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Festival of Neuroscience

Dublin, Ireland – 14th – 17th April 2019



British
Neuroscience
Association



Neuroscience
Ireland

BNA2019 POSTER ABSTRACTS**SESSION 1 – SUNDAY 14TH MARCH**

Poster number	Theme
PS001 – PS014, PS154	Attention, motivation, behaviour
PS015 – PS024	Developmental neuroscience
PS025 – PS039	Genetics and epigenetics
PS040 – PS063	Learning and memory
PS064 – PS095	Neurodegenerative disorders & ageing
PS096 – PS109	Neuroendocrinology and autonomic systems
PS110 – PS133	Neuronal, glial and cellular mechanisms
PS134 – PS151	Novel treatments & translational neuroscience
PS152 – PS153, PS155 – PS163	Psychiatry and mental health
PS164 – PS174	Sensory and motor systems

SESSION 2 – MONDAY 15TH MARCH

Poster number	Theme
PM001 – PM014	Attention, motivation, behaviour
PM015 – PM026	Developmental neuroscience
PM027 – PM047	Learning and memory
PM048 – PM066	Methods and techniques
PM067 – PM098	Neurodegenerative disorders & ageing
PM099 – PM112	Neuroendocrinology and autonomic systems
PM113 – PM123, PM125 – PM136	Neuronal, glial and cellular mechanisms
PM124, PM137 – PM153	Novel treatments & translational neuroscience
PM154 – PM166	Psychiatry and mental health
PM167 – PM177	Sensory and motor systems

SESSION 3 – TUESDAY 16TH MARCH

Poster number	Theme
PT001 – PT017	Attention, motivation, behaviour
PT018 – PT028	Developmental neuroscience
PT029 – PT054	Learning and memory
PT055 – PT088	Neurodegenerative disorders & ageing
PT089 – PT102	Neuroendocrinology and autonomic systems
PT103 – PT130	Neuronal, glial and cellular mechanisms
PT131 – PT147	Novel treatments & translational neuroscience
PT148 – PT150	Other (e.g. teaching, history, outreach etc)
PT151 – PT164	Psychiatry and mental health
PT164 – PT176	Sensory and motor systems

Poster number: PS001 (SP)**Theme:** Attention, motivation, behaviour**Differential effects of chronic corticosterone and interferon-alpha treatment on inducing anhedonia-like reward processing deficits in rats.****Authors:** Ms Lucy Lewis¹, Professor Emma Robinson², Professor Dominic Dwyer¹¹*School of Psychology, Cardiff University, Cardiff, United Kingdom*, ²*School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, United Kingdom*

Deficits in reward processing are common across several psychiatric disorders, such as Major Depressive Disorder (MDD), and include a reduced experience of pleasure (anhedonia), reduced motivation (apathy) and altered expectation of rewards in the environment (negative cognitive bias). Given the heterogeneity of symptoms expressed in patients suffering from such psychiatric disorders, the ability to parse the underlying neurobiology of each symptom individually is essential for identifying more specific targets for treatments.

Enhanced levels of glucocorticoids and pro-inflammatory cytokines are known risk factors for MDD, and chronic treatment with pharmacological agents related to these factors, e.g. corticosterone (CORT) and interferon-alpha (IFN- α), have shown to induce depressive-like phenotypes in rats. Previous studies have shown that both these substances induce negative cognitive bias, as measured in the affective bias test (ABT), but only CORT appears to induce anhedonia in the commonly used sucrose preference test.

Our study compares the effects of chronic treatment with CORT vs IFN- α on anhedonia-like behaviour in Sprague-Dawley rats, as measured in a more sensitive analysis of their licking microstructure when consuming 4% and 16% sucrose solutions. We demonstrate that CORT-treated rats displayed a significantly reduced average lick cluster size, indicating a lower hedonic response to sucrose reward. However, IFN- α treatment did not result in a change in lick cluster size.

These findings suggest distinct neurobiological roles of glucocorticoids and pro-inflammatory cytokines in the disruption of reward processing. Our future work will examine the effects of CORT vs IFN- α on motivational behaviour, completing the assessment of hedonic, motivational, and cognitive components of reward processing deficits, and thus characterising the psychiatric symptoms specifically associated with glucocorticoid and pro-inflammatory cytokine overproduction.

Poster number: PS002 (SP)**Theme:** Attention, motivation, behaviour**Effects of an Immunomodulator in a mice model of Social Isolation****Authors:** Ms Daniela Magalhães^{1,2,3}, Ms Myrthe Mampay³, Mrs Ana M Sebastião^{1,2}, Mr Graham K Sheridan³, Mrs Cláudia A Valente^{1,2}¹*Instituto de Farmacologia e Neurociências, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal*,²*Instituto de Medicina Molecular – João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon,*³*NeuroImmunology and NeuroTherapeutics Lab, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, United Kingdom*

Introduction: Social isolation (SI) is a psychological stressor, causing an alteration between the immune system and CNS communication^{1,2}. Therefore, the modulation of the crosstalk between immune system and CNS cells in a SI mice model was studied. FTY720, a nootropic and an inhibitor of the peripheral immune cell migration^{3,4}, was used to evaluate its effects upon anxiety-like behaviour and neuroinflammation induced by SI.

Methods: Young and Aged mice were studied and divided into 4 groups. Two groups were grouped house (GH) and the other two were SI for three weeks. Half of GH and half of SI received DMSO, while the other half was treated

with FTY720. Depression and anxiety were evaluated through Force Swim Test (FST) and Open Field (OF), respectively. Following the behaviour tests, molecular approaches were performed, specifically ELISA and Western Blot, to evaluate neuroinflammatory markers in hippocampus region, since they have a role in mental disorders.

Approach for statistical analysis: All the statistical analysis were performed using GraphPad Prism software (San Diego, CA, USA) and two-way ANOVA was used.

Results and conclusions: FST showed a decrease in immobility time in Young mice SI-FTY720 when compared to SI group, while OFT revealed a resilience in SI Aged mice treated group. Microglia activation analyses demonstrated that FTY720 decreased Iba-1 expression in SI Aged mice. Besides, inflammasome NLRP3 levels, which integrates the stress-associated signals⁵, were also diminished when given the drug to SI Young mice. This inflammatory complex is upstream in the activation of the pro-inflammatory cytokine interleukin-1 β (IL-1 β), which has also a key role in anxiety and depression⁵. Thus, IL-1 β expression was study and results showed a decreasing tendency in groups treated with FTY720. In conclusion, FTY720 treatment demonstrated a significant improvement in anxiety-like behaviour and a decrease in inflammatory mediators.

1. Stepanichev M, et al (2014). *BioMed Research International*, vol. 2014, Article ID
2. Wohleb ES (2016). *Nature Reviews Neuroscience*, 17(8), 497–511.
3. Brinkmann V, et al (2010). *Nature Reviews. Drug Discovery*, 9(11), 883–897.
4. Froestl W, Muhs A & Pfeifer A. (2014). *Journal of Alzheimer's Disease*, 41(4), pp.961–1019.
5. Yue N, et al (2017). *J Neuroinflammation*, 10;14(1):102

Poster number: PS003 (SP)

Theme: Attention, motivation, behaviour

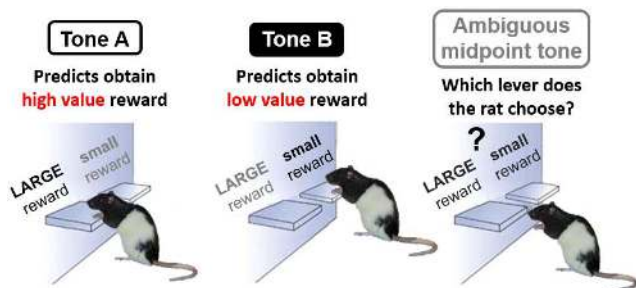
Targeted infusions with rapid acting antidepressants reveal a role for the prefrontal cortex in mediating affective biases and decision making

Authors: Dr Claire Hales¹, Julia Bartlett¹, Dr Roberto Arban², Dr Bastian Hengerer², Prof Emma Robinson¹

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Introduction: Affective biases are thought to be an important factor in the development, maintenance and treatment of depression, and can be measured in animals. Previous work has shown that acute, systemic treatment with rapid-onset antidepressants induce positive biases in decision making in a reward-based operant rodent judgement bias task (Hales et al., 2017). Here, we refine the site of action of three drugs shown to rapidly alter bias in this task by using targeted infusions into the rat medial prefrontal cortex (mPFC). To further elucidate the potential mechanisms involved we tested the GABA_A agonist muscimol.

Methods: Male lister-hooded rats were trained to discriminate between two distinct reference tones and respond on the appropriate lever to obtain high-value (four pellets) or low-value (one pellet) reward. Once trained, rats were implanted with mPFC guide cannula. Following recovery infusion studies were carried out using fully counterbalanced within-subject study designs. For experiment 1, rats were pretreated with either vehicle (PBS), ketamine (1 μ g/ μ l), scopolamine (0.1 μ g/ μ l) or muscimol (0.1 μ g/ μ l), while for experiments 2 and 3 rats were pretreated with either vehicle (10% 2-hydroxypropyl-cyclodextrin, 90% PBS) or CP-101,606 (1 μ g/ μ l or 3 μ g/ μ l respectively). Drugs were infused 5 minutes before twice-weekly test sessions (Tue/Fri) where judgement bias was measured by presenting midpoint ambiguous tones along with reference tones.



Schematic of the reward-based operant judgement bias task.
Rats are trained to discriminate between two reference tones (A and B) associated with large or small reward. Choosing the high-reward lever in response to the ambiguous tone is interpreted as expectation of high-value reward. A positive judgement bias occurs if more responses are made on the high-reward lever than the low-reward lever for the ambiguous cue, and vice versa for a negative judgement bias.

Approach for statistical analysis: Change from baseline in cognitive bias index (proportion of responses on the high-reward lever minus low-reward lever for vehicle session subtracted from drug session) was used as the main measure of judgement bias. Response latency and percentages of positive responses, omissions and premature responses were also analysed. Repeated measures ANOVAs with either one (treatment) or two (treatment and tone) factors were used as appropriate.

Results and conclusions: Ketamine, scopolamine and CP-101,606 (3µg/µl) induced specific positive changes in judgement bias for the midpoint tone (Fig.1), replicating effects seen using systemic treatments. Muscimol caused non-specific changes in behavioural measures across all three tones. This implicates the mPFC in the rapid-onset action of these drugs in altering decision making biases. These results also suggest the mechanism is more specific than inhibition of neurotransmission in the mPFC.

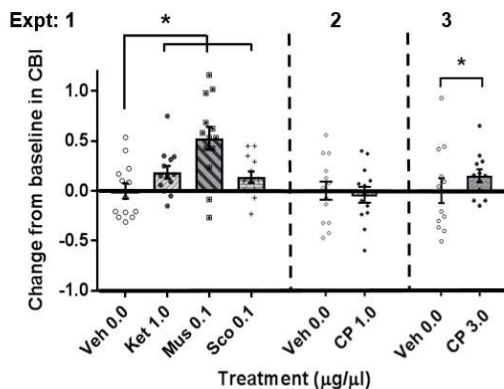


Figure 1 – Change from baseline in judgement bias caused by targeted mPFC infusions.
In experiment 1 (left), ketamine, muscimol and scopolamine all caused positive changes in judgement bias of the midpoint ambiguous tone. The lower dose of CP-101,606 (1.0 µg/µl; experiment 2; middle) had no effect on bias, but the higher dose (3.0 µg/µl; experiment 3; right) caused a positive change in bias. The effect of muscimol was non-specific, as it also caused large changes all other behavioural measures across all tones (data not shown), whilst the change in judgement bias were the only effects of the other drugs. Data shown represent mean ± SEM (block and error bars) as well as individual data points overlaid.

Poster number: PS004 (SP)**Theme:** Attention, motivation, behaviour**Not all rats like to be tickled****Authors:** Mrs Justyna K Hinchcliffe¹, Prof. Michael Mendl², Prof. Emma SJ Robinson¹¹*University of Bristol, School of Physiology, Pharmacology and Neuroscience, Bristol, United Kingdom,* ²*University of Bristol, School of Veterinary Sciences, Langford, Bristol, United Kingdom*

Introduction: Tickling and laughter have been primarily associated with humans and non-human primates, although this behaviour is thought to be observed in rats too (Panksepp J, Burgdorf J, 2003, *Physiol. Behav.*, 79(3): 533–47). Affective neuroscience research suggests that tickle-induced high frequency vocalisation patterns (50-kHz chirps), elicited by rough-and-tumble play, correspond to primitive human laughter and they may be related to their affective state. It also has been suggested that not all animals, like humans, encounter tickling as a pleasurable experience.

Methods: Male Lister Hooded rats (Harlan, N=16) were trained in the affective bias test (ABT for detailed method see Hinchcliffe JK et al., 2017, *Psychopharmacology*, 234(20): 3105-3116.), to enable a direct and individual measure of their affective state in response to tickling. The number of 50-kHz calls emitted during the 30s tickling sessions was then used to correlate with data from the ABT.

Approach for statistical analysis: The % choice bias data from the experiment were analysed using a one-sample t-test against the null hypothesised mean of 0% choice bias. Pearson correlation was used to analyse relationship between choice bias and the number of 50-kHz chirps.

Results and conclusions: Tickling induced a positive bias in rats in the ABT consistent with induction of a positive affective state at a group level ($t_{15}=4.753$, $p=0.0003$). There was a strong correlation between affective state and rats 'positive' vocalisations during the tickling episode (Pearson correlation, $r=0.8911$, $p=0.0001$). Moreover, we observed that not all rats respond to tickling in the same way, the animals that did not vocalise with 50-kHz calls also did not experience a positive affective state. Additional control experiment (hand approach test) revealed that these findings were not driven by direct or indirect effects of handling. This work demonstrates that individual differences in the amount of laughter induced by tickling are related to their affective response and, as seen in humans, not all rats like to be tickled.

Funding for this research was supported by a University of Bristol Research Postgraduate Studentship awarded to JKH. Additional funding was provided by a MRC project grant awarded to ESJR

Poster Number: PS005 (SP)**Theme:** Attention, motivation, behaviour**Differential effects of menstrual cycle and individual inhibitory control on activation and connectivity of the basal ganglia during a Stop Signal Task****Authors:** Ms Esmeralda Hidalgo-Lopez^{1,2}, Dr. Belinda Pletzer^{1,2}¹*Department of Psychology, University of Salzburg, Salzburg, Austria,* ²*Centre for Cognitive Neuroscience, University of Salzburg, Salzburg, Austria*

Introduction: Sex hormones fluctuations along the menstrual cycle are known to affect inhibitory control (IC) in women. Response inhibition can be assessed with the Stop Signal Reaction Time (SSRT), used as a clinical index in several disorders. Subcortical structures like basal ganglia (BG) are involved in the IC process and are known to

change in structure, activation and connectivity along the different cycle phases. Therefore, we aimed to investigate the BG activation and connectivity patterns related to IC across the menstrual cycle.

Methods: Thirty-six naturally cycling women were scanned three times locked to their menstrual cycle. During each session they performed a Stop Signal Task and saliva samples were collected to analyse hormonal levels.

Approach for statistical analysis: For the neuroimaging analysis we applied a two stage mixed effects model with SPM12, assessing the connectivity of bilateral BG with psychophysiological interaction (PPI). In order to analyze the behavioral data, the bilateral putamen BOLD-response and the effects of hormonal levels, statistical analyses were carried out through linear-mixed effects (LME) models.

Results and conclusions: We found an impaired SSRT during pre-ovulatory compared to menses, but only for those women who had better baseline IC. The BOLD-response in left and right putamen significantly decreased during luteal compared to pre-ovulatory for all women. Furthermore, the connectivity strength from the left putamen displayed an interactive effect of cycle phase and baseline IC. During pre-ovulatory compared to menses connectivity was significantly stronger for women with better IC, while it was decreased for women with worse IC in ACC and left IPL; and during luteal compared to menses in left SMA. The activation of the right putamen and differences in connectivity strength predicted the SSRT across participants. Therefore, we propose a compensatory mechanism for the hormonal changes across the menstrual cycle based on a lateralized pattern in putamens' activation and connectivity depending on the baseline IC.

Poster number: PS006 (SP)

Theme: Attention, motivation, behaviour

Activation of kappa opioid receptor (kor) potentiates cold sensation

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Introduction: Cold-evoked pain is commonly associated with peripheral neuropathy, and there is a limited progress in understanding the mechanism of cold pain, and here we are investigating the role of the KOR in mediating cold sensation and whether the presence/activation of TRPA1 channels modulates such an effect.

Methods: The cold plate assay was used to measure cold responsivity, C57BL/6 wildtype (WT) mice or TRPA1 KO were treated with U50,488 (U50) (KOR agonist, 5mg/kg i.p) or norbinaltorphimine (norBNI) (KOR antagonist, 10mg/kg i.p) to determine the nocifensive response. Thermal plantar assay was developed to assess how mice discriminate between the cold (3°C, 10°C) or warm temperatures (30°C). RNA *in situ* hybridization (ISH) fluorescent assay was used to determine the expression of KOR in the dorsal root ganglion (DRG) and its co-localization with TRPA1. To determine the calcium dynamics in DRG neurons, neurons were cultured from WT and treated with a TRPA1 agonist, mustard oil (MO) (100µM), U50 (10 µM), a combination of both and change in the intensity of the calcium indicator was quantified.

Approach for Statistical Analysis: A two tailed unpaired t-test and one-way ANOVA with Dunnett's Multiple Comparison test was used, and data is presented as mean ± SD.

Results: Mice injected with U50 showed significant potentiation in the number of jumps on the cold plate compared to controls at 3^oC. U50-induced nocifensive responses were attenuated in TRPA1 KO mice and norBNI administered mice. In the thermal plantar assay, WT spent less time in the cold zone when compared to their respective controls, which was higher in females. The hyperresponsivity to cold temperatures was higher at 3^oC vs. 10^oC. In ISH, the KORs colocalized with the TRPA1 in the DRG. Simultaneous application of MO, and U50 yielded a potentiated Ca²⁺ response when compared to the MO treatment, suggesting crosstalk between receptors in the DRG.

Conclusion: Activation of KOR potentiated cold sensation maybe via TRPA1 channel. The cold hyperresponsivity potentiated by KOR is temperature dependent and sex dependent. Colocalization of KOR and TRPA1 mediating cold responses in the DRG, and could potentially unravel the cold hypersensitivity associated with peripheral neuropathies.

Poster number: PS007 (SP)

Theme: Attention, motivation, behaviour

Towards an apathy phenotype: a behavioural analysis of aged mice

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Introduction: Apathy is a common behavioural symptom of aging, characterised by motivational deficit and emotional blunting. It is associated with poor quality of life and significant caregiver stress (Brodsky, H. *et al* 2010). Very few studies have explored the underlying mechanisms of apathy particularly in the context of normal aging, and as such treatment options are limited. The development of a suitable model for apathy to allow for assessment of its underlying neurobiology is therefore necessary. Here, we explore the impact of aging on behaviours relevant to apathy including sensitivity to reward, motivation for reward and emotional responsiveness to stress.

Methods: An aged cohort of 12 c57bl/6 male mice (15 months) provided by Eli Lilly and 12 sex and strain-matched controls (2 months) were used. Emotional responsiveness to stress was assessed using the novelty suppressed feeding test (NSFT). Motivation for reward was assessed using the progressive ratio task (PR) under food restriction and free food conditions, as well as the effort for reward (Efr) task. Sensitivity to reward was assessed using the sucrose preference test (SPT). Potential confounding factors such as differences in appetite and cognition were assessed using a consumption test and novel object recognition test (NORT).

Approach for statistical analysis: Performance in behavioural tests was compared between age-groups using an unpaired t-test. Where an additional factor including time/session was analysed, a repeated measures mixed model ANOVA with post-hoc unpaired t-test analysis was used.

Results and conclusions: Aged mice showed a reduced latency to eat in the NSFT and completed less trials in the PR task and EfR task (fig.1). However, mice failed to reach breakpoint under food restriction, and free food conditions removed the significant effect of age on PR performance. Aged mice also showed a reduced preference to sucrose solution in the SPT. The consumption test revealed aged mice eat more reward pellets when they are freely available compared to younger mice. The NORT revealed no difference in cognition between groups. Overall aged mice show evidence of blunted emotional and motivational arousal consistent with an apathy phenotype.

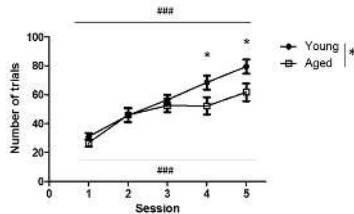


Fig.1 Number of trials completed over 5 consecutive sessions of the effort for reward task. Younger mice completed significantly more trials than aged mice at session 4 and 5. There was a significant effect of session on number of trials completed in both groups $n = 12$ per group, RM mixed model ANOVA with independent t-test post-hoc analysis. * $p < 0.05$, ### $p < 0.001$

Fig. 1.

Poster number: PS008 (SP)

Theme: Attention, motivation, behaviour

Differential behavioural effects of opioid receptor modulation on motivational state in the wistar 7yoto rat

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Major depressive disorder is the leading cause of disability worldwide¹ and inadequate response to antidepressant drug treatment is a serious issue. Wistar Kyoto (WKY) rats are considered to be a model of treatment-resistant depression (TRD) due to their increased immobility in the forced swim test (FST) and lack of response to standard selective serotonin reuptake inhibitor (SSRI) antidepressant treatments. In this study the WKY rat was used to examine the role of mu (MOR), kappa (KOR) and delta (DOR) opioid receptors in mediating mood and motivational behaviour in the forced swim test (FST) and a progressive ratio (PR) schedule.

WKY and control Sprague Dawley (SD) rats were tested in the FST, a measure of depressive-like behaviour, and a PR schedule, a measure of motivational behaviour. Opioid receptor modulators (MOR: cyprodime (10mg/kg), morphine (5mg/kg), RDC 2944 (0.1mg/kg); KOR: DIPPA (10mg/kg), U50 488 (5mg/kg); DOR: naltrindole (10mg/kg), SNC 80 (20mg/kg)) were administered s.c. 1hr before FST or 30min before PR schedule test. Fluoxetine (10mg/kg), an SSRI, was administered p.o. (once per day for 4 weeks). Hippocampal brain tissue was harvested post-mortem and analysed for neurogenesis by flow cytometry. Data were analysed by regular or repeated measures one- or two-way analyses of variance (ANOVA) followed by multiple comparison tests, where appropriate.

Increased immobility in the FST was observed in WKY rats in comparison to SD controls and treatment with the SSRI fluoxetine did not reduce this. Treatment with DIPPA or SNC 80 alone, or in combination, reduced immobility of WKY rats in the FST. Reduced breaking point (max responses per reinforcement) in the PR schedule was observed in WKY rats in comparison to SD controls and treatment with opioid receptor modulators failed to recover this. Reduced BrdU-labelled hippocampal cells were observed in WKY rats in comparison to SD controls. Treatment with DIPPA or SNC 80 alone, or in combination, attenuated this reduction. These data provide evidence to support the investigation of opioid receptor modulators for the management of TRD.

- 1) Rouine et al., *Opioid modulation of depression: A focus on imaging studies*. Prog Brain Res, 2018. 239: p. 229-252.

Poster number: PS009 (SP)

Theme: Attention, motivation, behaviour

An interaction between social affective biases and monetary offer amounts in human interpersonal negotiations

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¹University Of Oxford, Oxford, United Kingdom

Introduction: Negotiating the distribution of finite resources between parties who might have competing interests is an important part of human social interactions. Two key cognitive processes relevant to these social interactions are: (i) how people perceive their share of the resource distributions proposed by others, and (ii) the degree to which social affective biases (e.g. perceiving others' facial emotions more negatively than they actually are) influence these valuation mechanisms.

Methods: Participants (N=60) completed a brief facial emotion recognition task (bFERT) and rated various affective faces on a 9-point Likert scale (i.e. from negative to positive), allowing an assessment of social affective biases. A subset of participants (n=49) interacted with human confederates or a computerised opponent in a novel interpersonal monetary negotiation game which incorporates opponents' facial emotions, while undergoing pupillometry. All participants completed questionnaire measures of mood and social value orientation (e.g. Quick Inventory of Depressive Symptoms, Social Value Orientation Slider Measure).

Analysis approach: Affective biases were evaluated by fitting a 2-parameter probability weighting function to participant ratings in the bFERT. Participant choice behaviour was analysed using an ordinary least squares (OLS) regression model (e.g. regressors: opponent's facial emotion, offer amount, interaction term) as well as fitting formal computational models of the negotiation process. Pearson's correlation was used to evaluate linear relationships between psychological questionnaire scores and decision-making parameters.

Results and conclusions: Regression analysis of acceptance probabilities suggested that unfair offers coming from proposers with positive facial emotions were more likely to be accepted (based on Bonferroni corrected t-tests on regression coefficients, all $t > 3.508$, all $p < .001$). Model-based analysis suggested that social affective biases accounting for how people perceive others' emotional states are represented nonlinearly. Decision values, which guide participants' probability of accepting a condition in the negotiation game, are influenced by both the offer amount and an inequality term (i.e. difference between self and other's reward), which are further modulated by social affective biases.

Poster number: PS010 (PP)**Theme:** Attention, motivation, behaviour**Predicting successful inhibition using machine learning based on the brain's beta rhythm****Authors:** Ms Nadja Enz¹, Dr Kathy Ruddy^{1,2}, Dr Laura Rueda-Delgado¹, Dr Robert Whelan¹¹*Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland*, ²*Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland*

Introduction: The ability to inhibit unwanted behaviours is reliant upon effective inhibitory control in the brain. Poor inhibitory control is characteristic of a wide range of psychiatric conditions. The Stop-Signal Task (SST) is a lab-based measure that is sensitive to this deficiency, quantifying the time taken to cancel a response that has already been initiated (SSRT). A strong increase in the amplitude of brain oscillations in the beta (15-30Hz) frequency is registered in electroencephalography (EEG) recordings over the right inferior frontal gyrus at the moment of stopping a movement (Swann et al. 2009, Wagner et al. 2017). However, it is not clear whether this beta burst is directly instrumental in stopping the ongoing brain processes, or whether the pre-stop stimulus beta power influences successful inhibition. We hypothesise that if beta is instrumental to stopping, machine learning should be able to classify successful vs failed stop trials on the basis of beta power during stopping, but not of beta power prior to stopping.

Methods: EEG (64 channels) was recorded from 344 healthy participants while performing the SST. Beta power will be extracted at: i) the time of individual SSRT; and ii) in the 200ms before presentation of the stop signal.

Approach for statistical analysis: Penalised logistic regression will be used in our machine learning approach to predict the trial type (i.e. successful stop or failed stop). Nested cross-validation will be used to ensure stability of the model estimates (actual model). The entire procedure will be repeated using random-label permutation (null model). The accuracy of the null model will be compared to the accuracy of the actual model by performing a t-test. The actual model will be deemed to be successful if the area under the receiver operating characteristic curve of the actual model is larger than that of the null model ($p < 0.05$). The 95th percentile of the features of the null model will be used as a threshold on the actual model to identify spatial features (i.e. scalp locations) that best predict trial type. This procedure will be applied to an internal validation set and tested on an external validation set.

Poster number: PS011 (SP)**Theme:** Attention, motivation, behaviour**An empirical investigation of age-related differences in mind-wandering using triangulation of subjective, behavioural and electrophysiological measures****Authors:** Ms Catherine Moran^{1,2}, Ms Greta Warren^{1,2}, Mr Rónán Ó Grálaigh^{1,2}, Dr Joanne Kenney^{1,2}, Dr David McGovern⁵, Prof Alan Smeaton^{3,4}, Prof Paul Dockree^{1,2}¹*Trinity College Institute of Neuroscience, College Green, Ireland*, ²*School of Psychology, Trinity College Dublin, College Green, Ireland*, ³*School of Computing, Dublin City University, Ireland*, ⁴*The Insight Centre for Data Analytics, Dublin City University, Ireland*, ⁵*School of Nursing & Human Science, Dublin City University, Ireland*

Introduction: In mind-wandering, attention is disengaged from processing of the perceptual environment and redirected toward endogenously-generated mental content. However, little is known about how the phenomenology of these endogenous states differs between younger and older adults. This study classifies and measures the nature and frequency of mind-wandering states and investigates age-related differences.

Methods: A novel paradigm was employed using an adapted Continuous Gradual Target Detection task (McGovern et al., 2018; O'Connell et al., 2012) with triangulation of self-report, behavioural and electrophysiological assessments to decompose the signatures of mind-wandering. Thirty-eight participants completed the task requiring identification of contrast changes of a continuously presented flickering (25Hz) annulus stimulus for an intermittent gradual and smooth contrast reduction. The task was pseudo-randomly interrupted by experience sampling probes asking participants to subjectively discriminate the phenomenology and intentionality of their thoughts. Behavioural performance indices were measured, and electrophysiological signatures were tracked in real-time using continuous EEG and pupillometry.

Approach for statistical analysis: Preliminary analyses explored the nature and frequency of self-reported mind-wandering for younger and older adults. Additional analyses were designed to examine the electrophysiological changes that anticipate unintentional and intentional mind-wandering states in younger and older adults to elucidate the emergence of different subtypes of mind-wandering as a function of age.

Results and conclusions: Consistent with the literature, preliminary analysis showed that mind-wandering is frequent in human cognition. Groups differed in the propensity for and nature of mind-wandering. Older adults self-reported mind-wandering 31.38% of the time (20.82% unintentional; 10.56% intentional), while younger adults mind-wandered 53.01% of the time (31.13% unintentional; 21.88% intentional). Results are discussed in relation to the role of awareness in mind-wandering and different age-related metacognitive strategies.

Poster number: PS012 (SP)

Theme: Attention, motivation, behaviour

Lateral habenular-projecting hypothalamic neurons regulate food preference in a leptin dependent manner

Authors: Dr Richard M. O'Connor, Dr Maria V. Micioni Di Bonaventura, Dr Masago Ishikawa, Dr W. Matthew Howe, Dr Alexandra G. DiFeliceantonio, Ms Kavya Devarakonda, Dr Victor Mathis, Dr Paul Kenny
¹Icahn School of Medicine at Mount Sinai, New York, United States

Introduction: Rates of obesity are on the rise worldwide, resulting in a growing threat to public health. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of the complex neuronal mechanisms that control food choice. The lateral hypothalamus (LH) is considered a critical node in the maintenance of energy homeostasis. A major output of the LH terminates in the lateral habenula (LHb) which exerts a negative influence over motivated behaviours through inhibition of midbrain dopamine neurons. We tested the hypothesis that LH projections to LHb play an important role in food preference and food-related motivation through downstream influences on midbrain dopamine neurons.

Methods: Monosynaptic rabies tracing, Fibre Photometry, Behavioural analyses of Feeding

Approach for statistical analysis: Linear Mixed Effects Model

Results and conclusions: Using monosynaptic rabies tracing we found prominent innervation of ventral tegmental area (VTA) projecting LHb neurons originating in LH. Using fibre photometry, we found neuronal activity of these VTA projecting LHb neurons decreased in hungry animals during the retrieval of regular rodent chow rewards (homeostatic feeding) and in sated animals during palatable food consumption (hedonic feeding). In lean animals the magnitude of decreased neuronal firing from baseline was greatest for homeostatic food seeking compared to hedonic. Interestingly, this pattern switched when animals became obese through exposure to a cafeteria style diet. Ablation of LH inputs to the LHb increased consumption of palatable energy-dense food whereas decreased food consumption was observed when only standard (less palatable) chow was made available. Interestingly inhibition of

leptin activity in the LH of obese rodents lead to similar increases in preference for palatable food and rejection of standard chow suggesting the involvement of leptin in communication between the LH and LHb.

Based on these findings, we hypothesize that deficits in the LH – LHb - VTA circuit may emerge during weight gain and contribute to obesity-associated behavioural abnormalities.

Poster number: PS013 (SP)

Theme: Attention, motivation, behaviour

Intuition and reason: activity of the heart during moral judgement

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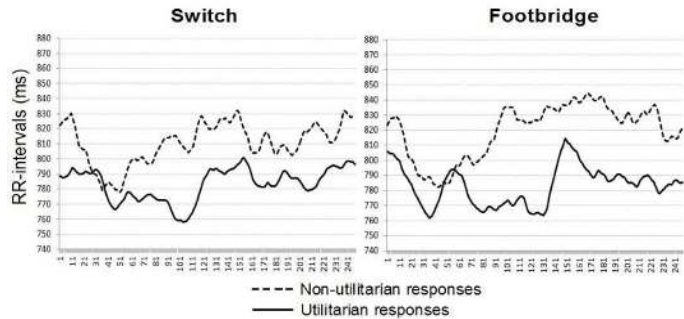
Introduction: Moral judgement is an important component of adaptive social behaviour. Harmful actions are usually associated with intense negative emotions and intuitively perceived as morally wrong. On the other hand, if harming someone results in a socially desirable outcome it can be judged as permissible. Utilitarian moral judgement (for example, allowing sacrificing one person's life to save more people) can be viewed as a conflict between intuition and reason (e.g. Greene et al., 2004). In this work we consider the intuitive and rational processes of moral judgement as an integral part of individual behaviour which is based on actualization of functional systems, the dynamic organization of physiological activity in the brain and the rest of the body which results in achieving an adaptive outcome (Anokhin, 1975; Shvyrkov, 1995; Alexandrov et al., 2000). This approach suggests that the heart is actively involved in the organisation of behaviour, and its activity should reflect the interplay between intuition and reason when making social judgements. In this work we tested a hypothesis that the dynamics of heart activity is different when individuals make utilitarian and non-utilitarian moral judgements.

Methods: ECG was recorded in 58 adult participants while they were evaluating permissibility of harmful actions in a set of moral dilemmas, including the traditional Trolley and Footbridge dilemmas. RR-intervals were analysed to describe the dynamics of heart rate (HR) and heart rate variability (HRV) indexes.

Analysis approach: HR and HRV indexes were compared using t-test and Mann-Whitney test (significance at $p < 0.05$) in situations when participants responded with utilitarian and non-utilitarian judgements.

Results and conclusions: Utilitarian moral judgements were accompanied by shorter RR-intervals, indicating higher HR, than non-utilitarian judgements (see Figure below). Lower HR had previously been reported to accompany the feelings of empathy and compassion to suffering others (Stellar et al., 2015). Lower HR in case of non-utilitarian judgements is consistent with the view on the role of negative social emotions, such as harm aversion, in moral judgement (e.g. Crockett et al., 2010). Overall, the results show that the intuitive and rational components of moral judgement are reflected in heart activity.

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The dynamics of mean values of interpolated RR-intervals (ms) during solving Switch and Footbridge dilemmas resulting in utilitarian (solid line) and non-utilitarian (dotted line) responses. Shorter RR-intervals, indicating higher heart rate, were observed when participants made utilitarian judgements compared to non-utilitarian judgements, Mann-Whitney U test: $U=4204$, $Z=16.58$, $p<0.001$ for "Switch"; and $U=4267$, $Z=16.54$, $p<0.001$ for "Footbridge"

Poster number: PS014 (SP)

Theme: Attention, motivation, behaviour

Investigation of opioid receptor modulation in recovery of object discrimination deficits in the IFN- α depression model

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Complaints of cognitive dysfunction are core symptoms of major depressive episodes. Research into current and potential antidepressant therapies does not often take this symptom into consideration. Given the renewed interest and potential efficacy of mu, kappa and delta opioid receptors (MOR, KOR and DOR respectively) in the treatment of affective disorders [1] we aimed to examine the 12eutrally12ve effects of opioid modulators in a rat IFN- α depression model. We investigated the effects of specific opioid receptor modulators (MOR agonist: RDC 2944 (0.5-0.1mg/kg); KOR antagonist: DIPPA (1.0-2.5mg/kg); and DOR: SNC 80 (1.0-5mg/kg)) alone, or in combination, on IFN- α -induced cognitive dysfunction.

IFN- α /saline treated male Sprague Dawley rats (170,000 IU, IFN- α or saline (0.9%) 3 times per week for 4 weeks) were examined in the novel object exploration task as a measure of cognitive function [1]. Briefly, animals were habituated to the arena before the sample phase where animals were exposed to 3 identical objects for 3x5min sessions with 5min intertrial intervals. 24hr later one object was exchanged for a novel object and the animals explored for another 5min in the test phase. DIPPA/vehicle was administered (s.c.) 23.5hr before test. RDC 2944, SNC 80 or vehicle were administered (s.c.) 30min before test. Data were analysed by regular or repeated measures one- or two-way analyses of variance (ANOVA) followed by multiple comparison tests, where appropriate.

Vehicle treated IFN- α rats were significantly impaired in the novel object exploration task compared to vehicle treated saline controls (** $p<0.0001$). The DOR agonist, SNC 80 (5mg/kg) alone recovered IFN- α -induced deficits in the novel object exploration task (* $p<0.05$). Combinations of DIPPA 2.5mg/kg & SNC 80 3mg/kg, DIPPA 2.5mg/kg & SNC 80 5mg/kg or SNC 80 (3mg/kg) & RDC2944 (0.5mg/kg) each recovered IFN- α -induced cognitive deficits (** $p<0.001$, ** $p<0.001$ and * $p<0.05$ respectively).

Together this data suggests opioid receptor modulation should be explored as a protagonist for depression related cognitive dysfunction.

1. Callaghan, C.K., et al., *Antidepressant-like effects of 3-carboxamido seco-nalmefene (3CS-nalmefene), a novel opioid receptor modulator, in a rat IFN-alpha-induced depression model*. *Brain Behav Immun*, 2018. 67: p. 152-162.

Poster number: PS015 (SP)

Theme: Developmental neuroscience

Development of dysfunctional feed-forward inhibition in the thalamo-cortical network of a mouse model of absence epilepsy

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Introduction: Childhood absence epilepsy accounts for approximately 10% of all paediatric epilepsies. While the hallmark spike-wave discharges seen in absence seizures arise from disturbances within the cortico-thalamo-cortical (CTC) network, the underlying mechanisms are unclear and appear to be multifactorial. Current antiepileptic drugs fail to suppress seizures in over 30% of patients. Hence, there is a need to understand the cellular and molecular mechanisms underlying seizure generation in patients from different genetic backgrounds. We recently reported reduced cortical AMPA receptor expression (predominantly GluA4-containing AMPARs) in parvalbumin-containing (PV+) inhibitory interneurons in the somatosensory cortex of the well-established stargazer mouse model of absence epilepsy. Fast spiking PV+ interneurons are responsible for feed-forward inhibition, which is essential to prevent runaway excitation within the brain. The aim of the current study was to investigate AMPAR subunit changes occurring during postnatal development to determine when these changes occur relative to seizure onset and thus if they could be contributory to seizure generation.

Methods: Quantitative western blotting was used to investigate the expression of AMPAR GluA1-4 subunits in the somatosensory cortex of epileptic stargazer and non-epileptic (NE) control mice at three critical time points; two before seizure onset (postnatal days (PN) 7-9 and 13-15), and one at seizure onset (PN17-18) in stargazers. Protein bands were analysed using Odyssey Image Studio Lite v3.1, with the relative intensity of each protein band normalized against its corresponding β -actin loading control band.

Approach for statistical analysis: Statistical differences in AMPAR expression levels between stargazers and their NE control littermates were tested using unpaired Mann-Whitney U test in GraphPad Prism 7.0, with statistical significance set at $p < 0.05$.

Results and Conclusions: Data analyses revealed a significant reduction in expression of AMPARs containing GluA1, 3 and 4 subunits but not GluA2 prior to seizure onset in the stargazers; reduction in GluA2-AMPA receptors occurred post-seizure. We conclude that while loss of GluA4-containing AMPARs (which are predominantly expressed in feedforward PV+ inhibitory interneurons and would therefore lead to dysfunctional feedforward inhibition) may be linked to seizure induction, the loss of GluA2-AMPA receptors is a secondary post-seizure change, which is most likely involved in seizure maintenance.

Poster number: PS016 (SP)**Theme:** Developmental neuroscience**Maternal vitamin d deficiency increases postnatal anxiety behaviour, changes proliferation and differentiation and epigenetic markers****Authors:** Ms Gulden Madi¹, Dr. Maria Toledo-Rodriguez¹, Dr. Preeti Jethwa²¹University Of Nottingham, School of Life Sciences, Nottingham, United Kingdom, ²University of Nottingham, School of Biosciences, Nottingham, United Kingdom

Exposure to sufficient vitamin D during early development is thought to be critical for neurodevelopment and yet the number of women of childbearing age deemed to have vitamin D deficiency (VDD) is increasing. The aim of this study was to investigate the impact of maternal VDD on postnatal neurodevelopment and explore the potential mechanism.

Virgin female C57BL/6J mice were fed a vitamin D sufficient (2.2IU D/g; CD) or deficient (0.0 IU D/g; VDD) diet for 6 weeks prior to being mated. At weaning offspring remained on their maternal diet for a further 8 weeks. At 8 weeks of age, spatial Learning and memory was investigated by spontaneous alternation while anxiety was measured using the elevated plus maze. At the end of the study, brains were dissected for: a) gene expression analysis of neurotrophins and epigenetic markers in hippocampus and hypothalamus, and b) immunohistochemistry to assess proliferation (Ki67) and differentiation (doublecortin) in dentate gyrus and sub ventricular zone. Four sections per animal were used for quantification in the dentate gyrus and sub ventricular zone. Images were analysed using ImageJ 1.43. All gene expression data was analysed using unpaired t-tests, using Prism 7 and significance threshold was set to P<0.05.

Mice exposed to VDD significantly increased anxiety like behaviour (P<0.05), while there was no significant difference in memory and learning (P=0.09) compared to CD offspring. Moreover, a significant increase in Ki67 immunoreactivity (IR) was observed in the sub ventricular zone of 8 weeks old males compared to CD offspring group (p<0.001). However, no significant changes were observed in doublecortin-IR in both tissues. Expression of neurotrophin genes brain-derived neurotrophic factor (BDNF; P<0.05) and VGF (P<0.0001) and, methylation markers KDM5A (P<0.001), KDM6B (P<0.001), UTX (p<0.001) and TH (P<0.05) but not Ezh2 was significantly increased in VDD offspring group compared to CD group of the 8 weeks old males.

VDD during early development promotes anxiety like behaviour in adult offspring, possibly due to modified proliferation and differentiation of neurones within the hippocampus. This may be associated with changes in the methylation of genes, ultimately leading to perturbed anxiety and memory.

Poster number: PS017 (SP)**Theme:** Developmental neuroscience**Do maternal glucocorticoids transmit the programming effects of maternal stress to the fetus?****Authors:** Ms Ying Sze^{1,2}, Ms Joana Fernandes^{1,2}, Dr Paula Brunton^{1,2}¹Centre for Discovery Brain Sciences, University Of Edinburgh, Edinburgh, United Kingdom, ²The Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom

Despite attenuated hypothalamo-pituitary-adrenal (HPA) axis responses to acute stress in pregnancy, chronic maternal social stress still exerts negative programming effects on the offspring. The mechanisms by which this occurs remains unclear, but excess maternal glucocorticoid transfer to the fetus could play a possible role. Local concentrations of glucocorticoids are modulated by 11 β -hydroxysteroid dehydrogenase (11 β HSD) enzymes. In the placenta, 11 β HSD2 converts corticosterone (CORT) into the inactive metabolite 11-dehydrocorticosterone (11-DHC), regulating glucocorticoid transfer across the maternal-fetal interface; whilst in the brain, 11 β HSD1 converts 11-DHC to CORT, regulating local glucocorticoid synthesis.

Pregnant rats were exposed to 10min social stress/day via the resident-intruder paradigm, from day 16-20 of pregnancy. Rats were killed following the final bout of stress and blood/tissues collected. Concentrations of CORT and 11-DHC in the maternal and fetal plasma, placenta, fetal brain and liver were quantified using liquid chromatography-mass spectrometry. *In situ* hybridisation was performed to quantify mRNA expression for 11 β HSD2 and glucocorticoid receptor (GR) in the placenta, and 11 β HSD1 in the fetal brain. Data were analysed by two-way ANOVA.

Plasma corticosterone concentrations were 3.7-fold greater in the stressed dams compared to controls. Maternal stress significantly increased circulating corticosterone concentrations in the female fetuses (1.3-fold), but not in the males. Similar changes were observed for plasma 11-DHC concentrations. CORT concentrations were significantly greater in the liver of both male (1.4-fold) and female fetuses (1.3-fold) following maternal stress; however no changes were detected in the fetal brain. Corticosterone concentrations and 11 β HSD2 mRNA expression were significantly greater in male, but not female placentae, from stressed dams compared with controls; with no changes in placental GR mRNA expression in either sex. 11 β HSD1 mRNA expression was greater only in the female fetal hippocampus after stress.

In conclusion, although repeated social stress activates the maternal HPA axis, the placental barrier appears intact, especially in the males, and the direct transfer of corticosterone from the maternal to fetal circulation is minimal. However, some changes in corticosterone metabolism still occur in the fetal liver and fetal brain. The data suggest that maternal glucocorticoids could exert effects on fetal glucocorticoid metabolism, but probably in an indirect, and sex-dependent manner.

Poster number: PS018 (SP)

Theme: Developmental neuroscience

Modelling of retinal mosaic formation using an agent-based model

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Individual retinal cell types exhibit semi-regular spatial patterns called retinal mosaics. These mosaics, enabling uniform sampling of visual information, are formed to varying degrees across cell subtypes. Retinal ganglion cells (RGC), amacrine, horizontal and photoreceptor cells are known to exhibit such layouts. In addition to cell body mosaics, dendritic arbours also form mosaics - dendrites of homotypic cells exhibit avoidance while dendrites of different types overlap.

Mechanisms responsible for the formation of such organised structures are still not well understood and they follow three main theories. (1) Homotypic cells prevent nearby cells from adopting the same type. (2) Cell tangential migration, with homotypic cells repulsing each other. (3) Cell death, with specific cell types (mainly RGCs) exhibiting high rates of apoptosis, increasing spatial regularity.

Here, we use BioDynaMo, an agent-based simulation framework, to build a detailed and mechanistic computational model of mosaic formation in 3D physical space. In particular, we investigate the implications of the three theories and their combinations.

To compare mosaics we use the regularity index, calculated by dividing closest average homo-type cell distance by the standard deviation.

We show that cell movement mechanism yields the most regular mosaics. Moreover, the longest cellular migration distance achieved in these simulations is in agreement with experimental observations. We also found that even if cell fate alone cannot create regular mosaics, it can enhance the mosaic regularity in combination with other mechanisms. Furthermore, we found that cell death can create regular mosaics only if 55-80% of the cells undergo apoptosis. Such a level of cell death precisely matches experimental findings, reporting 60-80% apoptosis in the RGC population. Finally, simulations of dendritic growth suggest a relationship between somatic mosaics and dendritic arbours morphology.

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Poster number: PS019 (SP)**Theme:** Developmental neuroscience**Characterising the molecular heterogeneity within human inhibitory interneurons – at single cell resolution****Authors:** Ms Francesca Keefe^{1,2}, Professor Anne Rosser¹, Professor Meng Li¹¹Cardiff University, Cardiff, United Kingdom, ²Wellcome Trust, London, United Kingdom

GABAergic inhibitory interneurons describe a diverse class of neurons. The critical role that interneurons play within their circuits has been highlighted by their implication in different pathologies. This emphasises the need to unravel the mysteries behind human interneuron diversity. By identifying genes that underpin interneuron subtype heterogeneity, we could better understand why specific subtypes are vulnerable in neurodevelopmental disorders. Moreover, this knowledge could be applied in vitro to direct interneurons towards a desired subtype. Here we describe the use of single cell mRNA sequencing (Fluidigm C1 RNA seq workflow), combined with immunohistochemistry, to determine the single cell expression profiles of human interneurons from early progenitor to late post-mitotic stages of development. This analysis was completed in reference to “authentic” inhibitory interneurons derived from the human medial ganglionic eminence (one of the main sources of interneurons in the foetal brain), and those derived in vitro from human embryonic stem cells. All human foetal tissue samples were obtained through voluntary abortions, and collected ages spanned from 9 to 15 weeks post-conception. Human embryonic stem cell derived interneurons were matured in vitro until post-mitotic stage. Repeated measures ANOVA, followed by Bonferroni post hoc test, was carried out to determine significant changes in marker expression over time. Single cell RNA seq analysis was performed using SINGuLAR Analysis Toolset. This included principal component analysis (PCA), which determined variation within each age group, and identified subpopulations. Weighted Correlation Network Analysis (WGCNA) identified differentially expressed genes between these subpopulations, and temporal changes in gene expression between age groups. Heterogeneity can be seen from early stages of interneuron development, with clustering of interneuron progenitors into subpopulations. By late development, transcriptomic profiles continued to diversify creating more distinct clusters (representing specific interneuron subtypes). This interneuron diversity and temporal changes were mirrored in both sources of interneurons, and confirmed at the protein level for the selected markers. Through this study we have identified candidate transcription factors that could be driving interneuron subtype diversity. Further work, using transcriptional activator dCas9 system, will be needed to directly determine the influence each candidate gene has on interneuron development in vitro.

Poster number: PS020 (SP)**Theme:** Developmental neuroscience**Altered VEP responses to illusory contours in children on the autism spectrum****Authors:** Dr Evan Myers¹, Mr. Zhewei Cao¹, Mr. Eric Nicholas¹, Dr. Edward Freedman¹, Dr. John Foxe¹¹University Of Rochester, Rochester, Ny, United States

Introduction: Perception of an object despite its incomplete presentation by ‘filling in’ missing segments is a fundamental visual process permitting recognition of objects that are partially occluded. This same process can lead to the illusory perception of contours, for example when showing Kanizsa figure stimuli consisting of equidistant ‘Pac-Man’ inducers. When these are oriented at a random rotational angle no illusory contour is observed, yet when oriented, as if they were the corners of a square, a completed square is reported. Two consistent effects occur when comparing EEG responses to presentation of these stimuli: [1] an increased amplitude in the N1/N170 peak, dubbed the *IC-effect* and [2] a sustained increased negative shift between 230 – 450ms, termed the ‘negativity for closure’ (N_{cl}) component. Both the *IC-effect* and N_{cl} component are most prominent from electrodes positioned over the lateral occipital cortex (LOC). Atypical sensory processing has been frequently reported in individuals with autism and are often correlated with symptom severity. Furthermore children diagnosed with an ASD show attenuated boundary detection.

The current study is an investigation of the VEP response following illusory contour versus no contour stimuli in neuro-typical (NT) compared to ASD children

Methods: Participants sitting in front of an LCD monitor were instructed to fixate on a central red target and to press a button following a brief color change to green. IC and NC stimuli were presented randomly for 80ms with an average frequency of once-per-second.

Approach for statistical analysis: Analysis of our EEG data using EEGLAB software thus far provides evidence of a differential VEP profile comparing the two groups.

Results and conclusions: In particular, we observe an attenuated *IC-effect* and N_{cl} component in the ASD group as compared to the NT group. Thus, this seemingly dampened contour perception may provide a neurophysiological marker of ASD as well as insight into the underlying differences in sensory processing in children on the spectrum.

Poster number: PS021 (SP)**Theme:** Developmental neuroscience**The anti-inflammatory peptide pat has no adverse effect on zebrafish embryonic development****Authors:** Prof. Bared Safieh-Garabedian¹, Dr. Michail Nomikos¹, Ms Malaz Elaidiq^{1,3}, Mr Alaaeldin Saleh¹, Prof. F. Anthony Lai^{1,3}, Dr. Gheyath Nasrallah^{2,3}¹College of Medicine, Qatar University, Doha, Qatar, ²College of Health Sciences, Qatar University, Doha, Qatar,³Biomedical Research Center, Qatar University, Doha, Qatar

Introduction: The synthetic peptide analogue of thymulin (PAT) has been shown to have potent anti-inflammatory and analgesic effects in animal models. However, as a potential therapeutic agent, its toxicity on the early developmental stages has not yet been investigated. In the present study, we have used zebrafish embryo model to evaluate any potential adverse effect of PAT on early developmental stages.

Methods: Mortality, teratogenicity, cardiotoxicity, locomotion and neurotoxicity, as well as hatching rate were employed to investigate any potential acute cytotoxic effects of PAT.

Approach for statistical analysis: Our findings showed that exposure to different doses of PAT (0.1, 1, 10, and 100 μM) do not induce any morphological or behavioral alterations in zebrafish embryos. The median lethal dose (LC50) and the no and the low observe effect concentration (NOEC) of PAT could not be calculated as no significant (>20%) mortality were recorded at any of the tested concentration. No significant teratogenic effects (including yolk and hear edema, scoliosis, eye and body size) were observed, suggesting that the low observe effect concentration (LOEC) was greater than the highest tested dose (100 μM). As the LOEC could not be calculated, we decided to use the 100 μM in all of the following toxicity assays. The hatching rate experiment showed that there was no delay on the hatching time of the PAT- treated embryos compared to the negative control ($p>0.05$), suggesting that PAT has no general detrimental effect on zebrafish embryo development. Furthermore, our results indicated that PAT does not induce any significant cardiovascular toxicity via examining the embryos' cardiac functions, including heart rate (beat per minute) ($p>0.5$), blood velocity ($p>0.5$), and diameter of blood vessels, compared to the negative control. Locomotion of the treated zebrafish embryos were also not affected, when assessed by spontaneous tail flick activity of the PAT-treated embryos compared to negative control ($p>0.5$), suggesting that PAT has no adverse effect on neuromuscular development of the zebrafish embryos.

Results and conclusions: In this study and taken together the results of the aforementioned toxicity assays, we provide evidence that besides its evolving therapeutic applications, PAT does not cause toxicity or adverse complications in zebrafish at early developmental stages.

Poster number: PS022 (SP)

Theme: Developmental neuroscience

Neural mechanisms of face-processing – an fMRI-study in 6- to 9-year-old healthy children

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The identification of facial expressions plays a key role in human social interaction. Although many studies have shed light on the neural network underlying face-processing in adults, only little is known about the neural correlates in children. The purpose of this study was to investigate whether the core face-processing network (*Fusiform face area*, FFA; *Occipital face area*, OFA and *posterior Superior temporal sulcus*, pSTS) and the extended face-processing network (e.g. amygdala and orbito-frontal cortex) are already fully developed in children and correlate with the location of face-processing regions in adults. Furthermore, the study aimed to investigate whether amygdala activity, which plays a central role in processing of emotions, can be robustly detected.

Functional brain activation for face-processing in 11 children (3 females, 8 males) aged between 6 and 9 years was being compared to activation in 10 adult subjects. Subjects were investigated using functional magnetic resonance imaging (fMRI) on a *Siemens Prisma 3-Tesla Magnetom* using a 64-channel brain array coil. During fMRI scanning subjects were presented a set of stimuli composed of images of male and female faces with neutral, sad and fearful facial expressions. Additionally, houses were presented as control stimuli. fMRI data were analysed using the software *Statistical Parametric Mapping* (SPM12). For normalisation of children data the toolbox *CerebroMatic* (implemented in SPM12) was applied. Statistical analyses were performed using *General Linear Models* (GLMs). Our analyses showed that the face-processing network is already well-developed in 6- to 9-year-old children. The core-network can be solidly portrayed on single-subject-level, showing robust bilateral activation of FFA, OFA and STS. However, the location and lateralization of the face-processing regions tends to be more variable in children compared to adults. Amygdala activity could be observed during face-processing in contrast to house-processing in some children. These results suggest that this paradigm can be applied to patients diagnosed with autism-spectrum-disorder (ASD) for generating a deeper understanding of their defective social interactions. We now use connectivity

analyses (in particular, *Dynamic Causal Modelling (DCM)*) to also assess the connectivity pattern in the face processing network.

Poster number: PS023 (SP)

Theme: Developmental neuroscience

Search organisation in multi-target displays can predict educational outcomes in children

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Introduction: The ability to organise one's search is an important skill, at least to those of us who frequently have to resort to running around the house after losing keys, phone, or other crucial items. In cognitive neuropsychology, tests of multi-target search organisation are frequently employed, and thought to reflect executive function. Here, we present the findings of a large (N>500) study in children aged 5-7.

Methods: Participants were tested with a custom-built cognitive testing suite that assessed (among other functions) verbal and spatial short-term memory, fluid reasoning, reading and maths fluency, and search organisation. The latter was tested using a multi-target visual search task, in which participants had to locate all targets among distractors. In one version, targets would be visibly marked off, and in another participants had to rely on memory.

Approach for statistical analysis: We employed dimensionality reduction (UMAP) and k-means clustering on search duration data from the marked and non-marked tasks. In addition, we employed structural equation modelling to test what structures of latent factors could best explain the observed data from the following variables: verbal short-term memory (digit recall accuracy), spatial short-term memory (dot matrix accuracy), fluid reasoning (Cattell Culture Fair series and classification sub-tests), search organisation (best R, intersection rate, and inter-target distance for visibly marked search), processing speed (inter-target time for both search tasks), reading proficiency (number of sentences correctly read in two minutes), and maths proficiency (number of correct sums in two minutes).

Results and conclusions: We found a reliable cluster solution with three groups characterised by quick search on both search tasks, slow search on both search tasks, and quick search only when targets were visibly marked. Two of the groups differed only on duration of the non-marked task, but these groups were of similar spatial short-term memory. They did differ in search organisation scores and educational outcomes. Our structural equation modelling suggested that short-term memory and search organisation were the main predictors of educational outcomes. In sum, search organisation is a simple and engaging test that explains unique variance in educational outcome measures.

Poster number: PS024 (SP)

Theme: Developmental neuroscience

Modelling the developing brain: Joint estimation of neonatal brain tissue shape and intensity from the developing Human Connectome Project

Authors: Dr Jonathan O'Muircheartaigh¹, Dr Emma Robinson¹, Prof Mary Rutherford¹, Dr Maximilian Pietsch¹, Dr Rui Pedro AG Teixeira¹, Dr Dafnis Batalle¹, Dr Jelena Božek⁴, Dr Andreas Schuh², Dr Antonios Makropoulos², Dr Emer Hughes¹, Dr Lucilio Cordero-Grande¹, Dr Anthony Price¹, Prof Stephen Smith³, Prof Jo Hajnal¹, Prof Daniel Rueckert², Prof Serena Counsell¹, Prof A David Edwards¹

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Introduction: Over the perinatal period, brain development is rapid and nonlinear [Makropoulos et al, 2016]. This represents a challenge when investigating clinical perinatal injury using MRI. Parametric statistical models of brain growth models can help, but often rely on strong assumptions. Here; we used a Bayesian non-parametric model estimation technique, Gaussian process regression (GPR), with multiple outputs [Álvarez & Laurence, 2011], to continuously estimate the intensity and shape of T1 and T2-weighted MR images over the perinatal period.

Methods: MRI data reported here were collected as part of the developing Human Connectome Project, described in Makropoulos et al. [2018]. The sample was 424 individual neonates (194 female) across a wide range of ages at scan (26 to 45 weeks post-menstrual age) and ages at birth (24-42 weeks).

Analysis Approach: T1 and T2 weighted volumes were non-linearly registered to a single common template space [Avants et al, 2011]. The GPy package (<https://github.com/SheffieldML/GPy>) was used for model design and fit. At every voxel, a GPR model (with 5-fold cross-validation) was estimated with age-at-scan, age-at-birth and sex as predictors and T1w / T2w image intensity and the deformations to template space as outputs. To investigate the clinical utility of these models, we manually outlined punctate white matter lesions (PWML) in a sub-sample of 40 neonates.

Results and Conclusion: The resulting model provided a continuous voxelwise prediction of brain shape and intensity changes. These predictions illustrate post-natal development; continuous changes in size, intensity and gyrification. In the 40 neonates with PWML, we calculated receiver-operating-characteristic curves (ROC) to test performance of the GPR model for detecting voxels containing manually labelled PWMLs. The GPR model provided a mean area-under-the-ROC of 0.95 (median 0.98).

The model shows good accuracy, especially in white matter. This framework permits single-subject inference of deviations in tissue intensity and shape changes, appropriate to the age and sex, and sensitive to pathology in individual neonates.

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Poster number: PS025

Theme: Genetics and epigenetics

Exploring neurodevelopmental gene expression changes in EHMT1 knockout mice

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Disruptions in epigenetic gene-regulators have been implicated in a number of neurodevelopmental disorders. *EHMT1* and *SETD1A*, which methylate lysine-9 and lysine-4 of histone H3 respectively, are such neurodevelopmental disorder genes. Mutations in these genes that result in loss of function of one copy are therefore likely to alter histone modifications and regulation of other genes. We want to examine these effects on gene expression in a mouse model using RNA-seq.

We will compare gene expression in the brains of *Ehmt1* heterozygous knockout (n=6; 3 male, 3 female) to wild-type mice (n=6; 3 male, 3 female) at E13.5. This neurodevelopmental timepoint was chosen because it represents the peak of *Ehmt1* expression in the brain. RNA will be extracted, and libraries prepared using KAPA mRNA hyperprep. RNA-seq will be performed in-house using an Illumina HiSeq 4000.

Differentially expressed genes (DEGs) will be compared using Fishers method and corrected for multiple test using Bonferroni. DEG datasets will also be examined for functional enrichment using Gene Ontology analysis where the probability of observing the number of DEGs in any given biological pathway is greater than or equal to the one observed by random chance. This will be calculated using Fishers method. Similarly, mouse Entrez IDs will be converted to human homologues and enrichment analysis performed to look for over-representation of genetic risk factors contributing to developmental delay and autism spectrum disorder. Finally, we will examine whether there is an overlapping molecular mechanism of action in the loss of function of one copy *Ehmt1* and *Setd1a*, by comparing our data to existing RNA-seq data from a *Setd1a* mouse model also generated in the lab.

Poster number: PS026 (SP)

Theme: Genetics and epigenetics

Investigating chromatin accessibility across human gabaergic interneuron differentiation

Authors: Mr George Andrew Inglis¹, Dr. Ying Zhou^{2,3}, Mr. Dillon Patterson⁴, Dr. Christopher Scharer⁴, Dr. Jeremy Boss⁴, Dr. Zhexiong Wen^{2,3}, Dr. Andrew Escayg¹

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Introduction: Inhibitory GABAergic interneurons play a critical role in the maintenance of normal brain function, and interneuron dysfunction has been directly linked to neurological disorders such as epilepsy and schizophrenia. However, little is known about the noncoding genetic regulatory elements that establish key expression pathways necessary for proper interneuron function. While ATAC-seq and other strategies to identify genetic enhancer elements have been performed on samples from different human brain regions or organoids, use of these heterogeneous samples may mask putative genetic elements that are exclusive to GABAergic interneurons. To better identify the genetic elements and pathways involved in interneuron development, we differentiated human induced pluripotent stem cells (iPSCs) to GABAergic interneurons and harvested cells at three developmental stages for ATAC-seq and RNA-seq.

Methods: Human iPSC lines were derived from two healthy male subjects. iPSCs patterned to the ventral forebrain fate were differentiated to GABAergic interneurons with ~80% efficiency. Cells were collected for ATAC-seq and RNA-seq analysis at three developmental time points: neural progenitor cells (NPCs), immature interneurons (4 weeks post-differentiation) and mature interneurons (8 weeks post-differentiation).

Approach for statistical analysis: We performed ATAC-seq on 2-3 replicates at each of the three developmental time points, for both iPSC lines (n=17). RNA-seq was performed on one iPSC line, with 2-3 replicates per time point (n=8). We used Bowtie2 and Cufflinks to map sequencing reads to the human genome (hg38), and MACS2 and Bioconductor to annotate reads and call peaks. Differentially accessible regions (DARs) and differentially expressed genes (DEGs) were identified based on FDR<0.05 and FC₂. A subset of DEGs were validated by qRT-PCR.

Results and conclusions: We found significant, widespread changes in chromatin accessibility and gene expression between each development time point, regardless of the iPSC line. We are currently analyzing the correlation between DARs and DEGs, as well as the identifying any transcription factor networks altered over the course of differentiation. Altogether, these results will provide important information on the genetic elements and pathways involved in GABAergic interneuron development. Future research could examine the specific contributions of specific DARs to gene expression, and target these elements to modulate GABAergic interneuron activity.

Poster number: PS027 (SP)**Theme:** Genetics and epigenetics**Caenorhabditis elegans as a genetic model for alcohol addiction****Authors:** Dr Jeff Barclay¹¹*University Of Liverpool, Liverpool, United Kingdom*

Introduction: Addiction to alcohol is a worldwide medical and social problem. Consumption is causally related to a multitude of diseases such as cancer, cirrhosis of the liver, depression, neurodegeneration and dementia; however, the underlying molecular mechanisms are incompletely understood.

To investigate all components of alcohol addiction requires long-term experimental manipulation and analysis of a whole-animal model. Excessive consumption and the consequent acquisition of dependence is partly determined by genetics and a major component of that genetic determinism is an individual's initial level of response. Here we characterise the nematode worm *Caenorhabditis elegans* as a whole-animal genetic model to investigate the neuronal effects of alcohol abuse and addiction. These assays allow us to investigate and compare genetic, environmental and pharmacological contributions to specific neuronal alcohol phenotypes over the entire lifespan of the organism.

Methods: *C. elegans* strains were grown and analysed under standard growth conditions. Genetic manipulations included forward genetics, RNAi, transgenics and gene editing. Phenotyping involved existing and novel assays performed over a broad range of ethanol concentrations.

Approach for Statistical Analysis: All data were compared by t-test or one-way analysis of variance (ANOVA) with an appropriate post-hoc test for multiple comparisons.

Results and Conclusions: Our experiments using *C. elegans* have been able to model a broad spectrum of alcohol phenotypes including low-alcohol-induced stimulation of the nervous system separate from high-alcohol-induced depression of the nervous system, alcohol-induced neuronal stress and progressive neurodegeneration and also behavioural plasticity phenotypes including alcohol preference and alcohol aversion.

From these results we have corroborated targets identified from human genetic association studies and GWAS, such as alcohol dehydrogenase (ADH) and β -klotho. Additionally, we have identified and characterised novel targets such as neuronal α -crystallin proteins and their associated cellular signalling pathways that respond to exogenous alcohol. These well characterised neuronal phenotypes can now be used as a whole-animal platform for larger-scale investigations into the mechanisms of addiction and future pharmacological interventions.

Poster number: PS028 (SP)**Theme:** Genetics and epigenetics**DNA methylation changes associated with symptom improvement in response to clozapine - a longitudinal EWAS study in treatment resistant schizophrenia****Authors:** Dr Amy Gillespie^{1,3}, Dr Eilis Hannon², Dr Alice Egerton³, Prof Jonathan Mill², Dr James MacCabe³¹*University of Oxford, Oxford, United Kingdom*, ²*University of Exeter, Exeter, United Kingdom*, ³*King's College London, London, United Kingdom*

Introduction: For patients with treatment-resistant schizophrenia, clozapine is the only evidence based treatment available. However, despite substantial research, we lack a full understanding of the processes underlying clozapine's unique efficacy. Animal studies indicate that clozapine influences histone modification and DNA methylation (dynamic "epigenetic" modifications), and a cross-sectional human study identified multiple differentially methylated

positions (DMPs) in clozapine-exposed samples. Our aim was to examine longitudinal, within-participant DNA methylation changes over the first 6 months of clozapine use, associated with symptom improvement.

Methods: We recruited 30+ participants with treatment-resistant schizophrenia, before clozapine prescription. We then collected whole-blood samples at baseline and follow-up (6 weeks, 12 weeks and 6 months after clozapine initiation), alongside clinical assessments of symptoms. We quantified whole-blood DNA methylation at ~ 480,000 sites across the genome using the Illumina 450 K HumanMethylation array.

Approach for statistical analysis: Following pre-processing, normalization and quality control, multi-level regression models identified associations between DMPs and changes in symptoms. Continuous measures of within-participant changes in PANSS symptoms - total, positive and negative- were used. Models controlled for age, sex, predicted cell counts, smoking, batch, medication use and repeated measures. Statistical significance was set at $p < 1 \times 10^{-7}$. Results were cross-referenced with the Blood Brain DNA Methylation Comparison Tool (<https://epigenetics.essex.ac.uk/bloodbrain/>)

Results and conclusions: In preliminary analysis of the first 22 participants: Five DMPs were significantly associated with within-participant changes in *total symptom severity*, three of which had prior evidence of correlated methylation in brain. One DMP was located within the promoter region of GLRA1, while another was located within the promoter region of NEFM. Three DMPs were significantly associated with within-participant changes in *positive symptom severity*, one of which had prior evidence of correlated methylation in brain. Fourteen DMPs were significantly associated with within-participant changes in *negative symptom severity*, five of which had prior evidence of correlated methylation in brain; two of these were in genes involved in cell adhesion.

These results align with literature suggesting that clozapine may normalise schizophrenia-associated biological dysfunction, but require replication and further studies to establish the causal role of DNA methylation in clozapine response.

Poster number: PS029 (SP)

Theme: Genetics and epigenetics

Functional analysis of novel epilepsy mutations in STXBP1

Authors: Dr Bangfu Zhu¹, Mr Alistair Jones¹, Dr Jeff Barclay¹, Dr Graeme Sills¹, Prof. Alan Morgan¹

¹University Of Liverpool, Liverpool, United Kingdom

Introduction: Epilepsy is a group of neurological disorders characterized by epileptic seizures. Genetics has been recognised to play an important role since some genetic variants associated with epilepsy have been identified recently. However, it is still unclear how mutations in the identified genes contribute to epilepsy.

Our research has focused on STXBP1 (Syntaxin-binding protein 1) -- the second most commonly mutated gene in infantile epilepsies. STXBP1 is a member of the Sec1/Munc18 family of membrane trafficking proteins essential for neurotransmitter release. Our aims are to characterise the functional effects of disease-causing mutations in STXBP1 and to search for genetic modifiers that can ameliorate the consequences of those mutations.

Methods: We first made epilepsy-associated mutations in human STXBP1 and then generated transgenic *C. elegans* with each of the 8 selected mutations in STXBP1. These humanised animal models have been analysed for alterations in neurotransmission and behaviour by Thrashing Assays, Aldicarb experiments and Electropharyngeogram (EPG) recordings. Meanwhile, the expression levels of wild type and mutated STXBP1 were also monitored by Western blotting and qPCR.

Analysis approach: For quantification, at least 3 independent experiments were performed. For statistical comparison of two groups, two-tailed Student's *t*-test was performed and a value of $P < 0.05$ was considered as statistically significant.

Results and conclusions: Our data show that 3 of the mutations in STXBP1 (namely E59K, V84D and R292H) resulted in significantly defective locomotion in worms, whereas other mutants displayed little difference with STXBP1/Munc18 wild-type. Protein expression levels decreased dramatically in all mutants compared to the wild-type STXBP1/Munc18 rescue although their transcriptional expression remained at a similar level, which suggests that STXBP1 proteins are destabilised due to mutations.

Aldicarb results indicate that all worms with mutations in STXBP1 show an increased response/sensitivity to acetylcholinesterase inhibitor Aldicarb (i.e. a HIC phenotype) compared to N2 wild-type worms. However, EPG recordings demonstrate that all 8 mutations lead to abnormal pharyngeal electric activity with a lower frequency of pharyngeal pumpings and irregular rhythm compared with the wild-type control, which implies these mutations in STXBP1 may cause epilepsy by altering electrophysiology of neurons in the brain.

Poster number: PS030 (SP)

Theme: Genetics and epigenetics

Micrnas as mechanistically and clinically relevant biomarkers for temporal lobe epilepsy

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Introduction: MicroRNAs are small non-coding RNAs that regulate translation of proteins and show potential as biomarkers of epilepsy. In recent studies the altered expression profiles of microRNAs have been reported in models of epilepsy. Here we propose a set of microRNAs as mechanistically relevant biomarkers for temporal lobe epilepsy.

Methods: Blood samples were collected and processed to obtain plasma at multiple time-points from three status epilepticus-based experimental models of temporal lobe epilepsy. MicroRNA profiling was performed using the OpenArray platform which provides genome-wide coverage of all rodent microRNAs. Biomarker performance was supported by analysis of plasma samples from patients with temporal lobe epilepsy. To test whether antiepileptic drugs interfered with these biomarkers animals with epilepsy were treated with AEDs twice daily (IP) for 3 days and plasma was analysed for changes in microRNA expression. In a separate study, we tested whether these miRNAs responded to an anti-epileptogenic treatment, injecting mice with an oligonucleotide antagomir targeting miR-134 shortly after status epilepticus and measuring miRNAs levels in plasma 2 weeks later.

Approach for statistical analysis: For experiments consisting of two groups a Student's *t*-test was undertaken. For experiments consisting of more than two groups a one-way ANOVA with a post-hoc Dunnett's test was employed.

Results and conclusions: Thirteen of the twenty most abundant microRNAs were common between the models, including miR-19b, miR-24 and miR-223. A total of 74 microRNAs were shared in all three models in samples from rodents with epilepsy, which included brain-restricted microRNAs not present in baseline samples. We validated a set of three up- and down-regulated microRNAs in epilepsy samples which were fully conserved between models.

Levels of the three microRNAs were similarly dysregulated in plasma from people with temporal lobe epilepsy. The expression of the three microRNAs were not affected by the currently available treatments, but were normalised by the disease-modifying microRNA-based therapy.

This study provides strong support for plasma microRNAs as conserved, mechanistic molecular biomarkers of temporal lobe epilepsy. It also demonstrates that our biomarkers are sensitive to the underlying disease and not to seizures alone.

Poster number: PS031 (SP)

Theme: Genetics and epigenetics

Beyond C4: Cognitive analysis of a complement gene pathway enriched for IQ in an Irish Sample

Authors: Ms Jessica Holland¹, Dr Donna Cosgrove¹, Dr. Denise Harold², Dr David Mothershill¹, Prof Aiden Corvin², Dr Derek Morris¹, Prof Gary Donohoe¹

¹NUI Galway, Galway, Ireland, ²Trinity College Dublin, Dublin, Ireland

Introduction: In the largest Genome wide Association Study (GWAS) of Schizophrenia (SZ) to date, the strongest association with SZ was found at a region of the genome that is synonymous with immune function¹. Although several studies have supported the relationship between immune genetics and SZ, few have examined the effect of these genetics in relation to cognition². Cognitive impairment can be predictive of functional outcome in SZ, with immune variants linked to deficits in general cognition and episodic memory². The current study analyses the effects of immune challenge on cognition, examining a set of genes related to complement, and how these are enriched for cognition or schizophrenia risk.

Methods: To test if genetic variants related to immune function impair cognition, a gene set corresponding to complement function was chosen from previous literature. This complement gene set was tested for enrichment for the phenotypes of IQ and SZ using MAGMA. This gene set was then brought forward for analysis in an Irish sample.

Analysis approach: Using PRSice, a PRS was computed for the complement pathway (34 genes). Block regression analysis was performed in SPSS, testing a relationship between PRS and cognition in 1238 schizophrenia sufferers and healthy controls.

Results and conclusions: Enrichment analysis suggests that the genes in the complement pathway are enriched for the phenotype of IQ ($p=0.017$). In analysing individual genes within the path, Complement factor H (CFH) was found to be highly enriched for the phenotype of IQ. Regression analysis suggests that the complement pathway contributes to variation in IQ ($p=0.037$), but this finding did not survive multiple testing correction. Across analyses, an association between the complement pathway and IQ was observed. The complement cascade may be an important target for study in relation to cognition in SZ, and could further elucidate aetiology of this disorder.

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Poster number: PS032 (PP)

Theme: Genetics and epigenetics

Analysis pipeline of whole genome sequencing data in neurodevelopmental disorders

Authors: Ms Fiana Ní Ghrálaigh¹, Dr Niamh M Ryan¹, Prof Louise Gallagher¹, Dr Lorna Lopez¹

¹Department of Psychiatry, Trinity College Dublin,

Introduction: Twin studies show that neurodevelopmental disorders (NDDs) are highly heritable (Sandin *et al.*, 2017). It is expected that a significant proportion of causal genetic variants of NDDs are rare and highly penetrant, *de novo* (arising spontaneously) or inherited variants (Gaugler *et al.*, 2014). Whole Genome Sequencing (WGS) allows analysis of all variant classes, frequencies and sizes across the genome. We aim to: 1. use WGS to identify putative pathogenic variants for NDDs using a family study approach; 2. evaluate the clinical significance of rare, segregating, putatively pathogenic variants in our families; 3. compare the putatively pathogenic variants identified within each family and perform inter-family analysis to identify enriched pathways/networks.

Methods: A cohort of multiplex extended families with one or more individuals affected with an NDD will be ascertained in Ireland (diagnosed to DSM-V standards). Samples will be selected for WGS from the cohort following genotyping to exclude probands with chromosomal abnormalities. One hundred genomic DNA samples (affected and unaffected) will undergo WGS to a target depth of 30X. Sequence reads will be aligned and single nucleotide variants (SNVs), insertion/deletion variants (indels) and copy number variants (CNVs) will be called and processed. Variant filtration will be carried out as per Figure 1.

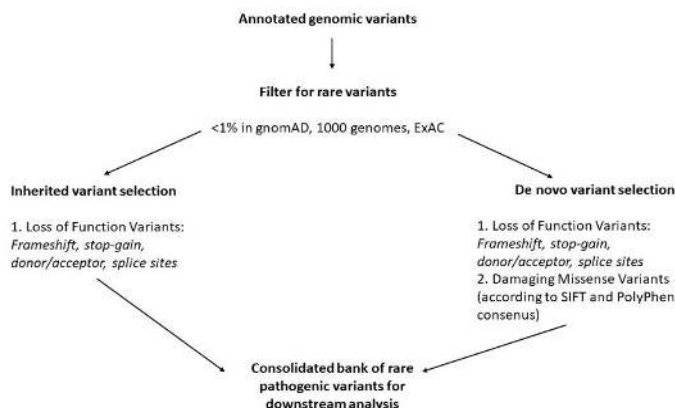


Figure 1 Variant Filtration Strategy: Variants will be filtered to a bank of rare genetic variants with a high likelihood of pathogenicity

Approach for statistical analysis: The resulting rare pathogenic variants (Fig. 1) will undergo statistical analysis to investigate disorder association. TADA (transmission and *de novo* association), a weighted, statistical model integrating *de novo*, transmitted and case-control variation will be run to increase power of association within families. Gene set enrichment analysis will compare cohort variants with previously associated NDD variants. Gene Network and Protein-Protein interaction analysis will investigate the burden of variants on pathways. Enrichment analysis will interrogate bias in frequency of inherited and *de novo* variants in affected versus unaffected individuals and bias in variant distribution across the genome.

References

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Poster number: PS033 (SP)

Theme: Genetics and epigenetics

MicroRNA Biomarkers of Paediatric Epilepsy

Authors: Dr Noelle Enright¹, Dr Gary Brennan¹, Dr Ngoc Nguyen¹, Professor Mary King², Professor David Henshall¹

¹Royal College Of Surgeons of Ireland, Dublin 2, Ireland, ²Children's University Hospital Temple Street, Dublin, Ireland

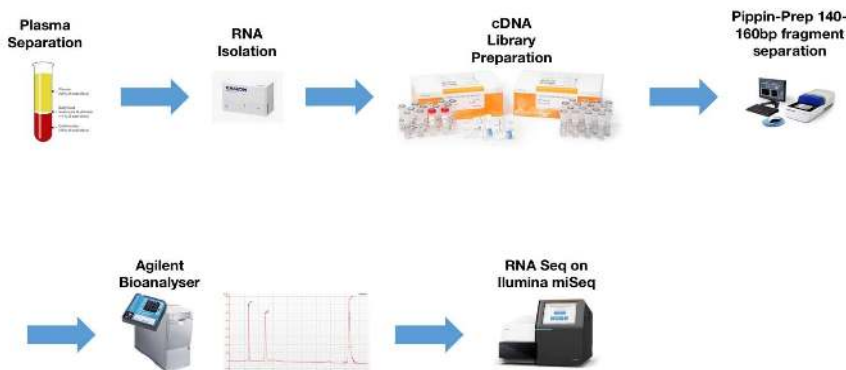
Introduction: Epilepsy is a prevalent chronic neurological disease in both children and adults. However, misdiagnosis is common, and only 50% of Magnetic Resonance Imaging (MRI's) in children with new focal seizures are abnormal (Gaillard *et al.*, 2009).

MicroRNAs (miRNA), small non-coding RNAs 22 nucleotides long (Bernardo *et al.*, 2012), function as an additional layer of gene expression by regulating protein expression (MacRae, 2013). They have been proposed as biomarkers in epilepsy as many are brain enriched, involved in processes central to epileptogenesis, identifiable in body fluids, and are stable in plasma (Ma, 2017).

This study aims to fill the gap in knowledge of miRNA profiles in paediatric epilepsy, and to identify a biomarker for lesional focal epilepsy, and for non-epileptic attack disorders both in children with epilepsy and those without.

Methods: Patients were divided into four groups (n=10) as follows; focal epilepsy with a normal MRI brain (Epi_FNM); focal epilepsy with an abnormal MRI (Epi_FAM); Epilepsy with non-epileptic attack disorder (Epi_N); Non-epileptic attack disorder (NEAD) (n=3). Controls were recruited from children with no neurological disorders having blood tests for another reason (Figure 1).

Figure 1. Methods.



Statistical analysis: Generated sequencing data was mapped to miRBase release 22 reference genome. RNA-seq analysis was performed using limma, Glimma and edgeR (Law *et al.*, 2016). Samples with low read counts and low numbers of miRNAs called present were filtered out prior to analysis; the remaining data was then normalised to account for batch effects and other technical biases. Differential expression analysis was then performed.

Results and conclusions: Seventeen miRNAs were shown to be differentially expressed between groups with an unadjusted p-value of <0.05. This study is the first to show differential expression (DE) of miRNAs between children with lesional and non-lesional focal epilepsy. These are an important biomarker as they have the potential to eliminate the need for MRIs in children with focal epilepsy. Other differentially expressed miRNAs show potential as biomarkers to diagnose both epilepsy and non-epileptic attack disorder. Importantly the majority of these DE miRNAs have been found to be DE in epilepsy in other studies and all are expressed in the brain.

Poster number: PS034 (SP)**Theme:** Genetics and epigenetics**MRNA expression profiling during status epilepticus and epilepsy**

Authors: Ms Giorgia Conte¹, Dr Alberto Parras^{2,3}, Ms Ivana Ollà², Dr Laura de Diego-Garcia¹, Dr Mariana Alves¹, Prof Raúl Méndez^{4,5}, Prof. David Henshall¹, Prof José J. Lucas^{2,3}, Dr Tobias Engel¹

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Introduction: Epilepsy is a chronic brain disorder involving abnormal neuronal activity characterized by the presence of seizures. In the 50% of the cases the pathology is acquired after a brain injury, it is developed in three phases: first the brain insult, then epileptogenesis and finally chronic epilepsy. Prolonged Status Epilepticus (SE), stroke or Trauma brain injury (TBI) are the most common causes of acquired epilepsy. It is still poorly known which transcriptional changes occur in the different stages of the pathology. For this purpose we investigated the gene expression changes after SE and during chronic epilepsy in an epileptic mouse model.

Methods: We injected kainic acid (KA) intra-amygdala to induce SE and consequently brain injury, and we performed a transcriptional profiling by microarray in mice hippocampus collected 8 hours and 14 days after SE, respectively during acute seizure and chronic epilepsy. We used this result to identify the biological pathway affected by the gene expression changes through DAVID Bioinformatics Resources 6.8. We identified the transcription factors involved in the regulation of the gene expression using Ingenuity Pathway Analysis (IPA) indicating cAMP response element binding protein (CREB) as the most implicated in all the conditions. A validation of the microarray results was performed by q-RT PCR. Finally, we injected KA and CREB inhibitor (666-15) to look at the role of CREB in the modulation of the gene expression and of the seizure severity in acute seizure.

Approach for statistical analysis: Graphpad was used to carry out t test and ANOVA

Results and conclusions: We found that during the acute seizure the number of up- and down-regulated genes was higher than during epilepsy, possibly due to the massive cell alteration that occurs during epileptogenesis. Calcium signaling pathway resulted to be downregulated in both pathological stages, suggesting a protective mechanism to reduce the neuronal hyperexcitability. We were able to confirm the downregulation of several genes involved in this pathway by q-RT PCR. Finally, CREB seems to modulate the downregulation of genes involved in calcium signaling pathway, while inhibition of CREB seems to decrease seizure severity during SE.

Poster number: PS035 (SP)**Theme:** Genetics and epigenetics**Differences in DNA Methylation Associated with Inflammatory Disease and Depression**

Authors: Mr. Anders Jespersen¹, Dr. Daniel McCartney¹, Dr. Riccardo Marioni¹, Prof. Andrew McIntosh¹

¹*University of Edinburgh, Edinburgh, United Kingdom*

Previous research has linked depression to inflammatory diseases and inflammatory blood markers, but the underlying molecular biology of the link is still unknown. DNA methylation (DNAm) is implicated in both depression and inflammatory diseases suggesting this could provide the link. Recent epigenome-wide association studies (EWAS)

have identified differentially methylated positions (DMPs) associated with depression (Jovanova et al 2018), as well as DMPs and differentially methylated regions (DMRs) associated with depression and inflammation (Crawford et al. 2018). In this study we tested the findings of previous studies and identified new DNAm signatures of inflammatory diseases and depression in a larger sample with a more robust and consistently measured depression phenotype.

Data from Generation Scotland were used; genome-wide DNAm measurements were obtained from blood samples using Illumina HumanMethylationEPIC BeadChips (n = 4,847). A clinical measure of depression was obtained using the Structured Clinical Interview for DSM-4 (SCID) Brief Screening Interview for Major Depression and a measure of inflammatory disease (self-report of diabetes, osteoarthritis, rheumatoid arthritis, COPD, or asthma – presence of any versus absence format). All models controlled for use of antidepressant medication (electronic healthcare-linked), white blood cell counts, age and sex.

An EWAS of a depression-inflammatory disease interaction revealed no genome-wide significant associations, but 5 CpGs with $P < 1 \times 10^{-5}$. A replication of the depression EWAS by Jovanova et al. (2018) showed an overlap of 5/15 (33.3%) DMPs with $P < 0.00625$. A replication of Crawford et al. (2018) revealed an overlap of 3/9 (33.3%) DMPs with $P < 0.0125$ for depression, none with the depression-inflammatory disease interaction, and 3/6 DMRs with $P < 0.0125$ for the depression-inflammatory disease interaction. However, a principal components analysis revealed that 6 DMRs could be collapsed to 4 suggesting that physical proximity may not be an important factor in coordinated multi-CpG methylation.

Our genome-wide analysis of DNA methylation, depression and inflammatory diseases identified several DMPs associated with a depression-inflammatory disease interaction approaching epigenome-wide significance. Furthermore, we demonstrated a good replication of results from previous EWASs of depression and depression-inflammatory disease interaction. Together these findings further elucidate the role of DNA methylation as a potential biological link between inflammatory diseases and the development of depression.

Poster number: PS036 (SP)

Theme: Genetics and epigenetics

Characterising the genetic and epigenetic architecture of neurological biomarkers in the Lothian Birth Cohort 1936

Authors: Mr Robert Hillary¹, Dr Daniel McCartney¹, Dr Sarah Harris^{2,3}, Ms Anna Stevenson¹, Ms Anne Seeboth¹, Mr Qian Zhang⁴, Mr David Liewald², Dr Kathryn Evans¹, Prof Craig Ritchie⁵, Dr Allan McRae⁴, Prof Naomi Wray⁴, Prof Peter Visscher⁴, Prof Ian Deary^{2,3}, Dr Riccardo Marioni^{1,2}

¹Centre for Genomic and Experimental Medicine, Institute Of Genetics And Molecular Medicine, The University Of Edinburgh, Edinburgh, United Kingdom, ²Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, Edinburgh, United Kingdom, ³Department of Psychology, The University of Edinburgh, Edinburgh, United Kingdom, ⁴Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia, ⁵Edinburgh Dementia Prevention, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, United Kingdom

Introduction: Aberrant plasma protein levels may serve as important markers of disease risk and progression in neurological conditions. However, the molecular mechanisms responsible for inter-individual variation in human plasma protein levels are poorly understood.

Methods: In this study, we have conducted genome- and epigenome-wide association studies on the levels of 92 neurological biomarkers to identify the genetic and epigenetic loci associated with their plasma concentrations (n = 750 individuals; mean age of 73).

Approach for statistical analysis: Following the identification of genetic and epigenetic associations with plasma biomarkers levels, we characterised these associations into *cis* and *trans* effects through bioinformatic analyses. *Cis*

effects were defined as loci residing within one megabase from the transcription start site. *Trans* effects were located outside of this region or on another chromosome. Upon identifying *cis* pQTLs, overlap with publicly available *cis* gene expression data (eQTLs) was examined to determine whether effects on protein levels were likely driven by changes in transcription. Bayesian tests of colocalization were performed to determine whether common causal variants underpinned modulation of transcript and protein levels.

Results and conclusions: We identified 3,128 genome-wide significant loci (or protein quantitative trait loci; pQTLs) in 38 proteins and 2,317 epigenome-wide significant sites associated with the levels of 10 proteins. Four proteins shared both genome- and epigenome-wide associations. Of the 3,128 pQTLs, 74 were determined to be independent. Of the independent genetic associations, 50 (67.5%) and 24 (32.5%) were *cis* and *trans* effects, respectively, whereas 1% of epigenetic associations were *cis* effects. 60% of *cis* pQTLs were also expression QTLs in the same gene in one or more tissue type. We observed a probability >75% that 7 independent *cis* pQTLs colocalized with eQTL variants. Furthermore, will perform summary-data-based Mendelian randomisation to determine whether proteins, including tau and poliovirus receptor, are causal in Alzheimer's disease. In summary, this study has identified genetic and epigenetic factors which may regulate neurological biomarker levels. Additionally, information from this study may be used to determine whether neurological biomarkers are causal in neurological disease states.

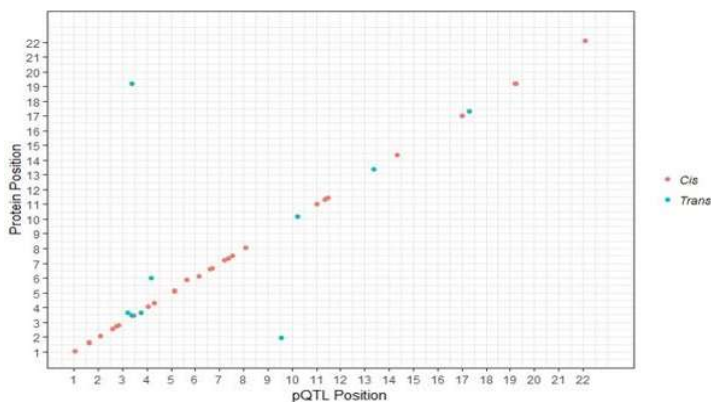


Figure 1 Genomic locations of pQTLs. The x-axis represents the chromosomal location of independent *cis* and *trans* SNPs associated with the levels of Olink neurology proteins. The y-axis represents the gene encoding the associated protein. Cis (red); trans (blue).

Poster number: PS037 (SP)

Theme: Genetics and epigenetics

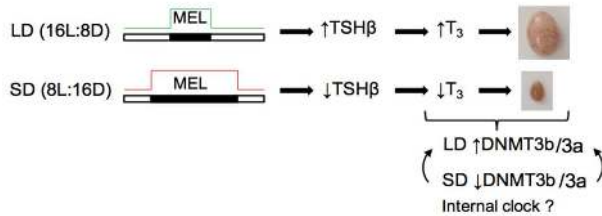
Photoperiodic and triiodothyronine regulation of DNA methyltransferase expression in the hypothalamus

Authors: Ms Elisabetta Tolla¹, Ms Anna Ashton², Professor Peter McCaffery², Dr Tyler Stevenson¹

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Introduction: Seasonal epigenetic modifications in the hypothalamus have been demonstrated to regulate long-term timing of reproduction and energy balance. In adult Siberian hamsters, there is a significant reduction in DNA methyltransferase enzymes (e.g. *dnmt3a/b*) in the hypothalamus exposed to short-winter photoperiods. This indicates that reduced neuroendocrine DNA methylation permits gonadal involution and body mass loss in this species. The mechanisms that govern the photoperiodic control of *dnmt1*, *dnmt3a* and *dnmt3b* are not well defined. Our objectives were to investigate the effect of thyrotrophin-stimulating hormone (TSH) and triiodothyronine (T3) on the photoperiodic regulation of DNA methyltransferase enzyme expression. If *dnmt1*, *3a* and/or *dnmt3b* are regulated by the photoperiodic response, we hypothesized that either TSH or T3 in short day hamsters would stimulate hypothalamic expression.

Methods: Two studies were conducted using *ex vivo* and *in vivo* analyses. Study 1 examined the effect of thyroid-stimulating hormone (TSH) on *dnmt1*, *3a* and *3b* expression in the Sprague Dawley rat hypothalamus using slice cultures. P10 rat hypothalamic slices were treated with TSH or vehicle control for 48 h, followed by qPCR analysis. In study 2, we investigated the sufficiency of T3 to stimulate hypothalamic *dnmt1*, *dnmt3a* or *dnmt3b* expression in adult female hamsters exposed to long days (LD) or short days (SD).



Approach for statistical analysis: ANOVA. *p* was considered significant if < 0.05

Results and conclusions: We did not detect a significant change in *dnmt1*, *dnmt3a* nor *dnmt3b* expression in response to TSH. Then, we examined the impact of daily T3 injections or saline on hypothalamic gene expression and female reproductive physiology. SD photoperiods were observed to reduce body weight and uterine weight. Unlike previous reports in male hamsters, daily T3 injections in SD females were ineffective to stimulate gonadal recrudescence. *Dnmt3a* and *dnmt3b* expression was reduced in SD hypothalamic, independent of T3. These data suggest that an alternative hormonal signal regulates *dnmt3a* and *dnmt3b* expression in female Siberian hamsters, or that cyclical *dnmt3a/b* expression reflect an endogenous circannual timing system. Moreover, it appears that additional supplementary cues are required to stimulate reproductive development in female hamsters.

Figure 1. Seasonal reproductive patterns between female long-day (LD) breeding Siberian hamsters and short-day (SD) non-breeding individuals. LD stimulate reproductive physiology through an increase in T3 and gonadal size (pictured in the photo). SD cause a decrease in T3 and gonadal size. Epigenetic enzymes *dnmt3a* and *dnmt3b* expression is reduced in SD independent of T3, suggesting that cyclical *dnmt3a/b* expression reflect an endogenous circannual timing system.

Poster number: PS038 (SP)

Theme: Genetics and epigenetics

Altered circadian rhythm in the Snord116-deleted mouse, an experimental model of PraderWilli syndrome

Authors: PhD student Maria Bolla¹, PhD student Matteo Falappa¹, Senior Researcher Tenured Laura Cancedda¹, Senior Team Leader Valter Tucci¹

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Prader-Willi syndrome (PWS) is a genomic imprinted disorder that is characterized by brain developmental, behavioral and metabolic abnormalities. Snord116 is a small nuclear RNA that controls the expression of many genes, including different clock genes in the suprachiasmatic nucleus. Snord116 is also a main regulator of sleep symptoms associated with PWS. Here, we analyzed the effects of the loss of paternal expression of Snord116 in the circadian rhythms of mice during light-dark (LD) and dark-dark (DD) where they express the capability of entrainment and free-running respect to external events, respectively. We found that loss of paternal expression of Snord116 in mice alters the circadian period during free-running, when the animals run according to their internal clock. In particular, mutant mice present with a reduced shortening of their circadian period in DD in comparison to their wild-type littermates. On the other hand, the circadian period during LD shows an unaltered circadian rhythm in mutants compared to wild-type mice. Our study indicates that Snord116 is involved in the regulation of circadian rhythms in mice and points out a new endophenotype for pre-clinical investigation into the pathomechanisms of PWS. Moreover, this research promotes the knowledge of how imprinted genes can contribute to the alteration of circadian rhythms.

Poster number: PS039 (SP)**Theme:** Genetics and epigenetics**Do damaging variants of SLC6A9, the gene for the glycine transporter 1 (GLYT-1), protect against schizophrenia?****Authors:** Prof David Curtis^{1,2}¹University College London, London, United Kingdom, ²Queen Mary University London, London, United Kingdom

Introduction: There is compelling evidence that impaired functioning of the glutamatergic N-methyl-D-aspartate receptor (NMDAR) can produce psychotic symptoms and is implicated in the pathogenesis of some cases of schizophrenia. Antagonism of functioning of the GlyT-1 glycine transporter enhances NMDAR activity. Therefore, genetic variants predicted to impair the functionality of *SLC6A9*, which codes for the GlyT-1 glycine transporter, are expected to be protective against schizophrenia.

Methods: In an exome sequenced sample of 4225 schizophrenia cases and 5834 controls variants occurring in *SLC6A9* were annotated.

Approach for statistical analysis: Weights were assigned to variants according to predicted effect on functioning using GENEVARASSOC. Genotype counts in controls and cases were compared using SCOREASSOC.

Results and conclusions: Variants predicted to be deleterious by SIFT and damaging by PolyPhen were examined. Genotypes at 1:44466494-G/A seemed likely to be erroneous. If these were ignored then there were 15 damaging variants in controls and 5 in cases. The results are consistent with the hypothesis that variants which damage *SLC6A9* are protective against schizophrenia but a larger sample would be required to confirm this.

Poster number: PS040 (SP)**Theme:** Learning and memory**Dopamine D1-like receptors in the dorsomedial prefrontal cortex regulate contextual fear conditioning****Authors:** Dr Christine Stubbendorff¹, Mr Ed Hale¹, Prof Helen J. Cassaday², Dr Tobias Bast², Dr Carl W. Stevenson¹¹School of Biosciences, University of Nottingham, Loughborough, United Kingdom, ²School of Psychology, University of Nottingham, Nottingham, United Kingdom

Rationale: Dopamine D1 receptor (D1R) signalling is involved in contextual fear conditioning. The D1R antagonist SCH23390 impairs the acquisition of contextual fear when administered systemically or infused locally into dorsal hippocampus or basolateral amygdala.

Objectives: We determined if state-dependency may account for the impairment in contextual fear conditioning in rats caused by systemic SCH23390 administration. We also examined if dorsomedial prefrontal cortex (dmPFC), nucleus accumbens (NAc), and ventral hippocampus (VH) are involved in mediating the effect of systemic SCH23390 treatment on contextual fear conditioning in rats.

Methods: In Experiment 1, SCH23390 (0.1 mg/kg) or vehicle was given before contextual fear conditioning and/or retrieval. In Experiment 2, SCH23390 (2.5 ug/0.5 uL) or vehicle was infused locally into dmPFC, NAc, or VH before contextual fear conditioning, and retrieval was tested drug-free. Freezing was quantified as a measure of contextual fear.

Results: In Experiment 1, SCH23390 given before conditioning or before both conditioning and retrieval decreased freezing at retrieval, whereas SCH23390 given only before retrieval had no effect. In Experiment 2, SCH23390 infused

into dmPFC before conditioning decreased freezing at retrieval, while infusion of SCH23390 into NAc or VH had no effect.

Conclusions: The results of Experiment 1 confirm those of previous studies indicating that D1Rs are required for the acquisition but not retrieval of contextual fear and rule out state-dependency as an explanation for these findings. Moreover, the results of Experiment 2 provide evidence that dmPFC is also part of the neural circuitry through which D1R signalling regulates contextual fear conditioning.

Poster number: PS041 (SP)

Theme: Learning and memory

Regulation of fear discrimination by the Kv3.1 voltage-gated potassium channel modulator AUT6

Authors: Christine Stubbendorff¹, Harriet Day¹, Jessica Smith¹, Ed Hale¹, Giuseppe Alvaro², Charles Large², Carl Stevenson¹

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Introduction: Various psychiatric disorders are characterized by impaired cognition and emotional regulation linked to disinhibition in corticolimbic circuits. Restoring the imbalance between excitation and inhibition in these circuits may therefore ameliorate certain symptoms in these disorders. Corticolimbic activity is regulated by inhibitory parvalbumin GABA interneurons that selectively express Kv3.1, a voltage-gated potassium channel. Kv3.1 modulators, such as AUT6, reverse cognitive and behavioural deficits in preclinical models of schizophrenia and mania. Our aim was to investigate the effects of AUT6 on fear generalization, a hallmark feature of anxiety-related disorders that is associated with corticolimbic disinhibition.

Methods: Female rats (n=9-10/group) underwent limited or extended auditory fear discrimination training that we recently showed leads to fear discrimination or fear generalization, respectively, based on cue-induced freezing at retrieval. We also assessed darting as an active fear response. Animals received injections of AUT6 or vehicle before discrimination training and/or retrieval testing. We also examined the effects of AUT6 on shock sensitivity and behaviour during open field testing.

Analysis approach: Discrimination at retrieval was inferred from freezing and darting levels during the CS+ and CS-. Discrimination ratios were also calculated from freezing and darting levels during the CS+ and CS- to account for inter-individual variability in, and potential drug effects on, these measures. Innate fear and locomotor activity were inferred from various behavioural measures in the open field test. Data were analysed using ANOVA or unpaired t-tests as appropriate.

Results and Conclusions: We found that limited training resulted in discrimination at retrieval based on freezing, but not darting, and that freezing-based discrimination was unaffected by AUT6. In contrast, we found that extended training resulted in generalization based on freezing, but discrimination based on darting, at retrieval. Moreover, AUT6 given before extended training enhanced discrimination at retrieval based on freezing (P<0.05), whereas darting-based discrimination was unaffected. These results were not due to non-specific drug effects on shock sensitivity during training or on locomotor activity during behavioural testing. Our findings suggest that modulation of Kv3.1 channels to influence corticolimbic inhibition mitigates the fear generalization phenotype that emerges with extended discrimination training, as indexed by passive but not active fear responding.

Poster number: PS042 (SP)**Theme:** Learning and memory**Targeted memory reactivation of competing memories during sleep induces forgetting****Authors:** Mr Bardur Joensen¹, Dr Sam Berens¹, Dr Scott Cairney¹, Dr Gareth Gaskell¹, Dr Aidan Horner¹¹*University Of York, York, United Kingdom*

When two memories interfere at retrieval, repeated retrieval of one of the competing memories has been shown to disrupt retrieval for the other competing memory (Wimber, Alink, Charest, Kriegeskorte, & Anderson, 2015), leading to forgetting ('retrieval-induced forgetting') (Anderson, Bjork, & Bjork, 1994). Although memory retrieval during wakefulness is thought to be distinct from reactivation processes in sleep, it has recently been shown that memory reactivation during sleep can, under certain conditions, also lead to forgetting (Oyarzun, Moris, Lugue, de Diego-Balaguer, & Fuentemilla, 2017, Antony, Cheng, Brooks, Paller, & Norman, 2018). Here we asked whether a similar retrieval-induced forgetting effect can be seen for overlapping pairwise associations when repeatedly cued via targeted memory reactivation (TMR). Participants learned several sets of overlapping pairwise associations (e.g., Hammer-Barack Obama, Hammer-Kitchen), where the object (e.g., Hammer) was always the overlapping element. Following learning, participants retrieved the individual associations belonging to half of the overlapping sets prior to sleep, and all the overlapping associations following sleep. During sleep, we presented half of the learnt object words auditorily, assuming that presentation of the object word (e.g., Hammer) would induce retrieval and reactivation of the associated elements (e.g., Barack Obama, or Kitchen, or both). We modelled memory performance using a generalised linear mixed-effect regression model and show that TMR during sleep induces forgetting of the more weakly encoded overlapping pairwise associations. However, we also show that prior testing protects these memories from forgetting during sleep, consistent with a recent proposal (Antony, Ferreira, Norman, & Wimber, 2017) that retrieval practice during wakefulness can induce a rapid 'online' consolidation process that reduces competition between overlapping memories. Our findings suggest that TMR can produce a form of retrieval-induced forgetting during sleep, but prior retrieval during wakefulness can protect against such forgetting.

Poster number: PS043 (PP)**Theme:** Learning and memory**Using hydrocortisone to modulate the U-shape between expectancy and memory****Authors:** Mr Jörn Alexander Quent¹, Professor Richard N. Henson¹¹*University Of Cambridge, MRC CBU, Cambridge, United Kingdom*

Introduction: In previous experiments using immersive VR, we demonstrated that spatial memory is a U-shaped function of object/location expectancy. Participants encoded objects in a virtual kitchen, located at unexpected, neutral and expected locations. The results are consistent with a neuroscientific model called SLIMM (van Kesteren et al, 2012), which postulates that the hippocampus is important for the memory advantage for unexpected locations, while the mPFC is crucial for the advantage for expected locations. If so, we should be able to selectively attenuate the advantage of unexpected locations by administering hydrocortisone, given that the hippocampus has a high density of glucocorticoid and mineralocorticoid receptors.

Methods: Participants will be either given a hydrocortisone or placebo tablet, with N = 25 per group based on 80% power to detect a U-shape within a group (effect size for cortisol manipulation unknown). Fifteen minutes after taking the tablet, participants will enter an fMRI scanner to measure changes in resting-state activity throughout the brain for a period of 45min. After scanning, participants enter the VR environment and spend 45sec encoding 20 objects in each of two rooms. After 2.5min of distractor task, spatial memory will be tested with a 3D location recall task, in which objects will be placed in VR, and 3AFC recognition task with two foil alternatives being approximately

matched for the expectancy based on prior norms (lasting approximately 20min in total). At the end, participants will rate the object/location expectancy on a continuous scale. Saliva samples will be collected before, after 45min and at the end of the experiment.

Approach for statistical analysis: We will analyse the performance data with mixed linear models with participant and object as random factors and group (hydrocortisone/placebo), expectancy, squared expectancy and the interaction between the last two as fixed factors. Any difference in quadratic components will be followed up by categorical tests of unexpected versus neutral trials. fMRI activity will be estimated as the variance over consecutive 5min windows, and activity in the hippocampus and mPFC will be correlated with the unexpected/expected memory advantages.

Poster number: PS044 (SP)

Theme: Learning and memory

How does learning to read shape the neural representation of spoken and written language?

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Introduction: Writing systems vary in the way they express the sounds and meanings of spoken language. Alphabetic writing systems contain information about phonological structure within the orthography due to regular systematic relations between graphemes and phonemes. Logographic writing systems encode less-fine-grained information about phonological structure via more arbitrary mappings between characters and syllables. We tested whether and how these differences impacted on the nature of emerging representations as adults learned to read novel words.

Methods: 24 participants were trained over 10 days on two artificial languages with alphabetic and logographic writing systems. Each language contained 24 words denoted by orthographic, phonological, and semantic components. Learning involved completing several computerised tasks each day and performance after training was assessed using behavioural tests without feedback. Following training, neural activity was recorded using fMRI whilst participants made meaning judgements about trained spoken and written stimuli (8 x 12-minute runs).

Approach for statistical analysis: Performance for both languages was compared using two-way repeated measures ANOVAs and paired-samples t-tests. Standard pre-processing was applied to raw data using a canonical HRF and univariate contrasts were cluster-level corrected at $p < .05$. Representational similarity analysis was chosen to investigate whether representations of spoken and written trained words were more phonemically and/or orthographically structured when associated with alphabetic compared to logographic writing systems. Prediction matrices were constructed based on shared sounds/symbols of spoken/written words within each language. These were correlated with neural dissimilarity matrices in ROIs for spoken and written language. Paired-samples t-tests were conducted to compare languages.

Results and conclusions: Alphabetic trained words exhibited stronger orthography–phonology mappings while orthography–semantic mappings were stronger for logographic writing systems. Spoken language and lexical/semantic processing regions were more active for alphabetic and logographic written words, respectively. When reading trained words, representations in spoken language processing regions exhibited clearer phonemic and orthographic structure for alphabetic compared to logographic writing systems. When listening to spoken words, representations in spoken language processing regions were more orthographically structured for alphabetic systems and representations in written language processing regions exhibited clearer phonemic structure for logographic writing systems.

Poster number: PS045 (SP)

Theme: Learning and memory

A role for the nucleus accumbens in the hippocampal learning-behaviour translation

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Introduction: The hippocampus is required for rapid place learning, but the pathways via which hippocampal place learning is translated into behaviour remain to be determined. The intermediate hippocampus is critical for the hippocampal learning-behaviour translation and combines neural substrates of accurate place encoding with links to prefrontal and subcortical behavioural control sites, which may contribute to this translation (Bast et al.,2009,PLoSBIol; Bast,2011,CurrOpinNeurobiol). The nucleus accumbens (NAc) is a main candidate due to strong hippocampo-NAc projections that have been implicated in behaviour based on place memory (Humphries&Prescott,2010,ProgNeurobiol).

Methods: We combined NAc functional inhibition in Lister Hooded rats by microinfusion of the GABA agonist muscimol with in vivo electrophysiological measurements around the infusion site to verify neural effects and with locomotor and startle/prepulse-inhibition (PPI) assays to rule out gross sensorimotor impairments (adapting methods from Pezze et al.,2014,JNeurosc). We then tested the impact of NAc muscimol on behavioural performance based on hippocampus-dependent 1-trial place learning using the watermaze delayed-matching-to-place (DMP) test (Bast et al.,2009), with muscimol infused between trial 1 (learning) and 2 (expression of memory).

Analysis: ANOVA was used whenever the independent variable had more than two levels or to analyse the impact of multiple independent variables.

Results and conclusions: Muscimol (125-250ng/0.5 µl/site) dose-dependently reduced NAc neuronal firing around the infusion site by 30-50% and caused moderate sensorimotor effects. Interestingly, NAc muscimol impaired between-session locomotor habituation. With habituation memory linked to the hippocampus (Fanselow,2000,BehavBrainRes), this is consistent with the idea that NAc is important for hippocampal memory expression. Our first watermaze experiment, testing the impact of NAc muscimol within-subjects, indicated that the NAc is required for DMP performance. However, there appeared to be a carry-over effect: after repeated testing with muscimol, rats failed to show the typical DMP search strategy (persistent searching in correct location) even on drug-free test days, possibly reflecting that NAc is required to reinforce the strategy. A second watermaze DMP experiment, using a between-subjects design to avoid carry-over effects, confirmed that NAc muscimol impairs expression of hippocampus-dependent rapid place learning.

Overall, these findings support that the NAc contributes to translation of rapidly-acquired place memory into behaviour.

Poster number: PS046 (SP)**Theme:** Learning and memory**Cannabinoid regulation of excitatory synaptic transmission at hippocampal ta-ca1 synapses****Authors:** Mr Adham Farah¹, Dr. Andrew J Irving², Dr. Jenni Harvey¹¹University Of Dundee, Dundee, United Kingdom, ²University College Dublin, Dublin, Ireland

Introduction: It is known that cannabinoids produce their biological effects via activation of CB1 and CB2 receptor subtypes¹, however in the CNS, the predominant receptor is CB1. Numerous studies have examined the modulatory effects of cannabinoids on excitatory synaptic transmission at hippocampal Schaffer collateral (SC)-CA1 synapses. Moreover, increasing evidence suggests that hippocampal CB1 receptors play a role in Learning and memory, and are also linked to neurodegeneration in Alzheimer's disease² (AD). However the effects of cannabinoids on excitatory synaptic function at the anatomically-distinct temporoammonic (TA) input to hippocampal CA1 neurons is not clear.

Methods: Standard extracellular recordings were used to examine the effects of different selective agonists for CB1 receptors on excitatory synaptic transmission at juvenile TA-CA1 synapses. Recordings were made from transverse hippocampal slices (350µM) prepared from 12-18 day old rats, perfused with oxygenated aCSF.

Approach for statistical analysis: Statistical analyses were performed using paired *t* test (two-tailed; 95% confidence interval) or repeated-measures ANOVA for comparison between multiple groups. *P* < 0.05 was considered significant with *n* representing the number of slices used from different animals.

Result and conclusions: Application of methanandamide (100nM; 15min) induced a long term increase (LTP; to 148±5% of baseline; *n*=4; *p*<0.001) in excitatory synaptic transmission via activation of CB1 receptors, as application of a CB1R- antagonist blocked this effect (AM251; 102 ± 1.1% of baseline; *n*=4; *p*>0.05). CB1R-induced LTP has a postsynaptic locus of expression, and was NMDA receptor-dependent as 50 µM D-AP5 inhibited this effect (*n* = 4; *p*>0.05). These findings may be important as the TA pathway plays a role in episodic memory³ and impairments in episodic memory is an early event in AD⁴.

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Poster number: PS047 (PP)**Theme:** Learning and memory**Testing the importance of subicular inputs to the rodent anterior thalamic nuclei for spatial working memory****Authors:** Dr Andrew Nelson¹, Professor John Aggleton¹¹Cardiff University, Cardiff, Cf10 3at, United Kingdom

The hippocampus and anterior thalamic nuclei conjointly support spatial memory. A key empirical question remains why there is apparent duplication of function between these two sites and whether interactions between the hippocampus and anterior thalamic nuclei support specific aspects of spatial memory. By combining DREADD technology with localised infusions of the DREADD ligand clozapine, we are now able to test the functional importance of anatomically-defined pathways for memory. To target subicular output pathways, rats will receive injections of the inhibitory DREADD AVV5-CaMKIIa-hM4D(Gi) into the dorsal subiculum. Indwelling cannula will be

inserted into the anterior thalamic nuclei to allow selective inactivation of subicular neurons that innervate the anterior thalamic nuclei. Control animals will receive injections of the same viral construct (AVV5-CaMKIIa-EGFP) that does not express DREADDS and will also receive clozapine infusions via indwelling cannula in the anterior thalamic nuclei. To assay spatial memory performance following inactivation of the subicular-anterior thalamic pathway, the animals will be tested on T-maze alternation, a measure of spatial working memory. In addition, to examine whether the subicular inputs to the anterior thalamic nuclei are required for selective aspects of spatial memory, the rats will be challenged with situations in which the available spatial information is restricted (e.g. nullify intramaze cues by rotating the maze between the sample and choice phase). The data will be analysed by ANOVA with a between subject factor of inactivation (DREADD versus control animals) as well as a within-subject factor of task variant (standard versus adapted).

Poster number: PS048 (SP)

Theme: Learning and memory

An Investigation into the effects of psychosocial stress on recognition memory

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Although wider research generally suggests that stress influences memory, research using psychosocial stress is less conclusive. This study systematically explored how psychosocial stress influences memory. We ran three experiments, each differing by one design element. Each experiment used both the Trier Social Stress Test and a cognitively matched low stress task. Each experiment used 36 participants, evenly distributed between conditions. Participants were all aged 18-30.

Stress levels were assessed at multiple time points using self-reports of anxiety (5 times: evenly spread throughout testing) and saliva samples to measure cortisol (3 times: before, during and after the experimental condition).

Overall changes in anxiety scores were calculated using an area under the curve analysis. Across all three studies, participants in the stress condition reported higher anxiety during the experiment than control participants, indicating an effective stress manipulation. Saliva samples are currently being analysed, however we expect them to be in line with anxiety ratings as previous research indicates a strong correlation between these measures.

During experiment 1, participants learned a list of 30 neutral words, and memory was tested using a remember-know recognition procedure. Stress was applied after Learning and memory was assessed immediately after learning and 24 hours later. Experiment 2 repeated this design and procedure using negative emotional, categorised neutral and random neutral words. Experiment 3 followed the same experimental design but used paired neutral words during learning, while memory was assessed using a combined old/new recognition task and word pair free recall.

We found no significant differences for any memory measures between the stress and control groups in any of these experiments (effect sizes of $d=0.02-0.42$), suggesting that post-learning psychosocial stress had minimal effects on word recognition. Additionally there were no significant correlations between anxiety and memory retention (correlation values of $r=-.155-.107$).

Our findings suggest weak effects of post-learning psychosocial stress on recognition and associative memory for lists of words. Consistent null findings across studies with a careful incremental design strongly support the suggestion that psychosocial stress has little influence on word consolidation. Future studies plan to build on this research by changing the time stress is applied.

Poster number: PS049 (SP)

Theme: Learning and memory

Activation of ER α induces a novel form of long-term potentiation at TA-CA1 synapses

Authors: Miss Leigh Clements¹, Dr Jenni Harvey¹

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Introduction: The actions of estrogen are well documented and hippocampal CA1 neurons are believed to be a major target for this multifaceted hormone. Indeed, estrogens are known to modulate hippocampal synaptic plasticity at Schaffer Collateral (SC)-CA1 synapses (1,2), however, the role of estrogens at the anatomically distinct temporoammonic (TA) pathway is unclear (3).

Methods: Standard extracellular recordings were used to examine the effect of estrogen receptor α (ER α) activation on excitatory synaptic transmission at TA-CA1 synapses. Transverse hippocampal slices (350 μ M) were prepared from juvenile (P11-24) male Sprague-Dawley rats and perfused with oxygenated aCSF. The CA3 region was removed in order to isolate the TA pathway and dopamine (100 μ M; 5 min) was applied routinely at the end of experiments in order to confirm stimulation of the TA pathway.

Approach for statistical analysis: Raw data was normalised and expressed as a percentage of baseline \pm SEM. Using repeated measures ANOVA for comparison of means within subject groups, $p < 0.05$ was considered significant.

Results and conclusions: Here we demonstrate that activation of (ER α) at TA-CA1 synapses induces a long-lasting increase (LTP) in excitatory synaptic transmission ($129 \pm 6.6\%$ of baseline; $p < 0.01$; $n = 4$). ER α -mediated LTP at TA-CA1 synapses is dependent on GluN2B-containing NMDARs. Moreover, ER α -induced LTP requires activation of the PI3-K signalling cascade as selective inhibitors of this pathway blocked LTP ($96 \pm 1.7\%$ of baseline; $p > 0.05$; $n = 4$). A role for ER α activation during activity-dependent LTP was observed as HFS (100Hz; 1 sec) failed to induce LTP in slices treated with a selective ER α antagonist ($100 \pm 3.2\%$ of baseline, $p > 0.05$; $n = 5$); an effect significantly different from HFS-induced LTP observed in control slices ($142 \pm 9.8\%$ of baseline, $p < 0.001$; $n = 5$). In immunocytochemistry studies, ER α -selective agonist PPT (25nM) increased the surface expression of GluA1 in hippocampal neurons ($173 \pm 7.0\%$ of control, $p < 0.001$; $n = 3$); an effect also blocked by the NMDAR antagonist D-AP5 ($89 \pm 3.5\%$ of control, $p > 0.05$; $n = 3$). These data indicate ER α activation induces a novel form of LTP at TA-CA1 synapses, which may have important implications for estrogenic regulation of CNS health and disease.

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Poster number: PS050 (SP)

Theme: Learning and memory

Tracking the emergence of location-based memory representations

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Introduction: Scene-selective regions of the human brain form allocentric representations of specific locations in our environment that are independent of heading direction, allowing us to know where we are regardless of our direction of travel. However, we know little about how these location-based representations form.

Methods: Using a representational similarity analysis (RSA) of fMRI data, we tracked the emergence of location-based representations in scene-selective brain regions. We estimated patterns of activity for sets of two distinct scenes (0° and 180°) taken from the same location before and after participants learnt they were from the same location. During a learning phase, we presented participants with a series of panoramic videos. Participants were shown two types of video: (1) an overlap video condition displaying two distinct scenes (0° and 180°) from the same location, and (2) a no-overlap video displaying two distinct scenes from different locations (that served as a control condition).

Approach for statistical analysis: Fisher-transformed correlation coefficients were used to measure the similarity of BOLD responses to different scenes within functionally defined regions of interest. These similarity estimates were then compared across conditions within a mixed-effects regression model.

Results and conclusions: In the parahippocampal place area (PPA) and retrosplenial cortex (RSC), representations of scenes from the same location became more similar to each other only after they had been shown in the overlap condition, suggesting the emergence of location-based viewpoint-independent representations. Whereas location-based representations emerged in the PPA regardless of subsequent behaviour, RSC representations only emerged for locations where participants could behaviourally identify the two scenes as belonging to the same location. These results demonstrate that we can track the emergence of location-based representations in the PPA and RSC in a single fMRI session and suggest that the RSC plays a key role in using such representations to locate ourselves in space.

Poster number: PS051 (PP)

Theme: Learning and memory

How pre-experimental knowledge benefits memory for congruent and incongruent events

Authors: Dr Andrea Greve¹, Ms Salmar Elnagar¹, Dr Elisa Cooper¹, Roni Tibon¹, Prof Richard Henson¹

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Introduction: Events that conform to our expectations, i.e. are congruent with our world knowledge or schemas, are better remembered than unrelated events. Yet events that conflict with schemas can also be remembered better, producing a “U-shaped” function of congruency: superior performance for both schema congruent and incongruent trials relative to unrelated trials. This prediction of the SLIMM (‘Schema-Linked Interactions between Medial prefrontal and Medial temporal region’) framework (van Kesteren et al, 2012) has recently been confirmed in studies testing experimentally trained schema (Greve et al., in press) but evidence for pre-experimentally acquired schemas, which are consolidated over an extended period of time, is still lacking and will be investigated here.

Methods: Pre-experimental knowledge of retail prices for objects is used to establish the relative value of randomly-paired objects that are either congruent, incongruent or unrelated with the expectations derived from prior knowledge. At study, object pairs are presented by showing multiple images of each object (1 to 3) and event memory for the number of objects on each trial is later tested.

Approach for statistical analysis: Memory accuracy (hits minus false alarm rates) is expected to be better for both congruent and incongruent trials, relative to unrelated trials, according to the SLIMM framework. This hypothesis will be tested using paired sample t-tests across conditions. Statistical analysis are modelled on comparisons previously reported for experimentally trained schemas (Greve et al., in press).

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Poster number: PS052 (SP)**Theme:** Learning and memory**Regulation of 22kHz ultrasonic vocalisations by stimulus detection in fear conditioning****Authors:** Dr Emma Cahill¹, Ms Maite Arribas¹, Ms Keemia Azvine¹, Mr Will Raby-Smith¹, Ms Jiaqi Zou¹, Prof Bastian Hengerer²¹*University Of Cambridge, Cambridgeshire, United Kingdom*, ²*CNS Department, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany*

Introduction: The development of new therapeutics for anxiety disorders is highly dependent on the identification and characterisation of animal models of anxiety. Recent investigations of rodent 22-kHz ultrasonic vocalisations (USVs) have shown that these might be a valid behavioural measure of anxiety. The hypothesis of this study is that the emission of USVs in a Pavlovian conditioned-fear paradigm is associated with hypervigilant behaviour. As such, this research intends to develop and refine an animal model of hypervigilance that could be used to screen new therapeutics.

Methods: Rats were trained in a fear-conditioning procedure, in which a tone (CS) predicted an unavoidable footshock (US). USVs and freezing were measured across a conditioning phase and a subsequent test phase. The CS was modified at test to reduce its detectability and salience, in order to screen for hypervigilance. In addition, a traditional measure of 'anxiety', the elevated plus maze was used. We also performed immunohistochemistry to establish which brain regions were activated, by measurement of cFos expression, with the expression of freezing and/or vocalisation.

Approach for statistical analysis: In order to analyse the effects of group and CS presentation on freezing and USVs, repeated measures ANOVAs with post hoc Sidak correction tests were performed. Baseline USVs were compared between groups using an independent samples, two-tailed t-test. Further investigation into the association between ultrasonic calling and freezing was conducted by dividing rats into groups of vocalisers and non-vocalisers and analysing the effect of vocalisation separately for the original tone group and modified tone group using a repeated measures ANOVA. The relationship between individual scores in the EPM and other variables were correlated using Pearson's correlation coefficient. Statistical significance was taken to be at $P < 0.05$.

Results and conclusions: The results suggest that the nature of the anxiety experienced during a fear-conditioning procedure is qualitatively different to that elicited by the elevated plus maze. Moreover, animals that vocalised froze significantly more during the test of fear learning despite having acquired conditioning to a similar level as non-vocalisers.

Poster number: PS053 (SP)

Theme: Learning and memory

Connecting the past and future: the role of the pre-commissural fornix in episodic autobiographical memory and simulation

Authors: Dr Angharad Williams¹, Mr Samuel Ridgeway¹, Dr Mark Postans¹, Prof Kim Graham¹, Prof Andrew Lawrence¹, Dr Carl Hodgetts¹

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The hippocampus and ventromedial prefrontal cortex (vmPFC) are critical for both episodic memory and future simulation. Damage to either structure impairs the ability to remember the past and imagine the future, and both structures are commonly activated during autobiographical memory retrieval and future simulation. There are strong anatomical connections between the prefrontal cortex and hippocampus, mediated by the fornix, consistent with the view that the prefrontal cortex and hippocampus operate interactively in support of memory and imagination. To date however, there has been no investigation of the importance of hippocampal-vmPFC structural connectivity in episodic memory and future thinking. Here, twenty-seven healthy young adult participants (aged 18-22 years old) were asked to recall past personal experiences and generate novel future events in response to a series of cue words (e.g. "holiday"). Past and future narratives were scored for episodic and semantic content according to the standardized autobiographical interview (AI) protocol. Diffusion weighted MRI and spherical deconvolution based tractography were employed to reconstruct the separate divisions of the fornix [the pre-commissural fornix (linking hippocampus with vmPFC) and the post-commissural fornix (linking fornix with anterior thalamus and mammillary bodies)]. Free water corrected microstructure properties (fractional anisotropy, FA) were calculated for each fornix division and correlated with scores from the past-future AI task. We found that pre-commissural - but not post-commissural - fornix microstructure was significantly correlated with the amount of episodic details contained in past *and* future autobiographical narratives. These results remained significant when controlling for grey matter volumes of the hippocampus and vmPFC. This study provides novel evidence for a key role of hippocampal-vmPFC connectivity in the (re)construction of events for one's personal past and possible future.

Poster number: PS054 (PP)

Theme: Learning and memory

Brain-heart cooperation during learning: results from non-linear analyses of EEG and heart rate complexity

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Introduction: The system-evolutionary theory (Shvyrkov, 2006) proposes to view behaviour as actualization of functional systems that are understood as temporal organizations of components localizing both in the brain and the rest of the body (Anokhin, 1974). According to the theory, learning is described as formation of a new functional system consisting of neural and visceral components, the joint activity of which provides the achievement of a new adaptive result for the whole organism. The goal of the study is to explore how neural and visceral components of functional systems cooperate during the acquisition of new behaviour. More specifically, we aim to describe the dynamics of the correlation between the measures of neural (EEG) and visceral (heart rate) activity at different stages of learning.

Methods: Long-Evans rats (3 - 9 months, n=10) will be trained to press a lever in order to obtain food in the feeder located at a 60 cm distance from the lever. Thus, the rats will perform a cyclic behaviour consisting of the following

behavioural acts: lever-pressing, feeder-approach, food consumption and lever-approach. The behavioural dynamics of learning will be described using the duration of behavioural acts and whole behavioural cycles. EEG (the retrosplenial, visual and motor cortical areas) and ECG will be recorded simultaneously during training sessions. Beat-to-beat intervals (heart rate) will be extracted from ECG. The sample entropy (estimation of complexity) will be calculated for the EEG and heart rate sequences within the periods of behavioural acts and cycles.

Approach for statistical analysis: We hypothesize that the complexity estimates for EEG and heart rate will concurrently decrease at the beginning stages of learning followed by their gradual increase during consecutive stages until the learning criterion is reached (Friedman test). Such dynamics can be considered as an indicator of changes in the structure of individual experience occurring when new functional systems are formed. We also expect that the correlation between the complexity estimates for EEG and heart rate dynamics will be lower during early stages of learning than the later stages due to the development of new inter-systems relations (Wilcoxon test of Spearman coefficients).

Poster number: PS055 (SP)

Theme: Learning and memory

MIA-induced osteoarthritis-like knee pain does not disrupt hippocampus-dependent place memory in Lister hooded rats

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Introduction: Chronic pain has been associated with changes in forebrain regions, including the hippocampus and prefrontal cortex, as well as impairments in related cognitive functions, including memory and attention (Baliki&Apkarian et al., 2015, Neuron; Moriarty et al., 2011, Prog Neurobiol). This suggests that pathologies associated with chronic pain, such as osteoarthritis, may disrupt cognitive functions. Here, we examine the impact of osteoarthritis-associated chronic pain on hippocampus-dependent memory in a rat model.

Methods: First, we adapted the monoiodoacetate (MIA) model of chronic osteoarthritis-like knee pain (Sagar et al., 2010, Arthritis Rheum) to adult male Lister hooded (LH) rats, which are more suitable for cognitive testing than the commonly used albino strains. Then, we used the watermaze delayed-matching-to-place (DMP) test, which is highly hippocampus-dependent (Steele&Morris, 1999, Hippocampus; Bast et al., 2009, PLoSBiol), to assess hippocampus-dependent place memory in LH rats injected into the left knee with 3mg/50µL MIA. Nociceptive behaviour (weight-bearing asymmetry; paw-withdrawal threshold) and selected sensorimotor functions (open-field locomotor activity; acoustic startle and its prepulse inhibition, PPI) were also measured at baseline and at several time points throughout a 93 day period after model induction. Knee pathology was scored at the end of the study.

Statistical analysis: Data were analysed by ANOVA, using treatment (MIA vs. control) as between-subjects factor and various repeated measures factors, as appropriate.

Results and conclusions: MIA injection caused robust pain behaviour, including weight-bearing asymmetry and reduced paw-withdrawal threshold (mechanical allodynia), as well as significant cartilage damage and synovitis in the knee. MIA-injected rats also showed reduced rearing from week 4 and reduced swim speed from week 7 after model induction. Mild PPI disruption was also observed at week 4, indicating some impact on the brain regions involved in PPI (Koch, 1999, Prog Neurobiol). However, there was no significant impairment in hippocampus-dependent rapid place learning performance on the watermaze DMP task, indicating that MIA-induced osteoarthritis-like chronic pain in LH rats does not substantially affect hippocampal function. This finding is consistent with previous human imaging

findings indicating that the hippocampus may be less affected in osteoarthritis than in other chronic pain conditions (Mutso et al., 2012, J Neurosci).

Poster number: PS056 (SP)

Theme: Learning and memory

Towards understanding one-shot place learning in spatial navigation: a reinforcement learning approach

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Introduction: Animals, including humans, can perform very fast, 1-trial, learning of new places [1,2,6]. The underlying mechanisms are the focus of ongoing research in experimental and computational neuroscience. We will present a new approach to modelling spatial learning and navigation of an agent in a circular open field maze with distal cues.

Methods: The approach comprises a combination of Temporal Difference (TD) learning, adapted from [5], and the Successor Representation (SR) [3,4]. TD models estimate a value function and a policy (best action to perform) in each state (place in the maze). In contrast, the SR provides a topological encoding of spatial information that allows to perform rapid path planning to novel goal locations in a familiar environment.

Analysis: Model performance is compared to one-trial place learning performance by rats and humans in the watermaze or watermaze analogues, respectively, when new goal locations need to be learned repeatedly [1,2,6].

Results and conclusions: We confirm previous findings [5] that the TD model can learn goal locations, although with only a gradual improvement in performance that does not capture the one-shot place learning shown by rats and humans [1,2,6]. The SR is able to simulate direct navigation to any goal locations in an open field environment similar to the watermaze, but its exact computation is very expensive [3].

We are currently investigating the combination of the two approaches. TD learning provides a gradual learning of the transition matrix of the states from which we computed the SR. The SR is then employed for path-planning to goal locations, once the rewards have been discovered. This combination will be employed to investigate the one-shot place learning shown by both rats and humans [1,2,6].

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Poster number: PS057 (SP)

Theme: Learning and memory

Spatial view cells in the primate hippocampus: properties demonstrated during active locomotion

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Video animations will be presented to illustrate the properties of hippocampal spatial view cells recorded in macaques during active locomotion in a 2.7x2.7 m open field foraging environment located in the middle of a laboratory which provided a rich scene. The place, head direction, eye position, and location being fixated on the walls of the room are displayed every 25 ms during the playback of the neuronal spikes in these new analyses. These neurons recorded in CA3, CA1 and the parahippocampal gyrus (1) respond primarily to a view of space 'out there', with much less information about the place where the monkey is located; (2) have responses that depend on where the monkey is looking, as shown by measuring eye position; (3) can still occur (especially for CA1 neurons) if the view details are obscured with curtains; (4) retain part of their 'space' tuning even in complete darkness, for several minutes (especially in CA1); (5) have an allocentric spatial representation; and (6) utilize independent encoding in that the information about spatial view increases linearly with the number of cells in the representation. A computational model shows that the spatial representation may be different from that of place cells in rats because of the smaller field of view of primates due to the primate fovea. Some hippocampal neurons encode for objects, others for spatial view in a room, and others for a combination of objects and spatial view, while a monkey is performing an object-place memory task in which the place is 'out there' in the room. This task and the one-trial object-place associations formed by these neurons is prototypical of episodic memory, and provides evidence that the primate hippocampus does associatively link information about objects and allocentric information about places 'out-there'. Recordings were made sufficiently long from 40 of the 708 neurons (5.6%) to provide evidence that they were spatial view neurons in this single environment, and in addition some neurons had place field responses.

Rolls, E.T. and Wirth, S. (2018) Spatial representations in the primate hippocampus, and their functions in memory and navigation. *Progress in Neurobiology* 171: 90-113.

Poster number: PS058 (SP)

Theme: Learning and memory

Investigating the role of group I PAK proteins in synaptic plasticity

Authors: Miss Miriam Durazo-Barba¹, Dr Daniel Whitcomb¹

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Introduction: Alzheimer's disease (AD) is the most common form of dementia with the characteristic symptom of progressive memory impairment. This is thought to be underpinned by the primary pathological features of neuronal and synaptic loss. The Group I p21-associated kinases (PAKs) are involved in regulating neuronal structure, which is crucial for the generation and maintenance of neuronal connections and functional signal transmission. Interestingly, evidence suggests that PAK levels are reduced in the brains of AD patients. The potential consequences of this for neuronal function will largely depend upon the roles PAKs play in neuronal physiology, the understanding of which is still being developed.

Synaptic plasticity is widely considered to underlie the cellular mechanisms of memory, and so has been the focus of extensive study in trying to understand the causes of cognitive impairment in AD.

Methods: First, we studied the role of PAKs in the long-term potentiation (LTP) form of synaptic plasticity, in acute hippocampal rat slices. Second, as PAKs regulate cellular morphology, we stimulated synapse growth in cultured

hippocampal neurons and examined the size of dendritic spines in the presence and absence of the PAK inhibitors using fluorescence microscopy. Finally, as increased intracellular calcium results in LTP induction we measured whether PAK inhibition by the aforementioned drugs produced calcium release using Fluo-4AM.

Statistical analysis: We used student's t-test when comparing two groups. Kruskal-Wallis was used for phalloidin staining experiments since these data did not meet the criteria for normality.

Results: Our electrophysiology experiments show that treatment of slices with IPA-3, a pharmacological PAK inhibitor, blocks LTP. However, a separate PAK inhibitor - FRAX486 - does not. Consistent with our electrophysiology data, we found that IPA-3-treated neurons showed marked reductions in size, and FRAX486-treated neurons and controls did not. We found that the effect of PAK inhibition was likely not due to disruptions in calcium signalling since we observed no effects on calcium release with application of the inhibitors to cultured hippocampal neurons.

Conclusion: These observations suggest that IPA-3 and FRAX486 act differently on PAK function and that PAKs may have an influence on steps in the signalling cascade that triggers LTP. Further characterisation of the physiological roles PAK proteins play in neuronal function will be important to understand the possible consequence of their decline in AD.

Poster number: PS060 (SP)

Theme: Learning and memory

The Effect of Gadolinium Brain Deposition on Hippocampal Neurogenesis

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Objective: Gadolinium-based contrast agents (GBCAs) are used worldwide to enhance the quality of magnetic resonance imaging. Post-mortem evaluation of human brain from patients who received GBCAs confirmed Gd retention. While the clinical significance of gadolinium deposition in the brain remains unsettled, it raises important questions concerning its long-term effects on Learning and memory in developing brains undergoing multiple MRI images. The purpose of the present study is to investigate whether multiple exposures to GBCA at young age have an impact on the stem cell niche in the hippocampus.

Methods: Young male Sprague Dawley rats (140-150 g) were given serial daily injections of two types of contrast agents: Dotarem (Gadoterate meglumine; Macrocylic GBCA) and Ominiscan (Gadodiamide, Linear GBCA) for a period of 20 days. A control group received Saline injection. Along with GBCAs, animals received BromodeoxyUridine (BrdU) injections every two days (Total dose= 300mg/kg; ip) to label newly formed cells in the brain. In order to assess the total number of *proliferating cells* in the dentate gyrus (DG) of the hippocampus, five rats from each group were sacrificed one day after GBCA exposure by cardiac perfusion. Furthermore, to determine the number of *maturing neuronal cells*, another 5 rats from each group were sacrificed one month after the last GBCA injection. The hippocampal tissues were then stained for BrdU⁺ and BrdU⁺/NeuN⁺ cells and analyzed using confocal microscopy.

The T-maze behavioral test was performed to assess the spatial working memory at day 10 and 20, and one month after the last GBCA exposure. Gadolinium deposition in the hippocampal region of the brain was quantified and confirmed using Inductively Coupled Plasma- Mass Spectrometry (ICP-MS) technique.

Results and conclusion: Gadolinium tissue concentration was approximately 1.03 mg/Kg and 1.45 mg/Kg in the hippocampal region following Dotarem and Omniscan exposure respectively. Preliminary behavioral data revealed

no significant changes in working memory; however, an alteration in the number of proliferating cells and maturing neurons in the DG of the hippocampus was observed. Our findings suggest that neurogenesis is a dynamic process in the hippocampus that might be affected by any change in the neuronal environment including Gadolinium retention.

Poster number: PS061 (PP)

Theme: Learning and memory

Do the rat anterior thalamic nuclei supply collateralized inputs to multiple cortical targets?

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The organization of cortical afferents from the anterior thalamic nuclei (ATN) follows a complex topography whereby individual thalamic nuclei preferentially project to different cortical areas. Additionally, projections from individual nuclei are topographically organized such that subdivisions within each nuclei projects differentially to the same cortical areas. Despite this overall topographical organization, many additional “non-specific” cortical projections have also been described originating from the anterior thalamic nuclei (Horikawa et al., 1988), but such projections are not seen in other studies (Sripanidkulchai and Wyss, 1986). So far, these analyses have largely been restricted to thalamic projections to the anterior cingulate and retrosplenial cortices. In the present study, we will re-evaluate the question of whether these non-specific projections exist and, if so, describe their specific cortical targets. Multiple combined unilateral injections of the two retrograde tracers *cholera toxin-b* (CTB) and *fast blue* (FB) will be positioned in orbital, medial prefrontal, anterior cingulate, and retrosplenial cortices, potentially also including the hippocampal formation, in order to reconsider the extent of fibre collateralization reaching these regions from the anterior thalamic nuclei and other, adjacent nuclei. Approximately 10 cases will be used to quantify collateralized projections to the frontal cortices, while the same number of cases will be used to analyse fibre collateralization between these same cortices and the retrosplenial cortex. The focus will be on the proportions of double-labelled cells following the various tracer injections. Control cases with tracer injections in bordering cortical regions may be included.

Horikawa, K., Kinjo, N., Stanley, L. C., & Powell, E. W. (1988). Topographic organization and collateralization of the projections of the anterior and laterodorsal thalamic nuclei to cingulate areas 24 and 29 in the rat. *Neuroscience research*, 6(1), 31-44.

Sripanidkulchai, K., & Wyss, J. M. (1986). Thalamic projections to retrosplenial cortex in the rat. *Journal of Comparative Neurology*, 254(2), 143-165.

Poster number: PS062 (SP)

Theme: Learning and memory

Beta-bursting in the retrosplenial cortex as a robust metric of environmental novelty

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Introduction: The ability to determine whether an environment is novel or familiar is something that many of us may take for granted. This is often affected in dementia, causing sufferers to be unable to remember places they have visited many times, sometimes even their own homes. There is currently a lack of robust metrics for determining whether a mouse recognises whether an environment is novel or familiar, limiting research into this facet of dementia. The retrosplenial cortex has been shown to have a role in spatial navigation and contextual memory, so

we utilised *in vivo* electrophysiology to look for changes associated with environmental novelty in the retrosplenial cortex of C57BL/6 mice.

Methods: 4-channel silicon probes were unilaterally implanted in the right retrosplenial cortex of male C57BL/6 mice. Following recovery, local field potentials were recorded while the animals underwent a novel/familiar environment test. Briefly, the animal is placed in a novel recording arena for 15 minutes, and given time to explore, after which, they are returned to their home cage for 15 minutes. Following on from this, the animal is returned to the same recording arena for another 15 minutes. This is repeated over 4 days, with the recording arena becoming more familiar to the animal. Finally, on day 5, the animal is placed in a new recording arena, in order to investigate changes due to novelty.

Approach for statistical analysis: Data was analysed offline using custom written MATLAB scripts, and the Chronux toolbox.

Results and conclusions: Upon inspection of the local field potential, oscillatory activity in the beta frequency range (20-30 Hz) seemed to occur in bursts of around 200ms duration. Upon investigating these “beta bursts”, we found that there were significantly more beta bursts in the retrosplenial cortex when the animals were in a novel environment (the first session of day 5), than a familiar environment (the second session of day 4) ($p < 0.05$). In conclusion, beta bursting activity in the retrosplenial cortex is associated with environmental novelty, and may be a valuable assay for investigating contextual familiarity.

Poster number: PS063 (SP)

Theme: Learning and memory

Precommissural and postcommissural fornix diffusion indices in healthy aging and cognition

Authors: Ms Emma Craig¹, Dr Beth Coad¹, Prof John Aggleton¹, Prof Seralynne Vann¹, Dr Claudia Metzler-Baddeley¹
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Introduction: The fornix is the principal white matter tract associated with the hippocampus and is important for a number of aspects of memory. Although the fornix is typically studied as a unified region, it is a complex bidirectional pathway with two principal components: the precommissural and postcommissural fornix (Poletti & Creswell, 1977). These pathways are connected to different brain regions, and preliminary research has suggested that they represent unique functional properties (Christiansen et al., 2016). This study aimed to investigate the relationship between age, cognition and white matter structure across the fornical subdivisions. Testing a large cohort of adults allowed the investigation of both the relationship between individual differences in the microstructure of fornix subdivisions and cognitive abilities, as well as how these regions are differentially affected by age.

Methods: A group of 166 healthy adults aged 35-75 underwent a battery of tests sensitive to memory, executive functioning, reasoning and intelligence.

Diffusion weighted MRI and spherical deconvolution based tractography were used to manually reconstruct precommissural and postcommissural tracts in order to extract the mean diffusivity, fractional anisotropy, isotropic signal fraction, intracellular signal fraction, orientation dispersion index and macromolecular proton fraction of these areas.

Approach for statistical analysis: Pearson’s correlations were carried out to investigate how the diffusion metrics of interest correlated with each other as well as other as well as participant age and cognitive test scores. Data were subjected to post hoc corrections for age, as well False Discovery Rate correction for multiple comparisons where necessary.

Results: The precommissural and postcommissural fornix could be distinguished on the basis of their diffusion metrics suggesting structural differences within these two divisions of the fornix. Precommissural fornix, postcommissural fornix and the fornix as a whole were affected by age but the different metrics showed different age-related patterns across fornix subdivisions. While there was some suggestion of functional specialisation across the two tracts, many of the correlations did not withstand correction for multiple comparisons.

Poster number: PS064 (SP)

Theme: Neurodegenerative disorders & ageing

L-Norvaline, a New Therapeutic Agent against Alzheimer's disease

Authors: Dr Baruh Polis¹, Dr Abraham Samson¹

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Introduction: Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder with an insidious onset. The disease is characterized by cognitive impairment and a distinct pathology with neuritic plaques and neurofibrillary tangles.

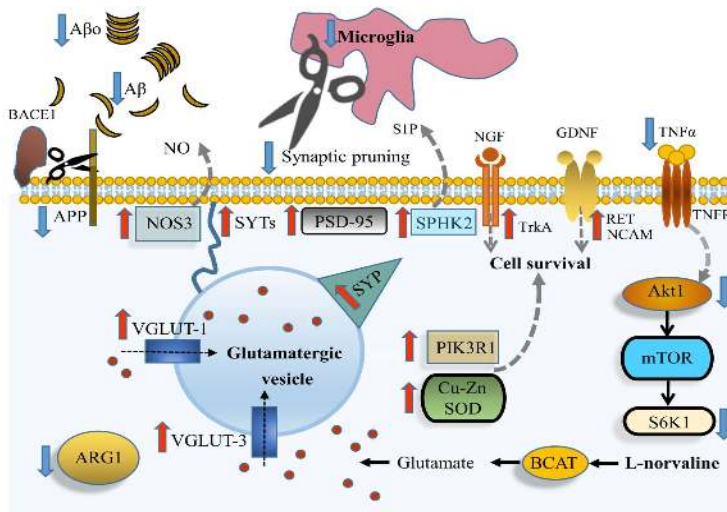
Growing evidence highlights the role of arginase activity in the manifestation of AD pathology. Upregulation of arginase was shown to contribute to endothelial dysfunction, atherosclerosis, diabetes, and neurodegeneration. Regulation of arginase activity appears to be a promising approach for interfering with the pathogenesis of AD and other metabolic disorders. Therefore, the enzyme represents a novel therapeutic target.

Methods: We administer an arginase inhibitor L-norvaline to four-month-old 3xTg-AD mice and wild-type control animals for two months. We tested their memory acquisition in various spatial memory-related paradigms (Morris water maze, Y-maze, novel object recognition test). Then, we evaluate the neuroprotective effect of the substance using immunohistochemistry, proteomics, and transcriptomics assays. Finally, we identify the biological pathways activated by the treatment.

Approach for statistical analysis: Pairwise comparisons were made using a two-tailed Student's *t*-test. For multiple comparisons, an ANOVA was performed followed by an appropriate post-hoc test. All data are presented as mean values \pm SEM. A *p*-value <0.05 was considered statistically significant.

Results and conclusions: We find that L-norvaline treatment reverses the cognitive decline in AD mice. We show the treatment is neuroprotective as indicated by reduced beta-amyloidosis, alleviated microgliosis and TNF α transcription levels. Moreover, elevated levels of neuroplasticity related protein PSD-95 were detected in the hippocampi of mice treated with L-norvaline. Furthermore, we disclose several biological pathways, which are involved in cell survival and neuroplasticity and are activated by the treatment.

Through these modes of action, L-norvaline has the potential to improve the symptoms of AD and even interfere with its pathogenesis. As such, L-norvaline is a promising neuroprotective molecule that might be tailored for the treatment of a range of neurodegenerative disorders.



Poster number: PS065 (SP)

Theme: Neurodegenerative disorders & ageing

Disturbances in slow wave sleep-related oscillations in the medial prefrontal cortex of a mouse model of Lewy body dementia

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Introduction: Sleep disturbances are an early and common symptom of Lewy body dementia (LBD). While most studies have focused on rapid-eye movement (REM) sleep, we are interested in changes that occur in slow-wave sleep (SWS), the deepest stage of non-REM sleep. Our aim is to identify electrophysiological SWS alterations in the A30P mouse model that over-expresses human mutant alpha-synuclein, the main component of Lewy bodies.

Methods: We used a 16-electrode probe to obtain electrophysiological recordings from the medial prefrontal cortex (mPFC) of young (2.5–4 months) adult transgenic A30P (n = 8) and control (n = 8) mice while under urethane-induced anaesthesia. After on-line and off-line spike sorting and preprocessing of the local field potential (LFP), we proceeded with automatic identification of the Up and Down states (UDS) that comprise SWS, and assessment of the timing of single neuron firing in relation to the UDSs. Waveform analysis was used to extract the power spectral density (PSD) on the Up-state for different frequency bands. Data from the 16 electrodes were grouped according to mPFC sub-region: anterior cingulate cortex, infralimbic, prelimbic cortices, dorsal peduncular region.

Analysis approach: After confirming normality of distribution for the LFP data, we applied repeated measures ANOVA with the mPFC sub-regions as the within-subjects variable and after establishing significance, with univariate ANOVAs for each region. Equivalent non-parametric tests were used to analyse neuronal firing timings.

Results and conclusion: Analysis of the LFP data revealed that A30P mice had a significantly faster slow-wave (0.1 – 0.9 Hz) oscillation frequency and shorter Up-state length and Up-state length variability over time compared to controls, in all regions. The A30P mice also showed significantly smaller LFP amplitude and amplitude variability over time in most regions. Neuronal firing analysis showed that in A30P mice a higher percentage of the total spiking occurred during the normally “silent” Down-state compared to controls. No differences were found in gamma and theta PSD between the two animal groups. These findings suggest a deficit in the tight control of UDSs in the A30P mouse as a consequence of abnormal alpha-synuclein expression.

Poster number: PS066 (SP)

Theme: Neurodegenerative disorders & ageing

The retinoic acid receptor as a novel therapy target for neuromuscular degenerative disease

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Introduction: The retinoic acid (RA) signalling pathway plays crucial roles in the central nervous system to promote cell survival. It is unexplored however whether the RA signalling pathway has a regulatory effect on the neuromuscular system and whether it may improve impaired motoneuron signalling in a motoneuron degenerative disease such as amyotrophic lateral sclerosis (ALS). The goals of our study are to evaluate the RA signalling pathway in the healthy and diseased neuromuscular system and whether it may provide a future therapeutic route for this devastating and yet untreatable disease of the neuromuscular system.

Methods: The expression and distribution of the RA synthesizing enzyme RALDH2 was investigated by immunohistochemistry in the neuromuscular system of wild type mice, using ChAT and VAcHT as markers of motoneurons and α -Bungarotoxin for labelling ACh receptors at the neuromuscular junction (NMJ). Expression of the type 1 cannabinoid receptor (CB1) as a downstream effector of the RA signalling system was also studied by immunohistochemistry. To investigate the influence of RA signalling on neuromuscular function electrophysiological changes in an impaired in-vitro neuromuscular preparation were measured to determine if these ligands improved function.

Approach for statistical analysis: All data were expressed using mean \pm SEM. Independent experimental groups were compared by the ANOVA test. $P < 0.05$ was considered as statistically significant.

Results and conclusions: The expression and distribution of RALDH2 in the motoneuron of the lumbar spinal cord, in the NMJ and muscle's sarcolemma suggests that endogenous RA plays a role in the adult neuromuscular system. The expression of the CB1r in the NMJ showed that RA might have neuroprotective and neuroplasticity promoting effects through the endocannabinoid signalling system in the NMJ. Electrophysiological recording showed that exogenously applied RAR ligand (1nM EC23) enhances nerve-evoked muscle tension for both twitch and tetanus when synaptic transmission is impaired. Further investigation of the RA signalling pathway is ongoing in the motoneuron and neuromuscular system to understand its interaction with other signalling systems and its potential association with, or amelioration of, the pathogenesis of ALS.

Poster number: PS067 (SP)

Theme: Neurodegenerative disorders & ageing

Inhibition of hemozoin-induced neuroinflammation in BV-2 microglia by skimmianine

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Introduction: Cerebral malaria (CM) is a severe neurological complication of *Plasmodium falciparum* infection. In CM, the accumulation of malaria pigment hemozoin induces inflammation leading to excessive production of pro-inflammatory cytokines which contributes to its pathology. The quinoline alkaloid, skimmianine has been suggested

to have anti-inflammatory activity. However, it is not known whether skimmianine could suppress hemozoin-induced neuroinflammation. In this study, we investigated the effect of skimmianine in hemozoin-induced microglia cells.

Methods: BV-2 microglia cells were treated with skimmianine (10, 20 and 30 μ M) 30 minutes before stimulation with hemozoin (400 μ g/ml). Levels of cytokines (TNF α , IL-1 β , IL-6 and IL-10) released were measured using ELISA while PGE₂ production was measured by enzyme immunoassay. Nitric oxide (NO) production was determined using the Griess assay. In addition, protein levels of COX-2, iNOS, κ B and phospho-p65 were evaluated with immunoblotting and immunofluorescence.

Analysis approach: Data were expressed as mean \pm SEM. Statistical analysis was performed using one-way ANOVA with post-hoc Student-Newman-Keuls test (multiple comparisons).

Results and conclusion: Skimmianine (10, 20 and 30 μ M) significantly ($p < 0.05$) reduced the production of TNF- α , IL-1 β , IL-6, NO and PGE₂ in BV2 microglia activated with hemozoin. Western blot experiments revealed that skimmianine reduced levels of iNOS, COX-2, phospho-p65 and phospho- κ B α protein expression, while immunofluorescent detection revealed reduced levels of p65 protein in the presence of skimmianine. These results suggest that skimmianine might be inhibiting neuroinflammation in hemozoin induced microglia cells by targeting NF- κ B signalling pathway. These results have significant implications in cerebral malaria.

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Poster number: PS068 (SP)

Theme: Neurodegenerative disorders & ageing

Microglia adopt a glycolytic phenotype in the aged brain and this change is attenuated by exercise

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Among the changes that occur with age, one is an increase in microglial activation, which is usually accompanied by neuroinflammatory changes. Exercise has been reported to attenuate these age-related changes, and to reduce the cognitive impairment observed in aged animals (Pérez-Domínguez et al. 2018). Recent evidence has indicated that inflammatory microglia are glycolytic (Holland et al., 2018), which may be driven by an increase in 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 enzyme (PFKFB3), the master regulator of glycolysis. Here we investigated whether microglia from aged animals exhibited a glycolytic signature and whether exercise exerted a modulatory effect on this metabolic profile.

Methods: Young (4 month-old) and aged (17 month-old) mice (n=8) were trained for 10 days on a treadmill. One day before sacrifice, animals were assessed in two behavioural tests, the novel object recognition test and the object displacement test. Animals were sacrificed immediately after the last bout of exercise, and microglial cells were isolated and cultured for 5 days. The metabolic profile of microglia was assessed using Seahorse Technology and cell function was assessed by analysing phagocytosis of latex beads. Data were analysed using a 2-way ANOVA.

Results and conclusions: Performance in both behavioural tests was significantly impaired in aged animals and exercise attenuated the age-related deficits. A significant increase in glycolysis and in glycolytic capacity was observed in microglia from aged animals and exercise also ameliorated these effects. An age-related increase in PFKFB3, the major regulator of glycolysis, was also observed and this, too, was ameliorated in aged animals that were assigned to the exercise group. Significantly, the age-related increase in glycolysis was coupled with a decrease in the phagocytic capacity of cells. The data suggest that exercise normalizes the metabolic profile of microglia and improves their phagocytic capacity.

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Poster number: PS069 (SP)

Theme: Neurodegenerative disorders & ageing

Age-related alteration in microglial phenotype and synaptic engulfment

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Introduction: Microglia, the resident innate immune cells in the brain, are responsible for the selective elimination of inappropriate synaptic connections. During development, synapses are opsonized and phagocytosed by microglia tagged with complement component 1q (C1q), the initiating protein in the classical complement cascade. In normal ageing, cognitive functions are impaired without evidence of neuronal loss. Interestingly, studies demonstrate that C1q is strongly overexpressed with age in the brain of adult mice. We hypothesize that age-related deterioration of neuronal functions are due to the inappropriate pruning of C1q-tagged synapses by microglia.

Methods: Brains of young (3-6 month-old), mature (9-12 month-old) and aged (18-26 months-old) mice were used to isolate synaptosomes and CD11b⁺ microglia for *ex vivo* experiments. Expression of synaptic markers and C1q in synaptosomes was assessed by western blot. Expression of C1qR, a receptor enhancing C1q-dependent phagocytosis, on CD11b⁺ microglia was assessed by flow cytometry. Microglial morphology and phagocytosis of synaptosomes were analyzed by immunocytofluorescence and confocal microscopy.

Analysis approach: Analyses were performed blindly. Multiple group comparisons were performed by one-way analysis of variance (ANOVA) followed by a Dunnett's or a Bonferroni's post hoc test.

Results and conclusions: C1q expression was significantly increased in synaptosomes with age. However, elevated C1q levels in synaptosomes from aged animals did not affect their phagocytosis by young microglia. Interestingly, a population of CD11b⁺ cells expressing C1qR was increased in both mature and aged compared to young mice. Microglia from mature mice had a significantly greater ability to phagocytose synaptosomes compared with microglia from young mice but phagocytic capacity in microglia from aged mice was significantly decreased. Together our results show that members of the complement pathway are increased in mouse brain with age, C1q in synaptosomes and C1qR in microglia, and these are associated with modification of phagocytic abilities. This suggests that the complement pathway may be involved in synaptic pruning in aged mice and that these changes precede synaptic and cognitive alterations.

Poster number: PS070 (PP)

Theme: Neurodegenerative disorders & ageing

Testing the antagonistic pleiotropy hypothesis of ApoE with cognitive and brain data from a healthy cohort

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Introduction: The Apolipoprotein E (ApoE) gene is implicated in neurodegeneration, specifically cholesterol metabolism, synaptogenesis, and the pathologies that characterise Alzheimer's Disease. Its three major alleles - $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ - have approximate proportions of 8%, 80% and 12% in the healthy Caucasian population. The $\epsilon 4$ allele has been associated with increased risk of neurodegeneration in old age, while the $\epsilon 2$ allele is hypothesised to be neuroprotective. Here we propose to use existing cognitive and brain data from a cohort of healthy people to test the "antagonistic pleiotropy" theory of Han & Bondi (2008), whereby the APOE $\epsilon 4$ allele has opposing effects on fitness across the lifespan: advantageous in early life but disadvantageous in later life. A second set of hypotheses relate to the possible protective effects of the $\epsilon 2$ allele in later life (Suri et al, 2013).

Methods: The cohort of ~700 adults aged 18-88 are part of the Cambridge Centre for Ageing and Neuroscience (CamCAN; www.cam-can.com). Cognitive variables will be measures of fluid intelligence (Cattell) and verbal memory (Story Recall); brain variables will be global measures of gray-matter (from T1+T2-weighted MRI scans), white-matter (from Diffusion-weighted MRI) and functional connectivity (from BOLD-weighted fMRI), using methods from previous papers that have examined ApoE in healthy volunteers.

Approach for statistical analysis: We will compare polynomial fits of age to the dependent variables as a function of $\epsilon 4$ -carrier versus $\epsilon 4$ -noncarrier, and $\epsilon 2$ -carrier versus $\epsilon 2$ -noncarrier (ignoring $\epsilon 2$ - $\epsilon 4$ individuals). For those variables that are inverted U-shape function of age, we will compare peak values (e.g, if they occur at an earlier age for those with $\epsilon 4$ allele). Bayes Factors will be used to assess the null hypothesis of no interaction between age and ApoE allele.

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Poster number: PS071 (SP)**Theme:** Neurodegenerative disorders & ageing**Influence of obesity and insulin resistance in septic encephalopathy in animal model****Authors:** Ms Andriele Vieira¹, Ms Mariane Rocha Abatti¹, Mrs Monique Michels Orben¹, Ms Heloísa Borges¹, Ms Amanda Goulart¹, Sr Filipe Fernandes Gabriel¹, Sr Felipe Dal Pizzol¹¹*Universidade Do Extremo Sul Catarinense, Criciúma, Brazil*

Introduction: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The brain damage severely contributes to increased rates of mortality. Sepsis and its consequences may be exacerbated when associated with a diagnosis of chronic inflammation, such as in obesity and insulin resistance. Both in obesity and in insulin resistance there is an increase in the levels of several pro-inflammatory cytokines, acute phase proteins, oxidative stress. These aspects could be potentiated when obese and insulin resistant patients are subject to an excessive inflammatory insult, verified in sepsis. Thus, the aim of the present study is to evaluate the susceptibility to septic encephalopathy in rats with obesity associated with insulin resistance.

Methods: To this aim, we used Wistar rats, aged 60 days, weighing 250-300g. For four months, the animals received hypercaloric nutrition to induce obesity and the animals with body mass index above that 24.9 Kg/m² were included in obese group. The glucose tolerance test was performed for the definition of insulin resistance. Sepsis was induced by intraperitoneal (i.p.) injection of fecal slurry (3 ml/kg body weight) administered through a 19G needle into the right lower quadrant of the abdomen, and the sham group received saline. The animals were killed at 24 hours and hippocampus and prefrontal cortex were removed to the determination of cytokines levels and verification of microglial activation by immunohistochemistry.

Approach for statistical analysis: Statistics were made by ANOVA with Tukey post-hoc test with of significance a value of p <0.05.

Results and conclusions: We observed that 24h after sepsis, proinflammatory cytokine levels were elevated in the sepsis + eutrophy group and obesity associated with insulin resistance potentiated this increase in the sepsis + insulin resistance / insulin group. The immunohistochemistry showed that in the sham + obesity / insulin resistance group there was microglial activation when compared to the sham + eutrophy group. The Sepsis + eutrophy group showed increased microglial activation and obesity + insulin resistance potentiated this increase. Thus, with our results and evidence from the literature, we can say that the obesity and insulin resistance exacerbates brain damage in animals subjected to sepsis.

Poster number: PS072 (SP)**Theme:** Neurodegenerative disorders & ageing**Effects of S100 β inhibition in the neuroinflammatory response in Sepsis****Authors:** Ms Mariane Rocha Abatti¹, Mrs Monique Michels¹, Ms Andriele Vieira¹, Mr Diogo Dominguni¹, Ms Heloisa Borges¹, Ms Amanda Goulart¹, Mrs Pricila Avila¹, Mr Felipe Dal Pizzol¹¹*Unesc, Criciúma, Brazil*

Background: Central nervous system is one of the first systems affected in sepsis, therefore the severity of sepsis is not only for it's high risk of mortality, but also for leading to cerebral dysfunction and cognitive impairment in long-term survival patients. The receptor for advanced glycation end products (RAGE) can interact with several ligands and its activation triggers a series of events in cell signaling, resulting in a hyperinflammatory condition related to sepsis. Recent studies shows that elevated levels of S100B (RAGE ligand) are associated with the pathophysiology of

neurodegenerative disorders, also participate in inflammatory brain diseases and may lead to increased activation of microglia, leading to neuronal death. This work aims to determine the effect of inhibition of S100 β on the neuroinflammatory response in sepsis.

Methods: Sepsis was induced in wistar rats by cecal ligation and perforation (CLP). There was three groups: Sham + saline, CLP + saline and CLP + 10 μ g / kg of monoclonal antibody (Anti-S100B) administered intracerebroventricularly (ICV). The animals were killed at 30 days after sepsis to perform behavioral evaluation by open field, novel object recognition and splash test. It was used hippocampus, pre-frontal and amygdala for the determination of S100B and RAGE proteins, by western blotting, evaluation of cytokines levels and verification of microglial activation by immunohistochemistry. Statistics were made by ANOVA with Tukey post-hoc test with of significance a value of $p < 0.05$.

Results: At 30 days, both Sham and CLP+anti-S100B decreased the numbers of crossings and rearings at test session, recovering the habituation memory at open field task. At novel object recognition, CLP+S100B group increased the recognition index at test session, when compared to training session. There wasn't any significant result in time of grooming in all groups. The levels of proinflammatory cytokines (TNF, IL1 β , IL6) were decreased when administrated anti-S100B, when comparing to CLP group. The immunohistochemistry showed that CLP+S100B group had a moderate decrease in microglial activation.

Conclusion: These results suggest that S100B has an important involvement in sepsis pathway, triggers inflammatory response and microglial activation.

Poster number: PS073 (SP)

Theme: Neurodegenerative disorders & ageing

The sphingosine 1-phosphate axis as a promising target in a murine model of Krabbe's disease: implications for inflammation and myelination

Authors: Ms Sibylle Bechet¹, Dr Steven Fagan¹, Dr Sinead O'Sullivan¹, Dr Justin Yssel¹, Prof. Kumlesh Dev¹
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Introduction: Globoid cell leukodystrophy (Krabbe's Disease, KD) is a rare infantile neurodegenerative disorder, caused by mutations in the galactocerebrosidase (*galc*) gene. A subsequent decreased enzymatic activity leads to a brain accumulation of the toxic metabolite galactosylsphingosine (psychosine). This causes profound demyelination and severe loss of oligodendrocytes, usually accompanied by neuroinflammation. Currently, clinical practice lacks a curative treatment and is mostly directed towards symptomatic relief. Recent findings give rise to the sphingosine 1-phosphate receptor agonist fingolimod as a potential therapeutic agent for KD. Our lab has previously shown that fingolimod attenuates psychosine-induced cell death of human astrocytes *in vitro* and demyelination in mouse organotypic cerebellar slices (1). This data thus prompted the current preclinical study investigating the effects of fingolimod in twitcher mice, a murine model of KD.

Methods: The direct impact of *in vivo* fingolimod-treatment was assessed via immunohistochemistry with markers for myelination, astrocytes, microglia and neurons. Additionally, western blots were carried out to quantify proteins of myelination and inflammation. Furthermore, PAS-histology was conducted to assess infiltrating multi-nucleated macrophages, a pathological hallmark of KD.

Statistical analysis: The difference in lifespan between treatment groups was examined by Kaplan-Meier log-rank analysis. Discrepancies on both behavioural and molecular/biochemical levels were analysed using a two-way ANOVA followed by a Bonferroni adjustment.

Results and Conclusion: Results indicate that treatment of twitcher mice with fingolimod significantly rescues myelination and regulates astrocyte and microglial reactivity. Furthermore, decreases in non-phosphorylated neurofilaments indicate that attenuation of demyelination is accompanied by neuroprotective and neurorestorative processes. These positive results are reflected in an increased lifespan of treated twitcher mice. In conclusion, findings of the current study suggest that fingolimod's mechanism of action reaches beyond that of immunomodulation, highlighting sphingosine 1-phosphate receptors as reliable drug targets for the devastating childhood illness KD.

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Poster number: PS074 (SP)

Theme: Neurodegenerative disorders & ageing

Using light-induced protein aggregation to investigate neurotoxicity of A β oligomerisation in novel *Caenorhabditis elegans* optogenetics model

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Introduction: Amyloid beta protein (A β) aggregation is a key characteristic of Alzheimer's disease (AD) and the current leading amyloid hypothesis of AD suggests a strong correlation between A β accumulation and AD pathogenesis. Recent research have examined whether oligomerisation of A β is sufficient to cause neurotoxicity, however a causative link between the two factors has not been established. We intend to investigate the relative role of soluble and aggregated A β protein on neurotoxicity using *Caenorhabditis elegans* as a model organism.

Methods: Cryptochrome 2 (CRY2) protein from *Arabidopsis thaliana* has been shown to induce rapid and reversible protein oligomerisation in response to blue light¹. We generated a novel *C. elegans* optogenetics model expressing CRY2-A β that exhibit light-induced aggregation of A β peptide. By growing the animals in light or dark conditions, we can manipulate the amount of A β aggregation at similar levels of A β peptide production. Using this model, we will compare the toxicity of soluble A β peptide and insoluble oligomers by performing metabolism assays and lifespan studies. All results of metabolism assays will be statistically analysed using ANOVA and the lifespan studies will be analysed using Kaplan-Meier survival analysis. We want to present this optogenetic model as a viable model to study neurotoxic effects of A β oligomerisation in *C. elegans*.

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Poster number: PS075 (SP)

Theme: Neurodegenerative disorders & ageing

A role for ER-shaping proteins in the regulation of autophagy

Authors: Dr Philippa Fowler¹, Dr Niamh O'Sullivan¹

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Hereditary spastic paraplegias (HSPs) are a group of inherited neurodegenerative disorders characterized by degeneration of the longest motor neurons in the corticospinal tract, leading to muscle weakness and spasticity of

the lower limbs. Pathogenic variants in genes encoding proteins that shape the endoplasmic reticulum (ER) network within axons are a leading cause of HSP. Despite this, the mechanisms by which loss of ER-shaping proteins lead to motor neuron degeneration in HSP remain poorly understood.

Using the dual-tagged mCherry-GFP-Atg8a reporter in an *in vivo* model of HSP in *Drosophila melanogaster*, we investigated the effect of targeted knockdown of the ER-shaping protein *Arl6IP1* on autophagic flux. We found that under normal conditions, autophagic markers in *Arl6IP1* RNAi flies were unchanged from controls. Starvation induces autophagy in control flies, enabling cells to recover nutrients by the degradation of cytoplasmic components. However, we found that starvation fails to induce autophagy in two independent *Arl6IP1* RNAi fly lines. Specifically, our analysis suggests that knockdown of *Arl6IP1* may impair the autophagic pathway by inhibiting the fusion of lysosomes with autophagosomes required to complete autolysosomal-dependent degradation. We next looked for evidence of defective protein degradation and found a significant increase in the accumulation of polyubiquitinated aggregates within the motor neurons and muscles of HSP model *Drosophila*.

These results propose a novel mechanism in which autophagic dysfunction may contribute to axonal degeneration underpinning some forms of HSP.

Poster number: PS076 (PP)

Theme: Neurodegenerative disorders & ageing

Generation of cell lines for the study of inherited motor neuron disease

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Hereditary Spastic Paraplegia (HSP) is an inherited axonopathy which affects the longest motor neurons in the cortical tract, resulting in lower limb spasticity and weakness. Variants in genes encoding proteins that shape the endoplasmic-reticulum (ER) network are a leading cause of HSP. Our lab as recently identified an important role for ER-shaping proteins in regulating mitochondrial morphology in the fruit fly *Drosophila melanogaster*. It is critical to understand the significance of these findings to HSP patients. The aim of my work is to generate human cell lines expressing disease-causing mutations in ER-shaping proteins.

The CRISPR based gene editing system allows precise genomic modifications. Models based on siRNA knock-down or plasmid-based overexpression work to transiently artificially decrease or increase protein expression. In contrast, CRISPR can create stable knock-out (KO) cells or cells expressing disease-causing variants. These lines can be used to study endogenous expression and localisation of disease-causing proteins and to establish robust gene-phenotype correlations. My work is focusing on the establishment and validation of KO cell models of the HSP-causing protein ARL6IP1.

The strategy for the future study of these models will be addressed by (1) testing markers for optimum visualisation of the ER and mitochondria within my cells; (2) using image analysis software to quantify organelle parameters relevant to my study; (3) screen for genetic modifiers of organelle disruption in my models of HSP.

Poster number: PS077 (SP)**Theme:** Neurodegenerative disorders & ageing**Leptin protects against abnormal mitochondrial fragmentation and dysfunction induced by amyloid-beta in hippocampal cells****Authors:** Ms Ying Cheng¹, Ms Alison Holiday¹, Ms Mizuki Morisaki¹, Dr Gayle Doherty¹¹*School of Psychology and Neuroscience, University Of St Andrews, Fife, United Kingdom*

Introduction: Mitochondrial dysfunction of neuronal cells occurs in an early and predominant manner in Alzheimer's disease (AD). Neuronal cells have high energy demands as they transmit signals over long distances and therefore rely on dynamic features of mitochondria to fulfil their energy requirements. Evidence from extensive studies supports that abnormal mitochondrial dynamics and function contribute to the progression of AD.

Methods: We have used differentiated mouse hippocampus neuronal cells (HT-22) to investigate the effects of leptin on mitochondrial fission and fusion dynamics and mitochondrial function during A β -induced neuronal loss. In this study, MitoRed staining was used to visualize mitochondrial morphology. Changes of mitochondrial membrane potential was monitored by JC-1 assay. ELISA, Western blot and immunocytochemistry (ICC) assay were performed to determine changes in mitochondrial proteins following leptin treatment.

Approach for statistical analysis: Image J was used for analysis of mitochondrial morphology and fluorescent intensity to obtain image data. To quantify the changes of mitochondrial morphology, indexes of count, size, mitochondrial fragmentation and interconnectivity were performed. Statistical analyses were performed using one-way analysis of variance (ANOVA) with Dunnett's/Dunn's(nonparametric) post hoc test for comparisons between multiple groups or independent-samples t test for comparisons between two groups. P < 0.05 was considered significant.

Results and Conclusions: It is found that leptin is able to inhibit A β -induced neuronal membrane permeability (p < 0.05, N=8) and prevent the associated loss of cells (p < 0.01, N=4). Furthermore, leptin attenuates abnormal mitochondrial fragmentation (p < 0.0001, N > 200 cells) induced by A β potentially through maintaining the level of mitochondrial fission protein Drp1 (p = 0.035, N=5). In addition, leptin prevents depolarization of mitochondrial membranes and enhances damaged mitochondrial membrane potential in the presence of A β (p < 0.001, N > 200 cells). Also, leptin downregulates the expression of A β -binding alcohol dehydrogenase (ABAD) implying that this may be central to leptin's anti-A β effects (p = 0.039, N=5). Taken together, leptin plays a neuroprotective role against in murine hippocampal cells by maintaining the balance of mitochondrial morphological dynamics and improving dysfunction of mitochondrial membrane potential and enzymes. Our findings strengthen the emerging evidence that leptin may be a potential therapeutic target for AD.

Poster number: PS078 (PP)**Theme:** Neurodegenerative disorders & ageing**Investigating the effect of a sphingosine-1-phosphate receptor modulator, fingolimod, on neuroinflammation in a rodent model of Alzheimer's disease****Authors:** Mr. Luke Davison¹, Dr. Steven Fagan¹, Prof. Kumlesh Dev¹¹*Trinity College Dublin, Dublin, Ireland*

Introduction: Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive memory loss and cognitive decline. At the molecular level, AD is characterized by accumulation of both amyloid beta (A β) protein extracellularly and hyperphosphorylated tau intracellularly, particularly in areas of the brain important for memory, learning and cognition such as the hippocampus and cortex. Glial activation is thought to contribute to

an inflammatory phenotype in the central nervous system (CNS) in AD, with the activation and subsequent release of pro-inflammatory cytokines from astrocytes and microglia recognised as being a significant addition to disease progression and severity.

Fingolimod (FTY720) is an immunomodulatory pro-drug used for the treatment of Multiple Sclerosis, due to its action as a functional antagonist of sphingosine-1-phosphate receptors on B and T lymphocytes, which are then internalised, preventing the egress of B and T cells from lymph nodes and ultimately preventing inflammatory demyelination in the CNS. We hypothesise that FTY720 can attenuate the inflammatory over-activation of astrocytes and microglia in AD, and also prevent demyelination in AD-relevant areas of the brain.

Methods: Rats with a single APP transgene aged 6 months, treated for 6 months with 1mg/kg FTY720 before sacrifice, will be assessed for astrocytic and microglial activation through Western Blot analysis of the glial markers GFAP (astrocytes) and Iba1 (microglia) from hippocampal and cortical brain homogenate, compared to water-treated wildtype (WT) rats, FTY720-treated WT rats and water-treated transgenic rats. Immunohistochemical analysis of parasagittal brain sections will stain for markers of astrocytes, microglia, neurons, axonal damage, early and late myelination markers in the hippocampus and cortex, and identify what effect FTY720 has on the activation/damage induced by AD on these cell types.

Approach for statistical analysis: Analysis of Western Blot and Immunohistochemical data will involve the use of Image J software for determination of the pixel density of protein bands and fluorescence intensity respectively. Statistical analysis will involve the use of Two-way ANOVA to account for the difference in genotype and treatment between groups. Tukey's post hoc test will be used to determine differences in the mean between pairs of groups.

Poster number: PS079 (SP)

Theme: Neurodegenerative disorders & ageing

Modulation of memory and oxidative stress bio-markers by resveratrol and environmental enrichment in rodent model of Alzheimer's disease

Authors: Dr MS Muhammad^{1,4}, Professor JO Ayo², Professor NM Danjuma³, Dr. Abdulwahab Al-hassan⁴, Dr. AS Isa⁴

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Introduction: Alzheimer's disease (AD) is the leading cause of dementia that affects one patient every seven seconds, with over 35 million people affected worldwide. In this study, we investigated the modulation of memory and oxidative stress bio-markers by resveratrol and environmental enrichment (EE) in aluminium chloride (AlCl₃) model of AD in mice.

Methods: Sixty three (63) male mice were used for the study, divided into nine groups, each comprising seven animals. Group I served as the negative control and received 0.2 ml normal saline/kg, Group II (positive control): 0.2 ml Carboxymethyl cellulose (CMC)/kg. Group III: resveratrol (200 mg/kg/), Group IV: CMC and kept in EE, Group V: AlCl₃ at dose rate of 50 mg/kg, Group VI: resveratrol at dose rate of 200 mg/kg and kept in EE, Group VII: AlCl₃ (50 mg/kg) + resveratrol (200 mg/kg) orally, Group VIII: AlCl₃ (50 mg/kg) and kept in EE, Group IX: AlCl₃ (50 mg/kg) + resveratrol (200 mg/kg) and kept in EE. All treatments were by oral and lasted for 8 weeks. Neurobehavioral assessments of memory was carried out 7 days before treatment, and at weeks 4 and 8 of the study, using passive avoidance test. The animals were sacrificed 24 hours after the last neurobehavioral assessment. Hippocampal samples were collected for biochemical analyses.

Analysis Approach: All analyses were done using one-way and mixed ANOVA followed by Tukey's and Bonferroni post-hoc tests, respectively.

Results and Conclusions: The results of memory evaluation obtained from the study showed a significant ($p < 0.05$) increase in step-down latency in $AlCl_3$ and resveratrol groups, at the fourth week of the study, followed by a significant decrease in the $AlCl_3$ group at the eight week of the study. These findings suggest that aluminium chloride induced memory deficit in a time dependent manner. Resveratrol significantly improved contextual fear memory at fourth week of the study. Both amyloid beta (A β) and nuclear factor erythroid 2-related factor 2 (Nrf2) concentrations significantly increased in $AlCl_3$ + EE + resveratrol treatment group, demonstrating beneficial role of independent treatments with either resveratrol and, or EE over the combined treatments in our study.

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Poster number: PS080 (SP)

Theme: Neurodegenerative disorders & ageing

Hypoglycaemia is a driver of lipopolysaccharide-induced sickness behaviour and cognitive impairment in mice

Authors: Dr John Kealy¹, Dr Carol Murray¹, Dr Ana-Belen Lopez-Rodriguez¹, Mr Dáire Healy¹, Dr Lucas Silva Tortorelli¹, Dr Michelle Doran², Dr Seán Doyle², Dr John P. Lowry², Dr Colm Cunningham¹

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Introduction: Systemic infection induces stereotypical changes known as sickness behaviour, including fever, lethargy, loss of appetite, and cognitive impairment. Severe infections can also cause acute neurological disturbances like delirium, especially in patients with an underlying neurodegenerative disorder. In the ME7 prion model of neurodegeneration, lipopolysaccharide (LPS) induces acute cognitive impairment in ME7-treated but not control mice and this impairment is dependent on systemic, not central, interleukin-1 β (IL-1 β) signalling. Here, we investigate whether LPS-induced hypoglycaemia instead drives these behavioural and cognitive changes.

Methods: LPS- (250 μ g/kg) and IL-1 β -induced (25 μ g/kg) hypoglycaemia was characterised in c57BL6/J and IL-1 receptor 1 knock-out (IL-1R1^{-/-}) mice. IL-1 receptor antagonist (IL-1RA; 10 mg/kg) was used to elucidate the role of IL-1 in LPS-induced hypoglycaemia. Blood glucose was measured using a veterinary glucometer. Central glucose was measured in cerebrospinal fluid using a clinical microdialysis analyser and in the parenchyma using amperometric glucose biosensors. The effect of hypoglycaemia on sickness behaviour as measured in the open field was investigated in c57BL6/J mice by using combinations of LPS, glucose (2g/kg), and 2-deoxyglucose (2-DG; 2g/kg). Hippocampal neurodegeneration was achieved in c57BL6/J mice via ME7 prion inoculation (with normal brain homogenate (NBH) as control). The effect of hypoglycaemia on working memory was assessed on the paddling T-maze using LPS, glucose, and insulin (400 μ g/kg). All drugs administered intraperitoneally.

Approach for statistical analysis: t-tests and ANOVAs (one-way and two-way, repeated measures or non-repeated measures - depending on experimental design) were performed in GraphPad Prism.

Results and conclusions: LPS induced long-lasting and robust hypoglycaemia both systemically and centrally in c57BL6/J mice. IL-1 β was sufficient but not essential to induce hypoglycaemia; IL-1RA only partially protected against hypoglycaemia in c57BL6/J mice and LPS still induced hypoglycaemia in IL-1R1^{-/-} mice. Systemic glucose concentrations correlated with locomotor activity and glucose pre-treatment prevented LPS-induced sickness behaviour. LPS caused cognitive impairment in ME7 despite equivalent levels of hypoglycaemia as in NBH controls. In ME7 but not NBH mice, insulin-induced hypoglycaemia mimicked LPS-induced deficits and glucose treatment could

partially reverse LPS-induced cognitive impairment. These data confirm that hypoglycaemia is a major driver of LPS-induced sickness behaviour and cognitive impairment.

Poster number: PS081 (SP)

Theme: Neurodegenerative disorders & ageing

The β (beta) network measured by electroencephalography discriminates dementia with lewy bodies from Alzheimer's disease

Authors: Mr Ramtin Mehraram^{1,2}, Prof Marcus Kaiser³, Dr Ruth Cromarty¹, Ms Alison Killen¹, Dr John-Paul Taylor¹, Dr Luis Peraza Rodriguez¹

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Introduction: Previous studies have shown that the brain network architecture and its connectivity strength—as assessed by electroencephalography (EEG)—are impaired in Alzheimer's disease (AD) patients compared with age matched healthy control people (HC). Here we performed a graph theory exploratory study to assess whether network measures discriminate Lewy body disease (LBD) patients, i.e. dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), from HC and AD participants.

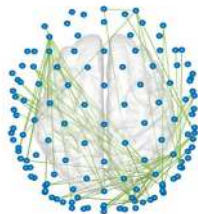
Methods: Resting state EEG signals (128 channels, 1024 Hz) were recorded from 18 HC, 22 PDD, 26 DLB, and 32 AD participants. Signals were filtered (bandpass: 0.5-80 Hz; notch: 50 Hz), noisy epochs were removed by visual inspection and artefactual components obtained by ICA were rejected. Connectivity strength was measured with weighted phase lag index (WPLI)¹. Network measures were computed using the Brain Connectivity Toolbox (BCT)², and the network edge densities ranged from 1% to 60% of the strongest WPLI values.

Approach for statistical analysis: Topological WPLI differences between groups were assessed with the Network Based Statistics toolbox (NBS)³. Differences in average WPLI and network measures were assessed by Kruskal-Wallis test ($p < 0.05$) followed by Mann-Whitney U test ($p < 0.05$, Holm-Bonferroni correction). Diagnostic accuracy was tested with the receiver operating characteristic (ROC) curves.

Results and conclusions: When compared with AD, graph measures indicated a less efficient β -band (14 - 20.75 Hz) network in DLB. The α -band (8 - 13.75 Hz) network was generally affected in the LBDs ($p < 0.05$ with Holm-Bonferroni correction) when compared with HCs. LBD networks were more segregated within the θ -band (4 - 7.75 Hz) compared with ADs (higher small-worldness and modularity).

Our study suggests that β -band network measures may be suitable as biomarkers for discriminating DLB from AD (sensitivity: 0.94, specificity: 0.56). These variations may be associated with impairment of attentional networks at rest in DLB.

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AD>DLB, β -band, NBS

Poster number: PS082 (SP)

Theme: Neurodegenerative disorders & ageing

Modular dissociation within brain networks shows segregated connectivity in the ageing brain and differentiated patterns in the neurodegenerative diseases

Authors: Dr Luis Peraza Rodriguez¹, Mr Ramtin Mehraram^{1,2}, Ms Julia Schumacher¹, Prof Marcus Kaiser^{1,3}, Dr John-Paul Taylor^{1,2}

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Introduction: It is hypothesised that the brain's modularity is a result of evolution where brain design allows for nuanced adaption of subsystems without altering its overall functional network. The ageing process alters the brain, and neurodegenerative diseases accentuate these alterations. Here, we investigated the brain's modularity and its variability and dissociation in healthy ageing and neurodegeneration.

Methods: Two neuroimaging databases were investigated; the 1000 functional connectome (N = 359) and the NKI Rockland sample (N = 297). Additionally, a cohort of neurodegenerative diseases was included (N = 97) which also comprised healthy controls (N = 34). Resting-state functional MRI data were pre-processed, brain connectivity matrices were estimated and thresholded at 10%, 20%, and optimal edge densities. To assess modular changes, we propose the novel index of modular dissociation, MD, which is defined as the difference between two weighted connectivity regimes: global and local threshold (Peraza et al., 2018).

Approach for statistical analysis: The neurodevelopmental databases were divided into young adults (YAs) and older adults (OAs), and the neurodegenerative database was divided by condition (Alzheimer's disease, Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), and OAs). Comparisons between groups were assessed by nonparametric permutations (5000), and results were considered significant at p-value < 0.05 FDR-corrected for multiple comparisons.

Results and conclusions: We found that with ageing the brain moves towards a segregated connectivity regime where modules in OAs demonstrate a tendency towards local connectivity, despite presenting with more variable modular patterns compared with YAs. The opercular cortices were the only regions that did not show modular segregation during ageing. When affected by neurodegeneration, the brain maintains a similar global pattern of segregation as seen in healthy older age. However at the local level, the brain regions showed differentiated patterns of MD, especially between DLB and PDD. This result suggests that these two conditions, DLB and PDD, may not be as similar as previously thought (Peraza et al., 2018).

Peraza LR, O'Brien JT, Blamire A, et al. (2018) The functional brain favours segregated modular connectivity at old age unless targeted by neurodegeneration. *bioRxiv*.

Poster number: PS083 (SP)**Theme:** Neurodegenerative disorders & ageing**Cannabidiolic acid rescues deficits in hippocampal LTP in two models of Alzheimer's disease****Authors:** Mrs Beatriz Gil^{1,2}, Dr Caroline Herron^{1,2}¹*SBBS, Conway Institute, University College Dublin, Dublin, Ireland*, ²*GW Pharmaceuticals plc, Cambridge, United Kingdom*

Introduction: Alzheimer's disease (AD) is a cognitive disorder diagnosed post-mortem by the presence of beta amyloid plaques (A β), and neurofibrillary tangles. Long-term potentiation (LTP) is a form of synaptic plasticity used to study potential therapies for AD. A β ₁₋₄₂ mediated attenuation of LTP in the hippocampal CA1 region can be reversed by pre-treatment with the phytocannabinoid, cannabidiol [1]. We have now examined the effects of cannabidiolic acid (CBDA) as a neuroprotective agent against A β in acute hippocampal slices and in the APP^{swe}/PS1^{dE9} (APP/PS1) mouse model of AD.

Methods: Extracellular field excitatory post synaptic potentials (fEPSPs) were recorded in hippocampal slices from C57BL/6 mice (8 weeks). The Schaffer-collateral pathway was stimulated every 30s (0.033Hz) prior to induction of LTP using high frequency stimulation (HFS; 2x100Hz, 1s). Slices were treated with CBDA (10 μ M), Beta Amyloid Derived Diffusible Ligands (A β ₁₋₄₂; 500nM) or a combination of CBDA+ A β . The level of LTP recorded at 60min was compared between groups.

LTP was also induced in slices from APP/PS1 mice and control littermates (9 months old; vehicle or CBDA treated; 30mg/kg; i.p. injections for 5 weeks). Paired pulse facilitation (range 10-150ms). LTP and post-tetanic potentiation (PTP) were assessed across groups.

Approach for statistical analysis: GraphPad Prism was used for graphing and analysis, Paired or unpaired t-test, or ANOVA were used, as appropriate.

Results and conclusions: Acute CBDA did not alter levels of LTP compared to control. A β attenuated LTP, while pre-treatment of slices with CBDA prior to A β significantly increased LTP compared to slices treated with A β alone. LTP in slices from vehicle treated APP/PS1 mice was significantly reduced compared to vehicle treated control littermates. CBDA (i.p) significantly increased the level of LTP in hippocampal slices from APP/PS1 compared to vehicle treated mice. PPF was significantly lower in vehicle treated APP/PS1 compared to vehicle treated controls and this was reversed in slices from CBDA treated APP/PS1 mice.

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Poster number: PS084 (SP)**Theme:** Neurodegenerative disorders & ageing**B2-adrenoceptor stimulation restrains microglial activation and attenuates advancements in dopamine cell loss and motor dysfunction in response to systemic inflammation: relevance to Parkinson's disease****Authors:** Mr Eoin O'Neill^{1,2}, Dr Andrew Harkin^{1,2}¹*Trinity College Institute of Neuroscience, Dublin 2, Ireland*, ²*School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland*

Microglia can become primed by ongoing neurodegeneration to respond more vigorously to an immune stimulus of systemic origin with potential neurotoxic consequences, which in turn may accelerate the course of

neurodegenerative disease. Here we assessed the impact of systemic inflammation on pre-existing microglial activation, dopaminergic neuropathology and motor dysfunction in the intra-nigral lipopolysaccharide (LPS) rat model of Parkinson's disease (PD). The immunomodulatory potential of pharmacologically targeting β_2 -adrenoceptors (β_2 -AR's) directly to interrupt the CNS response to systemic inflammation was also assessed. Our results indicate that a prior pathology in the nigrostriatal dopaminergic system predisposed to a heightened degree of Iba1⁺ reactive microgliosis and IL-1 β production upon subsequent peripheral exposure to a low dose of bacterial LPS. These findings were accompanied by exacerbated tyrosine hydroxylase-positive (TH⁺) dopamine cell loss in the substantia nigra and affiliated dopaminergic nerve terminal degeneration in the striatum, culminating in exaggerated motor deficits. Treatment with the long-acting, lipophilic, highly selective β_2 -adrenoceptor agonist formoterol curtailed the expansion of nigral microgliosis, restrained overt increases in IL-1 β production and prevented advancements in nigrostriatal dopaminergic neurodegeneration in response to peripheral immune challenge, facilitating astute improvements in motor function. Our data demonstrate that an acute episode of systemic inflammation can aggravate microglial activation and IL-1 β production in the inflamed substantia nigra, whilst expediting the progression of dopaminergic neuronal loss and the ensuing decline in motor function. Pharmacologically stimulating β_2 -AR's with formoterol halts advancements in Parkinsonian neuropathology and motor deficits promoted by systemic inflammation via immunomodulation of midbrain microglia.

Poster number: PS085 (SP)

Theme: Neurodegenerative disorders & ageing

An ovine model of Alzheimer's disease; investigating spontaneous tau pathology in sheep

Authors: Ms Emma Davies¹

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Research into Alzheimer's disease (AD) aims to elucidate the underlying pathological mechanisms of the disease and to identify potential therapeutic agents to stem or block pathological development. Research strategies have primarily relied upon *in vivo* rodent models of the disease. Whilst these models offer valuable insights into AD, they also have limitations as they are unable to fully recapitulate the complexity of the neurological disease due to a reduced complex brain structure and a comparatively shorter life span (JPND, 2014).

The development of large animal models which are capable of reflecting the complexity of human neurodegenerative disease is, therefore, increasingly important. Sheep have been identified as one such model (Jacobsen *et al.*, 2010), as this species demonstrates some of the primary histopathological characteristics of AD; Beta-amyloid plaques and hyperphosphorylated tau neurofibrillary tangles (Nelson 1994 & Reid *et al.*, 2017). However, although sheep spontaneously develop neurofibrillary tangles (insoluble forms of the tau protein), soluble tau oligomers are considered to be the more toxic form of the protein, triggering the neurodegeneration and pathogenesis associated with AD (Shafiei *et al.*, 2017). The aim of this study, therefore, was to further assess the suitability of sheep as an AD model, by profiling soluble and insoluble fractions of the ovine tau protein. The identification and analysis of normal and pathological tau isoforms in seven sheep over five years of age was performed by 1D and 2D SDS-Page, western blotting using phosphorylation specific antibodies, and liquid chromatography mass spectrometry.

Immuno-stained blot images were quantitatively assessed for significant differences between brain regions and individuals using a paired t-test or by one-way analysis of variance (ANOVA).

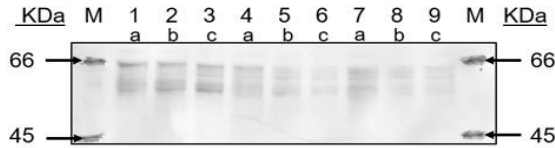


Figure 1: Western blot probed with phosphorylation specific Serine396 antibody showing recognition of pathological tau epitopes. Samples are from three sheep (1:1-3; 2:4-6; 3:7-9) with three brain areas respectively; a) Hippocampus, b) Entorhinal cortex, c) Frontal cortex, M) Low molecular weight marker.

A number of soluble tau isoforms were identified as positive for phosphorylation at amino acid Serine 396, in all sheep in a range of brain structures (hippocampus, entorhinal cortex and frontal cortex) (Figure 1). These preliminary data strongly suggest that AD-like pathological mechanisms may naturally occur in sheep thus making this species a good candidate model for the development of AD.

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Poster number: PS086 (SP)

Theme: Neurodegenerative disorders & ageing

The saturated fatty acid palmitate negatively affects morphology and function of primary hippocampal and cortical neurons via activation of the insulin pathway

Authors: Ms Aline Loehfelm¹, Dr. Alexander Tups¹

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Introduction: Insulin is not only important for glucose homeostasis in peripheral tissues, but also exhibits various functions in the brain. Accordingly, central insulin resistance, is a risk factor for the development of sporadic Alzheimer's disease (AD), the most common cause of dementia. A crucial risk factor for the development of Type 2 Diabetes (T2D) and, thus for the development of AD, is midlife obesity, which is mainly caused by the consumption of a diet high in long-chain saturated fatty acids and sugar. Considering these data, the aim of this study was to determine the negative effects of the saturated fatty acid palmitate (PA), the most abundant fatty acid in a Western style diet, on neuronal morphology and function, especially in regard to the development of Alzheimer's like pathologies. We further investigated the beneficial properties of the ω 3 poly-unsaturated fatty acid Docosahexaenoic acid (DHA) and the role of the insulin pathway in the PA-mediated changes.

Methods: All experiments were conducted in primary hippocampal or cortical cultures from P0/P1 Sprague Dawley rats. For morphological and functional analysis cells were treated with either 200 μ M PA, 200 μ M DHA or an equimolar combination of both. To determine the role of the insulin pathway, insulin and different inhibitors were applied. Dual label-immunocytochemistry was used to reveal morphological changes. Neuronal function was examined by calcium imaging.

Approach for statistical analysis: One-way or two-way ANOVA followed by Tukey's post-hoc analysis was used to determine statistically significant differences between groups.

Results and conclusions: Immunocytochemistry revealed that PA, but not DHA, leads to severe morphological changes in primary neurons, including swelling of the cell body and blebbing in axons and dendrites compromising healthy cell function. A three-dimensional analysis of synaptic input, visualised by Synapsin1 staining, furthermore exhibited a reduction in the number of synapses after PA treatment, leading to reduced cell excitability. Interestingly, DHA was able to prevent morphological changes, if applied simultaneously. Interestingly, it emerged that PA-mediated effects are caused by an increase in neuronal insulin signalling as shown by insulin stimulation and PI3K inhibition and not by overactivation of the GSK3 pathway.

Poster number: PS087 (SP)

Theme: Neurodegenerative disorders & ageing

Inherited motor neuron disease-causing genes regulate intracellular membrane compartments

Authors: Mr Dwayne Byrne^{1,2}, Dr Niamh O'Sullivan², Dr Craig Blackstone¹

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Introduction: Hereditary Spastic Paraplegias (HSPs) are a group of inherited neurodegenerative conditions in which length-dependent degeneration of the longest corticospinal tract neurons causes lower limb spasticity; thus, patients require walking aids or a wheelchair. Currently there are no treatments to cure or slow disease progression.

HSPs are highly heterogenous disorders, with >80 identified genetic loci identified. However, >50% of autosomal dominant HSPs are caused by mutations in endoplasmic reticulum (ER)-shaping proteins (Blackstone, 2018). Previous work (O'Sullivan et al, 2012; Fowler and O'Sullivan, 2016) found that reduced expression of two ER-shaping proteins, Reticulon-like 1 or Arl6IP1, in *Drosophila melanogaster* impair locomotor abilities but not longevity, reminiscent of HSP. Using these models, as well as novel knockout models I have generated by CRISPR/Cas9 gene-editing, I have investigated how loss of ER-shaping proteins disrupt intracellular organelles.

Methods:

- CRISPR/Cas9 gene-editing of *Drosophila melanogaster* to generate *in vivo* and models of HSP.
- Axons from HSP model and control flies expressing GFP-tagged mitochondria were imaged for 2 minutes. Kymographic analysis was used to quantify mitochondrial flux.
- LDs from HSP model and control flies were stained using Bodipy and LD analysis conducted using ImageJ software.
- In all studies a minimum of 15 flies per genotype from 3 independent experiments were investigated blind to genotype.
- Statistical analysis determined by t-test, one-way ANOVA and post-hoc analysis as appropriate.

Results and conclusions: Loss of ER-shaping proteins disrupts ER and mitochondrial organisation, specifically resulting in mitochondrial elongation. I examined whether mitochondrial trafficking within axons of *Drosophila* HSP models was disrupted, finding that mitochondrial mobility, both speed and proportion of trafficked mitochondria, was unchanged from controls. Therefore, loss of ER-shaping proteins is unlikely to directly regulate mitochondrial trafficking.

The ER is also the primary site for lipid biosynthesis and lipid droplet (LD) formation, which are disrupted in several published *in vivo* and cellular HSP models. Here, I show that knockout of ER-shaping proteins results in flies with significantly smaller LDs compared to controls, reflecting aberrant biosynthesis or clearance that might be relevant for HSP pathogenesis given the number of HSP gene products involved in this pathway.

Poster number: PS088 (SP)**Theme:** Neurodegenerative disorders & ageing**Investigating the genetics of cognitive resilience in healthy ageing****Authors:** Ms Joan Fitzgerald¹, Ms Laura Fahey¹, Prof Gary Donohoe¹, Dr Derek W Morris¹¹*Cognitive Genetics (CogGene), Neuroimaging, Cognition and Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland, Galway., Galway, Ireland*

Introduction: Age-related cognitive decline results in increased difficulty in performing tasks that require memory or rapid information processing and can have an increasingly detrimental effect on quality of life. Cognitive resilience is the ability to withstand the negative effects of stress on cognitive functioning. However, quantifying the contributors to resilience is challenging as it is necessary to identify individual differences in rates of change of performance over time. The genetic contribution to cognitive resilience is poorly understood as it is polygenetic and requires large data sets for analysis. The recent availability of data from the UK Biobank offers potential to advance research on the genetic and biological components of cognitive resilience.

Method: The UK Biobank general population cohort consists of UK residence aged between 40 and 69 recruited from 2006 to 2010. Using this cohort data, we created a longitudinal cognitive resilience phenotype by combining the phenotypic cognitive data parameter of current reaction time with a proxy phenotype of education years.

Analysis approach: We used this phenotype in a genome-wide association study (GWAS) using directly genotyped single nucleotide polymorphs (SNPs) only, and examined the resultant analysis using various bioinformatics tools to identify genes and gene sets that influence the biological pathways involved in resilience.

Results and conclusions: Data from 331,520 participants were included in the analysis. We found a total of 58 genome-wide significant SNPs ($p < 5 \times 10^{-8}$) associated with our phenotype. Further analysis showed that education years explained most of this association. However, comparing a GWAS of participants that showed expected resilience with a GWAS of those that showed high resilience highlighting 16 SNPs and 19 genes that are exclusively associated with resilience. These genes are all expressed in the brain with a variety of functions.

The creation of a longitudinal resilience phenotype using past education years and current reaction time is a potential tool for measuring resilience in large data sets. This analysis shows that of the many genes associated with education years (the length of time an individual spends in education), a proportion may contribute to cognitive resilience.

Poster number: PS089 (SP)**Theme:** Neurodegenerative disorders & ageing**Assessment of the impact of GDF-5-loaded collagen hydrogels on ventral mesencephalic grafts in a rat model of Parkinson's disease****Authors:** Ms Verónica Alamilla¹, Ms Silvia Cabré¹, Dr. Niamh Moriarty¹, Ms Rachel Kelly¹, Prof. Abhay Pandit², Dr. Eilís Dowd¹¹Pharmacology & Therapeutics, National University of Ireland, Galway, Ireland, ²CÚRAM Centre for Research in Medical Devices, Galway, Ireland

Introduction: A promising reparative therapy for Parkinson's disease is the transplantation of dopaminergic neurons harvested from foetal tissue. However, this is limited by poor survival leading to poor striatal reinnervation and motor recovery. We have recently shown that GDNF-enriched hydrogels have the potential to improve these graft

outcomes^{1,2}, suggesting that this approach merits extension to other neurotrophic factors. One potential neurotrophic factor to use in this context is growth differentiation factor 5 (GDF-5) which is a potent dopaminergic neuroprotective agent. Therefore, this study sought to determine the survival and efficacy of primary dopaminergic grafts in a GDF-5-loaded collagen hydrogel in a rat model of Parkinson's disease.

Methods: Forty Sprague Dawley rats received a unilateral medial forebrain bundle 6-hydroxydopamine lesion two weeks before transplantation surgery. They then received an intrastriatal transplant of E14 ventral mesencephalic (VM) cells (300k/6µl) with or without encapsulation in a collagen hydrogel with or without enrichment with GDF-5 (20µg/6µl). Methamphetamine induced rotations were assessed as a measure of functional restoration, while immunohistochemistry for dopaminergic neurons (tyrosine hydroxylase), microglia (OX-42) and astrocytes (GFAP) was used to identify graft survival, reinnervation, and host immune response post mortem.

Approach for statistical analysis: A randomised and blinded experimental approach was used throughout. All data were analysed using ANOVA (one-way or two-way with repeated measures where appropriate), with post hoc Bonferroni test as appropriate.

Results and conclusions: Surprisingly, we found that incorporation of GDF-5, but not the collagen hydrogel, into the transplantation process actually reduced the survival, reinnervation and functional capacity of the VM transplants suggesting that the GDF-5 was toxic to the cells. In conclusion, this study suggests that GDF-5, at the dose used in the present study, is detrimental to VM grafts. Therefore, it was not possible to determine if the collagen hydrogel provided any beneficial effects.

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Acknowledgements:

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Poster number: PS090 (PP)

Theme: Neurodegenerative disorders & ageing

Common pathological pathways between type 2 diabetes and dementia: investigating the role of the innate immune system

Authors: Dr Adam Dyer^{1,3}, Ms Isabella Batten¹, Dr Liam Townsend¹, Prof James Gibney², Dr Conor Woods², Dr Nollaig Bourke¹, Professor Sean Kennelly^{1,3}

¹School of Medicine, Trinity College Dublin, Dublin, Ireland, ²Department of Endocrinology, Tallaght Hospital, Dublin, Ireland, ³Department of Age-Related Healthcare, Tallaght Hospital, Dublin, Ireland

Introduction: Midlife Type 2 Diabetes (T2DM) is a potent, yet under-recognised, risk factor for the development of Alzheimer's disease and dementia in later life. Despite this, little is known about the putative pathophysiological links between the two conditions. Whilst circulating levels of pro-inflammatory cytokines have been shown to predict cognitive decline in T2DM, the underlying mechanisms remain unclear. Identifying common pathological pathways offers potential for development of novel biomarkers for cognitive decline in people with T2DM.

Methods: People with Type 2 Diabetes aged 40-65 will be recruited from the Diabetic Clinic and will undergo detailed health and diabetes status assessment as well as cognitive assessment. Controls matched for age and education level will be recruited by local advertisement. Cognitive assessments will be carried out using the standard Montreal

Cognitive Assessment (MoCA) as well as a detailed computerised neuropsychological test battery (CANTAB). A peripheral blood sample will be obtained for: (i) routine analysis for HbA1c and CRP, (ii) analysis of serum circulating pro-inflammatory cytokines (IL-1 β , IL-6 and TNF α using standard ELISA kits) and (iii) stimulation of peripheral blood mononuclear cells (PBMCs) using a range of innate immune inflammatory stimuli. Specifically, PBMCs will be isolated from individual patient samples using density centrifugation and incubated for up to eighteen hours with: (i) LPS, (ii) Amyloid B-42, (iii) LPS + Amyloid B-42, (iv) LPS + Nigericin and (v) Poly dA:dT. Immune activation will be assessed using ELISA for protein levels of IL-1 β , IL-6 and TNF α , and mRNA levels of inflammatory genes measured using qPCR using standard validated protocols in our lab. To date, all steps of the protocol has been optimised and patient recruitment has commenced.

Approach for Statistical Analysis: For between group differences, a t-test statistic will be used where data conform to a normal distribution, with appropriate non-parametric equivalents applied where this is not possible. Chi-squared tests will be used to compare count data between the two groups. Correlation analysis will be used to examine the links between neuropsychological performance and both circulating cytokines as well as cytokine response to the innate immune stimuli. Corrections for multiple testing will be applied.

Poster number: PS091 (SP)

Theme: Neurodegenerative disorders & ageing

Proteomic analysis of astrocytes carrying mutant TDP-43 reveals dysfunction of ubiquitin proteasome, energetics, cytoskeletal function and anti-oxidant responses: a case for therapeutics targeting glutathione and iron homeostasis

Authors: Prof Philip Beart¹, Mr Tong Chen², Dr Bradley Turner¹, Dr Hakan Muyderman²

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Introduction: The 43 kDa TAR DNA-binding protein (TDP-43) is a key disease protein found in ubiquitinated inclusions in neurons and astrocytes in >95% of Amyotrophic lateral sclerosis (ALS) cases constituting a histo-pathological signature of this disease. In ALS, astrocytes contribute to the pathogenesis of motor neuron injury through non-cell autonomous mechanisms. However, consequences of TDP-43 pathology in astrocytes have not been addressed. While mutant TDP-43 produces an ALS-like phenotype in transgenic animals and in humans, overexpression of wild-type TDP-43 does not produce ALS. Here we interrogated molecular mechanisms contributing to TDP-43 pathology in mouse astrocytes by expressing the TDP-43^{A315T} mutation, which produces familial ALS.

Methods: Primary mouse astrocytes were grown to confluence and used for experiments between 14-16 days when transfection of mCherry tagged TDP-43^{A315T} plasmid (Perera et al. PLoS One 9: e90449, 2014) was performed (Muyderman et al. Neurochem Res 35: 1771, 2010). At 72 h cytoplasmic and nuclear fractions were purified by 2D-electrophoresis and after silver staining, spots were excised for mass spectrometry. Western blotting, determination of cell viability and cytochemistry employed standard procedures.

Approach for statistical analysis: Treatments were compared to control sister cultures and performed in at least 3 independent cultures established from separate litters. Statistical analyses were performed on raw data by Student t-test or by ANOVA with Student-Newman-Keuls test. Results are mean \pm SD.

Results and conclusions: TDP-43^{A315T} produced substantial changes in astrocytic morphology as shown by cytochemistry with GFAP and F-actin at 72 h with increases in stress fibre formation, plus shortened processes and rearrangement of GFAP-positive intermediate filaments. Cell viability was unaffected. We identified a range of differentially expressed proteins predominantly involved in key pathogenic pathways implicated in ALS. Proteins involved in signal transduction, oxidative and cellular stress, and ubiquitin-proteasome system and protein

degradation accounted for >50% of changes in the proteome. Notable decreases were found in γ -glutamate-cysteine ligase regulatory subunit and ferritin heavy chain, both linked to ferroptosis. Ours is the first determination of roles of the proteome in astrocytic pathobiology in ALS and suggests pharmacological interventions increasing glutathione may have therapeutic potential.

Poster number: PS092 (SP)

Theme: Neurodegenerative disorders & ageing

Using *Caenorhabditis elegans* as a model for Charcot-Marie-Tooth syndrome

Authors: Mrs Iman Aolyamat¹, Dr Lee Haynes¹, Dr Jeff Barclay¹

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Introduction: Charcot-Marie-Tooth (CMT) syndrome is the most commonly inherited neurological disorder characterised by progressive muscular and nervous system dysfunction. CMT has been categorised into demyelinating type 1 (CMT1) and axonal type 2 (CMT2) neuropathies. Unfortunately, the disorder is still incurable. Small heat shock proteins (sHSPs) are low molecular weight proteins produced in response to stressful conditions. The most studied function of sHSPs is the prevention of protein misfolding and aggregation. Mutations in human HSPB1 and HSPB8 have been described in CMT2; however, the pathophysiological role of the associated mutated proteins remains unclear. We have created genetic models to investigate the pathophysiological impact of sHSP mutations in CMT2 using *Caenorhabditis elegans*.

Methods:

- Molecular biology and genetics.
- Age-dependent phenotypic methods.

Approach for statistical analysis: Data are presented as mean \pm standard error of means (SEM). Comparisons were made using ANOVA. Differences were considered significant when $P \leq 0.05$.

Results and conclusions:

- Human HSPB1 and HSPB8 genes were cloned, mutagenized and expressed transgenically in *C. elegans*.
- The genetic models expressing human HSPB1 and HSPB8 (wild-type and mutants) were phenotypically screened in-depth throughout the lifespan of the animal.
- The overexpression of wild-type HSPBs showed no negative effects on the strains phenotypes.
- The overexpression of certain mutant HSPB1 and HSPB8 showed a locomotion defect at different age groups.
- Overexpression of all mutant HSPBs caused a resistance phenotype to aldicarb at young age which suggests a defect in neurotransmitter release.
- Control nematodes and animals overexpressing wild-type HSPB1 and HSPB8 became hypersensitive to aldicarb at old age; however, animals expressing the mutant HSPBs showed an accelerated age-dependency.
- Overexpression of mutant HSPBs revealed normal levamisole sensitivity supportive of a presynaptic defect in neurotransmitter release.

To conclude, the created mutant strains replicate well HSPB-dependent human CMT2 phenotypes and can be used as a genetic basis for future mechanistic or therapeutic investigations.

Poster number: PS093 (PP)**Theme:** Neurodegenerative disorders & ageing**Investigating the potential of a dopamine genetic risk score to predict the incidence of impulse control disorders in Parkinson's disease****Authors:** Ms Alison Hall¹, Dr Ned Jenkinson¹, Dr Hayley MacDonald¹¹School of Sport, Exercise and Rehabilitation Sciences, The University of Birmingham, United Kingdom

Impulse control disorders (ICDs) are estimated to develop in 14-40% of Parkinson's disease (PD) patients treated in particular with dopamine agonists (DAs) (Kraemmer et al., 2016). DAs successfully treat symptoms of PD by augmenting depleted nigrostriatal dopamine. However, as DAs cannot be targeted only to dopamine depleted regions, dopamine is also increased in the relatively preserved medial prefrontal cortex and ventral striatum. The resulting hyperdopaminergic state in these regions can lead to ICDs. Dopamine levels and a person's response to dopamine medication is under the influence of many factors, including genetics. Our previous work has identified dopamine gene profiling as a potential method to quantify genetic levels of dopamine and predict how people will respond to DAs. Healthy adults with a higher dopamine genetic risk score (DGRS), reflecting higher starting levels of dopamine neurotransmission, showed impaired impulse control on DAs compared to placebo. We now want to extend these findings into PD patients who are taking DAs. The present study will use demographic, clinical and genetic data available from the Parkinson's Progression Markers Initiative (PPMI) cohort database to investigate the potential of our DGRS to predict patients at risk of developing ICDs. We hypothesise that patients with a higher DGRS, and therefore higher levels of dopamine, will present more ICD behaviours when dopamine is further increased with DAs than those with a lower DGRS.

This is a longitudinal study, encompassing data from PD patients contributing to the PPMI cohort database since 2010. ICDs will be identified via any positive score on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)-short. Each patient's DGRS will be calculated according to the presence or absence of mutations within the following genes: DRD1, DRD2, DRD3, COMT, DAT.

A mixed effects linear regression analysis will model (QUIP)-short score as a function of DGRS, DA dosage, time on DAs and their interactions. Age, disease severity and gender will also be included in the model while avoiding over-parameterization.

Kraemmer, J. et al. (2016) 'Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease', *Journal of Neurology, Neurosurgery and Psychiatry*, 87(10), pp. 1106–1111

Poster number: PS094 (SP)**Theme:** Neurodegenerative disorders & ageing**Biochemical studies in a conditional knockout mouse model related to Alzheimer's disease****Authors:** Ms Lauren Kavanagh¹, Ms Dzenana Becic¹, Mr Adam Rhodes¹, Professor Noel Buckley², Dr Vassilios Beglopoulos¹¹University Of Central Lancashire, Preston, United Kingdom, ²University of Oxford, Oxford, United Kingdom

Introduction: Alzheimer's disease (AD) is the major form of dementia and is pathologically characterised by progressive neurodegeneration, among other neuropathological features. Better understanding of the biochemical, cellular and molecular mechanisms underlying the pathology and symptoms of AD could contribute to the future improvement of treatment and diagnosis. This work focuses on the study of biochemical alterations in the brain, that

are possibly related to neurodegeneration in AD. To this end, a genetically modified (conditional knockout (cKO)) mouse model has been used, with a gene implicated in neurodegeneration conditionally inactivated in the brain.

Methods: All the work presented has been performed using brain tissue from cKO and control mice, and ethical approval has been granted. Tissue was lysed with appropriate detergents (denaturing conditions). Protein concentration was determined using a bicinchonic acid-based protein assay. Equal amounts of protein across different samples (from different mice) were loaded on Tris-glycine gels, and SDS-PAGE electrophoresis was performed. Following protein transfer to PVDF membranes, Western blot analysis was performed using a variety of antibodies. All experiments and analyses were performed blindly (the genotype was unknown to the experimenter until the analysis was completed).

Analysis approach: Four samples from each of the groups (cKO and control) were used. The analysis of the data was based on two approaches, a) visual comparison of the band intensity between the samples of the different groups, and b) quantification of the band intensity by densitometry and statistical analysis. In both approaches, the intensity of the signal corresponding to the original antibody was compared (and in the second approach normalised) to the that of a loading control, representing the levels of a “housekeeping” protein (beta-actin or alpha-tubulin), unlikely to change by the genetic manipulation. Statistical analysis was performed using t-test.

Results and Conclusions: Several marker proteins were analysed (MAP2, synaptophysin, Tau, Phospho-Tau), focusing on a) neuronal cellular compartments (dendrites, synaptic terminals), assessing the possibility of degeneration of these compartments in the cKO mice, and b) tau phosphorylation, an important process implicated in the neuropathology of AD, investigating the possibility that this process might be altered in the brain of the cKO mice.

Poster number: PS095 (PP)

Theme: Neurodegenerative disorders & ageing

Cognitive determinants and experience of hallucinations and presence phenomena in Parkinson’s disease

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Introduction: Parkinson’s disease (PD) is a neurodegenerative disorder that affects the motor system. Symptoms include tremor, rigidity, and gait problems (Lyons & Pahwa, 2011). In addition to motor system impairment, half of all patients will also experience some type of psychotic symptom, including hallucinatory phenomena, during later stages (Divac N, et al. 2016). A common hallucinatory phenomenon reported by patients is the sensation of a presence when there is nothing there to account for this feeling. There is very little research into the sense of presence phenomenon. This study aims to improve understanding by investigating the nature of this phenomenon and its relationship with cognitive variables, including general intelligence, memory, visual perception and executive function.

Methods: PD patients have been recruited from the Department of Neuropsychology, National Hospital for Neurology and Neurosurgery, Queen Square, London. PD patients who reported a sense of presence phenomenon have been interviewed using a novel questionnaire that assesses its nature and frequency, and elicits the patient’s understanding of its cause and meaning. All PD patients have undergone cognitive assessment, assessing IQ (WAIS-III), memory (Recognition Memory Tests), language (Graded Naming Test), visual perception (Visual Object and Space Perception Battery) and executive function (letter fluency, Stroop and Hayling Sentence Completion Test).

Approach for Statistical Analysis and Conclusion: This is a preliminary, investigatory study to (1) describe the lived experience of the sense of presence phenomena in PD, and (2) determine the cognitive variables that are associated

with this. Phenomenology will be described using qualitative and quantitative reporting methods, and independent t-tests and regression analyses will be used to reveal its cognitive determinants. Through this, the analysis will reveal the cognitive domains that differ in between patients that do and do not experience sense of presence phenomena.

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Poster number: PS096 (SP)

Theme: Neuroendocrinology and autonomic systems

Resiliency of prenatally stressed male and female rats following chronic mild stress exposure

Authors: Ms Daniela Schnitzler¹, Ms Ying Sze¹, Dr Paula Brunton¹

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Introduction: Repeated social stress experienced by pregnant dams 'programs' long-term changes in the offspring's brain and behaviour, including hypothalamo-pituitary-adrenal (HPA) axis dysregulation in both sexes and increased anxiety-like behaviour in the male offspring (1). This 'programming' may prepare the offspring for a suboptimal postnatal environment. However, a 'mismatch' between the predicted and actual postnatal environment may result in maladaptation. Here we aimed to test the resiliency of prenatally stressed (PNS) rats by investigating the impact of chronic stress in adulthood on anxiety-like behaviour and HPA axis activity.

Methods: To generate PNS offspring, pregnant dams were exposed to social stress (modified resident-intruder paradigm; 10 min/day) on gestational days 16-20. Control dams remained undisturbed. At 9-11 weeks of age, the male and female control and PNS offspring were either exposed to 7 days of chronic variable stress (CS) or undisturbed (no chronic stress; nCS). On the 8th day, anxiety-like behaviour was assessed using the light-dark box (LDB). Immediately afterwards, rats were killed, and trunk blood was collected. Plasma corticosterone concentrations were determined by radioimmunoassay.

Statistics: A two- or three-way ANOVA was used with Student-Newman-Keuls post-hoc tests. To compare two groups a Student's T-test was used. P<0.05 was considered statistically significant.

Results: As expected, PNS males showed more anxiety-like behaviour compared to control males, with no differences between control and PNS females. However, both CS PNS males and females displayed significantly less anxiety-like behaviour compared to their respective controls. Despite the similarity in behaviour, corticosterone responses were sexually dimorphic. After LDB exposure, plasma corticosterone concentrations were significantly greater in the CS PNS males compared to nCS PNS males, with no significant differences between the CS and nCS control males. In contrast, circulating corticosterone was significantly lower in the PNS females compared to the control females, regardless of chronic stress exposure.

Conclusion: The results support the 'maladaptive hypothesis' theory, in which PNS confers a degree of resiliency during chronic stress exposure in adulthood. In addition, chronic stress exposure abolishes the sex differences observed in anxiety-like behaviour induced by PNS.

1. Brunton, P.J., Russell, J.A., 2010. *J Neuroendocrinol* 22, 258–271.

Poster number: PS097 (SP)**Theme:** Neuroendocrinology and autonomic systems**Prolactin receptor-mediated stimulation of kisspeptin expression in periventricular nucleus projections to the oxytocin system in virgin mice****Authors:** Ms Shalini Kumar^{1,2}, Dr Rachael Augustine^{1,2}, Prof Colin Brown^{1,2}¹Centre for Neuroendocrinology and Department of Physiology, University Of Otago, Dunedin, New Zealand, ²Brain Health Research Centre, Dunedin, New Zealand

Introduction: Oxytocin is secreted from the posterior pituitary gland by magnocellular neurons in the supraoptic and paraventricular nuclei (SON and PVN) and is required for normal parturition. Kisspeptin expression in hypothalamic periventricular nucleus projections to the oxytocin system increases during pregnancy in rats and we have previously demonstrated that kisspeptin excites oxytocin neurons only in late pregnant rats. Periventricular nucleus kisspeptin neurons express prolactin receptors and placental lactogen, which acts on prolactin receptors, is chronically elevated throughout late pregnancy. Thus, we hypothesised that prolactin receptor activation might increase kisspeptin expression to excite oxytocin neurons in late pregnancy.

Methodology: Here, we determined the effect of prolonged prolactin infusion on kisspeptin and oxytocin neurons in virgin mice. Following subcutaneous infusion of ovine prolactin (1500 µg/day at 1µl/hr for seven days) or vehicle (0.01M NaHCO₃), double-label immunohistochemistry (IHC) for kisspeptin and oxytocin was carried out.

Approach for statistical analysis: All data were analysed using Graphpad Prism (Version 7.00). Values are expressed as means ± standard error of the mean (SEM). Two-tailed Student's t tests were used to compare between groups; *P* ≤ 0.05 was considered significant.

Results and Discussion: There was no significant difference in the mean number of kisspeptin-labelled cells in the periventricular nucleus of vehicle- and prolactin-infused mice (58.6 ± 23.7 and 49.1 ± 11.7, respectively; *P* = 0.20) or in oxytocin-labelled cells in the PVN (139.9 ± 22.8 and 138.1 ± 19.6, respectively; *P* = 0.47) or SON (48.8 ± 8.9 and 52.1 ± 2.5, respectively; *P* = 0.21). Kisspeptin fibre density was higher in prolactin-infused mice in the SON and perinuclear zone (PNZ) surrounding the SON (both *P* < 0.0001). However, the fibre density was not different between the two groups in the PVN. We observed, for the first time, that kisspeptin neurons formed close appositions with the oxytocin neurons in the PVN and SON. However, there was no difference in the number of appositions made between kisspeptin fibres and oxytocin neurons in prolactin-infused mice and vehicle-infused mice. Hence, prolactin receptor activation might contribute to increased kisspeptin expression in periventricular nucleus projections to the oxytocin system in late pregnancy, but might not drive the formation of new connections.

Poster number: PS098 (SP)**Theme:** Neuroendocrinology and autonomic systems**Investigating the role of the hypothalamic neuropeptide, QRFP, in arousal and body weight control****Authors:** Dr Christopher Cook¹, Dr Nicolas Nunn¹, Prof Simon Luckman¹¹FBMH, University Of Manchester, Manchester, United Kingdom

Introduction: A member of the RFamide family of peptides, pyroglutamylated RF-amide peptide (QRFP) is expressed exclusively in neurons surrounding the ventromedial nucleus (VMN) of the mediobasal hypothalamus. Early work identified orexigenic and hyperlocomotor responses to exogenous QRFP, and our laboratory and others have linked the peptide to both body-weight control and arousal. Currently, it is unclear whether QRFPs effects on body weight

are centrally mediated or via an unknown peripheral mechanism. Much remains to be discovered about the QRFP neuronal population, its role in normal physiology, the downstream targets that are responsible for QRFPergic effects, and whether QRFP neurons represent a homogeneous population. Our early functional results, suggest that the orexigenic and arousal effects of QRFP can be isolated, and we are currently characterising the separate pathways mediating the two effects.

Methods: We used a conditional *Qrfp* knock-out model (FIE*x-Qrfp*) to investigate the role of central QRFP in body-weight regulation and arousal. Body weight, composition and locomotor activity were measured in male and female littermates during 12 weeks of feeding with high-energy diet (HED).

Subsequently, by employing a mouse in which cre-recombinase is expressed under control of the *Qrfp* promoter, we have begun to interrogate the downstream targets of the QRFP neuronal population. Immunohistochemical techniques were employed to identify neuronal projections, thus identifying potential targets for future manipulation of the QRFP pathway.

Approach for statistical analysis: Statistical significance was tested for using a 2 way repeated measures ANOVA, with either Tukey's post-hoc test (body weight and composition study) or Sidak's post-hoc test (locomotion study) where appropriate, using GraphPad Prism 7.

Results and conclusions: FIE*x-Qrfp* homozygous mice display a lower whole-body adiposity in response to HED, when compared with wild-type littermates, and central rescue of *Qrfp* expression reverses this phenotype. In separate mice, *Qrfp* knock-out also led to a reduction in night-time locomotor activity.

QRFP neuronal fibres were found in numerous brain regions known to be involved in regulating arousal (locus coeruleus, raphe nuclei, ventral tegmental area and tuberomammillary nucleus), and metabolism (lateral and ventromedial hypothalamus).

Poster number: PS099 (SP)

Theme: Neuroendocrinology and autonomic systems

Acute myocardial infarction activates magnocellular vasopressin and oxytocin neurons

Authors: Dr Ranjan Roy¹, Dr Rachael Augustine¹, Dr Daryl Schwenke¹, Prof Colin Brown¹

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Introduction: Myocardial infarction is a leading cause of death worldwide. For those who survive the acute insult, a major long-term complication is chronic heart failure. Chronic heart failure is associated with increased circulating levels of the antidiuretic hormone, vasopressin, which is secreted from the posterior pituitary gland by magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei. However, it is not known whether acute myocardial infarction activates vasopressin neurons, or oxytocin neurons, which are also found in the supraoptic and paraventricular nuclei and promote natriuresis.

Methods: We used Fos protein as a marker of neuronal activation to determine whether magnocellular vasopressin and oxytocin neurons are activated 90 min after induction of myocardial infarction in adult male Sprague Dawley rats.

Analysis: The number of vasopressin-positive, oxytocin-positive and Fos-positive neurons were counted by an experimenter blinded to the groups. Comparisons were made using Student's t-tests.

Results and Conclusions: There were more vasopressin-positive and oxytocin-positive neurons in the supraoptic and paraventricular nuclei after myocardial infarction than after sham-operation, and a higher proportion of both phenotypes were Fos-positive. Fos is the protein product of the immediate early gene, *c-fos*, and acts as a

transcription factor to modulate the transcription of response genes in activated cells. Hence, increased Fos protein levels in magnocellular vasopressin and oxytocin neurons after acute myocardial infarction suggests that these neurons increase synthesis, and presumably secretion, of vasopressin and oxytocin, which might contribute to the development of chronic heart failure.

Poster number: PS100 (SP)

Theme: Neuroendocrinology and autonomic systems

Corticosterone in the hypothalamic arcuate nucleus regulates food intake and body weight

Authors: Dr Chioma Izzi-Engbeaya¹, Dr Yue Ma¹, Dr Niki Buckley¹, Dr Risheka Ratnasabapathy¹, Dr Errol Richardson¹, Dr John Counsell¹, Isabel Fernandes-Freitas¹, Mariana Norton¹, Gala Farooq¹, Zainab Mirza¹, Dr Sharon Cheetham², Prof Johanathan Seckl³, Prof Waljit Dhillon¹, Dr James Gardiner¹

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Introduction: Current medical treatments for obesity have limited efficacy and tolerability. Identifying novel pathways which control food intake could lead to effective therapies for obesity. Tissue-specific glucocorticoids are important in the development of obesity. *In vivo*, 11- β hydroxysteroid dehydrogenase type1 (11 β HSD1), converts the inactive glucocorticoid, 11-dehydrocorticosterone, to its active form (corticosterone). 11 β HSD1 is expressed in the hypothalamic arcuate nucleus (ARC), a major energy homeostasis-regulating centre. The role of 11 β HSD1 and corticosterone in the ARC on appetite regulation is unknown. We therefore investigated the effect of 11 β HSD1 expression in the ARC on appetite and body weight.

Methods: Experiments were performed using adult male Wistar rats fed a standard chow diet. In the first experiment, recombinant adeno-associated virus (rAAV) encoding 11 β HSD1 (rAAV-S11 β HSD1) was injected bilaterally into the ARC of 12 rats (overexpression group). rAAV expressing green fluorescent protein (GFP), rAAV-GFP, was injected bilaterally into the ARC of 12 rats (controls). In the second experiment, rAAV encoding small interfering RNA to 11 β HSD1 (rAAV-si11 β HSD1) was injected bilaterally into the ARC of 12 rats (underexpression group) and rAAV-GFP injected bilaterally in the ARC of 12 rats (controls). Body weight and food intake were measured 3x/week for 10 weeks starting 1 week post-surgery. Subsequently, tissues and plasma were collected for gene expression and hormone analysis.

Analysis Approach: Mann-Whitney tests were used to analyse non-parametric data, unpaired t-tests were used to analyse parametric data and generalized estimating equations were used to analyse longitudinal non-independent data.

Results and conclusions: In the overexpression group there was a 2.7-fold increase in ARC corticosterone levels compared to controls. This was associated with hyperphagia and 6% greater weight gain compared to controls. In the underexpression group ARC corticosterone levels were 47% lower compared to controls. This was associated with a 1.7-fold increase in intrascapular brown adipose tissue uncoupling protein 1 expression and a 5% lower weight gain. This data demonstrates that ARC 11 β HSD1 and corticosterone have important physiological roles in the regulation of energy homeostasis. Therefore 11 β HSD1 inhibitors, which target the central nervous system, could be an effective novel therapy for the treatment of obesity.

Poster number: PS101 (SP)**Theme:** Neuroendocrinology and autonomic systems**The apelinergic system in the circumventricular organs - a potential role in the control of arterial blood pressure?****Authors:** Dr Phil Griffiths¹, Dr Stephen Lolait¹, Ms Aarifah Bijabhai¹, Prof. Julian Paton², Dr. Anne-Marie O'Carroll¹
¹University of Bristol, Bristol, United Kingdom, ²University of Auckland, Auckland, New Zealand

A complex picture has emerged regarding the role that apelin, acting via the G protein-coupled receptor APJ, plays in the modulation of arterial blood pressure (ABP). Systemic administration of apelin decreases ABP, while central injection to discrete autonomic brain regions of anaesthetised rats activates pressor mechanisms. Interestingly, exogenous microinjection of apelin to the subfornical organ (SFO), one of the central circumventricular organs (CVOs) which lie outside the blood brain barrier, was shown to decrease ABP. The SFO, along with the vascular organ of the lamina terminalis (OVLT) and area postrema (AP), are thought to provide an interface between peripherally circulating signals and the brain through their projections to central autonomic structures. We hypothesised that the CVOs may contribute to the depressor effect of systemic apelin and that dysfunction in this system could contribute to chronic elevated ABP seen in hypertension. In this study the anatomical distribution of apelin and APJ gene expression in the CVOs of normotensive Wistar Kyoto (WKY) and spontaneously hypertensive (SHR) rats was investigated using branched chain *in situ* hybridisation histochemistry. 16µm sections at the level of the CVOs were processed using apelin- and APJ-specific probes with the RNAscope Multiplex Fluorescence Assay kit (Advanced Cell Diagnostics, USA). The total number of dots (corresponding to mRNA copies) per image was counted using an automated Plugin for Fiji (Wolfson Bioimaging Facility, University of Bristol) and verified by manual counting. Data is presented as median ± interquartile range and compared using a Mann-Whitney U test. APJ gene expression was increased in the SFO of SHR compared to WKY rats (1112±716 vs. 439±180, $P<0.05$, $n=4$). By contrast, both APJ (548±116 vs. 729±277, $P<0.05$, $n=4$) and apelin (281±64 vs. 638±434, $P<0.05$, $n=4$) gene expression was decreased in the AP of SHR compared to WKY rats. No significant difference in apelin or APJ gene expression was observed in the OVLT of SHR compared to WKY. This suggests that differences in the levels of apelin and APJ gene expression in the SFO and AP may be associated with the elevated ABP observed in SHR compared to normotensive controls.

Poster number: PS102 (SP)**Theme:** Neuroendocrinology and autonomic systems**Optogenetic stimulation of kisspeptin in the posterodorsal medial amygdala increases LH pulse frequency, which is modulated by GABA, in the female mouse****Authors:** Mr Geffen Lass¹, Dr Xiaofeng Li¹, Mr Ross de Burgh¹, Dr Shel-Hwa Yeo², Professor William Colledge², Professor Stafford Lightman³, Professor Kevin O'Byrne¹¹Department of Women and Children's Health, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom, ²Reproductive Physiology Group, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom, ³Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, The Dorothy Hodgkin Building, University of Bristol, Bristol, United Kingdom

Introduction: Kisspeptin within the arcuate nucleus of the hypothalamus is a critical neuropeptide in reproductive physiology. With neurokinin B and dynorphin, arcuate kisspeptin provides the oscillatory activity driving pulsatile secretion of GnRH and is believed to be a central component of the GnRH pulse generator. It is well established that the amygdala also influences LH pulsatility. The discovery of kisspeptin and its receptor within the posterodorsal medial amygdala (MePD), and our finding that intra-MePD administration of kisspeptin or its antagonist results in increased LH secretion and decreased LH pulse frequency, respectively, suggests an important role for amygdala kisspeptin in the regulation of the GnRH pulse generator, but these mechanisms are not established. This study

investigates this role of MePD kisspeptin using optogenetics, and whether MePD kisspeptin increases gonadotrophin secretion by disinhibiting GABAergic outputs on the GnRH pulse generator.

Methods: An AAV vector expressing channelrhodopsin was injected into the MePD of ovariectomised female Kiss-CRE mice together with chronic implantation of a fibreoptic probe. After a 60-min control period, animals were optogenetically-stimulated (473nm, 5-ms pulse width) at 0.5Hz, 2Hz or 5Hz for 90min. In another experiment, ovariectomised female Kiss-CRE mice were implanted with an optofluid cannula in the MePD and infused with a GABA_A antagonist (bicuculline, 68pmol/ul) together with 5Hz stimulation for 60min after a 60-min control period. Blood samples (5µl every 5min) were collected throughout for LH measurement.

Approach for statistical analysis: LH pulses were identified using DynPeak, and frequency analysed as LH inter-pulse interval. Data are presented as mean±SEM and one-way ANOVA used for statistical comparisons. N=3-7 per group.

Results and conclusions: Continuous optic stimulation at 5Hz decreased LH pulse interval (26.07±3.81 vs 16.64±0.83 min, n=7, p<0.05), which was not observed at the lower frequencies of 0.5 and 2Hz. In wild-type animals, continuous stimulation at 5Hz did not affect LH pulse frequency. Furthermore, intra-MePD infusion of bicuculline with optic stimulation increased LH pulse interval (25.00±2.89 vs 46.67±6.82min, n=3, p<0.05). These results demonstrate that selective activation of MePD kisspeptin neurones can modulate hypothalamic GnRH pulse generator frequency via a disinhibitory GABAergic mechanism.

Poster number: PS103 (SP)

Theme: Neuroendocrinology and autonomic systems

Kisspeptin enhances brain processing of olfactory and visual cues of attraction in men

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Introduction: Successful reproduction in mammals relies on the integration of sensory cues of attraction with emotions and behaviours. Kisspeptin (KP) is a potent activator of the reproductive axis with evidence that it may link reproduction with brain pathways controlling emotion and behaviour. KP receptors are expressed in brain regions related to olfaction, sexual function, and emotion but effects of KP on human sexual attraction are unknown.

Methods: We examined the effects of KP on brain activity during olfactory and facial attractiveness tasks using fMRI in 33 healthy heterosexual men. Participants received an infusion of KP or placebo (counterbalanced order), and brain responses were evaluated in response to a pleasant feminine scent and a viewing images of unfamiliar female faces from a validated database (facial attractiveness task).

Approach for statistical analysis: Imaging analysis was performed with FSL. Pre-processing: motion correction, smoothing (6mm), registration to a standard template, and high-pass filtering (0.01Hz). A GLM analysis modelled the occurrence of the stimuli, and included their temporal derivatives and head-motion regressors as confounds. Group analyses were random-effects (FLAME-1) models, with statistical maps thresholded at z=2.3, p<0.05 (cluster corrected). A set of a priori defined brain regions were used to extract data for region of interest (ROI) analyses.

Results and conclusions: KP significantly enhanced brain activity in response to a pleasant feminine scent, in regions related to olfaction and emotion (including the amygdala, striatum and insula). ROI analyses showed KP increased

brain activity in the main olfactory network ($p=0.008$) as well as in several limbic structures that express KP receptors and are associated with mood and olfaction: amygdala, hippocampus, thalamus, putamen, globus pallidus, caudate, insula and orbito-frontal cortex ($p<0.05$).

When viewing female faces, KP significantly enhanced brain activity in the medial prefrontal cortex (mPFC), an established aesthetic brain region. ROI analyses also showed enhanced activity in the mPFC during KP administration to faces rated high, medium, and low attractiveness ($p<0.01$).

Collectively, we demonstrate for the first time that KP administration enhances brain responses to olfactory and visual cues of attraction in humans. These data have important implications for our understanding of reproductive physiology and the development of therapeutics targeting the KP neurotransmitter system.

Poster number: PS104 (SP)

Theme: Neuroendocrinology and autonomic systems

In vitro optogenetic stimulation of vasopressin retinal ganglion cell axons in the hypothalamic suprachiasmatic nucleus

Authors: Dr Catherine Hume¹, Professor Gareth Leng¹, Professor Mike Ludwig¹

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Physiological circadian rhythms are orchestrated by the hypothalamic suprachiasmatic nucleus (SCN). The activity of SCN cells is synchronised by light information from the retina. However, it remains unclear exactly how light-responsive retina cells entrain SCM rhythms. Recently a population of vasopressin-expressing retinal ganglion cells (VP-RGC) have been characterised that project to the SCN and secrete vasopressin in response to light (Tsuji et al. J Physiol. 2017 595(11): 3497-3514). To determine whether vasopressin secreted from these VP-RGC influences the activity of SCN cells we used optogenetic tools to activate VP-RGC axons in the SCN and recorded changes in the electrical activity of SCN cells using *in vitro* electrophysiology.

Rats were subjected to intravitreal injections of A90-VP-ChR2mCherry (provided by Prof. Valery Grinevich, University of Heidelberg) to express ChR2 under the vasopressin promoter in VP-RGS. After 4-6 weeks acute brain slices were made. SCN cells were recorded from in a loose patch configuration and slices stimulated with pulses of blue light. The effect of blocking SCN vasopressin receptors was determined by adding a vasopressin V1A receptor antagonist to the extracellular solution ($(d(CH_2)_5^1Tyr(Me)^2Arg^8)$ -vasopressin).

Approximately 30% of SCN cells responded to optogenetic stimulation with increased firing rate ($\geq 10\%$ of baseline). Responses were classified into four groups based on firing pattern. (1) Gradual increase in firing rate throughout stimulation ($n=8$; baseline: 4.4 ± 1.3 spikes/s, stimulation: 6.4 ± 1.6 spikes/s; $p=0.007$, paired t-test). (2) Bursts of increased firing rate throughout stimulation ($n=6$; baseline: 2.5 ± 0.7 spikes/s, stimulation: 4.2 ± 1.6 spikes/s; $p=0.02$, Wilcoxon matched-pairs signed-rank test). (3) Initial single burst of increased firing rate ($n=5$; baseline: 3.9 ± 1.1 spikes/s, stimulation: 7.1 ± 2.4 spikes/s; $p=0.03$, Wilcoxon matched-pairs signed-rank test). (4) Increased firing rate at the end of stimulation ($n=3$; baseline: 2.8 ± 1.1 spikes/s, stimulation: 4.4 ± 0.1 spikes/s). In the presence of a V1A receptor antagonist, the firing rate of cells responding to optogenetic stimulation returned to baseline ($n=6$; baseline: 5.3 ± 2.5 spikes/s, stimulation: 9.2 ± 2.8 spikes/s, stimulation/antagonist: 5.3 ± 2.8 spikes/s; baseline vs. stimulation: $p=0.05$, baseline vs. stimulation/antagonist: $p>0.9$, Friedman test ($p=0.005$) with Dunn's multiple comparisons).

We have shown that the selective activation of VP-RGC axons in the SCN influences the electrical activity of SCN cells, potentially in a vasopressin dependent manner.

Poster number: PS105 (SP)

Theme: Neuroendocrinology and autonomic systems

Design of GPR54 (KISS1R) crosslinker peptides: new tools to study GPCR localization and function

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Introduction: The neuropeptide kisspeptin and its receptor, GPR54 (alias KiSS1R) play a central stimulatory role in mammalian reproduction. However, GPR54 localization is still incompletely mapped and its pharmacology only partially known. Receptor localization, identification of the peptide receptors, as well as receptor deorphanization remain important issues in drug discovery. To approach these problems, we designed new tools and used kisspeptin and its receptor to begin testing them.

Methods: By using furylalanine (FurAla) as a furan-containing amino acid, we created Kp analogs bearing a biotin tag (peptide 2: Biotin-linker-Tyr-Asn-FurAla-Asn-Ser-Phe-Gly-Leu-Arg-Tyr-NH₂; peptide 4: Biotin-linker-FurAla-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Tyr-NH₂). These molecules covalently bind GPR54. Two additional molecules were created based on peptide 2 and on the kisspeptin analog C6, that shows robust *in vivo* activity. One molecule (TMV-33-2a : N-palmitoyl-γ-glutamyl-Tyr-Asn-FurAla-Asn-Ser-Phe-GlyΨ [1,2,3-triazolyl]Leu-Arg(N^ω-Me)-Tyr-NH₂) was designed principally to improve its pharmacodynamics profile. The other one (TMV-34: Biotin-PEG₄-Tyr-Asn-FurAla-Asn-Ser-Phe-GlyΨ [1,2,3-triazolyl]Leu-Arg(N^ω-Me)-Tyr-NH₂) was designed to also bear a biotin to facilitate detection. *In vitro* activity was evaluated by a calcium mobilization assay in HEK-293 cells transfected with hGPR54. *In vivo* analysis was performed by measuring the effect on plasma LH level in adult C57BL6 mice.

Results and conclusions: In the calcium mobilization assay all analogs, but TMV-33-2a, were more potent than the endogenous agonist hKP10 (EC₅₀ = 0.5 nM) (Peptide 2 EC₅₀ = 0.001 nM; peptide 4 EC₅₀ = 0.0005 nM; TMV-33-2a EC₅₀ = 7 nM; and TMV-34 EC₅₀ = 0.05 nM). TMV-33-2a and TMV-34, when injected in male mice (0.4 nmol/mouse intraperitoneal), increased LH plasma concentration to a maximum of 10.9±2.9 ng·mL⁻¹ at 6 hours and 5.9±1.3 ng·mL⁻¹ at 20 minutes post-injection respectively. However, only TMV-33-2a showed a prolonged effect (LH increase over basal for more than 12 hours) whereas TMV-34 effect lasted only about 2 hours. Structural optimization is in progress to evaluate various combinations of chemical modifications and different tags to allow *ex vivo* receptor localization by crosslinking the receptor with the tagged analog. These preliminary results suggest that it is possible to develop highly potent and selective crosslinker molecules as new tools to study the kisspeptin system. More importantly, this strategy holds the promise to be applicable to study other targets.

Poster number: PS106 (SP)

Theme: Neuroendocrinology and autonomic systems

The elusive GnRH pulse generator: probing the hypothalamic KNDy neural network with optogenetic, neuropharmacology and mathematical modelling

Authors: Mr Ross De Burgh¹, Dr Xiao-Feng Li¹, Dr Margaritis Voliotis², Mr Geffen Lass¹, Professor Stafford Lightman³, Professor Kirasimira Tsaneva-Atanasova², Professor Kevin O'Byrne¹

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Introduction: Kisspeptin neurones located in the hypothalamic arcuate nucleus co-expressing Neurokinin-B (NKB) and Dynorphin (KNDy neurones) are a crucial regulatory component of the GnRH pulse generator controlling the reproductive axis. However, the neural dynamics that make this possible remain unclear. The pulsatile behaviour of the system under defined conditions can be predicted by a mathematical model¹. Using model predictions as a guide,

our aim is to gain a deeper understanding of the regulation of the GnRH pulse generator by investigating KNDy neurone dynamics using optogenetics and neuropharmacology.

Methods: An AAV vector expressing channelrhopsin was injected into the arcuate nucleus of intact female Kiss-CRE mice. A fibre optic probe was chronically implanted into the arcuate and a fluid cannula implanted in the third ventricle. After a control period of 60 min, animals were optogenetic stimulated (473 nm, 5-ms pulse width) at 0.5Hz or 5Hz with simultaneous infusion of kappa-opioid receptor (nor-BNI, 1.28nmol) or NK1 receptor (SB222200, 9nmol) antagonist respectively for 90 min. Controls received optic stimulation or drug alone. Blood samples (5µl every 5 min) were collected throughout the experiment for LH measurement.

Approach for statistical analysis: LH pulses were identified using DynPeak, and frequency analysed as pulses per hour. Data are presented as mean±SEM and one-way ANOVA used for statistical comparisons. N=4-6 per group.

Results and conclusions: The model predicts that the KNDy neural network has two equilibrium points which define if there is pulsatile or non-pulsatile dynamics. By investigating when the system switches from non-pulsatile to pulsatile kisspeptin release to drive GnRH pulses, we demonstrated that 0.5Hz stimulation failed to induce LH pulses whilst 5Hz evoked regular LH pulses in oestrus mice. Dynorphin antagonism increases LH pulse frequency when combined with 0.5Hz (increase to 1.6±0.19 from 0.17±0.17 pulses/h, P<0.05) whilst NK1 receptor antagonism blocked the stimulatory effects of 5Hz (decrease from 2.16±0.21 to 0.56±0.24 pulses/h, P<0.5). Drug alone had no effect. In conclusion, Dyn and NK1 signaling are crucial in regulating GnRH pulse generator frequency and act to decrease or increase respectively the sensitivity of the KNDy neural system to changes in network excitability.

¹Voliotis M et al 2018. doi.org/10.1101/245548

Poster number: PS107 (SP)

Theme: Neuroendocrinology and autonomic systems

The role of the amygdala in stress-induced delay of puberty in female mice

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Introduction: Post-traumatic stress (PTSD) is associated with altered pubertal timing in humans. Predator odour is a classical rodent PTSD model. Extra-hypothalamic kisspeptin neurones in the posterodorsal sub-nucleus of the medial amygdala (MePD) are thought to modulate pubertal timing, as well as anxiety and emotional processing. We test the hypothesis that psychosocial stress, processed by the MePD, is relayed to the hypothalamic GnRH pulse generator to delay puberty.

Methods: Female mice were exposed to predator odour, 2,4,5-Trimethylthiazole (TMT), for 14 days from postnatal day (pnd) 21. Anxiety was tested before (pnd 19-20), during (pnd 27-28) and after TMT-exposure (pnd 40-41) using the Elevated Plus Maze (EPM), Light/Dark Box (LDB) and social interaction. The effect of TMT-exposure on pre-pubertal luteinizing hormone (LH) pulses was measured, at pnd 26 and 29. In addition, kisspeptin-cre mice were bilaterally injected with hM3Dq-DREADD AAV in the MePD at pnd 14. From pnd 21 they were administered CNO via drinking water for 14 days and the onset of puberty monitored.

Approach for statistical analysis: All data was analysed using One-Way ANOVA with Brown-Forsythe test.

Results and conclusions: The TMT-exposed mice showed a significant delay of 5 days to first estrous (marker of puberty) (FE; p<0.001) without affecting body weight (BW). TMT-exposed mice spent less time in the open arm of

the EPM on pnd 28 (13±3 s) and pnd 41 (5±2 s) compared to control (pnd 28 32±5 s, pnd 41 31±6 s). They spent more time in the dark compartment of the LDB (TMT 180±12 s vs controls 121±13 s) and less time socially interacting (TMT 26.8±2.8 s vs controls 47.7±8.8 s) on pnd 27. The TMT-exposed group exhibited a reduction in LH pulse frequency on pnd 26 (TMT 0.1±0.1 pulses/2h vs control 0.9±0.3 pulses/2h) and 29 (TMT 0.2±0.2 pulses/2h vs control 2±0.7 pulses/2h). DREADD activation of kisspeptin neurones in the MePD advances FE ($p<0.05$) without affecting BW. Early exposure to predator odour delays puberty in female mice, reduces GnRH pulse generator frequency and has long-term consequences of enhanced anxiety behaviour, while selective chemogenetic activation of the kisspeptin system in the MePD advances puberty.

Poster number: PS108 (SP)

Theme: Neuroendocrinology and autonomic systems

Region specific deletion of beta-catenin leads to impaired glucose tolerance and increased body weight

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Introduction: β -catenin is a signalling molecule in the Wnt-signalling pathway, which has typically been associated with embryogenesis and tumorigenesis. More recently, new lines of evidence suggest that it may also be involved in the pathogenesis of type-2 diabetes. In its active form, β -catenin acts together with the transcription factor T cell-specific transcription factor-7-like-2 (TCF7L2) to activate target genes of the Wnt-signalling pathway. Impairment in this signal transduction pathway both in the pancreas and in the hypothalamus may contribute to the development of type-2 diabetes. Therefore, given the importance of β -catenin in the regulation of whole-body glucose homeostasis, we sought to determine the physiological role of β -catenin in the hypothalamus in regulating metabolism.

Methods: Using transgenic mice in which the β -catenin gene is flanked by LoxP sites (floxed), we performed bilateral injections of AAV2-mCherry-iCre virus into the arcuate nucleus (ARC) to specifically delete the β -catenin gene in that region (β -cat ARC KO). We kept the mice on normal chow for 4 weeks, and then swapped them to high-fat diet for a further 6 weeks, while measuring daily body weight and metabolic analysis.

Approach for statistical analysis: Statistical comparisons were performed with either one- or 2-way ANOVA with repeated measures tests, followed by Holm-Sidak for post-hoc analyses, where appropriate.

Results and conclusions: Whilst we did not see any difference in body weight when the mice were on normal chow for 4 weeks post-injection, the β -cat ARC KO animals did show impaired glucose clearance, only in males ($p=0.02$). In addition, when these mice were exposed to high-fat diet, both males and females in the β -cat ARC KO group showed a significant increase in body weight after 6 weeks compared to the control animals ($p<0.0001$ and $p<0.05$, respectively), with no difference in glucose tolerance. We next evaluated measures of energy homeostasis and found that even though there was no difference in energy expenditure among the groups, the maximal oxygen consumption in both males and females of β -cat ARC KO animals were significantly higher than the control animals ($p<0.0001$). This preliminary study indicates that β -catenin may have a critical role in regulating glucose homeostasis, and deleting β -catenin specifically in the ARC exacerbates diet-induced obesity.

Poster number: PS109 (SP)**Theme:** Neuroendocrinology and autonomic systems**Extra-retinal regulation of avian reproduction: a role for va-opsin and neuropsin****Authors:** Dr Jonathan Perez^{1,2}, Ms Elisabetta Tolla¹, Dr Ian Dunn², Dr Simone Meddle², Dr Tyler Stevenson¹
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Introduction: Photoperiod is well-established regulator of seasonal reproduction across vertebrate taxa. While detection of photic cues in mammalian species has been tied to melanopsin in retinal ganglion cells, avian species it has been localized to the hypothalamus. Multiple candidate photoreceptive opsins have been localized to the deep brain (VA-opsin, neuropsin and melanopsin), however, despite decades of research the identity of the photoreceptors necessary for the expression of seasonal breeding in birds remains unresolved. Using advancements in viral vector and RNA silencing techniques this study sought to establish causal involvement of the two leading photoreceptor candidates: VA-opsin and Neuropsin

Methods: A novel AAV2-viral construct expressing GFP and silencing RNA constructs targeting VA-opsin and neuropsin was injected into the third ventricle of photosensitive adult male Japanese quail (n=28) via stereotaxic surgery. Following surgery birds were held on short days (7L:17D) for three weeks for recovery and to allow expression of viral constructs. Birds were then transferred to long day (18L:6D) for 4 weeks to allow for full development of reproductive competence in control animals. Animals were then euthanized and tissues collected for subsequent analysis. Morphometric measurements were collected prior to photostimulation, immediately after, and weekly thereafter. All work was performed under Home Office licence (PPL 7007909) and accordance with local animal care and use guidelines.

Approach for statistical analysis: Morphometric data were analysed by linear mixed effects modelling of output by the main effects of time, treatment and their interaction, with repeated measures for individual animals to control for the effects of repeated sampling. Tissue and molecular analyses were statistically analysed by ANOVA.

Results and conclusions: RNA silencing of opsin expression resulted in increased rates of cloacal gland growth compared to sham controls. Treatment with RNAi targeting VA-opsin resulted in a decreased rate of mass gain compared to all other groups. However, there was no difference in final testes mass between treatments, with all animals showing enlarged testes characteristic of breeding preparation. Taken together these finds suggest that VA and neuropsin may provide tonic inhibition of some but not all aspects of seasonal breeding in birds.

Poster number: PS110 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Microglia and myelin are susceptible to BIP inducer X (BIX) induced damage in in-vitro spinal cord explant culture model****Authors:** Mrs Sravanthi Bandla¹, Ms Paula Arseni², Ms Lorna Hayden², Professor Christopher Linington², Dr Una FitzGerald¹¹School of Natural Sciences, Galway Neuroscience Centre, National University of Ireland, Galway, Ireland, ²Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, Scotland

Introduction: BIP inducer X (BIX, 1-(3, 4-dihydroxyphenyl) -2-thiocyanate-ethanone) preferentially induces the expression of endoplasmic reticulum (ER) chaperone B cell-immunoglobulin-binding protein (BIP) through the activated transcription factor 6 (ATF6) arm of the unfolded protein response (UPR). BIP has also been shown to be

significantly upregulated during normal myelination (Naughton et al, 2015) and its presence enhances the survival of myelinating oligodendrocytes in an EAE model of inflammatory demyelination (Hussein et al, 2017).

Aim: To determine if BIX enhances myelination in an *in-vitro* spinal cord explant culture model of myelination.

Methods: Myelinating spinal cord cultures were generated as described in Thomson *et al.*, (2008). The cultures were treated with BIX or DMSO (vehicle control) at days 18-28 *in vitro*, or between days 28-38, based on the specific objectives of the experiments. Fixation and staining protocols were performed as described by Linder and Linington (2014), to quantify: neurite density, myelination, microglia; cells of the oligodendrocyte lineage and astrocytes. Images were captured with an Olympus BX15 microscope and analysed using Ocular, CellProfiler software, (<http://www.cellprofiler.org/>) and ImageJ. A minimum of thirty images/parameter were analysed from three independent cultures for each biological replicate ($n \geq 3$) from at least three biological replicates per condition, unless otherwise specified.

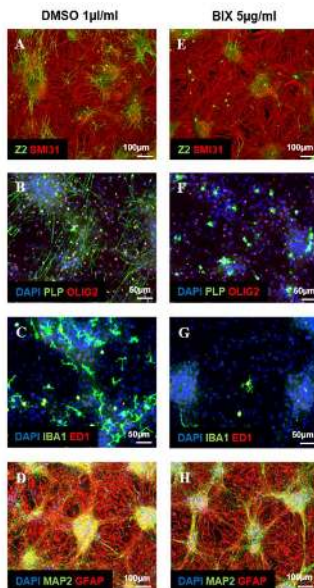


Figure 1: Representative images of myelinating cultures following treatment with BIX 5µg/ml from DIV 18-28. The cultures were fixed on DIV-28 and stained with antibodies against axons (SMI31), myelin oligodendrocyte glycoprotein (Z2), nuclei (DAPI), Oligodendrocyte lineage cells (Olig 2), myelinating oligodendrocytes (PLP), microglia (IBA1), phagocytic microglia (ED1), astrocytes (GFAP) and neuronal marker (MAP2). Vehicle control-DMSO 1µl/ml (Left panel) (A-D). Treated group-BIX 5µg/ml (right panel) (E-H). BIX is selectively toxic towards myelin, oligodendrocytes lineage cells and microglia while neurons and astrocytes were less affected compared to the vehicle control.

Approach for Statistical Analysis: Graph Pad prism 5.0 (Graph Pad, San Diego, CA, USA) was used to analyse the data. A two tailed unpaired t-test and one-way ANOVA with Dunnett's Multiple Comparison test was used to determine the statistical difference and data is presented as mean \pm SD. Significance was set at $P < 0.05$.

Results and Conclusions: A dose-response study (0.05-10 µg/ml) revealed that BIX is selectively toxic with respect to myelination ($p < 0.0001$), microglia ($p < 0.0002$) and oligodendrocyte lineage cells ($p < 0.0004$). Significant inhibition of myelination and loss of microglia was observed after 5 days (5 µg/ml) in the absence of any significant effect on neurite density or astrocytes. Withdraw experiments demonstrated these effects on myelination and microglia were irreversible. Although BIX inhibited myelination we found it was unable to mediate primary demyelination. BIX therefore appeared to have selective toxicity towards myelin and microglia.

Poster number: PS111 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Blocking stretch-activated cation channels prevents demyelination in the central nervous system****Authors:** Dr Maria Velasco-Estevez^{1,2}, Dr Kamal K.E. Gadalla³, Dr Stuart Cobb³, Prof Kumlesh K Dev¹, Dr Graham K Sheridan²¹Trinity College Dublin, Dublin, Ireland, ²University of Brighton, Brighton, United Kingdom, ³University of Glasgow, Glasgow, United Kingdom

Introduction: Demyelinating diseases of the central nervous system (CNS) are often characterised by both a breakdown of the myelin sheath and by secondary neuronal damage. Demyelination can cause excessive calcium influx into neurons leading to excitotoxicity which, in turn, accelerates oligodendrocyte degeneration. Current therapies for demyelinating disorders, such as Multiple Sclerosis, act predominantly as immune-modulators and are ineffective at protecting neurons against damage in the latter stages of disease. Furthermore, research in the past few years have strongly suggested a physical contribution to myelin initiation and repair. Here, we hypothesize that Piezo1 -a mechanosensitive cation channel- may play a role in regulation of myelination, and we present evidence that the peptide GsMTx4, a blocker of such stretch-activated cation channels, enhances developmental myelination *ex vivo* and prevents focal demyelination *in vivo*

Methods: The *ex vivo* organotypic slice culture model was used to analyse the effects of both activating and blocking Piezo1 on the myelin levels, neurons and glial cells. We also studied the effects of GsMTx4 *in vivo* using the LPC-induced focal demyelination injury in young adult mice by stereotaxic surgery.

Approach for statistical analysis: All statistical analysis was performed using GraphPad® Prism7. Each dataset was tested for normality using column statistics and D'Agostino-Pearson omnibus prior any other test. When only two groups were compared, a Student t-test was performed. In case three or more groups were to be compared, one-way ANOVA with Newman-Keuls post-hoc test was performed.

Results and conclusions: Our results show that the stretch-activated cation channel, namely GsMTx4, enhances developmental myelination in cerebellar slices, contrary to the Piezo1 activator, Yoda-1, which causes demyelination. Moreover, GsMTx4 prevented psychosine-induced demyelination *ex vivo*. This was corroborated *in vivo*, where GsMTx4 prevented the LPC-induced demyelination, neuronal and astrocytic toxicity and microglial activation. Piezo1 channels are expressed mainly by neuronal cell types in the mouse brain while seem to be absent in oligodendrocytes. Thus, our data suggest that targeting Piezo1 channels and attenuating excessive calcium influx blockage of stretch-activated cation channels, may help to prevent secondary progressive neurodegeneration in latter stages of demyelinating diseases.

Poster number: PS112 (SP)**Theme:** Neuronal, glial and cellular mechanisms

A functional analysis of nanotopographical designed platinum iridium electrodes

Authors: Ms Adriona Kelly¹, Dr. Nazar Farad², Dr. Michelle Kilcoyne³, Dr. Elaine Water³, Dr. Gerard O Conner^{1,2}, Dr. Manus Biggs¹¹Centre for Research in Medical Devices (CURAM), National University of Ireland, Galway, Galway, Ireland, ²National Centre for Laser Applications (NCLA), School of Physics, National University of Ireland, Galway, Galway, Ireland,³Carbohydrate Signalling Group, Microbiology, and National Centre for Biomedical Engineering Science(NCBES) School of Natural Sciences, National University of Ireland Galway, Ireland, Galway, Ireland

Introduction: The brain machine interface BMI describes a group of technologies capable of communicating with excitable nervous tissue within the central nervous system (CNS). These devices act to directly couple neural tissue with therapeutic stimulating devices or recording systems to control external devices.¹ BMI's have seen major advances in recent years, but these advances have been impeded due to a deterioration in the signal to noise ratio of recording electrodes over time following insertion into the CNS. This deterioration has been attributed to an intrinsic host tissue response, namely reactive gliosis, resulting in peri-implant encapsulation via the synthesis of pro-inflammatory signalling molecules and the recruitment of glial cells.² Modification of the nanoscale geometry of the implanted probe could enhance the electrode's electrical capabilities, and improve the physical coupling between the electrode and the surrounding neurons, whilst reducing gliosis.

Methods: In this study, commercially available platinum Iridium (Pt/Ir) microelectrodes and substrates were nanotopographically functionalised via femto/picosecond laser processing to generate Laser Induced Periodic Surface Structures (LIPSS). Four different topographies were analysed for their physical properties using scanning electron microscopy and atomic force microscopy. The electrochemical properties of these interfaces were then investigated using electrochemical impedance spectroscopy. The *in vitro* response of mixed cortical cultures (embryonic rat E14/E17), was subsequently assessed by confocal microscopy, ELISA and multiplex protein array analysis.

Approach for statistical analysis: Mann Whitney and Kruger Wallis statistical analysis was used. Electrochemical results were compiled from $n \geq 4$ ($p \leq 0.05$). *In vitro* results were compiled from $n \geq 3$ biological replicates ($p \leq 0.05$).

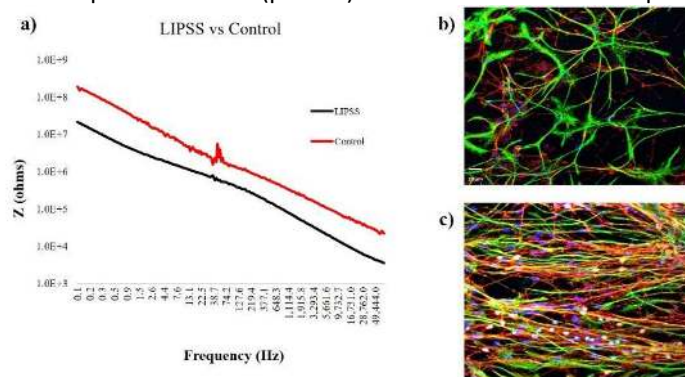


Figure 1. Significant reduction of Impedance for LIPSS a). Confocal analysis of neurons (red) and astrocytes (green) on control b) compared to orientated cells on LIPSS c)

Results & Conclusions: LIPSS features improved electrochemical properties of the electrodes (See Figure 1 a) and promoted cell alignment (See Fig 1 c). Protein array analysis also shows that proteins involved in activation of gliosis were downregulated in LIPSS features compared to control. Neuroelectrodes functionalised with nanotopographical features could promote chronic neuroelectrode functionality by reducing tissue encapsulation *in situ* and promoting organised interconnected neural network at the electrode interface.

References

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Poster number: PS113 (PP)

Theme: Neuronal, glial and cellular mechanisms

Fever and the brain in autism: temperature vs. Inflammatory effects

Authors: Dr Ana Belen Lopez Rodriguez¹, Dr Carol Murray¹, Ms Clodagh Towns¹, Dr Colm Cunningham¹

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Introduction: Autism is a collection of disorders (Autism Spectrum Disorder, ASD) that is predominantly developmental and genetically determined. However, there is evidence showing that environmental changes can impact on some symptoms. Fever has been reported to improve ASD symptoms, mainly based on carers' testimony describing that their children presented improvements during febrile episodes. There are limited data to support this, however one study showed that up to 25% of patients displayed an improvement in repetitive behaviours, stereotypy, irritability and speech when they had a fever of $\geq 38^{\circ}\text{C}$ [1]. Indications that symptoms can improve transiently implies that the circuits affected in ASD could perform relatively normally under certain conditions and its understanding offers hope to patients with ASD. The aim of this project is to ask whether is fever or inflammation that underpins these improvements. To do this, we used the whole body hyperthermia (WBH) protocol and acute systemic inflammation in C57BL6 (control) and C58J (ASD) mice.

Methods: 1) WBH protocol (38.5°C for 4 hours to achieve $39.5\pm 1^{\circ}\text{C}$ of body temperature) in C57BL6 to dissociate the effects of elevated body temperature and acute systemic inflammation (lipopolysaccharide, LPS $250\mu\text{g}/\text{Kg}$).

Immunohistochemical analysis at 4 and 24 hours after WBH/LPS have been run to analyse differential patterns of brain activation for immediate early genes in different brain regions. Preliminary data show a greater increase of cFos in LPS-treated animals than with WBH. Molecular analyses are ongoing to address changes at transcriptional level and autophagy proteins.

2) Assess the impact of these different paradigms on behavioural measures relevant to ASD in the C58/J strain, natural mutant showing ASD features. These are ongoing experiments that include the characterization of C58/J at baseline and the effects of WBH/LPS on behavioural tasks that are affected in animal models of ASD such as social interaction, locomotor function or repetitive behaviours.

Approach for statistical analysis:

Depending on the experimental design, we will use different tests:

- One-way ANOVA at a single time post-treatment.
- Repeated measures ANOVA for behavioural tests.
- T-test for two-group comparisons.

References:

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Poster number: PS114 (SP)

Theme: Neuronal, glial and cellular mechanisms

Reduced metabolic plasticity contributes to macrophage dysfunction in a murine model of alzheimer's disease

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Introduction: Inflammation drives Alzheimer's disease, with a progressive infiltration of peripheral immune cells, such as macrophages, observed in the brain. Macrophages from APP/PS1 mice, a murine model of AD, exhibit an inflammatory phenotype. Recently a link between inflammation and metabolism has been uncovered wherein, under inflammatory conditions, macrophages undergo a metabolic switch known as "Warburg metabolism" and produce ATP through glycolysis instead of traditional oxidative phosphorylation. This study aims to examine the metabolic phenotype of macrophages from APP/PS1 mice and establish whether aberrant metabolism contributes to altered macrophage function.

Methods: Bone marrow macrophages (BMDM) were harvested from 12 and 20 month old APP/PS1 and wildtype (WT) mice. BMDMs (5×10^5 cells/well) were stimulated with LPS ($100\text{ng}/\text{ml}$) + $\text{A}\beta_{1/40-1/42}$ ($10\mu\text{M}$) overnight and the SeaHorse Extracellular Flux (XF24) analyser was used to carry out bioenergetic analysis of cells. Supernatant samples

were assessed for concentrations of IL-1 β , TNF α , IL-6 by ELISA. Cells were stained for F4/80, and A β and the ability of mice to engulf A β was measured by confocal microscopy.

Analysis Approach: Two-way analysis of variance with *post hoc* Bonferroni tests, or two-tailed student t-test, was performed using Graphpad Prism and reported as mean \pm SEM, $p < 0.05$.

Results and Conclusions: Macrophages from 12 and 20 month-old APP/PS1 mice exhibited an increased glycolysis compared with macrophages from WT mice. Stimulation with LPS+A β increased glycolysis in macrophages from WT mice of both ages. However while LPS+A β increase glycolysis in macrophages from 12 month-old APP/PS1 mice, this effect was not observed in macrophages from 20 month-old APP/PS1 mice and in these samples, LPS+A β also failed to stimulate production of IL-6 and IL-1 β production. Significantly, macrophages from 20 month-old APP/PS1 mice exhibited a decreased ability to phagocytose A β compared with macrophages from WT mice. These data indicate that, with age, macrophages demonstrate a genotype-related decrease in plasticity, and specifically show an inability to respond to LPS+A β .

Poster number: PS116 (SP)

Theme: Neuronal, glial and cellular mechanisms

Probing activity-dependent dynamics of perisynaptic astrocytic processes using super-resolution microscopy

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Introduction: Astrocytes play an active role in shaping and maintaining neuronal circuits through their role in extracellular potassium buffering as well as their secretion and clearance of neurotransmitters. Whilst the molecular signal exchange between astroglia and synapses occurs in a highly heterogeneous microenvironment on the nanoscale, the spatial subcellular distribution of the underlying molecular machineries remains poorly understood. Previously we successfully imaged and analysed the nanoscale relationship between astrocytic processes and glutamatergic synapses. Here, we extended our study to investigate the plastic relationship between astrocytic processes and GABAergic synapses as there is very little known about astrocyte engagement of inhibitory synapses.

Methods: We employed immunohistochemistry of 30 μ m thick hippocampal sections followed by super-resolution single molecule localisation microscopy (SMLM) which can circumvent the optical diffraction limit and offers ease of use and flexibility not seen in electron microscopy. To achieve different conditions compatible with long-term synaptic potentiation or depression, we incubated acute hippocampal brain slices (350 μ m thick) with inducing reagents for LTP and LTD of excitatory synapses as well as LTP and LTD of the inhibitory systems (iLTP and iLTD, respectively).

Approach for statistical analysis: We analysed experiments using one way ANOVA with Bonferroni post hoc test to assess the level of significance between all of the groups. Significance values were represented as: * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

Results and conclusions: We employed SMLM to visualise the synaptic interactions in inhibitory systems in the hippocampus and quantified the structural differences due to the activity-dependent dynamics of astrocytic processes *in situ*. We were able to localise clusters of receptors and transporters in astrocytic and neuronal membranes in fixed brain slices. Moreover, through multi-colour imaging we were able to image and analyse the altered positional relationship between synapses and astroglial receptors and transporters in potentiated (iLTP) or depressed (iLTD) synapses. In a different set of experiments, we used multiphoton excitation imaging enabling us to investigate and characterise the physiological differences in the astroglia-neuronal relationship *in vivo*.

Poster number: PS117 (SP)

Theme: Neuronal, glial and cellular mechanisms

Live imaging of the inflammatory response to A β -producing neurons in drosophila

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Introduction: Chronic inflammatory responses involving microglia contribute to the progression of Alzheimer's disease (AD), with the most plausible microglial recruitment trigger being beta-amyloid peptide (A β) (Lee & Landreth, 2010; Wright et al., 2013; Sperling et al., 2014; Brown & Neher, 2014; Wang et al., 2018). Despite advances in understanding the likely mechanisms involved in microglial activation (Lull & Block, 2010), the factors controlling the migration of immune cells to the site of A β production and deposition are not well understood. A key reason for this is the inability to visualise the inflammatory response during neurodegeneration.

Methods: We address this problem by using live time-lapse microscopy in the genetically tractable *Drosophila* embryo, larvae, and pupae to offer exciting new insights into the A β -induced inflammatory response; with recruitment and activity of macrophages visualised in real time in the living animal. Our lab has led the way in developing this technique to live image the inflammatory response to tissue wounding and dissect the molecular mechanisms involved in the recruitment and activity of macrophages to the wounded area (Razzell et al., 2013; Evans et al., 2015).

Analysis approach: Quantitative cell tracking to measure macrophage speed and directional persistence; with mosaic expression of A β in neurons to assess if macrophages migrate preferentially towards A β -expressing neurons. Measurement of co-localisation of neuronal debris and A β within macrophages to determine the phagocytic capacity of macrophages in response to A β . Expression of photoconvertible GFP to label individual macrophages upon touching A β -producing neurons to see if contact affects subsequent behaviour. Expressing pan-caspase inhibitor, p35, to block apoptosis in neurons and identify if A β production is sufficient to trigger engulfment.

Results & Conclusions: In *Drosophila* driving human A β ₁₋₄₂ expression and secretion in neurons, a robust inflammatory response is initiated *in vivo* whereby macrophages accumulate around and actively engulf A β ₁₋₄₂-expressing neurons before overt cell damage is detectable (Figure 1). This response is strikingly similar to the macrophage recruitment in tissue wounding. As such, we hypothesise that an analogous pathway operates in the AD brain to drive inflammation that characterises early disease pathogenesis.

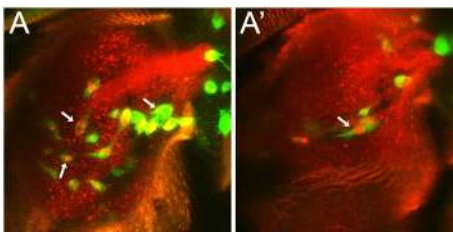


Figure 1: Live imaging of macrophage response to A β . In *Drosophila* pupal brains expressing and secreting human A β ₁₋₄₂ (A) and control (A'). A β ₁₋₄₂ initiates a robust inflammatory response *in vivo* whereby macrophages (green) accumulate around and actively engulf A β ₁₋₄₂ expressing neurons (red) compared to control. Notice accumulation of neuronal debris inside macrophages (arrows).

Poster number: PS118 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Neuropathology and pathogenesis of diaschisis lesion in an experimental white matter stroke model****Authors:** Professor Min-cheol Lee^{1,2}, Professor Kyung-Wha Lee¹, PhD Jong-Wook Cho², Professor Hyung-Ihl Kim²¹*Department of Pathology, Chonnam National University Medical School & Hospital, Gwangju, South Korea,*²*Department of Medical Science and Engineering, Gwangju Institute of Science and Technology (GIST), Gwangju, South Korea*

Neuropathology and Pathogenesis of Diaschisis Lesion in an Experimental White Matter Stroke Model

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Introduction: Cerebral functional insufficiency in stroke might be due to pathologic changes of the primary focal lesion as well as metabolic depression in brain areas remote from initial ischemic lesion, i.e. diaschisis. Previously, we showed that the development of diaschisis lesions by FDG-microPET study in a rat model of experimental photothrombotic infarct of the internal capsule. In the present study we hypothesized that the reduced neuronal and synaptic activities in the diaschisis lesion can be caused by the inhibitory action of GABA.

Methods: Tissue obtained from diaschisis lesions, focused by FDG-microPET image, studied by light and electron microscopy, especially immunostains for GFAP, neurofilament protein, Iba-1, GABA and MAO-B. Metabolic change of GABA synthesis checked using a reversible inhibitor of MAO-B, named KDS2010.

Approach for statistical analysis: Increased ramification of reactive astrocytes was assessed by Sholl analysis. Data were analyzed with statistical analysis software (Prism, V 7.0; GraphPad, San Diego, CA, USA). Differences between two different groups; hypertrophic astrocytes, microglia and number of synapses were analyzed with the two-tailed Student's unpaired t-test.

Results & conclusions: Experimental brain displays focal diaschisis lesions sustaining for more than 2 weeks in the ipsilateral cortex at day 7 after ischemic insults. Tissue obtained from diaschisis in the motor cortex reveals atrogliosis, microglial activation and minimal pathologic changes of neuron; swollen dendrites and multi-vacuolar degeneration of neuropils. Immunoreactivity of GABA and MAO-B was significantly increased in astrocytes in the cortical diaschisis lesions of stroke animals, compared to corresponding brain region of sham-operated animals. Significantly decreased volume of cortical diaschisis with recovery of glucose metabolism in the primary motor cortex observed by administration of KDS2010. The histopathology and hypometabolic state of diaschisis lesion possibly caused by astrocytic GABA suppression. MAO-B could be one of the key enzyme for the pathogenesis of diaschisis.

Poster number: PS119 (SP)**Theme:** Neuronal, glial and cellular mechanisms**The effect of menadione sodium bisulfate on ROS formation in THP1, SHSY5Y and 1321N1 cell lines****Authors:** Anna Stuczynska¹, Patrick McHugh¹¹*University Of Huddersfield, School of Applied Sciences, Huddersfield, United Kingdom*

Introduction: Oxidative stress is believed to be strongly involved in the progression of neuronal damage. Discovering new potential mechanisms of cellular protection could be beneficial for patients diagnosed with neurodegenerative diseases. Menadione sodium bisulfate (MSB), is a water-soluble form of menadione that can be converted into

vitamin K2 (Yoshihisa Hirota, 2013) and it is used in *in vitro* cell culture as oxidative stress generating agent. The aim of our study was to investigate the role of MSB on inducing oxidative stress in 3 different cell lines that mimicked blood and brain environment *in vitro*. Research into the mechanisms involved in the response to MSB could shed a light on the differences between cell line capabilities of providing cell protection.

Methods: ROS production was measured after exposure of different concentrations (5-15 μ M) of MSB within the multiple time course (5min – 48H). ROS generation was measured in live cells using GuavaCyte flow cytometer (Merck, Germany). The expression of *CAT*, *SOD1*, *SOD2*, *GPX1*, *NQO1*, *GSR*, and *NRF2* genes was measured using CFX96 Touch™ Real-Time PCR Detection System (BioRad Laboratories, USA) after 1, 4 and 24H of MSB exposure.

Approach for statistical analysis: All data analyses were performed using SPSS software (IBM Corp., USA). To determine statistical significance between treatment groups, data were analysed using one-way analysis of variance (ANOVA), followed by Bonferroni's t-test. Data are presented as normalized to control \pm SEM. A value of ($p < 0.05$) was accepted as statistically significant. Graphs were prepared using GraphPad Prism 7 (GraphPad Software, USA).

Results and conclusions: Comparison of ROS production within THP1 (monocyte), SHSY5Y (neuron-like) and 1321N1 (astrocyte-like) cell lines showed concentration and time-dependent differences. Overall, exposure to 15 μ M MSB lead to differences in ROS production and gene expression within cell lines. Nevertheless, further analysis of the co-culture *in vitro* models is needed to investigate how interactions between different cell types provide cell survival under oxidative stress.

References

Yoshihisa Hirota, \ddagger . N. (2013). Menadione (Vitamin K3) Is a Catabolic Product of Oral Phylloquinone (Vitamin K1) in the Intestine and a Circulating Precursor of Tissue Menaquinone-4 (Vitamin K2) in Rats*. *Journal of Biological Chemistry*, 33071–33080.

Poster number: PS120 (SP)

Theme: Neuronal, glial and cellular mechanisms

A new role for the hypothalamus to control body vitamin A homeostasis

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Introduction: Vitamin A is an essential micronutrient under tight homeostatic control in the body. The circulating form of the vitamin is retinol maintained at 1 mM concentration, only deviating from this at extremes of vitamin A deficiency or excess. This homeostasis is essential for life; however, its control is poorly understood. The hypothalamus is the key integrative region of the brain for regulation of body homeostasis and an obvious component in this retinol regulatory system, although the involvement of the brain in homeostasis of any vitamin has never been previously considered. It was conjectured that the hypothalamus can detect retinol through conversion of retinol to bioactive retinoic acid (RA) by cells lining the third ventricle known as hypothalamic tanocytes.

Methods: To test our hypothesis that the hypothalamus senses retinol and maintains retinol homeostasis via cells in the third ventricle, 5 mL of 100 mM of retinol, RA or DMSO (vehicle) were stereotactically injected into the third ventricle of the rat brain. Six and twenty-four hours after injection in the brain *mRNA* transcripts and proteins involved in retinol homeostasis were examined via qPCR and Western-blotting. Also, retinol and retinyl esters in the blood as well as liver as the main vitamin A storage organ, were quantified via HPLC.

Approach for statistical analysis: All results are presented as Mean \pm SEM of two independent experiments (n = 5) in technical triplicates. All data were subjected to a Student t-test and a *P*-value < 0.05 was considered statistically significant.

Results and conclusions: Retinol and RA injection in the rat hypothalamus induced significant changes in genes and proteins in the liver regulating retinol homeostasis. Similarly, HPLC quantification of retinol and its ester storage form showed significantly changed storage of retinyl palmitate in the liver, liver retinol and circulatory serum retinol following RA or retinol hypothalamic injection. There were distinctive reciprocal responses by the liver to hypothalamic RA versus retinol implying separate signals sent by these two stimuli from the hypothalamus. The results imply a sensor system for retinol in the brain that can regulate the retinol homeostatic regulatory system.

Poster number: PS121 (SP)

Theme: Neuronal, glial and cellular mechanisms

Electrophysiological and molecular characterisation of the mouse parasubiculum

Authors: Dr Rosanna Sammons¹, Mr Daniel Parthier¹, Mr Alexander Stumpf¹, Professor Dietmar Schmitz^{1,2,3}

¹Charité Universitätsmedizin Berlin corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, ²German Center for Neurodegenerative Diseases, ³Einstein Center for Neurosciences

Introduction: The parasubiculum lies centrally within the parahippocampal formation, receiving input from the CA1 and medial septum and projecting on to the medial entorhinal cortex (MEC). Cells in the parasubiculum express strong theta rhythmicity and several functional cell types have been described including head-direction, border and grid cells. Thus, it is likely that this brain region contributes significantly to spatial navigation circuits. However, the cellular composition of the parasubiculum and the border delineating the parasubiculum from its neighbouring structure, the MEC, are unclear.

Methods: We combine electrophysiology and immunohistochemistry in acute and fixed slices of adult mouse brain, to measure physiological properties of neurons in the parasubiculum and to obtain cell counts of different markers throughout the depth of the parasubiculum.

Approach for statistical analysis: We apply an unsupervised cluster approach (Ward's method) to classify neurons based on their electrophysiological properties, and model cell counts using generalised linear models.

Results and conclusion: We find that parasubicular neurons can be broadly separated into three clusters, with each cluster corresponding to a different immunomarker. The first cluster comprises of fast-spiking interneurons, putatively parvalbumin-positive. The second cluster describes non-fast spiking interneurons, many of which express reelin. Finally, the third and largest cluster comprises a homogenous population of principal cells, expressing the transmembrane protein WFS1. We further find that these different molecular markers show differential expression profiles throughout the superficial to deep axis of the parasubiculum. Moreover, we find two key molecular distinctions between the parasubiculum and the MEC; first, in the parasubiculum calbindin colocalises only with inhibitory neurons, whereas in the MEC calbindin is present in one of the major principal cell types. Secondly, the protein reelin is found predominantly in inhibitory neurons within the parasubiculum, while in the MEC reelin is expressed in a second class of principal cells. Thus, we are able to distinguish a border between these two neighbouring structures. This work forms an important basis for future studies investigating the functions of the parasubiculum, enabling us to detangle specific local connectivity patterns, as well as target-specific input and output projections.

Poster number: PS122 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Intraperitoneal injection of dimethyloxalyglycine (DMOG) modulates the inhibition of synaptic transmission by acute hypoxia in the isolated rat dentate gyrus****Authors:** Prof John J O'Connor¹, Ms Anna Carlene Moody¹, Ms Wai Wai Sin¹, Dr. Sinead M Lanigan¹, Assoc Prof Deirdre Campion²¹UCD SBBS, Conway Institute, University College Dublin, Dublin, Ireland, ²UCD Sch Veterinary Medicine, University College Dublin, Dublin, Ireland

Introduction: Long-term responses to hypoxia involve the stabilization of hypoxia inducible factor-1 α , which can be mimicked by inhibiting prolyl hydroxyl domains with compounds such as dimethyloxalyglycine (DMOG). However, when short duration hypoxic events occur in brain regions, neurons will depress synaptic activity, prepare for another hypoxic event (pre-condition) and full recovery may occur. In this study we have investigated the effects of 48 hr prior treatment with DMOG, on hippocampal synaptic transmission and the response to an acute hypoxic event.

Methods: Wistar rats (60 to 120g) were injected with DMOG dissolved in physiological saline (200 mg/kg, i.p.) under a national competent authority project license as per EU Directive 2010/EU/63. 48 hr later rats were euthanised and slices of the hippocampus were dissected and perfused with oxygenated artificial cerebral spinal fluid. Stimuli were applied pre-synaptically every 30 s in both the dentate gyrus and the CA1 regions of the hippocampus. fEPSP slopes were analyzed using WCP software (John Dempster, Strathclyde). To mimic a hypoxic event, N₂/CO₂ replaced O₂/CO₂ in the perfusing solution for 15 min. Long-term potentiation (LTP) was induced in both regions with 3 trains of 100 pulses (100 Hz, train interval 10 s).

Approach for statistical analysis: All values are given as mean \pm sem (n animals) and analysis was performed using one way ANOVA with post-hoc Bonferroni procedure.

Results and conclusions: 48 hr prior treatment with DMOG had no significant effect on LTP in both CA1 and DG regions with similar magnitude in DMOG treated and control animals (158.7 \pm 5.6%, versus 151.1 \pm 9.4%, and 140.0 \pm 4.4% versus 147.2 \pm 8.2%, respectively, n=5). Interestingly, DMOG treated rats showed an attenuation of fEPSP slope reduction in response to 15 min N₂/CO₂ perfusion in the dentate gyrus (74.2 \pm 4.7% vs 63.5 \pm 5.4% in control hypoxia; n=5; P<0.05) but not in the CA1 region (41.7 \pm 6.8% vs 48.2 \pm 7.1%; n=5). In conclusion 48 hr prior treatment with DMOG had no effect on synaptic plasticity in the hippocampus but altered the sensitivity of synaptic transmission to acute hypoxia in the dentate gyrus region only. These results may be important when investigating the effects of prolyl hydroxylase inhibitors in the clinic.

Poster number: PS123 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Three distinct hippocampal LFP states in anaesthetised rats: state-dependent LFP changes caused by hippocampal neural disinhibition****Authors:** Ms Miriam Gwilt¹, Dr Markus Bauer¹, Dr Tobias Bast¹¹School of Psychology, University of Nottingham, Nottingham, United Kingdom

Introduction: Hippocampal neural disinhibition (decreased GABA function) has been implicated in cognitive disorders, including schizophrenia and age-related cognitive decline. We have previously shown that hippocampal neural disinhibition in rats by picrotoxin (GABA-A antagonist) microinfusion disrupts memory and attention and

enhances hippocampal multi-unit burst firing recorded around the infusion site using 8-microwire arrays under isoflurane-anaesthesia (McGarrity et al., 2017, *CerebCortex*). Here we analysed the hippocampal LFP recorded alongside the multi-unit data. With GABA implicated in hippocampal oscillations, especially theta and gamma/beta, we expected frequency-specific picrotoxin effects. Importantly, we separately analysed three distinct states characterising the hippocampal LFP under isoflurane: 'burst' and 'suppression' states – occasional high-amplitude LFP-spike 'bursts' separated by low-activity 'suppression' – and a more 'continuous' medium-amplitude state (see figure).

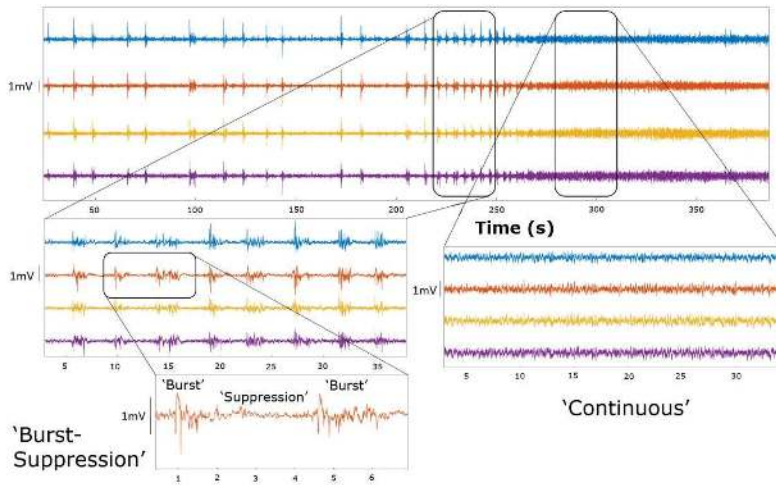


Figure: Three distinct LFP states in the hippocampus under isoflurane anaesthesia. The top plot shows a 400s long LFP recording from the temporal to intermediate hippocampus under isoflurane anaesthesia illustrating the transition from burst-suppression states (left), including burst and suppression states, to the continuous state (right). The middle and bottom panel show the different LFP states in expanded time lines.

Methods: We separated 'burst-suppression' and 'continuous' states using the kurtosis of the LFP-peak-amplitude distribution, then separated 'burst' and 'suppression' using semiautomatic amplitude thresholding. Power (FFT) and connectivity analyses were conducted using FieldTrip (Oostenveld et al., 2011, *ComputIntellNeurosci*).

Analysis: State-separated power and connectivity spectra were analysed using cluster permutation statistics comparing $\log(\text{post-infusion measure}/\text{pre-infusion measure})$ between saline and picrotoxin. State-dependence of picrotoxin-induced multi-unit changes was assessed by analysing state-separated and pooled post-infusion multi-unit data using two-factorial ANOVAs.

Results and Conclusions: The three LFP states showed different properties:

- Greater relative power at low compared to high frequencies in burst compared to suppression and continuous states;
- Higher 'functional connectivity' (across the 8 electrodes) at theta frequency in continuous compared to burst state, but higher connectivity at high-beta/low-gamma frequencies in continuous and suppression compared to burst state;
- Multi-unit firing and bursting tended to be higher in burst, compared to the other two states.

Picrotoxin increased power at lower frequencies (<20Hz) and decreased power and connectivity at higher frequencies (>20Hz) in burst and suppression states, with the power increases at 5.5-18Hz in burst state attaining significance. Unlike the LFP changes, picrotoxin-induced enhancement of multi-unit bursting was comparable across states.

Our results reveal three distinct hippocampal LFP states under isoflurane-anaesthesia. Hippocampal disinhibition tends to increase LFP power at frequencies <20Hz and decrease high-beta/low-gamma power and connectivity in burst and suppression states, but not continuous state (state-dependent); multi-unit changes were state-independent.

Poster number: PS124 (SP)**Theme:** Neuronal, glial and cellular mechanisms**The hypoxia-inducible factor 2 regulates brain remodeling after ischemic injury****Authors:** Mr Tristan Leu¹, Prof. Dr. Joachim Fandrey¹, Dr. Timm Schreiber¹¹*University of Duisburg-Essen, Essen, Germany*

Ischemic hypoxia results from insufficient blood flow and causes ATP depletion and rapid cell death in consequence of lacking adequate amounts of oxygen and nutrients. Contrary to previous assumption, the brain is capable of modest regeneration. Moreover, it was shown that hypoxia and hypoxia-inducible factor (HIF) are key factors in neural regeneration.

Especially HIF-2 α is distributed tissue specific and expressed in the developing brain. It modulates gene activity in response to low oxygen and protects neural progenitor cells and neural differentiation processes. But in general, the role of HIF-2 α during neural development is poorly understood.

To investigate the impact of HIF on neural regeneration, we established a murine neurosphere culture for wildtype (WT) and *Hif-2 α* -knockout (KO) cells. With this 3D model, we want to unravel the signaling pathways of HIF-2 under hypoxia and especially its function in basic processes of brain development like neural progenitor cell proliferation, migration, differentiation and apoptosis. This is fundamental to understand and clarify the role of HIF-2 in brain regeneration after ischemia such as an ischemic stroke.

With focus on the signaling pathway of HIF, we challenged proliferating and differentiating neurospheres with up to 4h oxygen/glucose-deprivation (OGD: 0.2% O₂; glucose free medium) to simulate an ischemic stroke *in vitro*.

Afterwards, we analyzed the migration capability of the cells. Before OGD, WT cells had significant better abilities to migrate than the KO. After OGD, neurospheres migrated significantly less in general, but not different considering the genotypes.

Additionally mRNA analysis showed a strong effect on the expression of genes involved in neurogenesis. Here, genes like *Nrg1*, which has a protective function against astrogliosis, or *Grin1*, which is critical for neuronal connectivity and survival, significantly differ between WT and KO cells after challenging the spheres with OGD.

These data suggest a restricted capability to regenerate from ischemia without HIF-2 α and decode its role in (re)modeling the CNS.

Poster number: PS125 (PP)**Theme:** Neuronal, glial and cellular mechanisms**Regulation of synaptic plasticity by the hypoxia-inducible factor 2 alpha in hypoxia****Authors:** Ms Theresa Quinting¹, Prof. Joachim Fandrey¹, Dr. Timm Schreiber¹¹*University of Duisburg-Essen, Essen, Germany*

Sufficient oxygen supply is fundamental for normal brain functions and to avoid hypoxia. In acute hypoxia, neuronal cells adapt in different ways to the decreased oxygen supply for protection of neurons including synaptic signaling decrease or changes in excitation and inhibition of neuronal and glial cells. However, in longer duration hypoxia synaptic depression goes beyond a neuroprotective role.

Key factors of the cellular response to low oxygen are the heterodimeric transcription factors "hypoxia-inducible factors" (HIF-1, HIF-2, HIF-3). HIFs alter the expression of oxygen-related genes and play an important role during brain development and neural regeneration after hypoxic events. Although the influence of hypoxia and HIF-1 on synaptic transmission and depression was investigated in many studies, the role of HIF-2 is enigmatic.

As several target genes of HIF-2 are known to have a significant part at the synaptic terminal, this study will investigate the role of HIF-2 α (oxygen-sensitive subunit) in synaptic transmission during normoxia and hypoxia. For this we created a conditional brain-specific *Hif-2 α* knockout mouse. To analyze synaptogenesis *in vivo*,

immunocytochemistry for synaptic markers in brain slices will be performed for wildtype or knockout mice during brain development. Additionally, differences in mature synapses will be analyzed using electron microscopy. We furthermore developed an *in vitro* neurosphere system to study changes in expression of synaptogenic factors using qPCR. To investigate the involvement of HIF-2 α in specific cell populations, the formation of synaptic contacts and the expression of synapse regulating molecules will be studied in hippocampal neuron-astrocyte co-cultures. Two further approaches will explore the role of HIF-2 α in regulating synaptic transmission. First, experiments will be carried out on acute tissue slides of wildtype or knockout hippocampi to measure field excitatory postsynaptic potentials and long-term potentiation. Additionally, we will conduct optogenetic studies by using our neuron-astrocyte co-culture. Excitatory neurons will be transfected with specific light-sensitive plasmids and co-transfected with a calcium sensor to measure synaptic transmission by Ca²⁺ increase in postsynaptic cells. Depending on the experimental set-up appropriate statistical methods will be used, i.e. unpaired, two-tailed t-test or 1- or 2-way ANOVA. For immunocytochemistry, semi-quantitative scorings will be adapted.

Poster number: PS126 (SP)

Theme: Neuronal, glial and cellular mechanisms

The effects of local energetic stress on mitochondrial transport in primary cortical axons

Authors: Dr Orla Watters¹, Dr. Niamh M. C. Connolly^{1,2}, Dr. Hans-Georg König¹, Dr. Heiko Düssmann^{1,2}, Prof. Jochen H. M. Prehn^{1,2}

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Introduction: Mitochondria play an important role in the maintenance of neuronal homeostasis by generating energy in the form of ATP. Mitochondrial transport in polarised neurons facilitates delivery of ATP to regions of localised high energy demand. Changes in cellular ADP / ATP ratio result in activation of the cytosolic energy stress sensor, AMPK. AMPK stimulates complex signalling cascades which work to restore energetic homeostasis in the cell. In this study, we investigate whether there is a direct link between mitochondrial transport and localised changes AMPK signalling.

Methods: Primary cortical neurons were nucleofected with 3 μ g mito-GFP and cultured within microfluidic devices to create physical isolation of axonal processes from the somato-dendritic regions. At 8 DIV, the movement of GFP-positive axonal mitochondria was monitored using time-lapse confocal microscopy. Kymographs were generated and analysed to assess changes in axonal mitochondria transport under conditions of localised AMPK activation.

Approach for statistical analysis: Repeated measures ANOVA and Dunnett's post-hoc test were used to compare the pooled data from each 30 min interval with their corresponding baseline values. A strict statistical significance threshold value of p-values ≤ 0.01 was set to account for alterations due to high-frequency imaging acquisition (0.25 Hz).

Results and conclusions: Pharmacological activation of AMPK at the distal axon (AICAR, 0.1 mM) induced a strong depression of the mean frequency, velocity and distance of mitochondrial transport in the adjacent axon. These effects were ablated by pharmacological inhibition of AMPK (compound C, 10 μ M).

Axons rely heavily on lactate as a substrate for ATP synthesis, provided through the astrocyte-neuron lactate transfer shuttle. To investigate AMPK activity in a more physiological setting we exposed the distal axon to lactate and induced localised nutrient deprivation in this region by inhibition of lactate uptake (AR-C155858, 10 nM).

Substitution of glucose to lactate as an energy substrate did not alter mitochondrial transport, whereas inhibition of lactate uptake resulted in a marked depression in the mean frequency, velocity and distance of mitochondrial transport in the adjacent axon. This effect was reversed by compound C, confirming the involvement of AMPK activity in mitochondrial transport induced during localised energy depletion.

Poster number: PS127 (SP)

Theme: Neuronal, glial and cellular mechanisms

Brain-wide activation changes caused by hippocampal neural disinhibition

Authors: Mr Stuart Williams¹, Ms Rebecca Hock¹, Dr Anja M Oelschlegel^{2,3}, Dr Jürgen Goldschmidt², Dr Tobias Bast¹
¹*School of psychology, University of Nottingham, Nottingham, United Kingdom*, ²*Leibniz institute for Neurobiology, Magdeburg, Germany*, ³*Institute of Anatomy, Otto-von-Guericke-University, Magdeburg, Germany*

Introduction: Hippocampal metabolic hyperactivity and neural disinhibition have been associated with early stage schizophrenia and age-related cognitive decline (Heckers & Konradi, 2015, *SchizophrRes*), although a causal link between disinhibition and metabolic hyperactivity remains to be demonstrated. Regional neural disinhibition may also cause activation changes in projection sites, which may contribute to some of the cognitive impairments caused by hippocampal disinhibition (Bast et al, 2017, *BrJPharmacol*; McGarrity et al, 2017, *Cereb Cortex*). Therefore, we examined the brain-wide activation changes caused by hippocampal disinhibition, using SPECT imaging in rats (Kolodziej et al, 2014, *Neuroimage*).

Methods: We combined ventral hippocampal picrotoxin (GABA-A antagonist) infusions (150ng/side) (McGarrity et al, 2017) with regional-cerebral-blood-flow (rCBF) measurements, using multi-pinhole SPECT (Kolodziej et al, 2014). Rats pre-implanted with hippocampal guide cannulae and a jugularis-vein catheter received hippocampal picrotoxin or saline infusions, followed 10 min later by intravenous injection of the radioactive tracer 99m-Technetium-HMPAO (over 10min). Brain-wide tracer distribution was then mapped by a 2-h SPECT/CT scan under isoflurane anaesthesia. Each rat received picrotoxin and saline infusions followed by SPECT/CT in a within-subjects design.

Analysis: SPECT data were co-registered to CT scans acquired in the same session, aligned to an MR brain template and global-mean normalised. Brain-wide activation changes after disinhibition and control were compared using voxel-wise paired t tests.

Results and conclusions: Picrotoxin increased rCBF around the infusion site in the ventral hippocampus, whereas rCBF in the dorsal hippocampus was markedly decreased, possibly reflecting reduced ventral hippocampal feedforward inhibition (Fig. 1A). This resembles the posterior hippocampal hypoactivation reported alongside anterior hippocampal hyperactivity in schizophrenia (Ragland et al, 2017, *NeuroImage: Clinical*) and suggests both changes may be caused by hippocampal disinhibition. Importantly, ventral hippocampal disinhibition caused marked extra-hippocampal changes in neocortical and subcortical sites. This included marked activation of medial prefrontal cortex and lateral septum (Fig. 1B/C), consistent with strong hippocampal projections to these sites (Petrovich et

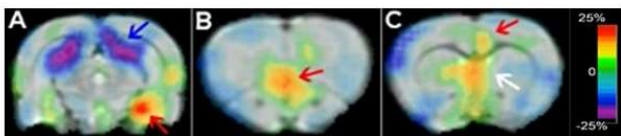


Figure 1: Changes in mean rCBF caused by ventral hippocampal neural disinhibition. Differences in SPECT tracer uptake after ventral hippocampal picrotoxin infusion as compared to saline infusion (n=12) are shown on MR templates of the rat brain. **A.** Ventral hippocampal disinhibition caused discernible activation around the infusion site in the ventral hippocampus (red arrow), and marked deactivation in the dorsal hippocampus (blue arrow). Additionally, ventral hippocampal disinhibition substantially increased rCBF in the mPFC (red arrows in B and C) and lateral septum (white arrow in C).

al, 2001, *BrainResRev*), and less pronounced changes in other sites, including ventral striatum activation, and deactivation of amygdala and piriform cortex.

The wide-spread, local and distal, activation changes revealed in the present study may contribute to cognitive and behavioural changes, including memory and attentional impairments and hyper-locomotion, caused by ventral hippocampal disinhibition (McGarrity et al, 2017).

Poster number: PS128 (SP)

Theme: Neuronal, glial and cellular mechanisms

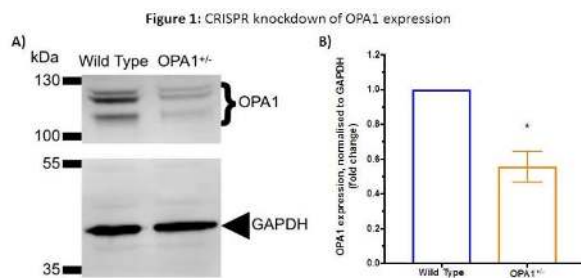
Optic atrophy (OPA)1 plays a key role in altered mitochondrial dynamics following neonatal hypoxic-ischaemic brain injury

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Introduction: Hypoxic-ischaemic encephalopathy affects 2-3 in every 1000 term infants and can bring about life-changing neurological consequences or death. Perturbation of mitochondrial function and subsequent induction of cell death pathways are key hallmarks in neonatal hypoxic-ischaemic (HI) injury, both in animal models and in term infants.

OPA1 is a dynamin-related guanosine triphosphatase, regulating both mitochondrial cristae junction formation and mitochondrial dynamics. Physiological function of OPA1 is mediated by interaction of its short (S-OPA1) and long (L-OPA1) forms generated by balanced action of Yme1L and Oma1 proteases. Previously we found that OPA1 was degraded in *in vitro* and *in vivo* models of HI.



CRISPR knockdown of OPA1 reduces protein expression to 53±6.9% in OPA1^{+/-} cells (A) Representative western blot, showing OPA1 protein knockdown, n=3. (B) Western blot OPA1 quantification normalised to GAPDH. Mean values ±SD plotted, n=3, *P<0.05

Methods: We used CRISPR to generate an OPA1 knockdown (53±6.9%) in a C17.2 cerebellar neural precursor cell line (OPA1^{+/-}) (Figure 1). Oxygen/glucose deprivation (OGD) using artificial cerebrospinal fluid was used as an *in vitro* mimic of HI. Cellular survival (lactose dehydrogenase release), mitochondrial function (MTT assay) and ATP production (ATPlite) were measured. Immunofluorescence microscopy was used to examine mitochondrial morphology. The Rice-Vannucci model of unilateral carotid artery ligation was used to induce hypoxia-ischemia *in vivo* in term equivalent, postnatal day 9 pups. OPA1 activity was determined *ex vivo* by GTPase assays of isolated OPA1 immune complexes.

Approach for statistical analysis: Experiments were independently repeated at least 3 times. Statistical analysis was performed using GraphPad Prism 7 Software. Data were assessed by a Student's t-test, One-way ANOVA or Two-way ANOVA with appropriate *post hoc* tests as necessary. Image analysis was performed using ImageJ.

Results and conclusions: We found fissioned mitochondrial morphology in the OPA1^{+/-} cell line compared with wild type cells. In addition, we found that OPA1^{+/-} cells have an increased susceptibility to OGD, specifically increased LDH release, reduced recovery of mitochondrial function and impaired ATP production after insult. We also found a reduction in OPA1 GTPase activity in Hypoxic-Ischaemic brain.

OPA1 warrants further investigation to determine its role in the regulation and recovery of mitochondrial dynamics following HI injury. Pharmacological interventions aimed at restoring OPA1 activity may provide additional methods of neuroprotection, where current therapies alone are inadequate.

Poster number: PS129 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Myelination status and its effects on integrin localisation and transport within CNS axons****Authors:** Dr Shmma Quraishie¹, Dr Melissa R Andrews¹¹*School of Biological Sciences, University Of Southampton, Southampton, United Kingdom*

Introduction: Growth-promoting proteins such as integrin receptors are widely expressed within developing CNS axons when the extracellular environment, including myelin is not fully developed. Integrin receptors interact with extracellular matrix ligands to promote neurite outgrowth, cell adhesion, migration and regeneration. In the mature CNS, expression of $\alpha 9$ integrin is downregulated despite an increase in the extracellular matrix ligand for $\alpha 9\beta 1$, tenascin-C, after injury (Andrews et al., 2009). This poses a problem for regeneration of damaged axons within the adult CNS as they are unable to grow through the injury site. Although forced expression of $\alpha 9$ using adeno-associated viruses (AAVs), can promote axonal elongation and neurite outgrowth *in vitro* as well as long distance sensory axon regeneration *in vivo* (Andrews et al., 2009; Cheah et al., 2016), forced expression of $\alpha 9$ within the adult sensorimotor cortex, is restricted to the somatodendritic compartment (Andrews et al., 2016) and does not extend beyond the axon initial segment. A number of studies have shown that if myelination is delayed, the permissive period for regeneration can be extended. Therefore a key event influencing the developmental loss of the regenerative capacity of the CNS is likely to be myelination of certain long tract fibres, such as the CST. The aim of this study is to determine if expression of $\alpha 9$ integrin by AAVs can be localised within unmyelinated axons in the adult CNS.

Methods: We investigated forced $\alpha 9$ expression following viral transduction of AAV5-CAG- $\alpha 9$ -V5 in adult Wistar rats, targeting three brain regions containing mixed populations of myelinated and unmyelinated axons; the hippocampus, striatum, and substantia nigra. Animals were sacrificed 4wks post-injection and assessed immunohistochemically for V5 expression alongside axonal and myelin markers.

Results and conclusions: Forced $\alpha 9$ expression was observed in neurons of the hippocampus, striatum and substantia nigra. Expression was not restricted to the somatodendritic compartment, as observed in the cortex, but was transported and localised in unmyelinated axons within the studied regions. These results suggest that distinct neuronal populations localise integrins within unmyelinated axons. Understanding the fundamental mechanisms underpinning integrin receptor expression, localisation, and transport will lead to improvements in future regenerative therapies.

Poster number: PS130 (SP)**Theme:** Neuronal, glial and cellular mechanisms**A computational study of astrocytic calcium homeostasis in the synaptic cleft****Authors:** Mr Marinus Toman¹, Prof Liam McDaid¹, Dr John J. Wade¹, Dr Jim Harkin¹¹*Computational Neuroscience and Neural Engineering (CNET) Research Team, Intelligent Systems Research Centre, Ulster University, United Kingdom*

Introduction: Calcium (Ca^{2+}) contributes to long-term and short-term synaptic plasticity in many ways and Ca^{2+} concentrations within the synaptic cleft fluctuate drastically during neuronal activity. Delivery of Ca^{2+} to the synaptic cleft can be regulated by astrocytes through transporters in their peripheral processes, e.g. through NCX and PMCA. Therefore, astrocytes may affect synaptic plasticity through Ca^{2+} homeostasis in the synaptic cleft.

The main aim of this work is to develop a biophysically realistic computational model of how astrocytes contribute to synaptic plasticity through regulation of synaptic Ca^{2+} levels. This work builds on recent research [1] which shows

that in thin astrocyte processes microdomains of sodium (Na^+) and potassium (K^+) forms at the perisynaptic cradle during neuronal excitation. The hypothesis that underpins this work is that elevated levels of Na^+ at the cradle could potentially reverse the NCX extruder thereby producing a local supply of Ca^{2+} . Efflux of this Ca^{2+} via the PMCA would dictate Ca^{2+} homeostasis in the cleft thereby affecting synaptic plasticity. The proposed model will be used to capture this signalling pathway.

Preliminary results will be presented which demonstrates that neuronal excitation modulates Ca^{2+} concentration in the synaptic cleft.

Methods: A biophysical model will be developed as a tool to investigate how the efflux of astrocytic Ca^{2+} effects Ca^{2+} homeostasis in the synaptic cleft and therefore plasticity. The model will consist of a mathematical framework which is constructed from existing biophysical models, including models for neuronal firing rates, synaptic transmission, astrocyte Ca^{2+} dynamics, probability of neurotransmitter release and synaptic plasticity.

Approach for statistical analysis: In the first instance, model data will be analysed and graphically represented to help visualise how neuronal excitation modulates Ca^{2+} in the cleft. This approach will continue as more data emerges on the relationship between plasticity, probability of neurotransmitter release, neuronal excitations, postsynaptic potentiation and $\text{Ca}^{2+}/\text{Na}^+$ levels in the perisynaptic cradle.

References:

[1] K. Breslin *et al.*, "Potassium and sodium microdomains in thin astroglial processes: A computational model study," *PLOS Comput. Biol.*, vol. 14, no. 5, p. e1006151, May 2018.

Poster number: PS131 (SP)

Theme: Neuronal, glial and cellular mechanisms

Examining the anti-inflammatory potential of cannabinoids in models of Alzheimer's disease

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The Alzheimer's disease brain is characterised by the accumulation of the toxic peptide β -amyloid ($\text{A}\beta$). This acts as the primary inflammatory stimulus, leading to the uncontrolled activation of glial cells, and subsequent deterioration in neuronal integrity. $\text{A}\beta$ induces its inflammatory effects through activation of toll-like receptors (TLRs) on microglia, in particular TLR2. Although primarily known for its ability to sense gram-positive bacteria such as common respiratory and skin infections, TLR2 plays a prominent role in regulating damage-induced inflammation. However its excessive activation in microglia can impair neuronal function (Costello *et al.*, 2015). No therapy currently exists to reliably alleviate the effects of AD pathology, although interventions which target inflammatory mediators have proven successful in attenuating $\text{A}\beta$ -induced microglial activation and the associated disruption of hippocampal synaptic function. Recent research on phytocannabinoid agents, primarily cannabidiol (CBD), has shown promise in the treatment of AD-related pathology in pre-clinical disease models (Hughes & Herron, 2018).

The current study interrogates the anti-inflammatory potential of CBD, and other phyto-compounds in microglial cells, and on inflammatory-induced neuronal dysfunction under control and AD-like conditions. We demonstrate that cannabinoid agents can effectively reduce TLR2-mediated release of the proinflammatory cytokine $\text{TNF}\alpha$, and the expression of inflammatory-related signalling molecules in microglia. Moreover, we show that the neuronal expression of iNOS and release of nitrite in response to TLR2 activation can be alleviated by cannabinoids, in both control cells and in neurons which express the dimeric form (S26C) of human $\text{A}\beta$ 42. We propose that phytocannabinoids may be an effective strategy to restore the inflammatory-related brain dysfunction associated with AD.

Poster number: PS132 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Short-term potentiation is potently inhibited by L-689,560 in the hippocampus****Authors:** Ms Rachael Ingram¹, Dr Arturas Volianskis¹¹*Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, QMUL, London, United Kingdom*

Introduction: Two forms of NMDAR-dependent synaptic potentiation are co-induced by theta-burst stimulation (TBS) of the Schaffer collaterals. The initial phase of potentiation (short-term potentiation, STP) declines in response to low frequency synaptic activation leading to a stable enhancement of synaptic transmission (long-term potentiation, LTP). STP and LTP are differentially sensitive to GluN2-preferring NMDAR antagonists and STP has been subdivided further into STP1 and STP2 [1]. Thus, STP1 and LTP are inhibited more potently than STP2 by D-AP5 and NVP-AAM077 (GluN2A-preferring antagonists). In contrast, STP2 is more sensitive to inhibition by Ro25-698 and UBP145, which are most potent at blocking GluN2B and GluN2D containing receptors, respectively. NMDAR open channel blocker ketamine is more potent at inhibiting STP2 than STP1 or LTP [2]. Concentration dependent effects of GluN1 inhibition on STP and LTP have not been described before and we investigated whether the GluN1 antagonist L-689,560 displays preference for either STP or LTP.

Methods: Hippocampal slices were prepared from male adult Wistar rats and kept submerged in ACSF. The Schaffer collaterals were stimulated and fEPSPs were recorded in the stratum radiatum of the CA1 area. L-689,560 was applied 30 min prior to induction of STP and LTP by TBS and results were compared to the controls without the compound application.

Approach for statistical analysis: Amounts of inhibition of STP and LTP were calculated in single experiments, concentration response curves were then constructed and fitted using nonlinear regression functions (Prism 7).

Results and conclusions: L-689,560 inhibited STP in a biphasic sigmoidal fashion with low (0.13 μ M) and high (2.2 μ M) IC₅₀ values that differed ~17 fold whereas it inhibited LTP in a single sigmoidal manner (IC₅₀ = 0.13 μ M). In conclusion, similarly to Ro25-698, UBP145 and ketamine, L-689,560 inhibits STP2 more potently than STP1 and LTP.

[1] Volianskis et al., (2013) *J Physiol* 591, 955–972.

[2] Ingram R et al., (2018) *Neuropharmacology* 142, 30–40.

Poster number: PS133 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Expression of alternatively spliced variants of the RNA editing enzyme, ADAR2 can regulate PIN1 gene expression in SH-SY5Y cell lines****Authors:** Dr Philip Chen¹, Ms Ilda Sethw Hassan¹¹*Royal Holloway, University of London, Egham, United Kingdom*

Introduction: RNA editing describes the modification of RNA transcripts so that the sequence differs from the original DNA. The first and most prevalent is A-to-I editing, where an adenosine is deaminated by a family of adenosine deaminases acting on RNA (ADARs) to form the base inosine. There are three members of the ADAR family (ADAR1-3) and ADAR2 is critical for editing the GluA2 subunit of AMPARs and impaired ADAR2 activity has been linked to a number of chronic neurodegenerative disorders including Alzheimer's disease and motor neurone disease. ADAR2 exists as multiple alternatively-spliced variants within mammalian cells and ADAR2a and ADAR2b differ by the

incorporation of a 120 bp *AluJ* sequence within the catalytic domain. The addition of the *AluJ* sequence in ADAR2b variants reduces RNA editing efficiency, however the physiological relevance of these splice variants and the post-transcriptional regulation of ADAR2 remains poorly understood.

We designed phosphorodiamidate morpholino oligomers (PMOs) to manipulate the alternative splicing of the 120 bp *AluJ* region and increase the expression of the more catalytically active ADAR2a variant. Subsequently, we examined the gene expression of a protein known to regulate ADAR2 activity, the nuclear peptidyl-prolyl *cis/trans* isomerase, Pin1.

Methods: PMOs were transfected into neuroblastoma SH-SY5Y cells over 24 hour incubation period. Editing levels were measured following RT-PCR of RNA extracted from transfected cells and densitometric analysis of a *BbvI* restriction digestion. Gene expression of Pin1 was quantified by qRT-PCR.

Approach for statistical analysis: All experiments were performed at least three times. Statistical significance was tested using ANOVA followed by Dunnett's multiple comparisons test.

Results and conclusions: We demonstrated that a PMO designed upstream of the 3' splice site of the *AluJ* region reduced incorporation of the *AluJ* sequence ($IC_{50}=3.13\pm 0.7 \mu M$) and increased expression of ADAR2a. Moreover, expression of ADAR2a increased GluA2 RNA editing efficiency compared to control PMOs by up to 30 %. Furthermore, expression of ADAR2a increased gene expression for Pin1. We suggest that the ADAR2a variant is able to regulate Pin1 expression and the interplay between both proteins could have important implications for their roles in neurodegenerative disorders.

Poster number: PS134 (SP)

Theme: Novel treatments & translational neuroscience

Translational assessment of the rapid-onset antidepressants ketamine and scopolamine in a rodent probabilistic reversal learning task

Authors: Mr Matthew Wilkinson¹, Professor Jack Mellor¹, Professor Emma Robinson¹

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Introduction: Deficits in reward processing are a key feature of major depressive disorder and can be assessed in rodents using translational probabilistic reversal learning tasks (PRLT) (Bari et al, 2010.

Neuropsychopharmacology;35(6):1290-1301). Recent advances in identifying compounds with rapid-onset antidepressant efficacy has led to a greater interest in understanding the psychopharmacological mechanisms underlying their action. This study sought to investigate the rapid-onset antidepressant compounds ketamine and scopolamine in a PRLT alongside utilising computational modelling to probe underlying cognitive processes.

Methods: We trained a cohort of 12 male rats in a PRLT. Briefly, rats were required to learn to spatially bias touchscreen responses to receive food reward. Stimuli were probabilistically rewarded so that there was a rich stimulus and a lean stimulus rewarded 80% and 20% of the time respectively. After 8 consecutive rich stimulus choices the reward contingencies were switched. Once baseline stability was established, rats were treated before testing with either ketamine (0, 1, 3, 10 mg/kg) or scopolamine (0, 0.03, 0.1 mg/kg). All data were fit to both a Qlearn1 and Qlearn2 model with a single or dual learning rate for positive and negative information respectively. Model fit was compared using vehicle data and parameters were generated using data from each individual drug dose to then generate model outputs.

Approach for statistical analysis: Parameters were assessed as appropriate with either one-way repeated measures ANOVA (treatment) or two-way repeated measured ANOVA (treatment, feedback type) using Sidak's correction for post-hoc analysis.

Results and conclusions: At odds with their role as rapid acting antidepressants both ketamine and scopolamine decreased reward learning performance alongside decreasing positive feedback sensitivity and motivation to complete the task. When analysed using the better fitting Qlearn1 model neither ketamine nor scopolamine had any effect on performance compared to a model predicted perfect strategy, however there was a significant negative effect of ketamine on learning rate. These results imply that the rapid-onset efficacy of ketamine and scopolamine is not mediated through differences in reward learning or changes in feedback sensitivity in this task with these results being more consistent with a non-specific general impairment caused by both drugs.

Poster number: PS135 (SP)

Theme: Novel treatments & translational neuroscience

Human leukocyte antigen-A critically determines neural stem cell immune tolerance

Authors: Mr Kwok Im^{1,2}, Dr. Kevin Doty², Dr. David Gate³, Dr. Brian Leung⁴, Dr. George Liu⁵, Dr. Terrence Town¹
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Introduction: One of the most successful applications of stem cell therapy is transplantation of non-matched fetal brain tissue into patients with Parkinson's disease. However, potential side-effects such as the immune-mediated microenvironment in the brain and histocompatibility of animal models to study human neural stem cell transplantation limit the progression of bench-to-bedside clinical application.

Methods: Here we report a model to investigate human neural stem cell immune tolerance by 'humanizing mice', which enables a comprehensive identification of human leukocyte antigen haplotypes relevant for allograft acceptance. Purified human hematopoietic stem cells were reconstituted into immunocompromised mice for 6 months before unilateral injections of human neural stem cells into the striatum for mix and match haplotype assays. After 2 weeks, animals were euthanized for downstream analysis.

Approach of statistical analysis: Immunohistochemistry, immunocytochemistry, fluorescent activated cell sorting (FACS), RTqPCR, and RNAseq were performed at the time of euthanasia of the animals. All statistical tests were performed by two way ANOVA and Tukey's post-hoc test. $p < .05$, *; $p < .01$, **; errors bars represent \pm SEM.

Results and Conclusions: Remarkably, we found immune tolerance of stem cell transplants with as much as 50% match at the HLA-A locus; irrespective to the degree of mismatch for HLA -B, -C, -DR, or -DQ. Furthermore, we have identified a high enrichment of human associated genes for neural development and immune activation in the striatal area transplanted with human neural stem cells, suggesting a fundamental HLA immune-dependent response to the engraftment of neural progenitor cells. Taken together, our results demonstrate that humanized mice are a critical pre-clinical tool to assess HLA-dependent stem cell transplant rejection and future immunotherapeutic applications.

Poster number: PS136 (SP)**Theme:** Novel treatments & translational neuroscience**Manipulating microglia to enhance anti-viral immunity in the central nervous system****Authors:** Ms Lorna Hayden¹, Ms Tiia Semenoff¹, Dr Julia Edgar¹, Dr Marieke Pinggen¹, Dr Xiaohong Shi², Prof Christopher Linington¹¹University of Glasgow, Glasgow, United Kingdom, ²Centre for Virus Research, Glasgow, United Kingdom

Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by opportunistic infection of oligodendrocytes by John Cunningham virus in immunocompromised individuals. Intrathecal synthesis of lipid-reactive IgM is associated with a decreased risk of developing PML (1); an observation suggesting these IgM antibodies may stimulate anti-viral activity in the CNS. To test this hypothesis we investigated the ability of O4, a sulphatide-reactive monoclonal antibody (2), to induce anti-viral responses in myelinated cultures derived from wild-type and IFNAR knock-out mice.

Methods: Transcriptional responses were analysed using gene microarrays and validated by RT-qPCR. Functional anti-viral activity was monitored using Bunyamwera virus (BUNV); viral replication being quantified by immunocytochemistry, RT-qPCR and plaque assay. Cells expressing *Ifnb1* and interferon-stimulated genes were identified by fluorescence *in situ* hybridisation.

Approach for statistical analysis: Raw microarray data were analysed using Partek Genomics Suite and Pathway. Statistical enrichment was determined by Mann-Whitney test with a *p*-value cut-off of 0.05. Data from all subsequent experiments were analysed by *t*-test, one-way ANOVA or two-way ANOVA using GraphPad Prism 5 software. RT-qPCR validations were quantified using the $\Delta\Delta CT$ method. Immunocytochemistry and *in situ* data were quantified blind using 10 random images per coverslip, data being expressed as percent positive cells.

Results and conclusions: Binding of mAb O4 to the myelin/oligodendrocyte surface induces an anti-viral signature within myelinated cultures. *Ifnb1* was induced in microglia, leading to IFNAR-dependent induction of interferon-stimulated genes in astrocytes, oligodendrocytes and neurons; a response that almost completely abolishes replication of BUNV in these cultures. Our data provide evidence for a previously unknown mechanism by which sub-lytic, antibody-mediated injury activates microglia to initiate an *Ifnb1*-dependent, CNS-wide anti-viral response. This could have major implications for the treatment of neurotropic viral infections, as well as for risk stratification of immunosuppressed patients.

1. Villar, et al. 2015. Ann Neurol 77, 447-57; (2) Brennan, et al. 2011. J Neuroimmunol 238: 87-95.

Poster number: PS137 (SP)**Theme:** Novel treatments & translational neuroscience**Blood borne biomarkers of neuropathic pain****Authors:** Dr Patrick McHugh¹, Dr David Buckley¹, Dr Jonathan Wren², Prof Dave Finn³¹Centre for Biomarker Research, University of Huddersfield, Huddersfield, United Kingdom, ²Oklahoma Medical Research Foundation, Oklahoma City, United States, ³Pharmacology & Therapeutics, National University of Ireland, Ireland

Introduction: Chronic neuropathic pain (CNP) is one of the most significant unmet clinical needs in modern medicine. Alongside the lack of effective treatments, there is a great deficit in the availability of objective diagnostic methods to reliably facilitate an accurate diagnosis. We therefore aimed to determine the feasibility of a simple diagnostic test

by analysing differentially expressed genes in the blood of patients diagnosed with CNP of the lower back and compared to healthy human controls.

Methods/Analysis approach: Refinement of microarray expression data was performed using correlation analysis with 3900 human 2-colour microarray experiments. Selected genes were analysed in the dorsal horn of Sprague-Dawley rats after L5 spinal nerve ligation (SNL), using qRT-PCR and ddPCR, to determine possible associations with pathophysiological mechanisms underpinning CNP and whether they represent translational biomarkers of CNP.

Results/ and Conclusions: We found that of the 15 potential biomarkers identified, tissue inhibitor of matrix metalloproteinase-1 (TIMP1) gene expression was upregulated in chronic neuropathic lower back pain (CNBP) ($p = 0.0049$) which positively correlated ($R = 0.68$, $p = \leq 0.05$) with increased plasma TIMP1 levels in this group ($p = 0.0433$). Moreover, plasma TIMP1 was also significantly upregulated in CNBP than chronic inflammatory lower back pain ($p = 0.0272$). In the SNL model, upregulation of the Timp1 gene was also observed ($p = 0.0058$) alongside a strong trend for the upregulation of melanocortin 1 receptor ($p = 0.0847$).

Our data therefore highlights several genes that warrant further investigation, and of these, TIMP1 shows the greatest potential as an accessible and translational CNP biomarker. We are currently looking at the gene expression differences in animal models of neuropathic pain and determining if these differences are clinically relevant to neuropathic pain in a bottom up translational approach.

References

O'Connor AB (2009). *Pharmacoeconomics*, 27(2): 95-112

Poster number: PS138 (SP)

Theme: Novel treatments & translational neuroscience

Sex- and time-dependent preventive effect of magnesium sulfate in a mouse model of cerebral palsy

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Introduction: Neonatal brain lesions can induce cerebral palsy (CP) defined as permanent disorders of movements and posture. Preterm birth and hypoxic-ischemic (HI) events are risk factors of CP. Moreover, boys display a greater vulnerability to develop CP than girls. A meta-analysis showed that magnesium sulfate (MgSO₄) administration to mothers at risk of preterm delivery reduces the risk of CP by 32%. Only two clinical studies have studied the long-term efficacy of MgSO₄. Therefore, long term effects, potential sex-dependent efficacy and potential side effects of MgSO₄ have to be investigated.

Methods: To address these questions, postnatal day 5 (P5) mice underwent a unilateral carotid ligation followed by hypoxia, with or without a MgSO₄ injection at 600 mg/kg. We evaluated MgSO₄ efficacy at short and long-term, in both sexes on cellular and behavioral levels. The latter consisted in evaluating sensorimotor abilities in pups. Moreover, in pups, we also quantified mRNA rates of proinflammatory cytokines. In adolescent mice, we measured cognitive and motor skills. At long-term, *via* cresyl-violet staining, brains were classified into: "no visible lesion" or "moderate to severe lesions", and a more detailed analysis allowed to determine the lost areas in different brain regions.

Approach for statistical analysis: For behavioral evaluation in pups and regional analysis in adolescent mice, analyses of variance were performed. For qRT-PCR experiments, behavioral evaluations and measurement of brain lesions at long-term, Kruskal-Wallis were performed. The significance threshold was set at $p < 0.05$.

Results and conclusions: In pups, HI induced sensorimotor deficits and increased TNF α and IL1 β mRNA rates, which was totally prevented by MgSO $_4$. At long-term, HI induced sensorimotor and cognitive deficits which were partially prevented by MgSO $_4$ only in females. However, as regards the hippocampus and thalamus, MgSO $_4$ prevented the increase of the lesion size only in males.

To conclude, at short-term, MgSO $_4$ had anti-inflammatory properties without presenting side effects. At long-term, MgSO $_4$ did not prevent motor nor cognitive impairments in males while it prevented histological damages in the hippocampus and thalamus. This discrepancy is consistent with clinical observations and raises the questions of the targets of MgSO $_4$ and the mechanisms underlying the sex-dependent efficacy of MgSO $_4$.

Poster number: PS139 (SP)

Theme: Novel treatments & translational neuroscience

CD146, a placental protein involved in the cortical angiogenesis impairments induced by in utero alcohol exposure

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Fetal alcohol syndrome (FAS) is the most severe expression of fetal alcohol spectrum disorders (FASD) and associates several neurodevelopmental troubles such as hyperactivity or learning deficits. FASD infants are frequently late or mis-diagnosed and challenge for clinicians consists in the early diagnosis of FASD to avoid the loss of precious years of care. While several biomarkers of prenatal alcohol exposure (PAE) have been characterized, there are currently no biomarkers of brain defects. Recent data from our Team showed in both human and mouse that PAE impairs cortical angiogenesis¹ and that the placental repression of PlGF mimics the vasculature disorganization observed in alcohol-exposed fetuses.² In addition to PlGF, CD146 is a soluble pro-angiogenic factor (sCD146) expressed by the placenta and a co-receptor of VEGFR-2, suggesting that it would be involved in alcohol-induced brain vascular defects. Subcutaneous injections of alcohol (3g/kg) from gestational day 15 (GD15) to GD20 were performed to characterize the effects of PAE on CD146 expression and *in utero* repression of placental CD146 by electroporation was done at GD13 to investigate the impact on the fetal cortical vasculature at GD20.

Statistical analysis was done using Mann Whitney and χ^2 tests.

First, characterization of CD146 expression showed that placenta is a major source of sCD146 and that, in fetal blood, sCD146 levels are markedly altered by PAE. Then, experiments revealed that PAE from GD15 to GD20 induced an opposite regulation of sCD146 in placenta and fetal brains. In particular, Western blot experiments revealed a strong decrease of sCD146 levels in the placenta whereas they significantly increased in the fetal cortex. Finally, the repression of CD146 expression in the placenta by *in utero* electroporation of CD146 CRISPR/Cas9 induced a marked reduction of CD146 levels in the placenta. This effect was associated to a disorganization of the vasculature in the fetal brain.

Altogether, these data support that placental CD146 is involved in the control of fetal brain angiogenesis and in the deleterious effects of alcohol on the cortical vasculature.

¹Jégou *et al*, *Ann Neurol*, 2012; ²Lecuyer *et al*, *Acta Neuropathol Commun*, 2017. ANR/Fondation de France/Fondation pour la Recherche en Alcoolologie/Fondation Paralysie Cérébrale/FEDER

Poster number: PS140 (SP)**Theme:** Novel treatments & translational neuroscience**The efficacy of nutritional phytochemical supplementation in improving cognition****Authors:** Alexander Marsh^{1,2,3}, Marion Mackonochie⁴, Momna Hejmadi¹, Vivien Rolfe⁴¹Univeristy of Bath, Bath, United Kingdom, ²Cardiff University, Cardiff, United Kingdom, ³University Hospitals Bristol NHS FT, United Kingdom, ⁴Pukka Herbs, United Kingdom

Introduction: The incidence of cognitive disorders is rising, resulting in a need for research into therapeutic interventions and prophylactic measures. The ingredients of various phytochemical supplements have had some success in improving cognitive outcome in preclinical studies, subsequently progressing to clinical trials. Now a number of published trials and reviews exist; however, confirmation of compelling evidence in support of routine use in (1) improving cognition in healthy individuals or (2) as prophylaxis and treatment against the cognitive sequelae of neurological insult, is yet to be established.

Methods: Informed by Cochrane guidelines, a novel systematic search strategy for RCTs exploring the effect of the active ingredients of commonly used phytochemical supplements on cognition in healthy and non-degenerative, cognitively compromised adults of working age (18-65) was conducted. PubMed, PsychINFO, and Web of Science were searched, in addition to consultation with experts and examination of reference lists to ensure a thorough review of the current literature.

Approach for statistical analysis: The search yielded 144 studies. Following screening, seven double blind, non-crossover, parallel RCTs examining either *Bacopa monniera*, *Ocimum sanctum* or *Cammelia sinesis* were finally selected for quantitative synthesis. No trials examining the other active ingredients met criteria. Participants were all healthy apart from those within the one *Cammelia sinesis* study, which examined Down's syndrome. Meta-analysis revealed no benefit of *Bacopa monniera* or *Cammelia sinesis* on processing speed, attention, working memory, language, psychomotor function or overall cognitive performance. *Ocimum sanctum* improved reaction times on an executive function task. *Bacopa monniera* demonstrated inconsistent but generally insignificant effect on memory function. *Cammelia sinesis* demonstrated no effect on memory.

Results and conclusions: Though, overall, no beneficial effects were seen, the limited number of trials, methodological issues and unclear risk of bias casts doubt on the validity of these findings. Further, methodologically robust trials are recommended to validate these findings.

Poster number: PS141 (SP)**Theme:** Novel treatments & translational neuroscience**Metabolism & inflammation in traumatic brain injury: testing potential therapeutic molecules in cell culture models****Authors:** Ms Killen MJ¹, Dr Susan Giorgi-Coll¹, Dr Carpenter KLH¹, Prof Hutchinson PJA¹¹Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, United Kingdom

Introduction: Traumatic Brain Injury (TBI) is a leading cause of death and disability, with 69 million people affected annually, worldwide^[1]. The initial trauma causes an immense disruption to brain homeostasis resulting in metabolic dysfunction and an inflammatory cascade. This can then promote further neurodegenerative effects for many months to years after, producing a 'secondary' injury. By investigating the link between inflammation and critical metabolic pathways, we aim to find potential supplements which alter the brain's response to acute injury and

improve recovery (Figure 1). Successful candidates will be explored further in clinical studies to improve patient outcomes as there is currently no standard neuroprotective drug treatment for TBI.

Methods: Primary rat mixed glial cell cultures^[2] were submitted to metabolic (rotenone) and inflammatory (lipopolysaccharide) stressors. The 'rescue' agents tested for potential therapeutic use, include; succinate, lactate, acetate, pyruvate and cyclosporine. After stress and rescue agents are applied, the resulting metabolic products released from cells into the culture media were collected at critical time points, and the dynamic response to stress was analysed using continuous monitoring methods.

Approach for statistical analysis: Concentrations of glucose, the lactate/pyruvate ratio (LPR), and cytokines in cell culture media were analysed as indicators of the cell's energetic and inflammatory state. LPR is an established indicator of brain energy status, with higher extracellular LPR correlated to worse outcomes in TBI patients^[3]. Statistical significance was calculated using Student's t test with Graphpad Prism software.

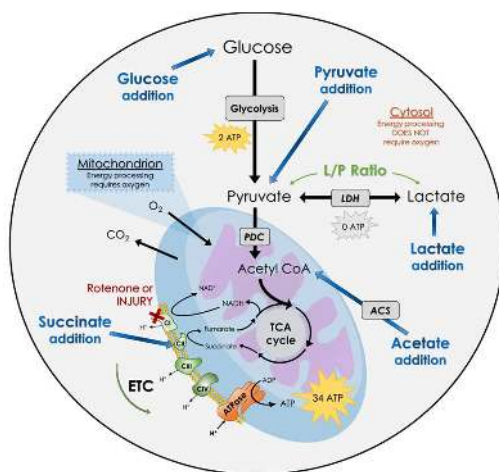


Figure 1. Illustration of metabolic pathways in the cell (in black text), and potential sites for supplementation (in blue text). The flow diagram depicts glycolysis, which produces two molecules of ATP per molecule of glucose, followed by downstream pyruvate processing. Pyruvate can be converted to lactate, which produces no molecules of ATP, or processed in the mitochondrion, through the tricarboxylic acid (TCA) cycle and electron transport chain (ETC), which can produce 34 molecules of ATP. Diagram copyright © 2018 Monica J. Killen

Results and Conclusion: Preliminary data suggest metabolic intermediate molecules are able to influence both metabolic and inflammatory markers of stress in our model. Addition of succinate, for example, decreased both rotenone and lipopolysaccharide induced stress, increasing activity of the efficient mitochondrial energy processing pathways. Early results also suggest that addition of metabolic intermediates can reduce concentrations of stress-induced IL-6, an important inflammatory signalling molecule.

By gaining insights into the brain's response to stress on a cellular level, this study will provide improved understanding of how to promote recovery, and which metabolic targets will have the best potential for future use in clinical trials.

[1] Dewan et al. 2018, JNS: 1-18.

[2] Giorgi-Coll et al. 2017, Sci Rep. 7:1003.

[3] Timofeev et al. 2011, Brain. 134:484-94.

Poster number: PS142 (SP)

Theme: Novel treatments & translational neuroscience

MSCs modulate peripheral stress-induced innate immune activation indirectly limiting the emergence of neuroinflammation and depressive / anxiety-like behaviors

Authors: Dr Denis Gallagher¹, Mr Fyyaz Siddiqui¹, Mr Maxwell Charlat¹, Ms Emaan Chaudry¹, Mr Siddiq Moolla¹, Dr. Andrée Gauthier-Fisher¹, Dr. Clifford Librach^{1,2,3,4,5}

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Introduction: Hyperactivation of innate immunity has been implicated in the etiology of mood disorders.

Mesenchymal Stromal Cells (MSCs) have demonstrated potent immunomodulatory capabilities which have yet to be exploited in stress-based preclinical models of mood disorders. We sought to test the ability of intravenously-delivered MSCs to modulate innate immune activation and behavioral patterns associated with murine repeated social defeat (RSD).

Methods: RSD-induced innate immune activation as well as depressive and anxiety-like behaviors were assessed in unstressed control, RSD and RSD + MSC groups as follows. Plasma concentrations of key cytokines were quantified using ELISA at several timepoints following infusion of 1×10^6 MSCs. Flow cytometry was used to quantify circulating Ly6C^{hi} monocytes and CNS inflammatory processes were assessed using immunohistochemistry (IHC). Social avoidance behaviour and dark / light preference tests were performed following RSD. Unbiased, whole body, MSC biodistribution studies were performed using the CryoViz™ cryo-imaging system at multiple timepoints post-infusion. Fate and interaction of pre-labelled MSCs with recipient innate immune cells was quantified using IHC and flow cytometry.

Statistical Analysis: ANOVA and Tukey's post hoc multiple comparison test were used to determine statistical significance. Graphs depicting mean and SEM are presented with statistical significance indicated as * $p < 0.05$ ** $p < 0.01$, *** $p < 0.001$, NS= not significant. N = 6-19 per experimental group.

Results and Conclusions: MSCs decreased stress-induced circulating pro-inflammatory cytokines and monocytes. MSCs also reduced neuroinflammation and limited the emergence of social avoidance and anxiety-like behaviours. However, biodistribution and IHC analyses revealed that infused MSCs distributed entirely within peripheral organs without homing to the brain. Fate studies indicated that infused MSCs provoked transient recruitment of recipient neutrophils and monocytes to the lungs within hours of intravenous administration. Infused MSCs and recruited neutrophils underwent apoptosis and were subsequently cleared by macrophages which accumulated in the lungs and spleen throughout RSD. We propose that clearance of both MSCs and recruited neutrophils, promotes a phenotypic switch towards CD206+ macrophages and ultimately resolution of systemic inflammation. Phagocytosis of infused MSCs and ensuing resolution of inflammation may provide downstream protection to distal organs in preclinical disease models in which peripherally-generated innate immune cells contribute to pathogenesis, including RSD. These data represent a novel avenue for translational MSC research and potentially identify unexpected targets in the periphery towards improved treatment of psychiatric disorders with an inflammatory component.

Poster Number: PS143 (SP)**Theme:** Novel treatments & translational neuroscience**Patient-derived iPSC for high grade glioma (PDI:HGG)**

Authors: Dr Daniel Mark Tams¹, Mrs Cath Fyfe¹, Dr Barbara da Silva², Miss Lauren Hindhaugh¹, Mrs Pawlina Dand¹, Mr David Wallbank¹, Dr Joe Mee¹, Mr John Gardner¹, Mr Kevin Bruce¹, Mr Ashley Barnes¹, Mr Ryan K Mathew², Dr Heiko Wurdak², Mr Aidan Courtney¹

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Introduction: PDI:HGG is an InnovateUK funded project to create an iPSC resource from primary patient high grade glioma (HGG) for use in phenotypic screening. This project focussed on HGG which makes up 45.2% of malignant primary brain and CNS tumours, typically affects patients aged 50-60 years, and is currently incurable.

Methods and Analysis: Glioma cell lines were isolated from primary tumour tissue at Leeds Institute of Medical Research at St James's and expanded as per published protocols¹. Each glioma line was reprogrammed using virally transfected Yamanaka factors. Whole genome sequencing at 60x resolution of tumour tissue, isolated glioma and reprogrammed iPSCs was performed at Edinburgh Genomics. Phenotypic screening was performed on the ArrayScan VTI HTS and statistical analysis was done using GraphPad.

Results: Primary glioma were expanded in culture and showed a high level of heterogeneity between and within each culture. Reprogramming of glioma was achieved using a feeder-dependant system and colonies of cells were shown to express the stem cell markers SSEA3, OCT4, NANOG, SOX2 and TRA-1-60. Colonies were expanded in culture and had a distinct iPSC-like cell morphology. Each iPSC line derived from glioma were sequenced at the genome level providing data on tumour mutations present in the iPSC line and how this compares to mutations in the original tumour tissue.

Differentiation of the iPSC lines derived from glioma to astrocytes and neurons was achieved and comparative data with normal iPSC control lines showed phenotypic differences in multiple assays.

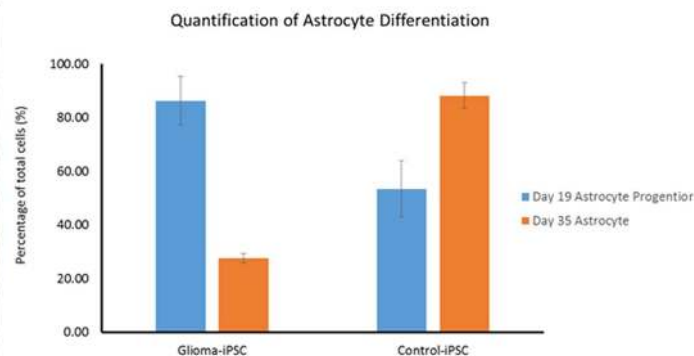
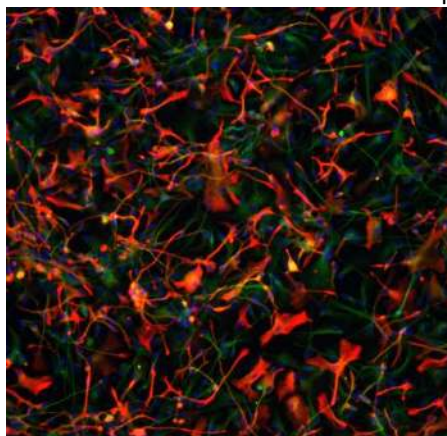


Figure 2 iPSCs derived from glioma and differentiated to Astrocytes. Neural progenitor cells derived from the iPSC line were matured to Astrocytes and imaged by immunocytochemistry GFAP (Red), Nestin (Green) (A). Quantification of S100b (astrocyte progenitor) and GFAP (astrocyte) expressing cells (B). n=3

Conclusion: This work demonstrates the application of iPSC technology to tumour tissue and describes the heterogeneous nature of the cells and the process of reprogramming. We show detailed characterisation data of the iPSC lines and differentiated cell types. Furthermore, we show data on the application of this technology to image-based compound screening.

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1. Wurdak H et al. *Cell Stem Cell*. 2010 Jan 8;6(1):37-47. PMID:20085741

Poster number: PS144 (SP)**Theme:** Novel treatments & translational neuroscience**The Development of Bolaamphiphiles as a Novel Drug Delivery System in the Treatment of Diseases of the Brain****Authors:** Ms Amy Maclatchy¹, Professor Jimmy Bell¹, Professor Annie Bligh², Dr Simon McArthur³, Dr Mark Odell⁴¹University of Westminster, London, United Kingdom, ²Caritas Institute of Higher Education, Hong Kong, China,³Queen Mary University of London, London, United Kingdom, ⁴University of Lincoln, Lincoln, United Kingdom

Introduction: The blood-brain barrier (BBB) is the principle regulatory interface between the blood and the central nervous system (CNS), maintaining homeostasis and protecting the brain from foreign molecules, including xenobiotics. The barrier selectively restricts entry to the brain, rendering treatment of brain diseases intrinsically challenging. While physical disruption of the BBB may overcome this barrier, it is non-specific and potentially damaging. Thus, novel drug delivery systems are urgently required. One such system is the bolaamphiphile compound GLH-20, derived from *Vernonia galamensis* oil. GLH-20 is a lipid with acetylcholine head-groups, capable of forming cationic, mono-layered membrane vesicles. GLH-20 vesicles can be packaged with multiple different cargoes and are selectively lysed by acetylcholinesterase, releasing their contents. We have investigated the ability of GLH-20 vesicles to transport tracer molecules across the BBB.

Methods: Bolaamphiphile GLH-20 vesicles encapsulating AlexaFluor 546 were produced by ultrasonication in solution and purified by Sepharose CL-4B gel filtration. Vesicle size and stability were determined by dynamic light scattering (DLS) and assessment of zeta-potential. Vesicle internalisation and lysis was assessed *in vitro* using several cell lines (SH-SY5Y neuroblastoma, BV2 microglia, hCMEC/D3 endothelia and HEK293T kidney epithelia) and confocal microscopy. Vesicle toxicity was assessed using the annexin A5-propidium iodide assay and flow cytometry. Entry of vesicles into the CNS was assessed *in vivo* by i.v. injection of C57BL/6 mice with AF546-containing vesicles (30 min circulation, 125 µl, N=4), followed by epifluorescent microscopic analysis.

Approach for statistical analysis: NIH ImageJ 1.49 was used to qualitatively assess vesicle uptake *in vitro* and *in vivo*. Tissue fluorescence was assessed quantitatively following homogenisation using a ClarioStar fluorescence plate reader. Data are presented as mean ± standard deviation.

Results and conclusions: Bolaamphiphile GLH-20 vesicles were synthesised and characterised. They were non-toxic *in vitro*. Vesicles were taken up by all cell types analysed, but were not opened in those cells known to lack acetylcholinesterase expression. GLH-20 vesicles penetrate the mouse brain parenchyma *in vivo*, within 30 minutes of administration. GLH-20 vesicles thus represent a novel, viable approach to deliver drugs to the CNS. We are currently determining the mechanism by which these vesicles cross the BBB, and their ability to deliver therapeutic agents to the brain.

Poster number: PS145 (SP)**Theme:** Novel treatments & translational neuroscience**Differential effects of NMDA antagonists on rat functional connectivity – a marker of psychotomimetic potential?****Authors:** Dr Jennifer Li¹, Mr Michael Conway¹, Dr Hugh Marston¹, Dr Gary Gilmour¹¹Eli Lilly & Co, Windlesham, United Kingdom

Introduction: Imaging studies show that regions of the brain engage in organized patterns of correlated activity to form resting state networks. Of these networks, the default mode network (DMN) has received attention for the role its disruption may play in neuropsychiatric disease. Using *in vivo* oxygen amperometry, task-induced decreases in

functional connectivity can be measured between DMN node pairs in freely moving rats. This study assessed how administration of NMDAR antagonists with proposed differing psychotomimetic potentials modulated DMN connectivity in comparison to a control network.

Methods: Rats were implanted with carbon paste electrodes in two DMN nodes: prelimbic and retrosplenial cortex; and two lateral cortical network nodes: anterior secondary motor and primary somatosensory cortex, jaw region. Rats were trained in a block design of four 15 minute alternating periods of instrumental responding (VI30 schedule) and unscheduled spontaneous behaviour. Animals were dosed s.c. with vehicle, 10 mg/kg S(+)-ketamine, 0.1 mg/kg MK-801 or 10mg/kg lanicemine in a within-subjects, cross-over design and signals recorded for the 1h session. **Approach for statistical analysis:** Linear correlations of slow fluctuations (0.01-0.1Hz) in the oxygen signal were calculated for 'rest' and 'task' blocks for each node pair under the different treatment conditions. Broadband correlation values were analysed by a Repeated Measures ANOVA with node pair, treatment and block type as within-subjects factors, followed by specific planned comparisons.

Results and conclusions: As previously shown, vehicle animals displayed significantly higher within- than between-network connectivity, and selective sensitivity of the DMN pair to reductions in connectivity during task compared to rest blocks. Task-induced modulation of DMN connectivity was abolished by ketamine and MK-801, but was unaffected by lanicemine. Ketamine also significantly increased between-network functional connectivity, whereas MK-801 reduced within-network connectivity. The psychotomimetic agents ketamine and MK-801 induced a pattern of effects suggestive of an overall disruption of intrinsic network integrity, while the non-psychotomimetic antagonist lanicemine had no effect on functional connectivity.

These results suggest that analysis of resting state network integrity in rodents may inform about the psychotomimetic potential of a test compound in humans. Pharmacological modulation of intrinsic network responses may offer a novel translational endpoint that may inform and predict human functional imaging and symptomatic outcomes

Poster number: PS146 (SP)

Theme: Novel treatments & translational neuroscience

Genomic and non-genomic pathways are both crucial for peak induction of neurite outgrowth by retinoic acid

Authors: Dr Thabat Khatib¹, Dr Pietro Marini¹, Dr David Chisholm², Professor Andrew Whiting², Professor Peter McCaffery¹

¹*Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom,* ²*Department of Chemistry, Durham University, Durham DH1 3LE, United Kingdom*

Introduction: Retinoic acid (RA), the active metabolite of vitamin A, is essential for many physiological processes; from its action to inhibit proliferation and induce differentiation. RA regulates genomic transcriptional activity via retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Much less studied though are a range of non-genomic actions, including RA regulation of ERK1/2 kinase phosphorylation. In this study we compare the ability of several synthetic RAR ligands to induce both genomic and non-genomic effects, and correlate this with their biological activity to induce neurite outgrowth.

Methods: The X-Gal based RA reporter and AlphaLISA[®] SureFire[®] Ultra assays were used to test the ability of RAR ligands to induce transcription (genomic) as well as ERK1/2 phosphorylation (non-genomic) activity, respectively in the neuronal SH-SY5Y cell line. Afterwards, the ability of ligands to induce neurite outgrowth was investigated by immunofluorescence analysis using the β III-tubulin antibody.

Approach for statistical analysis: All data are presented as mean \pm SEM of three independent experiments in triplicates. Data for the X-Gal and ERK1/2 phosphorylation were analysed using sigmoidal dose-response analysis of log (agonist) versus response curve (stimulation); non-overlapped 95% confidence interval limits (95% CI) was

considered statistically significant. Data for neurite outgrowth was analysed using one-way ANOVA with Newman-Keuls multiple comparison test; P value < 0.05 was considered statistically significant.

Results and conclusions: Synthetic RAR agonists have not previously been compared for genomic versus non-genomic activity and the capacity of an RAR ligand to activate gene transcription did not necessarily correlate with its ability to regulate ERK1/2 phosphorylation. Many of the RAR ligands that significantly ($P < 0.05$) induced both genomic and non-genomic activities could activate neurite outgrowth in SH-SY5Y cells at very low concentrations (10 nM) compared to RA that can do that at 10 μ M concentration. These results suggest that, to identify RAR ligand-based drugs of peak effectiveness, it is essential to screen for more than simply the capacity of the ligand to act on the genome to regulate gene expression, and the full potential of these drugs will not be realised until both genomic and non-genomic assays are applied.

Poster number: PS147 (SP)

Theme: Novel treatments & translational neuroscience

Cell energy status and cognition: physiological and behavioural effects of creatine supplementation

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¹*School of Psychology, University of Surrey, Guildford, United Kingdom*

Introduction: Altered or dysfunctional cell energy status is implicated in declining cognition in ageing as well as neurodevelopmental, neurodegenerative, psychiatric and acquired brain injury disorders. Creatine is involved in energy homeostasis, acting as an energy buffer in cells with high and fluctuating demands such as those in the brain. As such, creatine supplementation may play a role in neuroprotection or symptom alleviation in these conditions. Indeed, there is some evidence for this both prior to and after head injury, and evidence for creatine reductions after head injury, associated with worse cognition and reduced prefrontal BOLD tasks (Dean et al., 2015). This study aimed to test the mechanisms by which oral supplementation may effect cognition in a healthy population.

Methods: Neuroimaging data was acquired from ten vegetarian participants at three time points (baseline, placebo, creatine), one week apart. MRS was acquired for creatine concentration, and fMRI and EEG data was acquired during an n-back (0-, 2-, 4-back) task. Both placebo (maltodextrin) and intervention (creatine monohydrate) were taken as 5g of powder dissolved in 250ml of water/milk, two times a day (morning/evening).

Approach for statistical analysis: Repeated-measures ANOVA were carried out for each modality with factors "session" (Baseline, Placebo, Creatine) and "difficulty level" (0-, 2-, 4-Back). fMRI analyses were FWE corrected at $p < 0.05$.

Results and conclusions: Participants were faster ($F(4,36)=4$, $p=0.033$) and more accurate ($F(4,36)=4$, $p=0.006$) after creatine compared to baseline. Reduced BOLD response was seen after creatine in right prefrontal areas (BA8/9/46, DLPFC) compared to placebo and baseline. Increased P300 was observed after creatine compared to placebo ($p=0.01$), but not baseline ($p=0.055$). However, there was no significant change in creatine across sessions, and no correlation between creatine and behavioural performance, BOLD response or P300.

Creatine supplementation is associated with relatively subtle cognitive enhancement and altered neural functioning (reduced BOLD, increased P300), but no significant increase in neural creatine. This mixed picture suggest that either creatine increases are small, inconsistent or in other neural areas (e.g. white matter), or its effect may be mediated by another mechanism such as visceral creatine. Further research would be needed to untangle these factors.

Poster number: PS148 (SP)**Theme:** Novel treatments & translational neuroscience**Effect of Cannabidiol in two models of acute seizure****Authors:** Ms Mona Heiland¹, Dr Thomas Hill¹, Prof David Henshall¹¹*Royal College of Surgeons in Ireland Dublin, Dublin, Ireland*

Introduction: The phytocannabinoid cannabidiol (CBD) was recently approved as a new treatment for drug-resistant paediatric epilepsies, including Dravet syndrome. The efficacy of CBD for the treatment of other seizure-related disorders is uncertain. While studies have demonstrated the anticonvulsant effects of CBD in generalised seizure models (e.g. PTZ model) in rats, little is known about the effect of CBD in models of prolonged or focal-onset seizures. Here we investigated the effect of CBD in a mouse model of focal-onset status epilepticus (SE) (intra-amygdala (i.a.) kainic acid (KA) model). We also validated the seizure-suppressive effects of CBD reported in rats in the PTZ model using mice as a positive control.

Methods: Male C57/Bl6 mice were treated for five days twice daily with CBD (100, 200mg/kg) or vehicle control (n=10 per group). Mice were then assigned to one of two different seizure models (i.a. KA and PTZ model). In the i.a. KA model, SE was induced on the fifth day by an injection of KA into the ipsilateral amygdala. EEG was recorded to analyse seizure severity. Fluoro-Jade B staining was used to visualise neuronal damage 24 hours post-SE. In the PTZ model, seizures were induced on the fifth day by an i.p. injection of PTZ and seizures scored by a modified Racine's scale.

Approach for statistical analysis: Data were analysed for normal distribution using D'Agostino and Pearson omnibus normality test and presented as median and interquartile range. For the statistical analysis, a Kruskal-Wallis with a post hoc Dunn's multiple comparison test was performed and data was considered significant at $p \leq 0.05$.

Results and conclusions: CBD pretreatment had no effect on the severity of SE in the i.a. KA model in mice and histological damage in the hippocampal formation was similar between CBD-treated and vehicle animals. In contrast, CBD (200 mg/kg) significantly reduced seizure severity in the PTZ model. The findings confirm that CBD has anticonvulsant effects in mice but is not effective at SE. Since SE leads to chronic spontaneous recurrent seizures in this model, future studies could investigate if post-treatment with CBD is disease modifying (anti-epileptogenic).

Poster number: PS149 (SP)**Theme:** Novel treatments & translational neuroscience**Behavioural laterality predicts increased avoidance in a conditioned fear test in zebrafish****Authors:** Mrs Barbara Fontana¹, Mrs Madeleine Cleal¹, Dr. Matthew Parker¹¹*University of Portsmouth, Portsmouth, United Kingdom*

Introduction: Behavioural lateralization, the preferential use of one side of the body, is common in vertebrates, including humans, and is thought to be related to stress reactivity. For this reason, high levels of laterality bias has been linked to psychiatric disorders such as depression, schizophrenia and anxiety. Zebrafish (*Danio rerio*) is an increasingly popular animal model in neuroscience and biological psychiatry due its physiological homology, small size, easy maintenance and reproduction. Although zebrafish presents a robust behavioral repertoire, zebrafish behavioral lateralization has not yet been characterized in relation to stress reactivity. The objective of this study was to identify zebrafish with strong behavioral lateralization using an unconditioned y-maze search protocol, and evaluate if laterality bias played a role in a conditioned fear response.

Methods: 55 adult zebrafish were assessed in the y-maze for 1 hour. The mean and coefficient of variation for right and left bias was calculated for each animal and behavioral lateralization was considered when an animal presented >60% of preference for one arm. As well as general activity, various behavioral endpoints in the maze were evaluated including relative repetitions (rrrr + llll) and alternations (rlrl + lrlr). Following y-maze characterization, animals were pair housed for 24h and further tested on the shock avoidance test based on previously studies.

Approach for statistical analysis: Two-way ANOVA (shock avoidance task) and mixed two-way ANOVA (y-maze test) followed by the Newman-Keuls test were used to investigate bias effects. The results were considered significant when $p \leq 0.05$.

Results and conclusions: We showed, for the first time, that zebrafish present behavioral lateralization in the y-maze (right-biased 30.9 %, left-biased 23.7% and non-biased 45.7%). Left-bias fish showed significantly more repetitions ($p < 0.005$) when compared to non-biased animals. Also, both right- ($p < 0.05$) and left-biased ($p < 0.001$) animals had a significantly lower number of alternations. In the conditioned fear test, fish that showed clear behavioural lateralization showed a significantly stronger avoidance response to a shock stimulus than non-biased animals ($p < 0.05$). Our data suggest that, in zebrafish, behavioural lateralization is related to different behavioral phenotypes in the y-maze and predictive of performance on a conditioned fear test. Overall, our novel findings suggest that; 1) the y-maze test is a good protocol to measure behavioral lateralization in zebrafish and 2) that strongly lateralized zebrafish are a simple model for studying human psychiatric disorders related to stress reactivity.

Poster number: PS150 (SP)

Theme: Novel treatments & translational neuroscience

The noble gas xenon reduces secondary contusion volume, and prevents neuronal loss and microglial proliferation in a rat model of traumatic brain injury

Authors: Dr Rita Campos-Pires^{1,2,3}, Ms Nada Mohamed-Ali¹, Ms Maria Balaet¹, Dr Jitka Aldhoun¹, Ms Laura Abelleira-Hervas¹, Dr Phillip Aitken¹, Dr Christopher Edge^{4,5}, Professor Nicholas Franks⁴, Dr Robert Dickinson^{1,2}

¹Department of Surgery & Cancer, Imperial College London, London, United Kingdom, ²Royal British Legion Centre for Blast Injury Studies, Department of Bioengineering, London, United Kingdom, ³Charing Cross Hospital, London, United Kingdom, ⁴Department of Life Sciences, Imperial College London, London, United Kingdom, ⁵Royal Berkshire Hospital, Reading, United Kingdom

Introduction: Traumatic brain injury (TBI) is a complex and heterogeneous disorder. The 'primary injury' resulting from external forces is irreversible. Potentially preventable 'secondary injury' develops in the minutes, hours, days and weeks following trauma and is believed to underlie the functional impairments seen in TBI patients. Current TBI treatment is mainly supportive and no specific neuroprotective drugs are available. Xenon is neuroprotective in models of brain ischemia. We recently showed xenon was neuroprotective after TBI in mice¹. Here we evaluate xenon's neuroprotective efficacy on short-term histological outcomes in rats using the controlled cortical impact (CCI) TBI model.

Methods and Analysis: Young adult Sprague-Dawley male rats (n=22) were fixed in a stereotactic frame under anesthesia and underwent a cortical impact in the right parietal area. Sham animals underwent an identical procedure, but no craniotomy or impact were done. Core body temperature was maintained at 37°C throughout using a feedback-controlled heating pad. Animals were randomly assigned to control (75% nitrogen:25% oxygen) or xenon-treatment (50% xenon:25% oxygen, balanced with nitrogen) groups. Treatment was given for 3 hours, starting 30 minutes after TBI. Histological outcomes were measured at 30 minutes (contusion volume), and 24 hours (contusion volume, neuronal and microglial cell count) by researchers blinded to treatment. Statistical significance was assessed using Student's t-test, one-way and two-way ANOVA with Bonferroni's *post hoc* test.

Results and Conclusions: Xenon reduced secondary injury development by 34% at 24 hours after injury. In control TBI animals, neuronal cell number was significantly decreased in the ipsilateral retrosplenial cortex and contralateral motor cortex ($p < 0.05$) and microglial cells were significantly increased in the ipsilateral somatosensory cortex ($p < 0.01$) at 24 hours. Interestingly, neuronal and microglial cell counts in xenon treated animals were no different to uninjured shams.

Our results show for the first time that xenon is neuroprotective after TBI in rats. We demonstrate that xenon treatment after TBI reduces the development of secondary injury, and prevents neuronal cell loss and microglial proliferation in functionally relevant brain regions. These findings support the idea that xenon is neuroprotective and reduces inflammation after TBI.

¹Campos-Pires *et al*, 2015, Critical Care Medicine v43, p143

Poster number: PS151 (PP)

Theme: Novel treatments & translational neuroscience

Oral succinate pharmacokinetic study in healthy volunteers

Authors: Dr Mohammed Aftab Alam¹, Dr Adel Helmy¹

¹*Division of Neurosurgery, Department of Clinical Neurosciences, University Of Cambridge, Cambridge, United Kingdom*

Succinate plays a pivotal role in oxidative metabolism. Succinate is a tricarboxylic acid (TCA) cycle intermediate that interacts directly with the mitochondrial electron transport chain (ETC), enabling a route to ATP production via oxidative metabolism that bypasses complex 1. This has been suggested by Jalloh *et al.* (2017) as a potential therapeutic strategy for TBI. There is no available information on toxicokinetics and metabolism. An oral acute toxicity study of disodium succinate hexahydrate showed that this chemical did not cause any changes even at 2,000 mg/kg. The oral LD₅₀ value was considered to be greater than 2000 mg/kg bw in rats (MHLW, Japan: 2002).

The present study will establish the pharmacokinetics of succinate in blood and evaluate whether oral succinate intake influence the blood glucose levels. Subjects must be healthy consenting adult volunteers. Complying subjects will be fasting (permitted water only) for 8 hours before taking the succinate orally. 3 ml of blood will be drawn from an indwelling peripheral venous catheter before succinate intake (orally) and at 5, 15, 30 and 60, 90, 120 minutes following intake. The blood will be separated and the supernatant aliquoted, and subsequently stored in standard Eppendorf tubes at -80°C for subsequent analysis.

We will model the succinate concentration using a standard one compartment model in the first instance to allow derivation of Concentration(max), Volume of Distribution and half-life. We will also estimate oral bioavailability. The primary outcome would be (i) to model how succinate changes in blood following escalating concentrations of oral intake of succinate and (ii) to see if there is any statistical difference in serum concentrations of succinate between escalating concentrations of oral intake of succinate.

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Poster number: PS152 (SP)**Theme:** Psychiatry and mental health**Acamprosate effect on glutamatergic receptor subunit composition in dentate gyrus after long term self administration of ethanol****Authors:** Mrs Maria Nalberczak-Skóra¹, Kasia Radwańska¹¹*Nencki Institute of Experimental Biology, Warsaw, Poland*

Introduction: Alcohol addiction is a complex but common disease however it's biological processes are still not fully understood. The key factors of the disease are sustained drinking, withdrawal syndrome and reactivity to cues leading to relapse. Therefore, it is vital to understand how each of them affect the brain.

The glutamatergic receptor equilibrium on the membrane and subunit composition are known to play an important role in development of cocaine addiction. Identifying those changes in addiction of different types of drugs might lead to finding a common denominator and better comprehension of the disease.

Acamprosate is a drug which limits relapsing events in human alcoholics. It is identified to affect NMDA and GABA receptors, however it's direct biochemical process is still discussed. In order to recognise the neuronal pathway underlying relapsing behaviour it is valuable to understand the way of action of a drug which prevents it.

Methods and Analysis approach: IntelliCages are cages in which animals leave in groups and can be tested without human intrusion thanks to operant chambers placed in the corners. Mice were trained in IntelliCages for long-term self-administration of alcohol. Then, some of them were treated with acamprosate for 10 days. Subsequently, they were sacrificed during free alcohol access, after 6d withdrawal and 90 min of exposure to cue light associated with alcohol presence. To verify whether acamprosate plays a role in AMPA and NMDA subunit composition on DG membranes the tissue was cross-linked (BS3) and analysed with use of Western blot technique.

Results and Conclusions: Acamprosate prevents alcohol seeking and drinking behaviour after long term self-administration of alcohol in IntelliCages. The preliminary results from the analysis indicate that both AMPA and NMDA subunit composition changes after alcohol exposure and that those changes are regulated by acamprosate treatment.

Poster number: PS153 (SP)**Theme:** Psychiatry and mental health**Deficits of hippocampal-dependent learning and synaptic plasticity in a hemizygous cacna1c animal model of major psychoses****Authors:** Dr Cezar, M. Tigaret¹, Dr. Tzu-Chin, E. Lin¹, Dr. Lucy Sykes¹, Prof. Lawrence Wilkinson², Dr. Kerrie Thomas³, Prof. Jeremy Hall⁴¹*NMHRI, School of Medicine, Cardiff University, Cardiff, United Kingdom*, ²*School of Psychology, Cardiff University, Cardiff, United Kingdom*, ³*School of Biosciences, Cardiff University, Cardiff*, ⁴*School of Medicine, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom*

Introduction: Variants of the *CACNA1C* gene encoding the Ca_v1.2 subunit of L-type voltage-gated calcium channels are strongly linked with genetic risk across major psychiatric disorders^{1,2}. Common *CACNA1C* risk variants are thought to associate reduced expression of Ca_v1.2^{1,3}. We used a hemizygous *CACNA1C* rat model to study the mechanism of *CACNA1C* genetic risk. *Cacna1c*^{+/-} rats express ~ 50% of the Ca_v1.2 in the brain and exhibit impaired reversal learning⁴.

Methods: Synaptic plasticity experiments and two-photon Ca²⁺ imaging were performed in *ex vivo* hippocampal slices from 3-6 months old *Cacna1c*^{+/-} rats and wild-type littermates as described⁵. An independent cohort was tested for latent inhibition of Pavlovian contextual fear conditioning (LI). Phosphorylated ERK activation in dorsal hippocampus was assessed using immunohistochemistry.

Approach for statistical analysis: Ca²⁺ imaging data and phosphorylated ERK activation were compared across genotypes using independent sample t-test. LI was compared using between-subject design of variance analysis. Electrophysiology data were compared using paired t-test for samples with unequal variance.

Results and conclusions: *Cacna1c*^{+/-} rats showed an LTCC-sensitive impairment of LI and long-term potentiation (LTP) at glutamatergic Schaffer collateral (S/C) – CA1 synapses in the dorsal hippocampus.

Compared to wild-type littermates, action potential-evoked Ca²⁺ transients summated sub-linearly in dendritic spines in *stratum radiatum* from *Cacna1c*^{+/-} CA1 pyramidal neurons.

We found a deficit of MAPK/ERK cascade signalling in the *Cacna1c*^{+/-} hippocampus. Furthermore, activation of the ERK pathway using a TrkB/C selective agonist in *Cacna1c*^{+/-} rats rescued LTP at S/C – CA1 synapses.

Our data indicate that inadequate Ca²⁺-dependent MAPK/ERK signalling for induction of Hebbian plasticity at selected synapses underpins cognitive deficits associated with reduced *CACNA1C* gene dosage in *Cacna1c*^{+/-} rats.

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Poster number: PS154 (SP)

Theme: Attention, motivation, behaviour

Aberrant processing of context-specific information in Hemizygous CACNA1C rat model

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Introduction: Recent Genome-Wide Association Studies revealed *CACNA1C* gene, encoding subunit of Cav1.2 L-type voltage gated calcium channel (Ca_v1.2 LVGCC), is one of genetic risk factors highly associated with neuropsychiatric disorders such as bipolar disorder, schizophrenia and mood disorder. Dolmetsch *et al.* (2001) reported calcium influx via Ca_v1.2 LVGCC activates the MAPK/ERK signalling pathway and its downstream targets such as CREB and BDNF expression that are known to play critical roles in synaptic plasticity and Learning and memory. Present study used a novel *Cacna1c* heterozygosity rat model to examine the impact of *Cacna1c* haploinefficiency on latent inhibition of contextual learning, context preexposure facilitation effect and contextual discrimination in fear learning paradigms.

Methods:

- 2) Western blots and immunohistochemistry were used to investigate changes in basal activities of MAPK/ERK signalling pathway in our *Cacna1c* heterozygous rat model.
- 3) investigate the impact of *Cacna1c* haploinefficiency on context specific Learning and memory.

Approach for statistical analysis: Independent sample t-tests were after Western blot and immunohistochemistry to compare Ca_v1.2 protein levels and phosphorylated ERK activation in the subregions of dorsal hippocampus between WT and heterozygous rats. Between-subject design of variances analyses were used in analysing behavioural assays.

Results and conclusions: The results showed decreased Ca_v1.2 protein levels in the whole hippocampus and a reduction of phosphorylated ERK activities in DG, CA3 and CA1 of the dorsal hippocampus. We also observed behavioural deficits on contextual fear latent inhibition, context preexposure facilitation effect and context discrimination in the *Cacna1c* heterozygous rat model. Together these results show that *Cacna1c* haploinefficiency has profound effects on hippocampal and context-dependent forms of aversive associative learning.

Poster number: PS155 (SP)

Theme: Psychiatry and mental health

Learning and decision-making in adolescents with obsessive-compulsive traits

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Background: Past research has found that adolescents with OCD portray distinct cognitive profiles compared to adults with OCD. OCD in adolescents is associated with impaired learning and decision-making (Gottwald et al., 2018), which has profound implications for school performance and career attainment. Moreover, while cognitive inflexibility is regarded as an endophenotype of adult OCD, research on adolescents has shown mixed findings for this. This study aimed to investigate whether adolescents with obsessive-compulsive traits reveal impaired learning and cognitive inflexibility

Methods: Fifteen adolescents (aged 12-19 years) with high OC traits and 26 matched controls with low OC traits completed 4 cognitive tasks: 1) The Wisconsin Card Sorting task (WCST) to assess set-shifting, 2) a probabilistic reversal learning task to test cognitive flexibility and learning, 3) a Predictive-Inference task to assess whether learnt information guides decision-making (see Vaghi et al., 2017), and 4) a 4-Arm Bandit task to investigate explorative vs. exploitative decision-making

Results: There was no set-shifting deficit found in the adolescents with high OC traits as measured using the WCST. The High OC group revealed poor learning performance on the probabilistic reversal learning task, and a slight tendency to switch decisions following negative feedback suggesting that they may display overactive performance monitoring. Both High and Low OC adolescents showed a bias for model-free learning on the Predictive-Inference Task and rigid exploitative decision-making on the 4-Arm Bandit Task, which are results not typically found in adult studies.

Conclusions: This study provides very early indication of a learning impairment being present in adolescents with high OC traits. Furthermore, we have unexpectedly provided evidence for adolescents having different learning and decision-making styles from adults. These results warrant further investigation involving larger samples and other validated tasks of learning.

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Poster number: PS156 (SP)

Theme: Psychiatry and mental health

Computational psychiatry of reinforcement learning: relation to psychotic illness, clinical risk of psychosis and polygenic risk for schizophrenia

Authors: Ms Marcella Montagnese¹, Franziska Knolle, Joost Haarsma, Juliet Griffin, Alex Richards, Petra Vertes, Bea Kiddle, Michael Owen, Peter Jones, Michael Moutoussis, Peter Fonagy, Ed Bullmore, Ray Dolan, Ian Goodyer, Paul Fletcher, Graham K Murray

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Introduction: Schizophrenia is a highly complex disorder in which patients exhibit a heterogeneity of symptoms, including hallucinations, anhedonia and cognitive deficits in domains such as reinforcement learning (Albrecht et al., 2016). Given this complexity, the causal relations between genes and observed clinical symptoms are not well understood. Further, the explanatory gap between the two is too wide to be explained without considering an intermediary level. Thus, the aim of this project was to test the hypothesis that deficits in reinforcement learning (RL) represent an intermediate level in the pathway from polygenic influence to clinical symptoms.

Methods: The RL task administered was a version of the Go/NoGo task (GNG) by Guitart-Masip et al., (2012) and the behavioural data was modelled with a hierarchical Bayesian approach. Individuals who met the requirements for clinical or molecular genetic risk for schizophrenia were recruited. In study 1, we investigated whether genetic risk for schizophrenia in healthy individuals (n= 490), as measured by schizophrenia polygenic risk score (PRS), predicted performance on the modelled parameters from the GNG task. In study 2, we looked at group differences in task performance between controls (n= 29), people At Risk Mental State for psychosis (ARMS, n= 23) and FEP (First-episode psychosis, n= 26).

Approach for statistical analysis: Statistical techniques included standard multiple regressions with Benjamini-Hochberg correction between PRS (at p= 0.05) and the modelled GNG parameters (with first 5 PCA components, age and sex as covariates); ANOVAs for group differences in those at clinical risk for psychosis; and correlational analyses in both cohorts to establish if task performance correlated with clinical measures of psychopathology.

Results and conclusions: Results showed that PRS did not significantly predict performance on the GNG task in the general population and did not correlate with measures of psychopathology. Further, there were differences in the modelled parameters between controls and FEP, with the latter having impairments in overriding Pavlovian conflict, possibly due to higher cognitive deficits. We concluded that the RL deficits observed in patients were sensitive to illness stage, but similar RL impairments were not predicted by molecular genetic risk for the disorder in healthy individuals.

Poster number: PS157 (SP)

Theme: Psychiatry and mental health

A novel method for modifying frontoparietal network plasticity and its effects on decision-making

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Introduction: Across many neuropsychiatric conditions, decision-making is shifted away from goal-directed control, a flexible, computationally expensive strategy, towards habitual control, a fast, inflexible strategy. Previous single-site neurostimulation experiments have unsuccessfully attempted to shift decision-making towards goal-directed control.

Methods: We employed a dual-target neurostimulation approach in 30 healthy participants, using cortico-cortical paired associative stimulation (ccPAS) to target two key nodes: lateral prefrontal cortex (LPFC) and intraparietal sulcus (IPS), to test whether decision-making can be artificially shifted from habitual toward goal-directed control. Participants received three active stimulations, delivered at least six days apart (each involving 100 paired pulses over the IPS and LPFC, varying the interstimulus interval): two interventional, time-relevant ccPAS and one control, non-time-relevant ccPAS. Following stimulation, participants completed a two-step task, measuring goal-directed/habitual control, and a working memory task.

Analysis approach: We fit behavioural data from the 2-step task to a hybrid learning algorithm designed for this task (Daw *et al*, 2011). We analysed the effects of ccPAS condition on the weighting parameter w , the relative influence of model-free and model-based systems (within-subject design with three repeated measures; non-parametric analysis). We also analysed whether any changes in w were associated with changes in working memory under ccPAS (assessed using a visuospatial working memory task (Bays *et al*, 2009).

Results and conclusions: IPS→LPFC ccPAS (stimulating IPS, then LPFC with a 10ms interval) increased goal-directed and decreased habitual control compared to control ccPAS. This was independent of effects on working memory. LPFC→IPS ccPAS did not produce any effect. We report the first instance of neurostimulation successfully shifting decision-making from habitual to goal-directed control, putatively via inducing long-term potentiation between the IPS and LPFC. This could represent a novel intervention for disorders marked by increased habitual decision-making.

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Poster number: PS158 (PP)

Theme: Psychiatry and mental health

The effects of antipsychotics on human glial cells, inflammation and myelination

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Introduction: Schizophrenia (SCZ) is ranked among the top 25 leading causes of disability worldwide(1). There is increasing knowledge of the impact of glia on the neuropathophysiology of SCZ, with all three glial cell types showing structural and functional abnormalities(2). An active area of research examines the effects of typical and atypical antipsychotics on these neuropathophysiological mechanisms. The purpose of this work is to further understand the direct effects of typical and atypical antipsychotics on glial cell biology, neuro-inflammation and myelination.

Methods: Given the evidence for glial cell abnormalities, neuroinflammation and demyelination being associated with SCZ, these conditions can, in part, be simulated for experimental purposes in a laboratory. AIM 1 examines the effects of antipsychotics on human astrocyte biology, *in-vitro*, this will guide AIM 2 which examines the effects of antipsychotics on neuro-inflammation and myelin state in mouse organotypic brain slice cultures, *ex-vivo*. Findings

from aims 1 and 2 will influence an eventual AIM 3 examining the effects of antipsychotics in an animal model of inflammation/demyelination, *in-vivo*.

Analysis: Assays will examine astrocyte reactivity (immunocytochemistry), cell death/survival (MTT assay), cell migration, cell signalling (western blot and confocal) as well as cytokine levels and release (RT-qPCR and ELISA). Immunohistochemical assays will examine neuronal toxicity, markers of myelin and neuroinflammation. Sample size calculations assume Alpha of 0.05 and Power of 0.80, estimates of mean change and standard deviation will be based upon preliminary experiments and results from similar studies on literature review. One-way analysis of variance will be used to compare means from 2 or more groups. When two treatment groups with equal sample sizes are compared, a paired t-test will be used.

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Poster number: PS159 (PP)

Theme: Psychiatry and mental health

Inflammatory markers of antipsychotic weight gain and cardiometabolic dysfunction in youth mental health disorders

Authors: Dr Karen Conlan^{1,2}, Prof Louise Gallagher^{1,3}, Prof Jane McGrath^{1,4}, Dr Andrew Hogan^{2,5}, Prof Donal O'Shea^{2,6,7}
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Introduction: Second generation antipsychotics (SGAs) are prescribed to treat mental health disorders in children. There are concerns due to cardiometabolic side effects including weight gain with a risk of Type 2 Diabetes Mellitus. There is limited understanding of the factors increasing susceptibility to these side effects. It is established that increased adiposity associated with weight gain is mediated by the emergence of a persistent low-grade inflammatory state. However, there has been no research investigating the relationships between pro-inflammatory states in children and the cardiometabolic side-effects of SGAs and there are no clinical indicators of those at risk. We hypothesise that there is a subgroup of children who have pro-inflammatory immune profiles prior to starting SGA medication and that this subgroup are at increased risk of developing the cardiometabolic side effects of SGAs.

Methods: Children and adolescents (5-18 years) commencing SGA medication are recruited from CAMHS clinics. The cardiometabolic profile is assessed clinically and biochemically and serum and peripheral blood mononuclear cells (PBMCs) are obtained in order to measure levels of inflammatory markers. Through comparison with biobanked healthy control samples, we will determine if there is a subgroup at baseline with a pro-inflammatory profile. The patient groups will be assessed longitudinally at 3, 6 and 12 months to measure BMI percentile, blood pressure, heart rate, fasting lipids and glucose, prolactin, total insulin and C-peptide. Changes in immune cells and inflammatory markers will also be measured including IL-1, IL-10, IL-17, TNF- α and IFN- γ as well as Leptin, Ghrelin and Adiponectin in response to treatment with SGA medication. Enumeration and functional characterization of immune cells will be performed by flow cytometry.

Approach for statistical analysis: Statistical analysis will be completed in R 3.1.1 and GraphPad Prism 6. Group means and standard deviations will be calculated and compared with Students t-test or Mann-Whitney U as appropriate. Spearman and Pearson correlations will investigate possible relationships between explanatory and dependent variables. Linear regression models will be used to test the strength of the association. Input variables will include measures of inflammation and miRNAs. Dependent variables will include total BMI Z-score, metabolic syndrome score, triglycerides and cholesterol.

Poster number: PS160 (SP)

Theme: Psychiatry and mental health

Negative memory bias as a transdiagnostic cognitive marker for psychopathology

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Background: Depressed individuals have the tendency to remember information which valence matches their emotional state better. This is called a negative memory bias. Memory bias is believed to play an important role in the development and maintenance of depression. Although it is most frequently studied in depression, recent studies indicate that memory bias may be present in other psychiatric disorders as well.¹ Hence, memory bias may be a transdiagnostic marker for psychopathology in general. In this study, we critically investigate the presence of memory bias in a broad range of psychiatric disorders and examine the specificity of the underlying depressotypic processing style.

Methods: In this study, memory bias was tested using the Self-Referencing Encoding Task in 302 diagnosed psychiatric patients and 66 healthy controls. The psychiatric sample consisted of three subgroups: a group with stress-related psychiatric disorders (depression, anxiety and/or addiction), a group with neurodevelopmental psychiatric disorders (autism and/or ADHD) and a comorbid group with both types of disorders. Symptoms of depression, autism, ADHD and anxiety sensitivity were assessed using validated clinical questionnaires.

Results: Patients in the stress-related disorders group showed the highest mean negative memory bias score, while patients in the neurodevelopmental disorders group and the comorbid group also showed significantly higher negative memory bias scores compared to the control group. Further analyses showed that (comorbid) depressive symptoms may underlie the presence of negative memory bias in all individuals.

Conclusions: Memory bias was found in all three patient groups, which strengthens the hypothesis of memory bias as a transdiagnostic marker for psychopathology in general. We also found that, regardless of the type of psychiatric disorder, memory bias seems to be a depressotypic processing style. This may be driven by underlying negative cognitive schemas.²

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Poster number: PS161 (PP)

Theme: Psychiatry and mental health

Peripheral complement system proteins in schizophrenia: a systematic review and meta-analysis

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Introduction: The complement system is a specific component of the innate immune system which has been implicated in the pathogenesis of schizophrenia. For example, genetic susceptibility for schizophrenia is related in part to allelic variation of the complement component 4 gene¹. Peripheral complement proteins may represent potential as biomarkers of schizophrenia. Several studies have attempted to measure complement proteins in schizophrenia patients, although there is variation in the individual proteins tested, heterogeneous methods and small sample sizes. The primary objective of this review is to systematically evaluate the literature measuring complement factors in schizophrenia to answer the question: in adult patients with schizophrenia, are serum/plasma complement protein levels altered in comparison to controls? And if so, how?

Methods: We will search MEDLINE, Embase and PsycINFO from inception to current date using the following basic search strategy: schizophrenia OR psychosis AND complement. Inclusion criteria will include: case-control or cohort studies; comparing serum or plasma complement protein levels in cases (people with schizophrenia, however defined) to controls (people without schizophrenia). Exclusion criteria will include: genetic or RNA expression studies; animal studies; no control comparison group; studies focusing on psychiatric disorders other than schizophrenia/related psychoses. The primary measure for each study will be mean complement factor levels in schizophrenia patients vs. controls. A variety of other data will be extracted from each included study (for example, case and control definition, matching criteria, laboratory methods and other information to assess risk of bias).

Approach for statistical analysis: We will assess heterogeneity using the I² statistic. If studies are not excessively heterogeneous (with particular respect to method of complement factor measurement and definition of cases or controls), and the number of included studies allows, then we will perform a meta-analysis. We will calculate effect size estimates (for example, by Hedges' *g*) for individual complement factors that are analysed in more than one study and present these summary data using forest plots. Assuming a fair degree of heterogeneity, we plan to use a random-effects model.

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Poster number: PS162 (SP)

Theme: Psychiatry and mental health

Machine Learning to Predict Outcomes and Functionality in Adolescents with Psychotic Experiences

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Introduction: It has been shown that children and adolescents who experience psychotic symptoms are at increased risk of psychosis later in life.¹ Establishing early predictors of later psychosis is therefore a highly desirable goal as it provides both potential clinical value and insight into the etiopathophysiology of psychosis.

Methods: A cohort of 212 children was interviewed as part of a longitudinal study to follow the outcomes of children with psychotic experiences (PE). This project used a subset of that data, examining the clinical and cognitive data of 165 participants collected at 11-12 years of age. The dataset was analysed via an elastic net-based machine-learning algorithm in order to better detect subtle relationships and to contribute to a larger machine-learning project that will encompass the entire dataset.

Approach for statistical analysis: The data was pre-processed via SPSS and Microsoft Excel. Variables were removed from analysis if greater than 10% of variable data was missing, otherwise the variable was imputed. Missing values from binary variables were imputed with standard outcomes. Missing values from continuous variables were imputed to the median value. Variables that were neither were re-coded as such. One participant was removed due to missing data. The machine-learning algorithm was an elastic net-based approach provided by Professor Whelan's lab. The algorithm was run in MATLAB 2018a for ten iterations per outcome. Model fit, beta values, surviving features at the 90th percentile, and logistic regression results were output.

Results and conclusions: It was found that clinical measures of psychosis are highly associated with PEs and cognitive tests were found to be associated with functionality, suggesting external validity. Logistic regression identified a number of variables correlated to PEs for further investigation in the integrated model. We found that machine-learning models can replicate known outcomes and identify further variables for investigation as predictors of psychosis later in life.

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Poster number: PS163 (SP)

Theme: Psychiatry and mental health

Electrical stimulation rescues midbrain dopaminergic neurodegeneration of vulnerable depressive-like rats

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Introduction: Although deep brain stimulation has been proposed as a potential therapy for patients with treatment-resistant depression, the neural mechanisms of resilience and vulnerability in depression still remain largely obscure. In this study, we investigated the effects of high-frequency stimulation (HFS) in different brain regions on various depressive-like behaviours using the stress resilience and vulnerable rat depression models.

Methods: Animals were exposed to chronic unpredictable stress procedures (CUS) for 3 weeks. Vulnerable and resilience animals were characterized based on their sucrose consumption levels during CUS procedures. CUS-treated rats received HFS in the lateral habenula (LHb), ventromedial prefrontal cortex (vmPFC), nucleus accumbens (NAc) and they were tested for depressive-like behavioural experiments. The morphological changes of dopaminergic neuron were determined by immunohistochemical staining methods and the level of stress hormone was measured using radioimmunoassay approach.

Analysis approach: The data normality distribution was examined using the Kolmogorov-Smirnov test. The results for behavioural and immunocytochemical studies were analyzed by specific Analysis of Variance (ANOVA, with repeated-measures) and Bonferroni post-hoc tests for multiple comparisons, as appropriate. Independent sample t-test was

used for data consisting of two groups. If data were not normally distributed, non-parametric Kruskal-Wallis or Mann-Whitney U test was used, as appropriate. All p -values < 0.05 was regarded as significant.

Results and Conclusion: CUS exposure for 3 weeks increased number of animals (51%) exhibiting reduced sucrose consumption, separating the resilience and vulnerable group of CUS-induced model. Interestingly, vmPFC HFS significantly reduced anxiety response, increased hedonia and motivation levels for food intake in the vulnerable group compared to the resilience group, while HFS in other brain regions did not show difference. HFS in vmPFC and LHb also showed reduced behavioural despair in both CUS vulnerable and resilience group. In histochemistry, our results demonstrate that vmPFC HFS rescued the stress-induced dopamine neuron degeneration in the dorsal raphe nucleus. These results suggest that vmPFC HFS effectively restores depressive-like behaviours by mechanisms of dorsal raphe dopaminergic neurons restoration in the vulnerable CUS-induced model. Future studies are needed to further elucidate the underlying mechanisms of HFS on the resilience and vulnerable group of CUS-induced depression models.

Poster number: PS164 (SP)

Theme: Sensory and motor systems

Virtual reality modulates vestibular evoked potentials

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Introduction: The popularity of Virtual Reality (VR) has increased rapidly in recent years. However, a troublesome problem is that up to 80% of users will experience unpleasant side-effects such as nausea, disorientation, blurred vision, and headaches – a malady known as *Cybersickness*.

Cybersickness may be caused by conflicting sensory inputs for self-motion: while vision signals that the user is moving in a certain direction with certain acceleration, the vestibular organs do not. To resolve this sensory conflict and enjoy the VR experience - the brain must adjust sensory information to rely on visual instead of vestibular self-motion signals. This may be supported by altered vestibular experiences occurring following VR exposure. Here we investigated the effects of VR on vestibular processing by measuring reflex responses to real vestibular stimuli (vestibular evoked myogenic potentials, VEMPs) during short duration immersion in a VR environment.

Methods: Cervical VEMPs were measured according to standard procedures. VEMPs were elicited via 100dB, 500Hz tone-burst stimuli into the ear, and muscular responses were measured on the sternocleidomastoid ipsilateral to the vestibular organ stimulated. VEMPs were recorded while participants were immersed in a simplified VR scenario displaying either a random or expanding field of dots, with the latter inducing a sensation of linear vection.

Approach for statistical analysis: VEMPs P1-N1 amplitudes were estimated for each participant in each experimental condition. A 2 (Side: left muscle vs right muscle) x 2 (Stimulus: vection vs random) repeated measures ANOVA was used to investigate changes in VEMPs amplitudes. A paired t -test was used to investigate changes in VEMPs asymmetry ratios.

Results and conclusions: No significant main effects of vection ($F(1, 23)=2.26$, $p=.15$, $\eta_p^2=0.089$) or side ($F(1, 23)=0.75$, $p=.40$, $\eta_p^2=0.03$) were found on VEMPs amplitudes. However, a significant interaction was found ($F(1, 23)=4.42$, $p=.047$, $\eta_p^2=0.16$). The VEMP amplitude was increased on the left muscle following exposure to vection compared to random visual stimuli ($t(23)=2.80$, $p<.01$, Cohen's $d=0.40$). Accordingly, asymmetry ratios were increased following exposure to vection ($t(23)=-2.14$, $p<.05$, Cohen's $d=0.42$). Our results suggest that exposure to VR modulates vestibular processing, which may explain common after-effects of VR.

Poster number: PS165 (SP)

Theme: Sensory and motor systems

Brain resting-state network analysis in a neuroinflammatory cause of chronic pain

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Introduction: It is well established that pain information arriving at the spinal cord dorsal horn is modulated by top-down brain efferents (Fields & Basbaum, 1978; Eippert, et al., 2009).

The periaqueductal grey (PAG) is an important component in this descending modulatory system and exerts inhibitory and facilitatory effects via the rostral ventromedial medulla (RVM), whilst the PAG is itself under the influence of many cortical areas (Bingel & Tracey, 2008).

Research in this area is predominated by animal studies and/or acute pain paradigms. Addressing this imbalance, here we present MRI resting state brain data from neuromyelitis optica (NMO) patients with chronic pain.

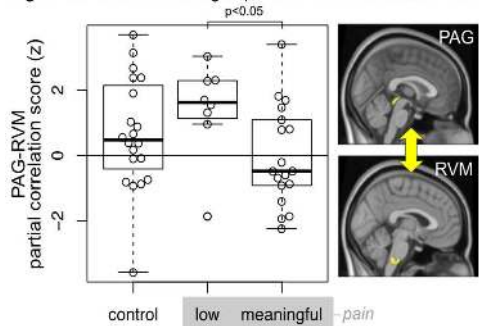
Methods: 27 NMO patients; 20 healthy controls. Isotropic MP-RAGE (TR:2.3s; TE:3.9ms) and EPI (128 measurements; TR:2.4s; TE:30ms); Siemens Verio 3T MRI (12-channel head coil; 4-channel neck coil; FMRI, Oxford). Pain measurement: Brief Pain Inventory Pain Severity Index (PSI) (Cleeland & Ryan, 1994).

Approach for statistical analysis: Images pre-processed and analysed using FSL (Jenkinson, et al., 2012). Subject-level data de-noised (MELODIC; PNM). Seed-based analyses: brain-wide and sub-regions (e.g. brainstem; Harvard-Oxford-atlas) (Desikan, et al., 2006); 7T-derived PAG-mask seed (Ezra, et al, 2015; FEAT). Network analysis using a total of six nodes including PAG, RVM, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsolateral prefrontal cortex (dlPFC), and thalamus (FSLNets, ridge-regression, $\rho=0.1$). Higher-level statistics: Randomise (5000 permutations).

Results and conclusions: PAG-seed connectivity correlated significantly with chronic pain severity in the dlPFC, ACC, PCC and RVM. PAG-RVM connectivity negatively correlated with pain however cortical-PAG connectivity was unexpectedly positively correlated.

Network analyses incorporating the thalamus abolished significant correlations with cortex-PAG connectivity, corroborated the negative correlation with PAG-RVM connectivity, and revealed an interesting distinction between low pain patients and other groups (figure 1); a distinction previously observed in this cohort but with PAG glutamate concentrations (Kong, Y., et al, 2015. ISMRM 2015).

One interpretation is that low-pain NMO patients adapt (or are pre-adapted) to the presence of a chronic pain trigger and tonically engage descending inhibition.

Figure 1. Pain and control groups' PAG-RVM correlation scores

Control and meaningful-pain group correlation scores appear strikingly similar when compared to the low-pain group. There is thus the suggestion that low-pain patients adapt (or are pre-adapted?) to the chronic pain cause, and engage descending inhibition via the PAG-RVM pathway.

PSI, pain severity index; PAG, periaqueductal grey; RVM, rostral ventromedial medulla; 'low pain' = $PSI \leq 12$; 'meaningful pain' = $PSI > 12$; p-value family-wise-error corrected.

Poster number: PS166 (SP)

Theme: Sensory and motor systems

Pharmacological and molecular characterisation of latent sensitisation in a rat model of postoperative pain following inguinal hernia repair

Authors: Ms Emer Power^{1,3,4}, Ms Orlaith Mannion^{1,3}, Ms Stephanie Bourke¹, Mr Bradley K. Taylor⁵, Mr Mads U. Werner⁶, Mrs Michelle Roche^{2,3,4}, Mr David P. Finn^{1,3,4}

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Background and Aims: In latent sensitisation, hyperalgesia in remission may be re-instated by inverse-agonists/antagonists at the Mu-opioid receptor (MOP)^{1,2,3}. Some evidence also implicates the delta(DOR) and kappa(KOR) opioid receptors^{4,5}. We examined latent sensitisation in our rat model of postoperative pain following inguinal hernia repair(hernioplasty).

Methods: Thirty-two adult male Lister-Hooded rats underwent hernioplasty or sham procedure (n=16/group). Behavioural measures included locomotor activity and von Frey testing(VF) for mechanical allodynia at baseline(-24hrs) 4, 24, 48hrs post-surgery. Six- and twelve-days post-surgery, rats received 3mg/kg(s.c.) naloxone (MOP inverse agonist) or vehicle (n=8/group) and behavioural tests were conducted at 30mins, 90mins and 4hrs post-injection. Another cohort of rats also underwent sham or hernioplasty (n=8 /group). This cohort was euthanised at day 12 post-surgery and brain/spinal cord tissue was extracted. Tissue was analysed by qRT-PCR for opioid receptor and peptide mRNA.

Approach for Statistical Analysis: Normality was tested via the Shapiro-Wilk test. Behavioural results were analysed using the Kruskal Wallis test followed by Mann-Whitney tests with Bonferroni-Holm correction. PCR data were analysed using an independent t-test. Differences were considered statistically significant at $p < 0.05$.

Results & Conclusions: Hernioplasty reduced locomotor activity and caused mechanical allodynia at 2-24 hr post-surgery, which resolved within 48 hr. On days 6 or 12 after hernioplasty (but not sham), naloxone significantly increased (i.e. reinstated) mechanical allodynia. qRT-PCR revealed a significant increase in mRNA coding for KOP in

the periaqueductal grey(PAG) and proopiomelanocortin(POMC) expression in the ipsilateral spinal cord and contralateral amygdala following hernioplasty, compared with sham controls. MOP expression was unchanged in all tissues.

This study provides evidence for endogenous opioid receptor analgesia and changes in opioid receptor/peptide mRNA post-surgery. The lack of change in MOP expression suggests that constitutive activity at the receptor may be responsible for the latent sensitisation effect.

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Poster number: PS167 (SP)

Theme: Sensory and motor systems

Layer IV gates disinhibition to govern the critical period for feed-forward visual plasticity

Authors: Aaron McGee^{1,3}, Dr. Michael Frantz¹, Dr. Taruna Ikrar², Dr. Xiangmin Xu²

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Introduction: Perturbing sensory experience can disrupt developing neural circuitry. In primary visual cortex (V1), depriving one eye of vision (monocular deprivation, MD) during a developmental 'critical-period' permanently degrades cortical responsiveness to that eye, a phenomenon termed ocular dominance (OD) plasticity. Yet where and how this experience-dependent visual plasticity emerges and propagates within the laminar circuitry of V1 is controversial.

Methods: Here we explored how OD plasticity is governed with a conditional mutant of *nogo receptor 1 (ngr1)*, a gene required to close the critical period. We performed multi-unit electrophysiologic recordings in anesthetized mice to measure eye dominance for units across all cortical layers. In parallel experiments, we performed laser scanning photostimulation (LSPS, 'glutamate uncaging') to evaluate the strength and distribution of excitatory synaptic inputs onto both pyramidal neurons and parvalbumin-positive interneurons in L2/3. Last, we examined the progression of OD plasticity by measuring eye dominance with shorter durations of deprivation.

Approach for statistical analysis: Pairwise non-parametric tests were identified prior to initiating the study. Both Kruskal-Wallis pairwise tests and cumulative distributions were employed to evaluate statistical significance of differences between experimental and control groups.

Results and conclusions: Deleting *ngr1* selectively in the thalamo-recipient layer 4 (L4) prevented the critical period from closing. Deletion of *ngr1* in L4 was accompanied by a sustained capacity for disinhibition by reduction of excitatory synaptic drive onto parvalbumin-positive (PV) interneurons with 1-2 days of MD. After only 2 days of MD, OD plasticity was significantly greater in L4 than L2/3 or L5 in both adult mice lacking *ngr1* selectively in L4 and critical-period WT mice.

Poster number: PS168 (SP)

Theme: Sensory and motor systems

Neurophysiological Underpinnings of the Diminished Capacity for Regulating Speed-Accuracy Tradeoffs in Older Age

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Introduction: The ability to adjust decision making strategies to account for changing demands for speed versus accuracy is an essential component of adaptive choice behaviour. It has consistently been observed that older adults have diminished flexibility in this regard but it is unclear how this manifests in neural signatures of decision formation.

Methods: In the present experiment, older adults (65–80 years) and younger adults (18–35 years) engaged in a two-alternative contrast discrimination task (n=60), consisting of two superimposed leftward/rightward gratings which changed in relative contrast. Stimuli were presented under two conditions emphasising accuracy/speed, imposed via verbal instruction and feedback in the form of points. Continuous 128-channel EEG data were recorded to allow for probing of the distinct stages of the sensorimotor hierarchy.

Approach for statistical analysis: Both ERP and time frequency analyses were carried out. For the former, ERPs were created for each participant by averaging across single trials. For the latter, Short Time Fourier Transforms were used. Group differences were primarily assessed using mixed factorial ANOVAs.

Results and conclusions: In keeping with the findings of previous studies, older adults were less amenable to speed accuracy manipulations at the behavioural level. Although the age groups were matched for accuracy and reaction time when accuracy was emphasised, the reaction times of older adults were significantly slower than those of younger adults when speed was emphasised. Analysis of beta band activity indicated that this effect was at least partly attributable to differences at the level of motor preparation. While young participants exhibited markedly greater motor preparation at trial onset under speed compared to accuracy emphasis, this modulation was less pronounced among the older adults. Potential compensatory mechanisms were also at play, with older adults exhibiting stronger sensory evidence encoding signals (Steady State Visual Evoked Potentials), indicating better discrimination at the sensory level. Older adults did not earn fewer points than younger adults in the task, suggesting a lack of functional impact of their reduced flexibility. These results add insight to performance differences between younger and older adults in the domain of decision making.

Poster number: PS169 (SP)

Theme: Sensory and motor systems

Expertise differences in neural events during action prediction in football: an analysis of eeg event related potentials, alpha power and signal detection measures

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Introduction: We investigated the influence of expertise on neural events involved in the observation and prediction of another person's actions, in a time-critical football scenario.

Methods: Skilled male football players (N=15); and novices with little or no experience of competitive play (N=17) viewed point-light video clips of footballers dribbling the ball towards the viewer then turning to the left or right,

either without deception (50% of stimuli) or with a *stepover* action to feign moving in one direction before going in the other (50% of stimuli). Clips (2000 ms) were temporally occluded; at -160, -80, 0 or 80 ms relative to the frame in which the player's foot contacted (genuine trials) or passed in front of (deceptive trials) the ball. Participants predicted the ball direction following a visual prompt presented 100 ms after the end of each clip.

Analysis approach: Sensitivity to predicted direction was calculated as d' ; and EEG was analyzed as event-related potentials (ERPs) and event-related bandpower in the alpha range (9-11 Hz).

Results: There was a significant adverse effect on d' of deception overall, a significant interaction between deceptive / genuine moves and occlusion, and skilled players were significantly superior to novices specifically on deceptive moves. Alphanpower was greater in experts than novices before and during the video. However, relative to the pre-stimulus peak there was greater alpha desynchronization during action observation in experts. Over a similar time-course, from 500 ms after video onset, ERP showed a sustained right frontal negativity, greater in amplitude in skilled players, and more prominent on deceptive moves. Conversely, ERP amplitudes to the prompt stimulus itself were greater in novices.

Conclusion: The results support a nuanced view of "neural efficiency" in which skilled players showed more differentiation of neural activity in response to the rapidly changing task demands over time.

Poster number: PS170 (SP)

Theme: Sensory and motor systems

Differentiating the roles of the cerebellum and motor cortex during visuomotor adaptation using either hand or whole arm reaching movements

Authors: Mr Matthew Weightman¹, Dr John-Stuart Brittain², Dr Ned Jenkinson¹

¹*Sport, Exercise and Rehabilitation Sciences, University of Birmingham, United Kingdom*, ²*School of Psychology, University of Birmingham, United Kingdom*

The control of proximal versus distal upper limb movements are believed to be subserved by somewhat distinct neural pathways (Lawrence & Kuypers, 1968a, b). Direct connections from the primary motor cortex (M1) to distal muscles supports the key role of M1 in the production and control of hand/finger movements (Bortoff & Strick, 1993). Alternatively, impaired reach behaviour after cerebellar lesions and ataxia point to the cerebellum as a vital neural substrate contributing to whole arm reaching (Bhanpuri et al., 2014). Here, we aimed to further elucidate the roles of both the cerebellum and M1 during specific motor tasks using either movements of the hand and fingers or the whole arm.

Young healthy participants received anodal transcranial direct current stimulation (TDCS) over the lateral cerebellum, M1 or sham stimulation during a visuomotor rotation task requiring either hand/finger movements or whole arm reaching movements. Participants made fast 'shooting' movements towards the targets using either a hand-held joystick (requiring finger/hand movements) or 2D robotic manipulandum (requiring reaching movements) while a 60-degree rotation was unexpectedly added. Mixed effect models, repeated-measures and one-way ANOVAs were used to compare adaptation rates/stages between stimulation groups.

It was found that cerebellar TDCS enhanced adaptation for participants completing the reaching task, as they displayed significantly reduced error at the end of the task compared to the M1 or sham group. Conversely, M1 stimulation resulted in improved adaptation performance during the hand task compared to cerebellar or sham groups. This effect on adaptation did not persist after a 50-minute break (40 minutes without stimulation), when re-tested on the same task. These results demonstrate an effector specific effect of TDCS over M1 and the cerebellum during visuomotor adaptation and could prove important in the use of TDCS as a viable clinical tool for the treatment of upper limb motor deficits moving forward.

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Poster number: PS171 (SP)

Theme: Sensory and motor systems

Differential effects of optogenetic modulation of rat anterior cingulate cortical glutamatergic neurons on the aversive and sensory components of pain in male and female rats

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Introduction: The anterior cingulate cortex (ACC) plays an important role in top-down control and the affective component of pain. *In-vivo* optogenetics is a technique in which light-sensitive proteins, opsins, are used to modulate target populations of neurons with high temporal control in awake behaving animals. Commonly used opsins are channelrhodopsin-2 (ChR2) and archaerhodopsin (ArchT) to activate or silence neurons, respectively. Optogenetic methodology has been a valuable tool in a wide range of neuroscience fields including pain research. The aim of this study was to investigate the effects of optogenetic modulation of glutamatergic neurons in the ACC on formalin-evoked aversion and nociceptive behaviours in rats.

Methods: Adult female and male Sprague-Dawley rats underwent stereotaxic injection of adeno-associated virus (AAV) and implantation of optic fibres into the ACC. The AAV encoded control fluorophores, ChR2, or ArchT under regulation of calmodulin kinase II alpha (CamKII α) promoter for selective expression within glutamatergic neurons. Four weeks later, the effects of optogenetic stimulation on formalin-induced nociceptive behaviour and formalin-induced conditioned place aversion (F-CPA) were assessed.

Approach for statistical analysis: Data were analysed using one-way or repeated measures ANOVAs followed by Tukey post-hoc analysis where appropriate.

Results and conclusions: We found that optogenetic inhibition of glutamatergic neurons in the ACC abolished F-CPA in males, while activation of the same neurons did not significantly affect F-CPA, compared with rats expressing the control fluorophore. However, optogenetic activation of glutamatergic neurons in the ACC resulted in decreased nociceptive behaviour at discrete timepoints during the late stage of the 60-minute formalin trial in male but not female rats. Together these data suggest that glutamatergic neurons in the ACC play differential and sex-dependent roles in the sensory and aversive components of pain processing.

The present study was carried out with financial support from Science Foundation Ireland (SFI) and co-funded under the European Regional Development Fund under Grant Number 13/RC/2073.

Poster number: PS172 (SP)**Theme:** Sensory and motor systems**Visualizing native N-type calcium channels****Authors:** Ms Krishma Ramgoolam¹, Dr Manuela Nieto-Rostro¹, Professor Annette Dolphin¹¹*UCL, London, United Kingdom*

CaV2.2 constitutes the pore subunit of N-type calcium channels, which are important for neurotransmitter release in the central and peripheral nervous system. Immunohistochemical detection of native CaV2.2 has not been possible until now due to the low expression of these channels and lack of suitable antibodies. We have now developed a constitutive knock-in (KI) transgenic mouse, expressing CaV2.2 with an epitope tag (2xHA) inserted in the extracellular loop between S3 and S4 of Domain II (CaV2.2_HA KI). The tag did not affect the function of the channel when expressed in vitro (Cassidy et al., 2014). In the peripheral sensory nervous system, our data show CaV2.2_HA to be expressed on the cell surface of dorsal root ganglion neurons (DRGs). In the spinal cord, CaV2.2_HA is predominantly in the superficial laminae LI and LII of the dorsal horn, mainly in the primary afferent terminals, since HA staining is reduced following rhizotomy. These mice will be instrumental in the future to understand the presynaptic role of N-type calcium channels in physiological and pathological states and will also be of use to examine the trafficking and recycling of the channels in several neural cell types.

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Poster number: PS173 (SP)**Theme:** Sensory and motor systems**Motor cortex neurotransmitters relate to retention, but not adaptation in a visuomotor rotation task****Authors:** Ms Caroline Nettekoven^{1,2,3}, Ms Sinead Brady^{1,2,3}, Mr Jacob Levenstein^{1,2,3,4}, Dr Uzay Emir⁵, Dr Ned Jenkinson⁶, Dr Charlotte Stagg^{1,2,3}

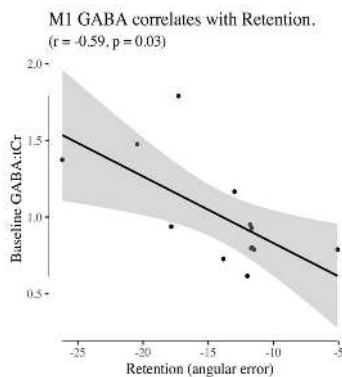
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Introduction: Neurotransmitter concentration levels in the primary motor cortex (M1) relate to motor learning. For example, M1 gamma-aminobutyric acid (GABA) baseline levels and its practice-related reduction have been associated with motor learning in model-free learning tasks. However, if this translates to model-based learning tasks has yet to be elucidated.

Methods: Using a within-subject design (N=15 healthy participants) magnetic resonance spectroscopy data (7T) were acquired from the left hand area during the performance of a visuomotor joystick task. During one session (adaptation session) the visual feedback was rotated, and participants adapted their movements to the perturbed feedback. This was followed by a washout period (no offset), which allows to quantify the retention of the compensatory movement. During the other session (control session) no rotation was imposed.

Statistical analysis: Task performance was quantified using a model-free approach (averaging the error). Spearman's rank-order correlations and partial correlations were calculated.

Results: Model-free analysis revealed that M1 GABA at baseline ($GABA_{Baseline}$) correlated with retention ($r_{13}=-0.59$, $p=0.03$), but not adaptation ($r_{14}=0.19$, $p=0.51$): participants with high $GABA_{Baseline}$ retained more compensatory movement. Additionally, M1 Glutamate at baseline ($Glu_{Baseline}$) correlated with retention ($r_{11}=-0.58$, $p=0.04$). Further analysis showed that $GABA_{Baseline}$ and $Glu_{Baseline}$ were highly correlated ($r_{14}=0.72$, $p=0.01$) and suggested that the relationship with retention was driven by the shared variance of GABA and Glutamate. As expected, $GABA_{Baseline}$ did not correlate with retention ($r_{11}=-0.25$, $p=0.38$) or adaptation ($r_{11}=-0.22$, $p=0.51$) in the control session. In summary, we provide evidence that inter-individual differences in performance on a model-based motor task correlate with magnetic resonance spectroscopy-assessed neurochemical concentration levels in M1.



Poster number: PS174 (SP)

Theme: Sensory and motor systems

Gating without swinging: a new model of hair-cell mechanotransduction with bilayer-mediated cooperativity

Authors: Dr Francesco Gianoli¹, Dr Thomas Risler^{1,2}, Dr Andrei Kozlov¹

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Introduction: Mechano-electrical transduction (MET) is the fundamental process of hearing that transforms auditory stimuli into electrical signals intelligible to the brain. It occurs when auditory stimuli open mechanosensitive ion channels located in the hair cells of the internal ear. Since 1988, the gating-spring model developed by Howard and Hudspeth(1) has been the main explanation for this phenomenon: the stimulus-driven deflection of the stereocilia tense the tip link that transmits force to a single MET channel and thus opens it. Although this model has been very successful, the predicted size of the movement associated with the channel's opening is unrealistically large for a single channel(2). Furthermore, experiments indicate that each tip link connects to two channels rather than one and there is strong evidence that the lipid bilayer that supports the channels modulates their open probability(3,4).

Methods: We developed a new model of mechanotransduction that features two channels per tip link, which interact through membrane-mediated elastic forces.

Results: By using only realistic parameters, the model not only quantitatively reproduces all the main physiological properties of MET, but it also accounts for experimental results that were previously unexplained.

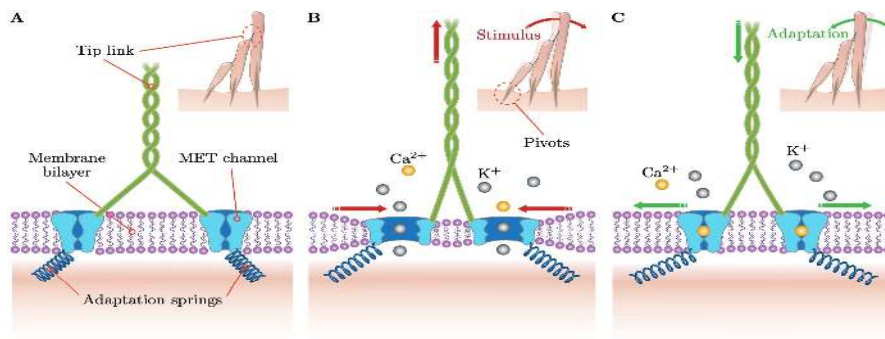


Illustration of the model and its main features. (A)–(C) The upper inserts show a side view of a typical mammalian hair bundle with three rows of stereocilia. The main panels show an enlarged view of the lower end of a single tip link, connected to two MET channels within the lipid bilayer. The channels are linked to the cell cytoskeleton via two adaptation springs. Three configurations are shown: (A) in the absence of a stimulus, (B) when a positive stimulus is applied, and (C) when fast adaptation takes place.

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Poster number: PM001 (SP)**Theme:** Attention, motivation, behaviour**Early sensory activity and motor preparation during rapid value-biased decisions****Authors:** Ms L. Alexandra Martinez Rodriguez¹, Prof. Simon P. Kelly¹¹*University College Dublin, Dublin, Ireland*

The aim of this study is to investigate the effects of value on early sensory neuronal responses and motor preparation dynamics, during rapid sensorimotor decisions. Different accounts have been developed that try to explain the mechanisms underlying value biases during the decision-making process. The starting point bias account suggests a shift in the starting point of the evidence accumulation, in the direction of the more valuable alternative. A different model suggests that the mean tendency of the decision variable (drift rate), varies as a function of value. While most studies have supported a starting point bias approach, recent work (Afacan-Seref et al., 2018) suggests that drift rate biases may also be part of the decision-making dynamics. One possible source of such drift rate biases is the modulation of the sensory representations of evidence in the low-level visual cortex. Our study examines these by recording EEG (Biosemi), eye-position (Eyelink) and EMG of the flexor pollicis brevis muscle, while participants perform a value-biased orientation discrimination task under a strict deadline.

Similar to Afacan-Seref and colleagues (2018), behavioural data was best accounted for by a model in which the evidence representation—and hence, rate of accumulation—was itself biased by value and it was non-stationary, increasing over the short decision time frame. Adding a value biased urgency signal to this model showed a similar fit, suggesting a possible role of these signals in the biasing mechanism. Regarding the neural processes involved during this task, the lateralized motor preparation reflected in the Lateralized Readiness Potential (LRP), showed signs of a starting point bias around cue onset that increased with time. However, the initial, “C1” component of the visual evoked potential (VEP), showed no signs of significant value modulation. Our results show that drift rate biases don’t occur at the sensory level, but it is as yet unclear whether they arise from biases between urgency signals or modulations of the sensory readout.

Poster number: PM002 (SP)**Theme:** Attention, motivation, behaviour**Possible cortical mechanisms involved in creative design****Authors:** Prof Roger Orpwood¹¹*University of Bath, Bath, United Kingdom*

There have been an increasing number of papers investigating the creative process from a neuroscience perspective. The majority of these have been imaging studies seeking to identify those areas of the brain that are active when creative acts are taking place. However some have argued that little consensus has emerged from this work, and that perhaps the focus of research exploring creativity should shift to exploring the potential mechanisms involved (eg Dietrich and Haider, 2017). This paper attempts to consider mechanisms by examining the manipulation of sensory and motor representations in the cortex. It focusses on the design of a mechanical device, and only considers the ideation phase of creativity.

Deriving a design for a mechanical device involves being provided with a desired behaviour, and then imagining potential objects whose behaviour is acceptably close to that desired. Representations of objects and representations of behaviour are known to be present in sensory and motor cortices, and that these representations are activated during imagination (eg de Borst and Gelder, 2017). There are many reciprocal connections between these representations, and the paper argues that these links could enable associations between objects and behaviours to be learnt. The paper goes on show how these associations could be used in iterations between the

sensory and motor areas to compile novel structures whose imagined behaviour is acceptably close to that desired. It shows how the originality of the solution could be increased through broadening the range of sensory representations included, and through manipulations of representations at a lower level of the sensory and motor cortical hierarchies.

A simulation study is presented which models the interconnections between a sensory and motor network, together with an external executive control that manages the manipulation of representations. Although quite limited, the simulation shows that the mechanism described is feasible.

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Poster number: PM003 (SP)

Theme: Attention, motivation, behaviour

The effects of daily stress, risk-taking, and impulsivity, on fluctuations in alcohol use in healthy drinkers: A pilot study

Authors: Mr James Clay¹, Dr Matthew Parker¹

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Introduction: Hazardous drinking, if chronic, can escalate into an alcohol use disorder (AUD), presenting a global health issue. The mechanisms underlying the transition from controlled social drinking to uncontrolled alcohol misuse are multifaceted, hence our current inability to predict those most at-risk of misusing alcohol, or developing AUD. Our previous research suggests that impulsivity mediates laboratory induced stress to predict alcohol craving and consumption in normative populations. In this study, we aimed to determine whether our prior findings could be generalised in a naturalistic setting, using a semi-longitudinal design, by testing the hypothesis that in a sample of social drinkers, those with a greater level of impulsivity/risk-taking would consume a greater volume of alcohol following daily stress.

Methods: We characterised impulsivity/risk-taking in 23 participants (12 female; mean age = 24.59 [SD = 5.34]) using a battery of questionnaires (explicit assessment) and computer tasks (implicit assessment). We then collected daily subjective stress assessments and physiological measures of alcohol use via portable breathalyser over 30 days.

Analysis approach: To test our hypothesis, we fit a series GLMMs with blood alcohol concentration (BAC) as the outcome variable. After running null models, we determined our random effect structure and that our data were gamma distributed. We controlled for the effect of weekend (Friday – Sunday) by sub-setting our data into two data frames: 1) Monday – Thursday; 2) Friday – Sunday. We then grouped covariates based on what they quantified e.g., impulsivity, risk-taking, previous alcohol use etc., running a separate model for each group and employing a backwards elimination technique, sequentially removing the largest p -values until only $p_s < .05$ remained.

Results and Conclusions: We found support for our hypothesis, with higher risk-taking and impulsive participants drinking more following daily stressors. However, the picture was not clear, with participants drinking greater volumes of alcohol at weekends, and the interactions of stress x personality trait often differing on weekdays. Overall, this was the first study to demonstrate that using digital biomarkers to observe risk for alcohol misuse is feasible, supporting our previous work and providing further evidence that impulsive individuals may be more at risk of stress induced alcohol craving/consumption.

Poster number: PM004 (SP)**Theme:** Attention, motivation, behaviour**Impact of hippocampal neural disinhibition on latent inhibition in a conditioned emotional response procedure****Authors:** Mr Stuart Williams¹, Ms Miriam Gwilt¹, Ms Rebecca Hock¹, Dr Carl Stevenson², Professor Helen Cassaday¹, Dr Tobias Bast¹¹*School of Psychology, University of Nottingham, Nottingham, United Kingdom*, ²*School of Biosciences, University of Nottingham, Nottingham, United Kingdom*

Introduction: Hippocampal neural disinhibition, i.e. reduced GABAergic inhibition, is a key feature of schizophrenia pathophysiology (Heckers & Konradi, 2015, *SchizophrRes*). The hippocampus is a crucial component of the fear circuit and positively modulates striatal dopamine (Bast et al, 2011, *CurrOpinNeurobiol*), which plays a significant role in salience modulation (Kapur, 2003, *Am J Psychiatry*). Therefore, we examined the contribution of hippocampal neural disinhibition to impairments in fear conditioning and salience modulation associated with schizophrenia (Jensen et al, 2008, *Neuropsychopharmacology*).

Methods: We examined the effect of ventral hippocampal disinhibition by picrotoxin (GABA-A antagonist) infusion (150ng/side) (McGarrity et al, 2017, *Cereb Cortex*) on latent inhibition (LI) of fear conditioning, using a conditioned-emotional response paradigm (Nelson et al, 2011, *Jpsychopharm*). Rats received light (CS)-foot shock (US) pairings. Conditioned suppression of the lick response was used as a measure of conditioned fear. Reduced conditioned suppression in rats pre-exposed (PE) to the CS, compared to non-pre-exposed (NPE) rats was used as measure of LI. Picrotoxin or saline was infused prior to both pre-exposure and conditioning.

Analysis: Conditioning to the CS was measured using latency to make 50 licks without CS (A) and time taken to complete 50 licks following CS onset (B) to calculate a suppression ratio $A/(A+B)$. Data was analysed by ANOVA with infusion group and pre-exposure as between-subject factors.

Results and conclusions: In contrast to saline-infused rats, rats that received hippocampal picrotoxin did not express LI, while picrotoxin rats in the PE and NPE groups showing comparable conditioned suppression (Fig.1, left). Abolished LI in picrotoxin-infused animals is explained by reduced conditioned suppression in the NPE group as compared to saline-infused rats, indicating reduced fear conditioning to the light CS. Hippocampal picrotoxin also reduced contextual fear conditioning, indicated by reduced latency to lick compared to the saline group during re-exposure to the context after conditioning (Fig.1, right).

Overall, rats with ventral hippocampal disinhibition did not express LI, showing similar levels of conditioning regardless of CS pre-exposure. However, this mainly reflected that hippocampal disinhibition impaired fear conditioning to the CS, resembling the reduced aversive cue conditioning in patients with schizophrenia (Jensen et al, 2008), as well as the impaired contextual fear conditioning seen in the present study.

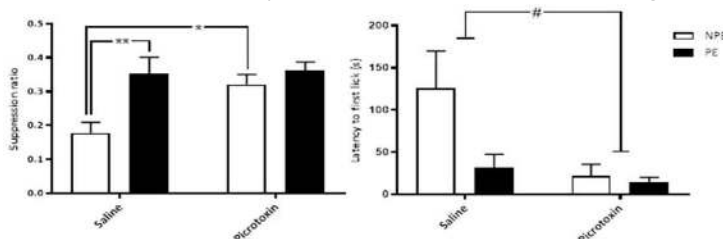


Figure 1: Left: Conditioning to the light CS, as reflected by the mean suppression (+SEM). Note: the lower the suppression ratio, the stronger the conditioning to the CS. * Indicates significance between saline and picrotoxin NPE groups ($p < 0.05$), ** significance between control and NPE ($p < 0.01$). Right: Conditioning to the context (chamber), as reflected by the mean latency (+SEM) to lick when re-exposed to the context after conditioning. # indicates main effect of infusion ($p < 0.05$).

Poster number: PM005 (SP)

Theme: Attention, motivation, behaviour

A neutrally-constrained process model of prior-informed decision making

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Introduction: How does the brain exploit prior information about stimulus probability when selecting actions in response to noisy sensory stimuli? Most behavioural modelling studies account for the influence of priors through a single parameter – typically starting point bias – but it is unclear whether these parsimonious models truly reflect the underlying neural computations. Here we avail of recently characterised electroencephalography (EEG) signals reflecting decision formation at key sensorimotor processing levels to construct and constrain a model of prior-informed decision making.

Methods: We recorded EEG from 20 human subjects performing a motion direction discrimination task with prior cues indicating the likely direction of motion. Building on the “sequential sampling” framework, in which sensory evidence is accumulated up to action-triggering thresholds, we explicitly modelled two decision levels guided by neurophysiological signals—a motor-independent representation of cumulative evidence feeding build-to-threshold motor signals that receive additional dynamic urgency components. The motor level had starting points directly constrained by neural signals and built to a fixed threshold at response. We examined two versions of the model: one in which prior bias was captured by the starting point alone and one which also included drift rate bias. We compared their performance to similarly parameterized standard diffusion models.

Approach for analysis: We used the Akaike Information Criterion for model comparisons.

Results and conclusions: The neutrally-constrained model accurately accounted for behaviour across three task conditions (easy, speed pressure, and weak evidence), and outperformed the standard diffusion model which failed to capture the fast guesses and lack of skew in the response-time distributions for the more difficult conditions. When simulated based on the behavioural fit, it recapitulated an array of condition- and outcome-related effects in the neural decision signals which were not directly used to inform the model. Most interestingly, the neutrally-informed model indicated that priors are incorporated not only by starting point biases as assumed in standard models, but also by significant drift rate biases. Our approach demonstrates how incorporating neural data in tandem with behavioural modelling can provide much-needed constraints while elucidating multi-level mechanisms that would not be discernible from behaviour alone.

Poster number: PM006 (SP)

Theme: Attention, motivation, behaviour

Differential behavioural effects of opioid receptor modulation on motivational states in a rat IFN- α depression model

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Introduction: There has been a renewed interest in opioid modulators for the treatment of depression in recent years. However, the role individual opioid receptors play in mood and motivation remains unclear [1]. Here, we explore effects of mu (MOR), kappa (KOR) and delta (DOR) opioid receptor modulation in the rat interferon-alpha (INF- α) model of depression.

Methods: IFN- α /saline-treated Wistar rats were tested in the forced swim test (FST), a measure of depressive-like behaviour, and a progressive ratio (PR) schedule, a measure of motivated behaviour. Opioid receptor modulators (MOR: cyprodime (10mg/kg), morphine (5mg/kg), RDC 2944 (0.1mg/kg); KOR: DIPPA (10mg/kg), U50 488 (5mg/kg); DOR: naltrindole (10mg/kg), SNC 80 (20mg/kg)) were administered s.c. 1hr before FST or 30min before PR schedule test. Fluoxetine treatment (10mg/kg p.o. for 4 weeks) was included as a comparative antidepressant treatment. Hippocampal brain tissue was harvested post-mortem and analysed for neurogenesis by flow cytometry.

Analysis approach: Data were analysed by regular or repeated measures one- or two-way analyses of variance (ANOVA) followed by multiple comparison tests where appropriate.

Results and Conclusions: IFN- α -treated rats demonstrated increased immobility scores in the FST compared to saline-treated rats. Administration of fluoxetine, DIPPA or SNC 80 alone, or in combination, recovered immobility scores in the FST. IFN- α treated rats showed an increased breaking point (max responses per reinforcement) in the PR schedule compared to saline controls, which was reduced by morphine, DIPPA or U50 488 alone, or a combination of DIPPA and SNC 80. SNC 80 alone, or in combination with DIPPA, recovered IFN- α -induced decreases in neurogenesis. Together these data indicate that opioid receptor modulation plays a key role in the regulation of motivational states and warrants further investigation.

1. Callaghan, C.K., J. Rouine, and S.M. O'Mara, *Potential roles for opioid receptors in motivation and major depressive disorder*. Prog Brain Res, 2018. 239: p. 89-119.

Poster number: PM007 (SP)

Theme: Attention, motivation, behaviour

Daily variation in electrophysiological sensitivity to nicotine within the medial habenula

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Introduction: Circadian signalling is widespread throughout the brain, driving daily rhythms in physiology and behaviour. The habenula, a small bilateral structure of the epithalamus implicated in reward and addiction processes, is one such area, demonstrating circadian rhythmicity in molecular and neuronal activity. The medial portion of the habenula (MHb) has remarkably dense expression of several different nicotinic acetylcholine receptor (nAChR) subunits. This has led to a wealth of research firmly implicating the MHb as a crucial centre mediating nicotine withdrawal. Intriguingly, studies in both humans¹ and animals^{2,3} have provided evidence for daily rhythms in nicotine intake and withdrawal, raising the possibility of a circadian influence on the cholinergic circuits of the MHb.

Therefore, we set out to investigate whether there was evidence of diurnal patterns in sensitivity to nicotine within the MHb, and to characterise time of day differences in the network properties of the MHb.

Methods: Using *in vitro* electrophysiological approaches, both spontaneous firing rates and responses to nicotine were examined in mouse MHb at defined time points across the day-night cycle to investigate whether these properties were under circadian influence.

Approach for statistical analysis: All data was tested for normality using the Shapiro-Wilk test. Comparisons between 2 time points were analysed using the Student's t-test, or Mann-Whitney U test in the cases where data significantly differed from a normal distribution. The proportions of response types between time points were analysed using Fisher's exact test.

Results and conclusions: Our investigations have demonstrated that there is a tendency for higher spontaneous firing activity in the 4 hours preceding lights-off compared to the 4 hours immediately following lights-on. This is also mirrored by larger responses to nicotine in the late circadian day than the early morning. These results suggest that cholinergic signalling is under circadian control. Current work is investigating time of day related changes in the MHb expression of specific nAChR subunits.

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Poster number: PM008 (PP)

Theme: Attention, motivation, behaviour

Investigating the role of the Prader-Willi syndrome critical interval for behavioural phenotype

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Introduction: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by hyperphagia, hypotonia, learning disability, and in some cases a range of secondary features including psychotic episodes, impaired attention span and autism. PWS is caused by loss of function mutations affecting the expression of the imprinted cluster on chromosome 15q11.2-q13. Among the genes of the PWS cluster are two non-coding RNAs, *SNORD116* and *IPW* which are collectively known as the Prader-Willi syndrome critical region (PWS-cr). The deletion of PWS-cr is sufficient to induce PWS in humans. However, while PWS-cr contributes heavily to the core features of PWS, including the hyperphagia and hypotonia, it is unclear whether and to what extent it plays a role in the behavioural phenotypes typical of the syndrome. Previously, behavioural studies of a full genetic mouse model of PWS have demonstrated increased schizo-typal behaviour and deficits in attention when the expression of the entire 15q11.2-q13 cluster is disrupted. The aim of this study is to assess whether the PWS critical interval plays a role in the manifestation of these behavioural abnormalities with the use of a PWS-cr^{+/-} mouse model.

Methods: In order to examine the effects of PWS-cr on behaviour we will perform behavioural tasks of relevance to the phenotypes characteristic of PWS on a PWS-cr^{+/-} mouse model, focusing on anxiety, schizo-typal behaviour and attention. The open field and elevated plus mazes will be used to measure anxiety levels, the acoustic startle and prepulse inhibition tests will be used to measure levels of schizo-typal behaviour and the 5-choice serial reaction time task will be used to assess attention and impulsivity. Further on an RNA sequencing study on brain tissue from the PWS-cr^{+/-} mouse model will be used in order to inspect the effect of PWS-cr on gene expression and post-transcriptional modifications.

Approach for statistical analysis: All data from the behavioural tasks will be analysed with R studio using ANOVA and repeated measures ANOVA with the main between subject factors being genotype (wild type and PWS-cr^{+/-}) and sex (male and female). Bonferroni post-hoc corrections will be used where necessary.

Poster number: PM009 (SP)

Theme: Attention, motivation, behaviour

Differential role of amygdala PPARs in conditioned fear-related behaviour in the presence or absence of nociceptive tone

Authors: Ms Jessica Gaspar^{1,3,4}, Dr Bright Okine^{1,3,4}, Dr Alvaro Llorente-Berzal^{1,3,4}, Mr David Dinneen¹, Dr Michelle Roche^{2,3,4}, Professor David Finn^{1,3,4}

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Introduction: Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors¹. There is evidence for their involvement in pain², cognition³, and anxiety⁴. However, their role in pain-fear interactions is unknown. In this study, we aimed to investigate the effects of systemic and intra-basolateral amygdala (BLA) and central amygdala (CeA) administration of PPAR α , PPAR β/δ and PPAR γ antagonists on nociceptive behaviour, fear-conditioned analgesia (FCA), and conditioned fear in presence or absence of nociceptive tone in rats.

Methods: Male Sprague-Dawley (SD) rats received footshock (FC) or no footshock (NFC) in a conditioning arena. 23.5h later, rats received intra-plantar injection of formalin and intra-peritoneal vehicle, PPAR α (GW6471), PPAR β/δ (GSK0660) or PPAR γ (GW9662) antagonists, before re-exposure to the arena for 15 minutes, and behaviour recorded. In subsequent experiments, rats underwent a similar protocol except PPAR antagonists or vehicle were microinjected intra-BLA or intra-CeA 15 minutes prior to formalin or saline administration. Pain- and fear-related behaviours were assessed for 30 minutes and amygdalar neurotransmitters/endocannabinoids were measured post-mortem.

Analysis Approach: Data were analysed using repeated-measures or two way ANOVA followed by Student Newman-Keuls post-hoc test or Mann-Whitney followed by Kruskal-Wallis when appropriate.

Results and conclusions: Systemic administration of all antagonists potentiated context-induced freezing in the presence of formalin-evoked nociceptive tone, with no effect on nociceptive behaviour. Intra-BLA administration of PPAR α or PPAR γ antagonists potentiated freezing in the presence of nociceptive tone in FC rats. Blockade of all PPARs in the BLA increased freezing and BLA dopamine levels in NFC rats in the absence of nociceptive tone. Administration of PPAR α , PPAR β/δ or PPAR γ antagonists intra-CeA did not affect freezing duration in the presence of nociceptive tone. Formalin-injected FC rats receiving intra-BLA PPAR α and PPAR γ antagonists had higher levels of dopamine in the BLA. In conclusion, PPAR α and PPAR γ in the BLA play a role in expression and extinction of conditioned fear in the presence or absence of nociceptive tone.

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Acknowledgments

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Poster number: PM010 (SP)

Theme: Attention, motivation, behaviour

Effects of pharmacological modulation of the endogenous opioid and cannabinoid systems on affective responding in a rat model of autism

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Introduction: In addition to social and communication deficits, autism spectrum disorder (ASD) is associated with alterations in nociceptive and affective processing. Anxiety-related behaviour and altered pain responding have been demonstrated in rats prenatally exposed to valproic acid (VPA), a validated preclinical ASD model. The opioid and endocannabinoid systems are key modulators of affect and nociception, and alterations in these systems have been reported in the VPA model.

This study examined the effect of enhancing opioid and endocannabinoid activity on thermal nociception, anxiety- and depressive-like behaviour in saline- and VPA-exposed rats.

Methods: Pregnant female Sprague Dawley rats received VPA(500mg/kg;s.c.) or saline at GD12.5. Female adolescent offspring (PND33-43;n=10-12) received the Mu-opioid receptor agonist morphine(2mg/kg;s.c.), the anandamide degradation inhibitor PF3845(10mg/kg;i.p.), the 2-arachadonicglycerol degradation inhibitor MJN110(5mg/kg;i.p.) or vehicle and underwent testing in the hotplate test (HPT), elevated plus maze (EPM), open field test (OFT) and forced swim test (FST).

Statistical analysis: Data were analysed using two-way ANOVA followed by Fisher's LSD *post hoc* or Kruskal-Wallis followed by Mann-Whitney U-test where appropriate. P<0.05 was deemed significant.

Results and Conclusion: In the HPT, morphine, but not PF3845 or MJN110, increased response latency in both saline- and VPA-exposed rats. Morphine did not alter anxiety-related behaviour or distance moved (DM) in the EPM or OFT in saline-exposed rats, but reduced time in centre of the OFT in VPA-exposed rats. Morphine increased immobility in the FST, an effect only significant in saline-exposed rats. PF3845 reduced time in the open arms (OA) of the EPM in saline-, but not VPA-exposed rats. PF3845 did not alter responding of saline- or VPA-exposed rats in the OFT or FST. MJN110 reduced time in the OA and increased DM in the EPM in both saline- and VPA-exposed rats. MJN110 increased immobility in FST and time in centre of the OFT in saline- and VPA-exposed rats, respectively. Mass spectrometry confirmed that PF3845 and MJN110 increased cortical levels of anandamide and 2-arachadonicglycerol respectively in saline- and VPA-exposed rats.

These data demonstrate differential effects of enhancing opioid and endocannabinoid activity on affective responding in saline- and VPA-exposed rats.

Acknowledgements

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Poster number: PM011 (SP)**Theme:** Attention, motivation, behaviour**Effects of MAGL inhibition and CB₂ receptor antagonism in the anterior cingulate cortex on fear-conditioned analgesia, formalin-evoked nociceptive behaviour and levels of endocannabinoids and neurotransmitter in the rat nucleus accumbens****Authors:** Mr Darragh Mattimoe^{1,3,4}, Dr. Louise Corcoran^{1,3,4}, Dr. Michelle Roche^{2,3,4}, Prof. David Finn^{1,3,4}¹*Pharmacology and Therapeutics, School of Medicine, Galway, Ireland*, ²*Physiology, School of Medicine, Galway, Ireland*, ³*Galway Neuroscience Centre, Galway, Ireland*, ⁴*Centre for Pain Research, Galway, Ireland*

Introduction: Fear-conditioned analgesia (FCA) is a powerful form of endogenous analgesia. The anterior cingulate cortex (ACC) is involved in the cognitive-affective component of pain and pain modulation. Our previous research revealed that intra-ACC administration of an inhibitor of monoacylglycerol lipase (MAGL), the primary degradatory enzyme for the endocannabinoid (EC) 2-arachidonoyl glycerol (2-AG), attenuated FCA, an effect which was not CB₁ receptor-dependant. The ACC projects to the nucleus accumbens (NAc), a region typically associated with reward but having a role in pain modulation. Modulation of the ACC-NAc projection modulates pain behaviour in awake free-moving rats. We aimed to determine the role of MAGL and CB₂ receptors in the ACC on FCA and formalin-evoked nociceptive behaviour and associated alterations in EC and neurotransmitter (NT) levels in the NAc.

Methods: Male Lister-Hooded rats (n=10/group) were used. Rats had cannulae bilaterally implanted 1mm above the ACC. Rats were placed in a clear Perspex arena and received 1 footshock/minute for 10 minutes, control animals received no footshock in the arena. 23.5 hours later rats received an injection of intra-plantar formalin and intra-ACC microinjection of DMSO vehicle, MJN110 (MAGL inhibitor), AM630 (CB₂ receptor antagonist) or MJN+AM630. Rats were returned to the Perspex box 15 minutes post drug administration and behaviour was recorded for 30 minutes. NAc tissue was isolated by Palkovits punching and HPLC-MS/MS used to measure EC and NT levels.

Approach for statistical analysis: Parametric data were analysed by two-factor analysis of variance followed by Fisher's LSD test. Non-parametric data were analysed by Kruskal Wallis analysis of variance by rank followed by Mann-Whitney U tests. P<0.05 was considered significant.

Results and conclusions: Intra-ACC administration of MJN110 attenuated FCA, an effect blocked by the AM630. AM630 alone reduced nociceptive behaviour in non-fear-conditioned rats. Thus, a MAGL substrate in the ACC may modulate FCA and 2-AG-CB₂R signalling in the ACC and suppress this form of endogenous analgesia. Fear-conditioning and/or modulation of 2-AG-CB₂ signalling did not alter EC or NT levels in the NAc which argues against their involvement in ACC-mediated control of FCA or formalin-evoked nociception through a 2-AG-CB₂ signalling mechanism.

Acknowledgements

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Poster number: PM012 (SP)**Theme:** Attention, motivation, behaviour**Chemogenetic silencing of the anterior cingulate cortex differentially affects intradimensional and extradimensional attentional set-shifting in rats****Authors:** Ms Emma Bubb¹, Prof John Aggleton¹, Dr Andrew Nelson¹¹*Cardiff University, Cardiff, United Kingdom*

Introduction: Behavioural flexibility, or the ability to update responding as environmental contingencies change, is a key executive function mediated by the rodent prefrontal cortex. However, behavioural flexibility encompasses a range of different cognitive processes that are in-turn supported by diverse frontal, corticostriatal and corticothalamic systems.

Methods: To examine the contribution of the anterior cingulate cortex to these processes, rats received injections of the inhibitory DREADD AAV5-CaMKIIa-hM4Di-mCherry or a non-DREADD expressing viral control AAV5-CaMKIIa-EGFP virus into the anterior cingulate cortex. The rats were tested on an attentional set-shifting task that measures both the ability to attend to stimuli dimensions that are reliable predictors of reinforcement (intra-dimensional shift) as well shift attention from one stimulus dimension to another, previously irrelevant, dimension, when contingencies change (extra-dimensional shift).

Approach for statistical analysis: Number of trials taken to reach criterion for the attentional set-shifting task were analysed using two-way ANOVA, where stage (eight levels) was a repeated-measures factors and group (DREADD virus or viral control) was a between subjects factor.

Results and conclusion: In stark contrast to the effects of prefrontal damage on this task, DREADD mediated inhibition of the anterior cingulate cortex impaired intradimensional shifts but, paradoxically, improved performance on extradimensional shifts, relative to controls. This pattern of results suggest the anterior cingulate cortex is vital for attending to those stimulus dimensions that reliably predict reward. Silencing of anterior cingulate activity allows poor predictors of reward to usurp attentional control, impairing the ability to attend to the currently relevant stimulus dimension (intradimensional shifts) while facilitating performance when a previously irrelevant stimulus dimension becomes predictive of reward (extradimensional shifts). Notably, damage to the anterior thalamus, a site richly interconnected with the anterior cingulate cortex, produces precisely the same pattern of results. The implication of these findings is that the anterior thalamic nuclei and anterior cingulate cortex form a functional circuit that mediates attention to the best predictors of reward.

Poster number: PM013 (PP)**Theme:** Attention, motivation, behaviour**Influences of social cognition and reward processing on autism symptoms in Prader-Willi Syndrome****Authors:** Ms Sarah-Marie Feighan¹, Professor Louise Gallagher¹¹*Trinity College Dublin, DUBLIN, Ireland*

Introduction: Prader-Willi Syndrome (PWS) is a neurogenetic syndrome caused by the loss of expression of paternally expressed genes from the paternally inherited copy of chr15q11-13 (Bittel et al., 2005). PWS is characterised by the onset of hyperphagia and insatiable hunger in childhood leading to morbid obesity. Hyperphagia in PWS individuals is due to an impaired satiety response and an increased reward value of food (Miller et al., 2011). Autism Spectrum disorder (ASD) symptoms, including atypical social cognition, are prevalent in PWS cases and intriguingly, appear to increase in PWS across childhood (Bennet et al., 2015). The social motivation theory of ASD proposes that social

cognition impairments are largely driven by social motivational deficits (Chevallier et al., 2012). We hypothesize that the onset of hyperphagia may reduce the reward value of social stimuli and contribute to the relative increase of ASD symptoms seen in later childhood in PWS cases. Our aim is to investigate: 1. if reduced valence of social reward underpins ASD symptoms in PWS; and 2. if reduced valence of social reward is related to the onset of hyperphagia.

Methods: We will phenotype ASD symptoms and hyperphagic behaviour in individuals with PWS (n=60, age 4-40y) and age/IQ matched controls. We will characterise social cognition comprehensively using a battery of accessible and validated eye-tracking paradigms. To test the relationship between reward valence for social cognition and hyperphagia, we will compare reward processing for food stimuli; social stimuli; and non-food/non-social stimuli. A dynamic preferential looking paradigm will be used to investigate differences in attentional bias between PWS cases and controls in hungry and satiated conditions.

Approach for statistical analysis: To ensure each task is measuring social cognition deficits as opposed to general intellectual disability, the performances of PWS cases and controls on the eye-tracking batteries will be compared using t-tests. Regression analysis will be used to test if performance on the social cognition battery is predictive of ASD symptoms in PWS. Lastly, the relationship between attentional bias for social stimuli and food stimuli will be explored in both PWS cases and controls in a satiated condition.

Poster number: PM014 (SP)

Theme: Attention, motivation, behaviour

Restriction of dietary protein leads to rapid preference for protein and elevated activity in ventral tegmental area

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Introduction: Adequate intake of amino acids is essential for health and survival. Accordingly, regulation of dietary protein intake has been demonstrated across several species, with protein intake being prioritised over carbohydrate and fat. However, there is still little understanding of the underlying neural mechanisms. Moreover, it is unclear whether, in the case of protein deficiency, the drive for dietary protein is specific and immediate or a learning-based adaptation.

Methods: During a 4-day conditioning session, protein-restricted (5% casein diet) and non-restricted (14% casein) control rats were trained to discriminate between protein (4% casein) and carbohydrate (4% maltodextrin) solutions. A preference test followed, with both solutions available at the same time. Throughout experiments, neural activity associated with licking behaviour was measured by expressing the calcium indicator, GCaMP6s, in ventral tegmental area (VTA) and using fibre photometry to record fluctuations in emitted fluorescence.

Approach for statistical analysis: Photometry signals were divided into discrete trials by aligning data to licking and calculating fluorescence changes, relative to baseline. For licking and neurophysiological data, two-way repeated measures ANOVA was used. Casein preference was determined vs. no-preference (0.5) using a one-sample t-test.

Results and conclusions: Protein-restricted rats showed a strong preference for protein whereas control rats showed no preference. Moreover, VTA activity was greater in protein-restricted rats consuming protein than carbohydrate. After switching diets between groups, a new preference test conducted without additional conditioning sessions revealed a rapid shift in preference in newly protein-restricted rats. Further investigation in a separate cohort demonstrated that protein preference in protein-restricted rats developed within the first 3 minutes of exposure to solutions, despite the lack of conditioning session with protein-containing solutions.

Overall, we show that protein-restricted rats exhibit a strong protein preference that develops rapidly with minimal experience. In addition, VTA activity reflects protein content of food when rats are protein-restricted. To further assess the role of VTA in encoding the nutrient value of food across distinct physiological states, future experiments will analyse how VTA activity is modulated by the first encounter with protein-rich food during protein restriction and how this activity evolves across multiple exposures.

Poster number: PM015 (PP)

Theme: Developmental neuroscience

Impact of substance use on the development of functional modules associated with sustained attention in adolescence

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Introduction: Inhibitory control and sustained attention improve through adolescence (e.g., Ordaz et al., 2013). However, little is known about developmental changes of brain connectivity, and its modularity (the extent to which there are separable groups of interconnected brain regions), and how these are related to age-related improvements in inhibitory control and sustained attention. Additionally, some adolescents may show deficits in inhibitory control in both experimental settings and everyday life, as it is seen in the adolescents' early consumption of alcohol, nicotine and hash. This may be due to differences in the brain's modularity that could affect sustained attention and ultimately prevent successful inhibitory control.

Here, we aim to investigate the relationship between brain connectivity development and deficits in sustained attention as they pertain to substance use and misuse.

Methods: 1400 participants from the IMAGEN project performed a reaction time task both at age 14 and age 19 under functional MRI. From the fMRI, we will extract the averaged time-series in regions of interest and calculate wavelet coherence at 0.06-0.12 Hz in three windows of 105 volumes per time point. A connectivity matrix with the coherence measure will be built per layer. We will apply modularity maximization for multilayer networks per time point (Mucha et al., 2010; Bassett et al., 2011). For this, optimal structural and temporal parameters will be searched in a subset of the sample. Optimal parameters will be used for the final modularity maximization. This will result in the allocation of regions of interest to specific functional modules. Within-module connectivity, (i.e. *functional integration*) and between-module connectivity will be calculated across all modules (i.e. *functional recruitment*).

Approach for statistical analysis: We will use scores on alcohol, nicotine and cannabis use from on the European School Survey Project on Alcohol and other Drugs to group participants into low, medium and high users. We will assess the effect of substance use on the functional integration and recruitment using linear mixed effects models.

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Poster number: PM016 (PP)

Theme: Developmental neuroscience

The effects of a ketogenic diet during pregnancy on the developing mouse brain

Authors: Dr. Denis Barry², Mr. David Lee², Dr. Robin White¹

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Introduction: A ketogenic diet (KD), characterized by increased fat and decreased carbohydrate consumption, leads to the production of circulating ketone bodies that serve as an alternative energy source to glucose. As ketone bodies can cross the placenta during pregnancy, maternal ketosis exposes the developing fetus to elevated blood ketone bodies. Recent studies have shown differences in overall body size, gross brain anatomy, and postnatal behaviour in offspring of rodents on a maternal ketogenic diet, suggesting that a maternal ketogenic diet leads to persistent changes in the central nervous system (CNS). The proposed research aims to investigate potential effects of a maternal ketogenic diet on CNS compartment formation and white matter patterning at key stages of development in the brain and spinal cord. We hypothesize that a ketotic environment during development will result in altered neuronal and glial differentiation, migration, and subsequent synapse formation.

Methods: The effects of a maternal KD on nervous system development will be assessed using both *in vivo* and *in vitro* approaches. Female mice will be fed either a KD (67.4% fat, 0.6% carbohydrate, and 15.3% protein) or a standard diet (SD; 5% fat, 76.1% carbohydrate, and 18.9% protein) for 30 days prior to mating and throughout pregnancy. Precursor cell lineage and brain architecture will be investigated using immunohistochemistry and histological staining, respectively, at embryonic day (E)11.5, E13.5, E15.5 and E17.5 as each of these time points reflect a key stage in CNS formation. In addition, primary neurosphere cell culture isolated from the cortices and spinal cords of embryos aged E13.5 and E15.5 will be induced to differentiate and proliferation, migratory potentials, and cell fate will be measured.

Approach for Statistical Analysis: Based on normality of data, either parametric or nonparametric two-way ANOVAs (time x diet) followed by post-hoc analyses will be used to determine differences in cell number and distribution between KD and SD in different brain compartments. Student's t-tests or Mann-Whitney tests will be used to assess differences in proliferation, migration, and differentiation of neurosphere cell culture between the two diets.

Poster number: PM017 (SP)

Theme: Developmental neuroscience

Contrasting effect of overexpressing the neurotrophin receptors TrkA and TrkB during development

Authors: Mrs Laura Cassels¹, Professor Yves-Alain Barde¹, Dr. Xinsheng Nan¹

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Introduction: In the developing nervous system, specific populations of neurons depend on nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF) for their survival. While NGF binds to and activates the tyrosine kinase receptor TrkA, BDNF binds to TrkB, and this activation is known to prevent programmed cell death. To test the possibility that growth factor receptors may have signalling functions in the absence of ligand activation, here, TrkA and TrkB were overexpressed in all cells during the earliest stages of mouse development. Previous experiments

addressing a similar question used a strategy leading to the overexpression of TrkA and TrkB restricted to post-mitotic neurons¹. Under these conditions, TrkA, but not TrkB, caused the death of all developing neurons.

Methods: *TrkA* and *TrkB* cDNAs preceded by *LoxP* sites flanking a STOP cassette were inserted into the ubiquitously expressed *Rosa26* locus and a *Cmv^{Cre}* driver used to excise the stop cassette in all cells from the earliest stages of development. Embryos were examined by standard histological techniques, immunohistochemistry and iDISCO.

Statistical analysis: After testing the normality of the data, two-way ANOVAs with post-hoc tests were used to assess significance.

Results and conclusions: TrkA-induced cell death, marked by active caspase-3 staining, turned out to be restricted to post-mitotic neurons endogenously expressing TrkA (Table 1). Whilst cell losses in these ganglia resulted in perinatal lethality, the embryos appeared to be otherwise surprisingly normal. In particular, there was no evidence of increased cell death in cells not normally expressing TrkA. As these results are indistinguishable from those obtained with *Ngf^{-/-}* mutants, it appears that TrkA acts to capture target-derived NGF, thus preventing its interaction with expressed by neurons requiring NGF for survival. Overexpression of TrkB did not compromise the development, survival or even fertility of the animals, in spite of significant losses of cranial sensory neurons (Table 1). This contrasts with the results obtained with *Bdnf^{-/-}* animals and possible explanations for this surprising result will be presented.

Table 1 Number of surviving ganglia neurons in E18.5 TrkA- or TrkB-overexpressing mice

	TrkA Litters			TrkB Litters		
	Control (±SD) ^(N)	TrkA-over expressing (±SD) ^(N)	Remaining % vs. Control ⁽ⁿ⁾	Control (±SD) ^(N)	TrkB-over expressing (±SD) ^(N)	Remaining % vs. Control ⁽ⁿ⁾
Sensory Ganglia						
Dorsal Root (C1)	5728 (±1060) ⁽⁴⁾	1640 (±274) ⁽⁵⁾	29 % ^{***}	7798 (±1357) ⁽⁴⁾	4167 (±1725) ⁽⁵⁾	53 % [*]
Trigeminal	40494 (±4383) ⁽⁴⁾	10136 (±3980) ⁽⁵⁾	25 % ^{***}	43385 (±9484) ⁽⁴⁾	30704 (±2563) ⁽⁴⁾	71 % [*]
Vestibular	5144 (±713) ⁽⁴⁾	4801 (±711) ⁽⁶⁾	93 % ^{NS}	4842 (±473) ⁽⁴⁾	2689 (±364) ⁽⁵⁾	56 % ^{***}
Nodose-petrosal	5332 (±335) ⁽⁶⁾	4373 (±331) ⁽⁷⁾	82 % ^{NS}	4192 (±440) ⁽⁴⁾	774 (±167) ⁽⁵⁾	18 % ^{***}
Sympathetic Ganglia						
Superior Cervical	23510 (±4456) ⁽⁴⁾	14700 (±2415) ⁽⁵⁾	63 % ^{**}	26695 (±7422) ⁽⁴⁾	35461 (±4672) ⁽⁵⁾	133 % ^{NS}

Neuronal counts were determined from haematoxylin and eosin stainings. SD – standard deviation. Number of embryos analysed are indicated in superscript brackets. Two of each ganglia were counted per embryo and averaged. NS - not significant, * - $p < 0.05$, ** - $p < 0.01$, *** - $p < 0.001$ compared to littermate controls (two-way ANOVA with Bonferroni pairwise comparisons, except the vestibular ganglia where one-way ANOVA was performed).

References

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Poster number: PM018 (SP)

Theme: Developmental neuroscience

Investigating the effects of ketone supplementation on neuroepithelial and neuronal cell growth, lineage and health

Authors: Dr Robin White², Mr David Lee¹, Dr Jennifer England¹, Dr Mohammad Alherz¹, Dr Denis Barry¹

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Introduction: The ketone diet (KD) replaces glucose for ketone bodies by reducing carbohydrate and increasing fat and protein intake. The diet is growing in popularity as a method of weight loss and health maintenance. As such, the numbers of pregnant women engaging with the KD or variants of it are increasing. However, it remains unclear what the effects of glucose replacement with ketones are on neural cell development and differentiation from the multipotent neuroepithelium. Evidence is emerging to suggest that pregnancy in a ketogenic state has effects on

regional brain and organ development. We placed a spotlight on the impact of ketone supplementation and glucose deprivation on the growth, differentiation and metabolic activities of neuroepithelial stem cells and neurons.

Methods: The effects of beta-hydroxybutyrate (β HB) supplementation were compared in NE-4C (neuroepithelial) and SHSY-5Y (neuroblastoma) cells grown under regular and glucose-free conditions for 7 days. Both cell types were differentiated into neuronal/glia and neuronal phenotypes respectively using retinoic acid to determine the effects of β HB on cell maturation and lineage. Mitochondrial health was assessed using an MTT assay, and fluorescence indicators of mitochondrial membrane potential and cell viability. To test cell proliferation, cells were exposed to the synthetic nucleotide BrdU for six hours with subsequent protein quantification. Immunocytochemical analysis markers of neuronal and glial lineages were used to determine differentiation capacity. Cell growth and connectivity were analysed using actin expression, neurite outgrowth assays and synaptophysin expression.

Approach for statistical analysis: Following normality testing, one-way ANOVAs with subsequent post-hoc tests were used to evaluate quantitative differences between experimental groups in each experimental assay.

Results and conclusions: 5 and 10 mM β HB rescues both NE-4C and SHSY-5Y cells from glucose deprivation in short term cultures, but is cytotoxic at high and low concentrations. Normal growth patterns, rates of proliferation, and differentiation potentials of SHSY-5Y cells and NE-4C cells are altered with increased concentrations of β HB over time. These data shed new light on the effects of ketone supplementation on the growth, development and health of brain stem and neuroblastoma cells, revealing benefits and potential risks associated with the ketone diet during pregnancy.

Poster number: PM019 (SP)

Theme: Developmental neuroscience

Maternal and neonatal outcomes of gestational exposure to SSRI antidepressants in the rat

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Introduction: Selective serotonin reuptake inhibitor (SSRI) antidepressants are the most prescribed psychotropic drugs in pregnancy¹. SSRIs alter synaptic availability of serotonin, an important embryogenesis growth factor, and such gestational exposure pose risks to neonatal development including preterm birth, low birth weights and developmental delays². Currently, physicians face a dilemma selecting an SSRI when pregnant women are treatment-naïve. This study aims to mimic such a scenario by examining the maternal and neonatal effects of exposure to the SSRIs paroxetine (PRX), sertraline (SERT), citalopram (CIT), and fluoxetine (FLX) using a clinically relevant approach³.

Methods: Female Sprague-Dawley rats (~4 months) were mated and singly housed. From gestation day 7 until littering, dams received either vehicle, PRX (1.25, 2.5, or 5 mg/kg), CIT or SERT (2.5, 5 or 10 mg/kg), or FLX (2.5 mg/kg) via oral gavage (n=9-13/group). Maternal weights and food intake were measured. Littering characteristics such as litter size and mortality were recorded. Somatic and behavioural data were collected to measure the physical and behavioural maturation of the offspring.

Analysis: Data were analysed using either one or two-way ANOVA, Kruskal-Wallis or Chi-Squared tests; $p < 0.05$ was deemed statistically significant.

Results/Conclusions: During gestation, SERT (10 mg/kg) significantly reduced maternal weight gain and food consumption. Although litter characteristics did not differ across groups initially, within the first week pup mortality significantly increased for PRX (2.5, 5 mg/kg) and SERT (10 mg/kg) exposed dams; no deleterious somatic

development consequences were detected. There were significant decreases in surface righting behaviour on day 2 for SERT (2.5 mg/kg males) and CIT (10 mg/kg females) and day 4 for FLX (2.5 mg/kg males), following littering. Overall, these data demonstrate that at pharmacological doses, SERT decreased maternal weight gain and food consumption. Furthermore, PRX and SERT have profound effects on neonatal mortality and SERT, CIT and FLX have some deleterious behavioural effects in exposed pups. Such findings in an animal model could have implications for prescribing SSRI antidepressants during pregnancy and for perinatal care of SSRI-exposed infants.

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Acknowledgements: College of Science, NUI-Galway postgraduate fellowship.

Poster number: PM020 (SP)

Theme: Developmental neuroscience

Mapping differential responses to cognitive training using machine learning

Authors: Ms Mengya Zhang¹, Mr Joseph Rennie¹, Dr Duncan Astle¹, Dr Erin Hawkins¹, Dr Joe Bathelt¹

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The prospect of enhancing working memory (WM) and associated skills via cognitive training has received considerable interest from both researchers and commercial enterprises. Traditional approaches to analysing cognitive training data, such as group level ANOVAs followed by pairwise t-tests, suffer several limitations, which in turn have implications for theoretical and methodological progress. In an attempt to overcome previous limitations when modelling and analysing cognitive training data, the current paper explores the use of two relatively simple, yet effective, machine learning techniques. Specifically, we used self-organising maps (SOMs) and K-Means clustering to ask the following questions of previously acquired datasets: Are SOMs capable of representing multivariate cognitive data?; Does training alter between-task relationships?; Are there subgroups with different profiles of change following training? SOMs provide a means to represent relationships in multivariate cognitive datasets and make predictions based on this representation. Applying this approach to understand working memory training, our results suggest that between task-correlations remained relatively stable, with the exception of a pair of tasks both purporting to measure WM, the implications of which are discussed. K-means clustering analysis revealed three statistically meaningful subgroups with distinct performance profiles in an independent large sample (N=617, mean age= 9.16 years, range: 5.16-17.91 years). Further analysis involving the allocation of individuals from combined training studies (N = 179, mean age: 9.00 years, range: 7.08-11.50 years) into these same three subgroups both before and after training, revealed differentiable improvement trajectories. Moreover, scores on a separate measure of fluid intelligence were shown to be predictive of a participant's improvement trajectory. In summary, self-organizing maps coupled with K-means clustering appear to be a useful addition to the research toolkit that can help in the modelling and analysis of cognitive training data. In particular, the approach taken here highlights the need to reconsider the interpretation of training-related gains as it suggests that underlying mechanisms tapped by training might be task-specific rather than domain-general, and subject to individual differences.

Poster number: PM021 (SP)**Theme:** Developmental neuroscience**The RED App: a free, open-source and cross-platform touchscreen application for cognitive assessment in children****Authors:** Mr Giacomo Bignardi¹¹*MRC Cognition and Brain Sciences Unit, Cambridge, UK*

Introduction: Few children enjoy taking exams, yet many cognitive tests are based on traditional pencil-and-paper methods. We present a novel touch-based cognitive assessment application, designed with the aim to create brief, reliable, and engaging tasks for children aged 7-13. We validated the measures in a large developmental cohort, from the Resilience in Education and Development (RED) study.

Methods: The application was developed using the Unity Game Engine, and currently runs on different platforms (including Android, iOS and Windows). The initial release targets a range of cognitive domains, including working and short-term memory, visuospatial attention, phonological processing, number sense, evidence accumulation, educational attainment and questionnaire responses. We validated the app measures in a large and heterogenous sample of children within the RED longitudinal study (N>600). School year groups were tested in their own classrooms, using iPad tablet computers, in addition to teacher assessments of academic ability and behaviour.

Approach for statistical analysis: We detail the psychometric properties of the tasks, including their reliability and external validity to predict teacher-rated educational attainment, using latent variable and general linear models.

Results and conclusions: Most tasks had generally good psychometric properties, and we found that children enjoyed completing the majority of tasks, requiring minimal prompts to stay focused on the tests even when testing a classroom of 30 children simultaneously. We conclude that testing children with engaging tablet-based assessments is a viable way to collect cognitive and questionnaire data.

Poster number: PM022 (PP)**Theme:** Developmental neuroscience**Cognitive and Neuroanatomical Associations of Cavum Septum Pellucidum in a Pediatric Population****Authors:** Mr Zachary P Christnesen¹, Dr. Edward G Reedman¹, Dr John J Foxe¹¹*University of Rochester, Rochester, United States*

Introduction: The septum pellucidum is a thin membrane that separates the anterior horns of the ventricles. Prenatally a fluid-filled space separates the septum, forming cavum septum pellucidum (CSP). Typically this space closes soon after birth and the septum fuses along the midline. In some instances the septum does not fuse, resulting in a persistent CSP. Although CSP is found in neurotypical populations, estimates of its frequency are highly variable. The presence of CSP in adult populations has long been associated with chronic head trauma and more recently a variety of psychopathology, particularly psychopathy. The focus of the present study is to characterize CSP in a neurotypical pediatric population and determine its potential as an indicator of emerging psychopathology.

Methods: The adolescent brain and cognitive development (ABCD) study is a longitudinal, 21 site study that aims to follow children, recruited at ages 9-10, for a ten-year span. The initial population sample (Release 1.0) consists of 4521 children. All children are screened for psychopathology prior to enrolment. Neuroimaging will be collected biennially and cognitive assessments annually from children throughout the ABCD study.

The focus of this investigation is the relationship between CSP presence and measures from KSADS-V diagnostic interviews, the prodromal psychosis scale, the youth prosocial survey, sum mental health scores, and structural

connectivity. Total symptoms present within each KSADS-V diagnostic subscale will be used as a proxy for degree of subclinical manifestations of each psychopathology subscale. The prodromal psychosis scale will be used to derive the weighted distress score for each child. The total scores from the prosocial behaviour survey will be used to further characterize social behaviour. Structural connectivity measures will be derived from diffusion weight images using the human connectome pipeline.

Approach for statistical analysis: The association between structural connectivity measures and CSP will be modelled using cross validation of a generalized lasso to identify the association between select structural measurements. Factor analysis will be used to identify underlying latent factors within psychopathology measures. Upon identification and characterization, these latent factors will be modelled in relation to CSP using mixed effect models to control for study site.



Pediatric brain with cavum septum pellucidum

Poster number: PM023 (SP)

Theme: Developmental neuroscience

Altered thermal and mechanical nociceptive responding following TLR4, but not TLR3 activation in the valproic acid rat model of autism

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Introduction: Increasing evidence indicates that individuals with autism spectrum disorders (ASD) exhibit altered pain perception and expression^[1]. Recent studies in our lab have demonstrated altered nociceptive responding in a clinically relevant ASD animal model, the prenatally exposed valproic acid (VPA) rat. ASDs are also associated with altered immune responses^[2], which may underlie the altered pain perception associated with this disorder. Thus, this study investigated the impact of toll-like receptor (TLR)3 and TLR4 activation on nociceptive responding in the VPA rat model.

Methods: Pregnant female Sprague Dawley rats received VPA(500mg/kg;s.c.) or saline at GD12.5. Adolescent female offspring (PND41-45, n=9-12) underwent baseline nociceptive testing in the hotplate test (HPT; thermal nociception) and von Frey test (VFT; mechanical nociception). Animals received either a TLR3-agonist (polyI:C; 3mg/kg;i.p.), TLR4-agonist (LPS; 1mg/kg;i.p.), or vehicle (saline) and were re-tested for nociceptive responding at 3, 6 and 24hrs post-immune challenge.

Statistical analysis: Data were analysed using two-way ANOVA followed by Fisher's LSD *post-hoc* or Kruskal-Wallis followed by Mann-Whitney U-test. $P < 0.05$ was deemed significant.

Results and Conclusion: Baseline testing revealed that VPA-exposed rats exhibited an increased response latency in the HPT and higher paw withdrawal threshold (PWT) in the VFT, when compared to saline-exposed counterparts. In saline-exposed rats, LPS reduced response latency in the HPT at 3hrs and increased PWT in the VFT at 3 and 6hrs. VPA-exposed rats exhibited reduced response latency and higher PWT in the HPT and VFT respectively, at 3hrs post vehicle administration, when compared to saline-exposed counterparts. LPS did not alter response latency of VPA-exposed rats in the HPT, but reduced PWT in the VFT at 3hrs when compared to vehicle-counterparts. PolyI:C administration did not alter nociceptive responding of either group. Systemic LPS and polyI:C administration reduced bodyweight 24hrs post-challenge in both groups.

In conclusion, VPA-exposed rats exhibit altered thermal and mechanical nociceptive responding prior to and following TLR4, but not TLR3, activation. These data indicate that TLR4-mediated immune responses may underlie the altered nociceptive responding associated with autism.

Acknowledgements:

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Poster number: PM024 (SP)

Theme: Developmental neuroscience

Graph theory application in functional brain network architecture of healthy neonates using data from the developing human connectome (dHCP)

Authors: Ms Megan Ni Bhroin¹, Dr Arun Bokde¹, Dr Eleanor Molloy²

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Graph theory based approaches model the brain as a complex network represented as a graph comprising nodes and edges. Using this approach, we can better understand the developmental trajectory in the functional brain network architecture, which is largely unknown. Studies have shown that important, highly connected brain areas or hubs are mostly located in association cortices in adults. In the present study, we used data from the developing human connectome project (dHCP) to characterize functional brain connectivity of healthy neonates using graph theory measures.

High resolution structural and functional MRI data from 37 term-born neonates (21 male, 13 female) were acquired through the first release of the dHCP. Images were processed and analysed in SPM8 and the CONN toolbox. Residual time series for all voxels within the 90 cortical and subcortical ROIs were averaged to represent the BOLD signal for that particular region. These ROIs are based on the AAL parcellation and mapped to neonates by Shi et al. Characteristics graph metrics included; betweenness centrality, degree centrality, clustering coefficient and global efficiency.

Regionally, brain hubs were found to be well-established by the time of birth. Specifically, the hubs in neonates, calculated with betweenness centrality, were found to be located in the precuneus, which were adult-like, and in lateral regions including the rolandic operculum and sensorimotor regions which were neonate-specific ($P < 0.001$, in all cases, FDR-corrected). Moreover, degree centrality hubs we identified, the parietal lobule and the cuneus have also been consistently located in adults. The top clustering coefficient and global efficiency hubs were also found to be located in sensory and motor regions ($P < 0.001$, in all cases, FDR-corrected).

Our results show that cortical hubs in healthy full term infants are bilaterally connected and can be mainly found in homodal primary sensorimotor brain regions. This suggests that primary sensorimotor networks are highly functioning at birth which is highly consistent with behavioural observations. This is in contrast to what is seen in adults where the majority of cortical hubs and hub-related networks are located in heteromodal association cortex. Taken together, our findings indicate that hub patterns while not fully mature in the neonate brain – are transitioning to an adult configuration.

Acknowledgments:

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Poster number: PM025 (SP)

Theme: Developmental neuroscience

Modelling Evidence Accumulation in children using a random dot kinematogram iPad app

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Introduction: Evidence Accumulation has been characterised and modelled extensively in adult humans and animal models (e.g. Gold and Shadlen, 2001; Wyart et al., 2012), however it's development in children, and it's role in school attainment & cognition has been little studied. Here we present an iPad-based assessment-game, which could easily provide a rich measure of evidence accumulation processes in children. We report on the findings from the first time-point in a longitudinal study.

Methods: As part of a wider project investigating cognitive and social skills in primary school children (600, 7-9 years olds) were assessed in class using an iPad app and a teacher questionnaire. Amongst measures of socioeconomic status, maths and English attainment, standardised school tests, working memory, attentional control, number sense, phonological awareness, and other tasks, an app-based evidence accumulation task was used.

A random dot kinematogram (characterised as a 'snow cloud') showed a varying amount of coherent movement which changed over time, and in half of the trials showed conflicting directions. The child had to drag a figure in the direction that they thought most of the dots were moving. This allowed us to record a continuous response to the current weight of evidence.

Statistical Approach and Analyses: First, a simple correlation of the current weight of evidence over time with the Y position of the child's finger placement was undertaken. The responses were fitted to contemporary models of evidence accumulation. The model parameters were then compared with the working memory, short term memory, attentional control, search organisation, attentional control, number sense, and educational outcomes, using bayesian general linear modelling.

Results and Conclusion: Due to the variability in the children's responses not all data is fitted well under the models, but within each participant there is a number of viable trials for data analysis — the richness of the measure only require a few trials to fit. We find associations with both the simple correlation between response and evidence over 'valid' trials, and also certain model parameters, with cognitive and educational outcomes. This shows we are able to model evidence accumulation in children with a relatively quick assessment.



Screenshot of the iPad based evidence accumulation task. A changing random dot kinematogram indicates which side to move the snowman to. The location of the child's hand is shown by the cartoon hand.

Poster number: PM026 (SP)

Theme: Developmental neuroscience

Maternal exposure to stressful life events and early brain development in preterm neonates

Authors: Miss Alexandra Lautarescu¹, Dr Diliana Pecheva¹, Dr Suresh Victor¹, Dr Michael Craig², Prof David Edwards¹, Prof Serena Counsell¹

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Introduction: Prenatal stress exposure is associated with a range of adverse outcomes in the offspring, including an increased risk for neurodevelopmental and psychiatric outcomes. The biological basis for this is poorly understood. In vivo brain imaging studies of children exposed to maternal stress in utero have reported decreases in grey matter volume, as well as changes in white matter microstructure. The aim of this study was to investigate the association between maternal stress and offspring early brain development in the context of preterm birth.

Methods: 207 infants born prematurely (mean age=29.99, SD=2.12, range 23.57-32.86) underwent magnetic resonance imaging (MRI) around term equivalent age (mean age=42.24, SD=1.57, range 37.86-45.29). MRI scans were acquired on a Philips 3 Tesla MR system using an eight-channel phased array head coil. Mothers completed a questionnaire measuring the number and severity of stressful life events experienced in the year prior to the study visit. Women who reported alcohol and drug abuse during pregnancy, and cases with major focal lesions were excluded from analysis. Ethical approval was obtained from the Hammersmith and Queen Charlotte's Research Ethics Committee (09/H0707/98).

Approach for statistical analysis: Multiple regressions were used to examine associations between maternal stressful life events and offspring brain development, controlling for gestational age at birth, postmenstrual age at scan, maternal age, socioeconomic status, and total days on parenteral nutrition. Structural MRI data analysis included volumetric data for several regions of interest (relative to total brain volume): hippocampus, amygdala, and thalamus. Diffusion MRI data analysis included the uncinate fasciculus tract, and a control tract, the inferior longitudinal fasciculus.

Results and conclusions: Increased maternal stress as measured by exposure to stressful life events was associated with altered white matter microstructure (increased axial, radial, and mean diffusivity) in the uncinatus fasciculus, but not in the control tract. Maternal stress was not significantly associated with volume changes in any of the regions of interest. In conclusion, these findings suggest that prenatal stress exposure may be associated with altered development of specific fronto-limbic pathways in preterm neonates as early as term equivalent age.

Poster number: PM027 (SP)

Theme: Learning and memory

NMDAR-dependent mechanisms influence the claustral place field remapping in darkness

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The claustrum is an enigmatic and underexplored brain structure, with conflicting views regarding its functions. Determining the precise organisation and function of the claustrum remains a challenge given the difficulty in reliably targeting claustral neurons for physiological and anatomical investigation. This lacuna has been addressed by recent research focused on the anatomical, electrophysiological and behavioural properties of the claustrum. Previous studies conducted in our lab (Jankowski MM and O'Mara SM, 2015) demonstrated the presence of place cells in the claustrum with the hypothesis that they may be anchored to visual stimuli. To further explore this issue, we describe here, for the first time in the claustrum, possible cellular mechanisms whereby place fields are remapped when visual cues are eliminated in the environment through manipulations of ambient lighting conditions. Through implantation of tetrodes into the anterior claustrum of freely-moving rats, we performed in vivo electrophysiological recordings while they navigated different environments. Neuronal plasticity plays a fundamental role in the place field formation during navigation. Therefore, we performed spatial navigation experiments following intraperitoneal injection of the NMDAR antagonist ((±) - 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP)) and the NMDAR co-agonist D-Serine. Our results show claustral place fields remap when the visual input removed, and this remapping appears to be under the control of NMDAR-dependent mechanisms.

Poster number: PM028 (SP)

Theme: Learning and memory

Too little and too much: impact of functional inhibition and disinhibition of the medial prefrontal cortex on behavioural flexibility assessed using an operant strategy-shifting task

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Introduction: Attentional performance requires balanced medial prefrontal cortex (mPFC) activity, with functional inhibition or disinhibition by micro-infusion of the GABA agonist muscimol or antagonist picrotoxin, respectively, causing impairments (Pezze *et al.*, 2014, *JNeurosci*). Aspects of behavioural flexibility, linked to the mPFC and local GABA transmission (Brady&Floresco, 2016, *JoVE*), may also require balanced mPFC activity.

Methods: We examined how mPFC muscimol (62.5ng/side) and picrotoxin (300ng/side), as compared to saline control infusions, affect behavioural flexibility in male Lister Hooded rats, using an operant strategy-shifting task. The task involved 'shifts' (across three sessions) from a spatial-response condition, where food reward was associated

with left or right lever responses, to a cue light-based response condition, where food reward was associated with panel light illumination, or vice versa (Brady&Floresco,2016)(see Figure).

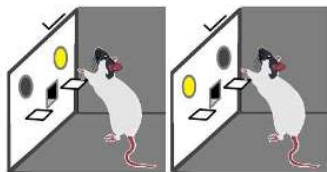
Analysis: Trials to criterion and percentage of correct responses, omissions and errors (perseverative or never-reinforced) were analysed by ANOVA using infusion group as between-subjects factor and, if appropriate, shift session as within-subjects factor. Fisher's LSD test was used for post-hoc comparisons.

Results and conclusions:

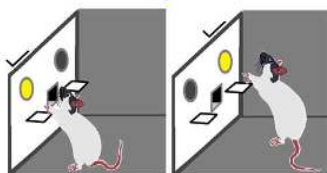
Remarkably, irrespective of infusion, to shift from spatial-response to cue light-based responses, Lister hooded rats required three times as many trials as reported in previous studies in other strains (e.g. Brady&Floresco,2016). These slow shifts were not impaired by mPFC inhibition or disinhibition. However, in addition to increasing trial omissions, disinhibition impaired spatial-response expression and, during shifts, reduced perseveration of the spatial-response condition.

Although Lister-Hooded rats struggled with spatial-response-to-cue-response shifts, they readily acquired cue-based responses when they had not first been trained in the spatial-response condition. Moreover, they then readily performed cue-to-spatial-response-strategy shifts. Interestingly, there was a strong trend for mPFC disinhibition to slow down the cue-to-spatial-response-shift, with picrotoxin-infused rats showing a lower percentage of correct responses than saline-infused rats during shift session 2.

In conclusion, although Lister hooded rats readily acquired both spatial-response and cue strategies they were slow to shift from the spatial-response strategy. This was unaffected by mPFC inhibition or disinhibition. In contrast, they readily performed a cue-to-spatial-response-strategy shift, and prefrontal functional disinhibition, but not inhibition, tended to disrupt this shift.



Spatial Response Condition: Lever on one side (e.g. here the right lever) is correct, irrespective of cue light



Visual Cue Condition: cue light indicates correct lever, irrespective of lever side

Poster number: PM029 (SP)

Theme: Learning and memory

Fan cells in lateral entorhinal cortex are critical for recognition of object-place-context configurations

Authors: Dr Brianna Vandrey¹, Dr Derek Garden¹, Miss Veronika Ambrozova², Professor Matthew Nolan¹, Dr James Ainge²

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Introduction: Episodic memory relies on the hippocampus and its surrounding cortical network. The superficial layers of entorhinal cortex provide substantial input to the hippocampus within this network. Recent evidence suggests that the lateral entorhinal cortex (LEC) is required to bind together features of an episode¹. However, the role of discrete circuit components is unclear. Fan cells in layer 2 (L2) of LEC which project to the dentate gyrus (DG) are of particular interest given that L2 manifests early pathology in Alzheimer's Disease². Here, we ask if suppressing output from fan cells in L2 of LEC affects the ability to integrate object information with the contextual and spatial features of an episode.

Methods: We used Sim1:Cre mice to obtain genetic access to fan cells in LEC L2³. Injection of adeno-associated virus (AAV) encoding green fluorescent protein (GFP) into the LEC of Sim1:Cre mice labeled neurons with morphological and electrophysiological characteristics of fan cells⁴. Subsequently, AAV encoding tetanus toxin light chain (TeLC) or GFP was injected into the LEC of a further cohort of Sim1:Cre mice (21 TeLC; 17 GFP control). These mice were tested on novel object recognition, object-context (OC), and object-place-context (OPC) tasks.

Approach for Statistical Analysis: A discrimination ratio was calculated for each task⁵. One-sample t-tests were conducted to determine whether ratios for each group were above chance, and univariate ANOVAs were used to compare groups. Pearson's R was calculated to determine relationships between virus expression and behaviour.

Results and Conclusions: OPC recognition was significantly impaired in mice in the TeLC group in comparison to controls. However, mice in the TeLC group maintained recognition of novel objects and OC configurations. Performance on the OPC task was correlated with the extent of virus expression in the TeLC group. These findings indicate that fan cells in L2 of LEC are critical for associating the features required for episodic memory.

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Poster number: PM030 (SP)**Theme:** Learning and memory**Novel 2-dimensional spatial navigation tasks in awake head-fixed mice****Authors:** Dr Sarah Stuart¹, Dr Jon Palacios¹, Professor Jack Mellor¹¹*University of Bristol, Bristol, United Kingdom*

Introduction: Novel approaches to allow stable neurophysiological recordings in awake behaving mice are necessary to advance our understanding of the neural networks associated with cognitive behaviours such as Learning and memory. The most commonly used techniques either require full physical restraint or employ linear treadmills in combination with virtual reality. More recently however, a novel method in which a head-fixed mouse can move around an air-lifted Mobile Homecage and explore a tangible 2-dimensional environment offers the potential to assess a variety of behaviours simultaneously with high-precision neurophysiological recordings and/or 2-photon imaging. However, the extent to which these animals can perform reward and cue-associated spatial navigation tasks in this system has not yet been investigated.

Methods: Learning behaviour was assessed in cohorts of adult male C57BL/6 mice in 3 reward-associated behavioural tasks. In a spatial reversal learning task, animals learned to associate one arm of a T maze with reward delivery before the location of the reward was then changed to the opposite arm. In a cued reward-localisation task, the mice explored a circular track using tactile and visual cues and were required to wait within a target location for 2s to obtain reward. In a third task, animals were trained to use left/right light cues to find the location of reward in a T maze.

Analysis Approach: Learning curve data was analysed using one- or two-way repeated measures ANOVA where appropriate.

Results and Conclusions: Mice demonstrated a clear reversal of arm choice and time spent in each arm in the spatial reversal learning task. In both tactile and light cued reward-localisation tasks, the mice reached ~70% accuracy over the course of 2 weeks of training. These data indicate that the animals are able to effectively learn three goal-directed behaviours under conditions presented in the Mobile Homecage system, and provide the basis for future experiments investigating the neural and molecular mechanisms underlying spatial navigation and memory in head-fixed mice.

Poster number: PM031 (SP)**Theme:** Learning and memory**Spatial coding in the subiculum requires intact input from anterior thalamus****Authors:** Dr Bethany Frost¹, Professor John Aggleton², Professor Shane O'Mara¹¹*Institute Of Neuroscience, Trinity College Dublin, Dublin, Ireland,* ²*School of Psychology, Cardiff University, Cardiff, UK*

Introduction: Network interactions involving the anterior thalamus (ATN), hippocampal formation, and retrosplenial cortex (RSP) are critical to spatial mnemonic processes. Hippocampal area CA1 comprises a major projection to the subiculum. The ATN also project directly to the dorsal subiculum, and lesions of the ATN induce significant deficits in spatial navigation.

The majority of CA1 neurons display a strong spatial signal (place cells). Neurons in the subiculum show a heterogenous spatial code, with place, head-direction and grid cells among the neuronal phenotypes present. Here, we sought to understand the origins of the heterogenous spatial signal in subiculum and further our understanding of the neural basis of ATN lesion-induced dysfunction.

Methods: Simultaneous single-unit and local field potential (LFP) recordings in the dorsal subiculum combined with LFP recordings in the RSP were conducted during exploration and behaviour tasks in control (n=3), sham (n=3) or ATN-lesioned (n=6) rats. In addition, a further six rats underwent single-unit and LFP recordings in the dorsal subiculum and RSP during temporary inactivation of the ATN using muscimol.

Approach for statistical analysis: Spike sorting was performed using TINT (Axona Ltd, UK) to isolate single units based on waveform features. Spatial properties of spike clusters were investigated using custom-written MATLAB (MathWorks, USA) code, and statistical analyses were performed in R (R-Project, Austria).

Results: Place, head-direction and grid cells were recorded in the dorsal subiculum of control rats. Unexpectedly, given the intact spatial projection from CA1, no spatial units were recorded in the subiculum of ATN-lesioned rats, and spatial alternation task performance dropped to chance. There was no impairment in bow-tie maze performance in ATN-lesioned rats, indicating recognition memory remained intact.

Within-animal studies showed that temporary inactivation of the ATN reversibly disrupts spatial signal in the subiculum and causes a temporary deficit in spatial alternation behaviour.

Conclusion: The absence of ATN input to the hippocampal formation causes disruption in spatial signal processing in the subiculum, suggesting that the spatial responses found in the subiculum are the result of thalamic input rather than hippocampal. Spatial signal in the subiculum requires input from the ATN, and does not depend on input from CA1.

Poster number: PM032 (PP)

Theme: Learning and memory

Identifying neural and computational markers of age-related changes in reinforcement learning

Authors: Ms Laura Rai¹, Ms Gabi Pragulbickaite¹, Ms Catherine Baker¹, Ms Laura Brosnan¹, Ms Hannah Rice¹, Mr Rory Boyle¹, Dr Francesca Farina¹, Prof Robert Whelan¹

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Introduction: Probabilistic reinforcement learning refers to the process of using unreliable feedback in order to learn the value of stimuli and guide decision-making. It has been shown to decline with age, however the mechanisms underlying this decline remain poorly understood. The Probabilistic Selection Task measures individual differences in learning from reinforcement relative to punishment, and it has been shown that dopaminergic state modulates such learning (Frank et al., 2004). The aim of the present study was to examine age-related cognitive changes in reinforcement learning.

Methods: A sample of healthy young adults (N = 40) and healthy older adults (N = 80) completed the training and test phases of the Probabilistic Selection Task under EEG, alongside a measure of spontaneous eye-blink rate as an index of dopamine functioning.

Approach for statistical analysis: Performance on the PST will be compared between younger and older participants. Using the drift diffusion model of decision-making, we will use computational modelling to bridge the behavioural and neural data in order to examine age-related differences in reinforcement learning. The Hierarchical Drift Diffusion Modelling toolbox (Wiecki et al., 2013) will be used to model trial-by-trial behaviour alongside EEG theta power (4-8 Hz). In addition, standard group comparisons between the younger and older age-groups will be made on the behavioural PST data and event-related potentials (ERPs) in the training and test phases.

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Poster number: PM033 (PP)

Theme: Learning and memory

Does adolescent exposure to a cafeteria-diet potentiate the effect of neuroinflammation on memory during adulthood in rats?

Authors: Dr Sarah Nicolas^{1,3}, Dr Ciarán S. Ó Léime^{1,3}, Dr Alan E. Hoban¹, Dr Cara M. Hueston¹, Prof. John F. Cryan^{1,2}, Dr Yvonne M. Nolan^{1,2}

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Introduction: Overconsumption of high energy diets rich in saturated fat and sugar (cafeteria-diet) leads to an increased prevalence of obesity, metabolic disorders and memory impairments and is thus a major health concern in developed countries. Adolescence is a critical period of development of plasticity-driven neural circuits in the hippocampus and associated Learning and memory function. The hippocampus is particularly susceptible to the pro-inflammatory cytokine interleukin-1 β (IL-1 β), with elevated levels in adulthood implicated in memory and stress-related disorders. We hypothesize that the adolescent hippocampus may be particularly susceptible to hippocampal-associated impairments induced by a cafeteria-style diet, which may impact upon behaviour and resilience to inflammation in later life.

Thus in this study, we will investigate whether consumption of a cafeteria diet during adolescence induces memory, inflammatory and metabolic impairments in adulthood, and whether it potentiates the negative effect of IL-1 β on memory during adulthood.

Methods: Male Sprague Dawley rats had free access to a cafeteria diet during the adolescent period (P28 – P56). At P56 (early adulthood) a lentivirus causing overexpression of IL-1 β was injected into the hippocampus and allowed to overexpress IL-1 β for six weeks to induce chronic neuroinflammation. Hippocampal-associated behaviours (recognition and contextual memory) were carried out three weeks after viral integration. The impact of the cafeteria-diet during adolescence on adult metabolism, inflammation and hippocampal neuroplasticity will be assessed by measuring the levels of hormones (insulin, leptin, adiponectin), and inflammatory cytokines (IL-1 β , IL-6, TNF- α) in the circulation, and the expression of plasticity markers (synaptophysin, PSD95, BDNF) in the hippocampus.

Statistical analysis: We will analyse the behavioural data generated from the memory tasks, and plasticity markers to determine the potential interaction between adolescent consumption of cafeteria-diet and adult neuroinflammation on behaviour and plasticity. The means (+/- SEM) will be analyzed via one-way or two-way analysis of variance (ANOVA) tests, followed by a post-hoc analysis, in order to characterize both the effect of cafeteria-diet in adolescence, the injection of IL-1 β and the interaction between these 2 interventions.

This work was supported by Science Foundation Ireland (SFI/IA/1537)

Poster number: PM034 (SP)**Theme:** Learning and memory**Cognitive impairment at an early age in animal model of sensitivity to stress is accompanied with marked neurophysiological alterations****Authors:** Ms. Maryia Bairachnaya¹, Mr. Alexey Shnayder¹, Dr. Anton Sheinin², Prof. Albert Pinhasov¹, Dr. Izhak Michaelievski¹¹Ariel University, Ariel, Israel, ²Tel-Aviv University, Tel-Aviv, Israel

Introduction: Uncovering the mechanisms underlying age-related cognitive changes is one of the most important challenges in neuroscience. The multiplicity of evidence indicates a strong correlation between the impact of stress on brain functionality and ageing-related cognitive impairments. Using a unique mouse model of sensitivity to stress developed in our lab by selective breeding according to their social behavior (dominance (Dom) or submissiveness (Sub)), we found that Subs exhibit stress-sensitivity signs, e.g. depressive- and anxiety-like behavior after exposure to chronic mild stress (CMS), in contrast to the stress-resilient Doms. Moreover, in a novel object recognition paradigm, Subs exhibited a marked cognitive decline at an early age, been accompanied with alterations in short- and long-term synaptic plasticity.

Methods: In this study, electroencephalography (EEG) recording was used to monitor brain electrical activity during novel object recognition (NOR) test. Cognitive performance in Dom and Sub animals was evaluated in different age groups (3, 6 and 9-month old) before and after CMS exposure.

Approach for statistical analysis: Performance of each group in the memory task was compared using the ANOVA method, followed by Bonferroni post-hoc tests. Power spectrum density was calculated with custom-written MATLAB-based programs (MathWorks, Natick, MA).

Results and conclusions: We found that cognitive deficiency in Subs from an early age was accompanied with changes in frequency bands on EEG, e.g. significantly lower power in delta (1-4 Hz), theta (4-8 Hz) and low gamma (20-40 Hz) frequency bands in hippocampus during novel object exploration. Moreover, after CMS exposure inherent stress susceptibility in Sub mice correlates with alterations in multiple frequency bands in mPFC: increased power in delta (1-4 Hz) and theta (4-8 Hz) frequency bands and low power in low gamma (20-40 Hz). These findings reveal a correlation between early age cognitive decline in stress susceptible animals and power alterations of frequency bands. Further studies would allow a better understanding of corticolimbic neurophysiological events that are linked to early manifestation of age-related cognitive impairments.

Poster number: PM035 (SP)**Theme:** Learning and memory**Destabilising instrumental memories: influence of reinforcement schedule and reinforcer magnitude during memory reactivation****Authors:** Dr Antonio Ferragud¹, Mr Craig Burns¹, Dr Omar Perez², Ms Holly Hellawell¹, Ms Alexa Netty¹, Ms Natasha Seaton¹, Mr Vikram Thakur¹, Mr Nikolay Zhelyazkov¹, Dr Amy Milton¹¹University Of Cambridge, Cambridge, United Kingdom, ²California Institute of Technology, Pasadena, USA

Introduction: Whether instrumental memories reconsolidate has been a contentious question. While early work suggested that they did not, more recent research has shown that instrumental memories will reconsolidate with reinforcement schedule changes during memory reactivation. Exton-McGuinness et al. (2014) showed that variable, but not fixed, ratio schedules of reinforcement at reactivation induced a previously trained instrumental memory to

destabilise and become sensitive to disruption with an NMDA receptor antagonist. Here, we sought to further characterise and understand other factors that induce instrumental memory reconsolidation, with the hypothesis that destabilisation would occur when prediction error was induced during memory reactivation.

Methods: Rats were trained on a fixed ratio (FR)-1 schedule over 10 days. 24 hours after the completion of training, animals were re-exposed to the conditioning chamber, with different groups experiencing different schedules of reinforcement. These included variation of: reinforcement schedule predictability (fixed ratio, variable ratio, and random ratio schedules), reinforcer magnitude, and the effort required for the instrumental response. In separate groups, we also tested whether temporal expectation of reinforcement could induce destabilisation in rats trained on variable interval schedules. The persistence of the memory was tested in a drug-free, unreinforced operant session 24 hours after memory reactivation.

Approach for statistical analysis: Differences in test performance were analysed with ANOVAs, with Condition (reactivation) and Drug (vehicle vs MK-801) as between-subjects factors. Reactivation performance was assessed in a similar manner, to test for acute behavioural differences produced by drug administration. Animals were matched for training performance before assignment to experimental conditions using repeated measures ANOVAs, with Session as a within-subjects factor and prospective Drug and experimental Conditions as between-subjects factors.

Results and conclusions: In addition to replicating the findings of Exton-McGuinness et al. (2014) that a shift to a variable ratio, but not fixed ratio, schedule at reactivation induces reconsolidation of an instrumental memory, we observed that changes in reinforcer magnitude induced memory destabilisation. Altering the amount of effort, or the expected timing of reinforcer delivery, did not induce reconsolidation. This work is the most extensive analysis of the conditions that support instrumental memory reconsolidation to date.

Poster number: PM036 (SP)

Theme: Learning and memory

MSK1 and its role in inducing synaptic changes after environmental enrichment

Authors: Ms Pippa Richardson¹, Mr Daniel D. Cooper¹, Professor Bruno G. Frenguelli¹

¹University Of Warwick, Coventry, United Kingdom

Introduction: Environmental enrichment has many positive effects on the brain including improved cognition and increased dendritic spine density. The most probable molecular pathway involved is the enrichment-induced release of brain-derived neurotrophic factor (BDNF). We have shown that mitogen- and stress-activated protein kinase 1 (MSK1), which is activated by BDNF and regulates transcription through CREB phosphorylation, is necessary for the enhancement of miniature excitatory postsynaptic synaptic currents (mEPSCs) post-enrichment (Correa *et al.*, 2012; Lalo *et al.*, 2018).

Changes in cell surface expression of AMPA receptors (AMPA receptors) is a likely mechanism for regulating these effects since synaptic AMPAR levels correlates with the efficiency of neuronal transmission. Our current hypothesis is that MSK1 is necessary for trafficking AMPARs to the synaptic membrane, to elicit enhancement of synaptic transmission and cognition after enrichment. To determine how MSK1 regulates enrichment-induced effects, we used mice that contain a mutation that removes MSK1's kinase function (MSK1 KD).

Methods: We are comparing across four groups of wild-type and MSK1 KD mice, raised under either standard or enriched conditions over various lengths of time, ranging from juveniles to adults. Using western blotting, we investigated total AMPAR levels in hippocampal tissue and will use cell surface biotinylation and immuno-gold electron microscopy to determine AMPAR localisation. How MSK1 regulates behaviour is being investigated using novel object recognition and spontaneous alternation tasks.

Approach for statistical analysis: Four groups will be compared within these experiments, with n=4 per group for biochemical assays and 10-14 for behavioural tasks. Two-way ANOVA statistical analysis will determine any effects of housing condition and genotype.

Results and conclusion: We have established that total levels of AMPAR subunits, GluA1 and GluA2, are not different across either housing or genotypes after 1 week of enrichment. To determine the basis of the impairment of synaptic transmission in the MSK1 KD mice we will use cell surface biotinylation and immuno-gold electron microscopy against GluA subunits.

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Poster number: PM037 (SP)

Theme: Learning and memory

The time-course of human memory consolidation in preclinical Alzheimer's disease

Authors: Mr Alfie Wearn¹, Miss Esther Saunders-Jennings¹, Mr Volkan Nurdal¹, Dr Michael Knight¹, Dr Risto Kauppinen¹, Dr Elizabeth Coulthard^{1,2}

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Memory consolidation over days and weeks requires a brain network including hippocampus, thalamus and neocortex (Aggleton 2014; Barry et al. 2018), but the temporal dynamics of regional recruitment in humans is unclear. Structural changes, prominently in medial temporal lobe (MTL), cause long-term memory consolidation deficits present in preclinical stages of Alzheimer's disease (AD). Therefore, participants at various stages of AD provide a window onto how brain changes impact long-term memory consolidation.

By observing the strength of correlations between volumetric measures of brain structure, and delayed recall probed over long periods, we test the hypothesis that hippocampus is the critical node in the network for early memory consolidation (with different temporal functionality within its subfields), whereas neocortex is required for long-term storage and thalamus is critical in the transfer of information between the two.

We present analyses from two cross-sectional studies in which participants were tested for immediate and delayed verbal recall and had a structural MRI scan. Study 1 included 65 participants (17 with mild cognitive impairment; MCI) and study 2 included 60 participants (16 MCI). Verbal memory was assessed using Hopkins or California Verbal Learning Tasks, respectively (HVL/CVLT). Delayed recall was tested after a short delay (~30 minutes) and after either 24 hours (study 1) or 4 weeks (study 2). Volumetry was conducted using FreeSurfer v6.0 and ASHS (Automatic Segmentation of Hippocampal Subfields).

In both studies, all timepoints of delayed recall correlate with MTL volume, whereas, thalamus volume predicts performance exclusively at 30m. Ventromedial prefrontal cortex (vmPFC) thickness significantly correlates with all timepoints in study 2, but none in study 1, possibly reflecting the increased difficulty of CVLT. All MTL subfields except CA3 positively correlate with verbal memory at both short and long-delay timepoints, in both studies. These data emphasise the critical role for hippocampus in short and long-term memory consolidation. In contrast, thalamus has a temporally specific role in shorter-term memory consolidation and vmPFC is recruited for a harder memory task, perhaps because effective memory required protection from distracting information. Overall, we have demonstrated specific roles for regions within the network underpinning orchestration of human long-term memory.

Poster number: PM038 (SP)

Theme: Learning and memory

Modelling Learning and memory using behavioural analysis, confocal imaging and whole-mount in situ hybridisation with immediate early genes in zebrafish

Authors: Dr Sandra Toledo-Rivera¹, Dr Anton Nikolaev¹

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Introduction: The brain is a unique kind of machinery with the capability of adaptation to learn and forget things all the time, modifying itself while for instance, you are reading this. This ability is what we know as brain plasticity. Here we describe different behavioural, molecular and imaging methods that aim to contribute in the identification of how this mechanism works on the wild-type zebrafish, chosen as a model for the many advantages that it offers such as the close homology that shares with humans.

Methods: Visual Lateralisation Novel Object Recognition (VLNOR) and the classical Novel Object Recognition tests along with Whole-Mount in situ hybridisation (WISH) using the Immediate Early Gene *c-fos* were tested in zebrafish over 5 days post-fertilisation. Additionally, *in vivo* confocal imaging on nacre *NBT:GCaMP3* line of late-stage zebrafish larvae was done to characterise the different responses retrieved according to different visual memory stimuli given, mainly in the optic tectum neuropil and peri-ventricular neurons.

Analysis approach: Computerised video and image processing and analysis methods were performed to assess the relation of the ZF regarding the angle and distance within the object per frame (25 fps) using custom-written scripts for Python. WISH was done using Pentylentetrazole-treated fish as a positive control of *c-fos*. Finally, the voxel-wise method described in Bergmann et al. 2018, was used for the confocal imaging analysis through a custom written code for Igor Pro 6.3.

Results and conclusions: WISH in up to 22 days post-fertilisation zebrafish was achieved successfully, opening the possibility to perform this technique on fish submitted to behavioural tests only and with other IEG such as Arc and Homer1a. The use of zebrafish behavioural analysis, whole-mount In situ hybridisation, and confocal imaging are ideal tools for memory formation research, offering us an affordable approach that would result in a number of useful applications for future memory research, including therapeutic targets for a variety of neurodegenerative disorders regarding memory such as Alzheimer disease, ageing memory-loss prevention, among others.

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Poster number: PM039 (SP)

Theme: Learning and memory

Noradrenergic modulation of the hippocampal CA1 network

Authors: Mr Travis Bacon¹, Prof Tony Pickering¹, Prof Jack Mellor¹

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Introduction: The hippocampus encodes new memories by strengthening synaptic coupling to create ensembles of principle neurons. Release of neuromodulators within the hippocampus regulates this process and is therefore predicted to determine which memories are encoded. The locus coeruleus (LC) is a brainstem nucleus that projects

diffusely throughout the cortex, releasing noradrenaline (NA) to co-ordinate multiple brain areas and mediate a variety of cognitive processes, including learning, memory, vigilance, and sleep¹. Within the hippocampus NA release acts as a novelty signal, with the LC switching from tonic firing in familiar spaces to burst firing when an animal enters a novel environment². The effects of such a switch on synaptic dynamics, ensemble recruitment and memory formation are still poorly understood.

Methods: To explore the relatively understudied modulatory effects of NA on various hippocampal synaptic inputs and post-synaptic firing properties we have used a combination of whole-cell patch-clamp recording in *ex vivo* hippocampal slices, optogenetic manipulations and computational modelling.

Approach for statistical analysis: Raw data were analysed in MATLAB or Excel before tests for normality and statistical analyses were conducted in GraphPad Prism.

Results and conclusions: At Schaffer Collateral-CA1 (SC-CA1) synapses bath-applied NA attenuated both excitatory and feedforward inhibitory responses, this resulted in little change in Excitatory-Inhibitory (E-I) ratio yet a reduced spike probability. Conversely, when NA was evoked from LC terminals using optogenetics, we instead observed an increase in spike probability, arising from a reduction in the spike threshold. It is possible that concentration differences underlie these distinct results and we are in the process of elucidating the receptors and mechanisms behind these findings.

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Poster number: PM040 (SP)

Theme: Learning and memory

Calcineurin (phosphatase 2B) is involved in the impairment of early- but not late-phase of LTP induced by protein synthesis blockers

Authors: Dr Alexander Maltsev¹, PhD Natalia Bal¹, Prof., PhD Pavel Balaban¹

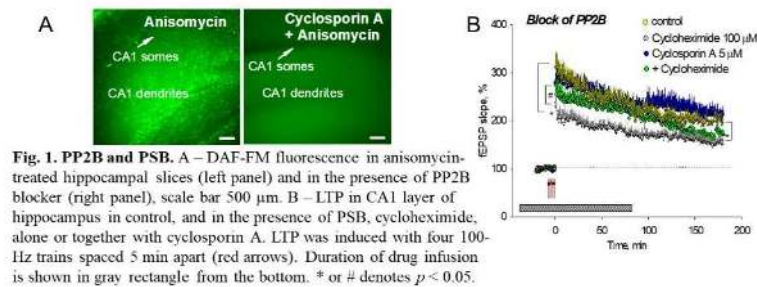
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Introduction: Long-term potentiation (LTP) is strengthening of synaptic transmission between neurons which persists for a long time after the impact on afferent pathways. LTP is one the key forms of synaptic plasticity involved in Learning and memory. It is possible to distinguish the early (E-LTP, several min – 1h) and late (L-LTP, many hours) phases of the potentiation's development. For several decades is well known the ability of blockers of protein synthesis (PSB) to suppress the L-LTP in different brain regions. However, the mechanisms of PSB's influence are still not fully understood.

Methods: In this work we investigated changes in field potentials (fEPSPs) in the CA1 hippocampus, and performed fluorescent microscopy of hippocampal slices stained by the NO-sensitive DAF-FM probe.

Approach for statistical analysis: Results are presented as mean \pm S.E.M. of *n* slices from at least three different animals. Changes in fEPSPs and DAF-FM fluorescence were analyzed by ANOVA (*post-hoc* by Bonferroni test); $p < 0.05$ reveals statistically significant differences (*, #).

Results and conclusions: Using direct measurement of NO-sensitive DAF-FM probe fluorescence, it was shown that the PSB application in the absence of tetanic stimulation leads to significant increase in the NO (Fig. 1A). Tetanization of the PSB-treated slices resulted in a further increase in NO production, recorded mainly in the CA1



dendrites. NO increase impaired the paired-pulse facilitation (PPF) in slices, suggesting an influence on the presynaptic plasticity. Pretreatment of slices by NO synthase blocker, L-NNA, or NO scavenger, PTIO, totally prevented NO synthesis and the impairment of L-LTP, rescuing the amplitude and slope of fEPSPs to the control values. Moreover, L-NNA or PTIO rescued the PPF in PSB-treated slices up to control. Established phosphatase 2B inhibitor, cyclosporin A, itself practically does not influence the LTP, but prevented the PSB-induced E-LTP decline (Fig. 1B). Direct measurements of NO synthesis revealed that cyclosporin A also abrogated the DAF-FM fluorescence in PSB-treated hippocampal slices without/with tetanic stimulation (Fig. 1A). Taken together, these data suggest that calcineurin (phosphatase 2B) is involved in the PSB-induced NO production.

Work was supported by a Program of Russian Academy of Science, RFBR grants 17-00-00216 and 17-04-01796.

Poster number: PM041 (SP)

Theme: Learning and memory

Influence of magnesium-rich marine mineral dietary supplementation on synaptic plasticity, neurogenesis and memory function in young and old rats

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Introduction: Emerging research indicates that dietary factors play a crucial role in brain health and cognitive function. A diet lacking adequate minerals, in particular magnesium and calcium, is considered a risk factor for cognitive decline and the development of dementia in older age through impairments in activity-dependent neuroplasticity, neurogenesis (a form of brain plasticity) and memory formation. Previous studies indicate that magnesium compounds can act as positive regulators of synaptic plasticity and promote memory function in young as well as aged rats. The food supplement Aquamin-FTM is a natural multi-mineral derived from the red algae *Lithothamnion corallioides*, rich in bioactive calcium and magnesium, as well as 72 other trace minerals. Recently it has been shown using primary neuronal cell cultures that Aquamin-FTM has direct anti-inflammatory effects. In addition, Aquamin-FTM in combination with the magnesium-enriched seawater-derived food ingredient Aquamin-Mg²⁺TM (Marine Mineral Blend (MMB)) significantly enhances gut microbiota diversity and alters short chain fatty acid (SCFA) profiles in the gut of adult male rats. Given the significant impact of gut microbiota on the regulation of neuroinflammation as well as brain function and behaviour, here, we will investigate whether the anti-inflammatory properties of this MMB can abrogate the decline in neurogenesis, neuroplasticity and hippocampal-associated memory decline associated with ageing.

Methods: Two cohorts (young cohort: aged 12 weeks, aged cohort: aged 16 months) of adult male Sprague Dawley rats were maintained for a period of 6 weeks on MMB-enriched chow. The other two cohorts of control rats (young cohort: aged 12 weeks, aged cohort: aged 16 months) were fed standard rat chow. Rats were tested using several hippocampal-dependent memory tasks (Y-Maze, novel object recognition, modified spontaneous location recognition task). To evaluate the impact of MMB on memory function, we will analyse the behavioural data generated from the memory tasks. We will also assess neuroplasticity (synaptophysin, PSD95, BDNF) and neurogenesis (DCX) in the hippocampus.

Approach for statistical analysis: Two-way ANOVA will be used to identify treatment or age effects, or interaction between both factors. If significant effects are found, post-hoc comparison will be conducted using Bonferroni's post-tests.

Poster number: PM042 (SP)

Theme: Learning and memory

Genomic investigation of mitogen- and stress activated kinase 1 function in the molecular mechanisms of experience-dependent synaptic plasticity

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Introduction: To date, pharmaceutical therapies have been largely unsuccessful at ameliorating or preventing the effects of dementia-related neurodegeneration. Environmental enrichment (increased social contact, exercise and complex surroundings) has however been shown to be effective at stimulating neurogenesis and improving cognitive function in many animal models. The molecular mechanism of this improvement is currently not fully characterised, but establishing this could aid understanding molecular changes during memory formation, and potential enhancements to this process.

We have previously shown that mitogen- and stress-activated protein kinase 1 (MSK1) has a regulatory role on synaptic structure and function in response to environmental stimuli (Corrêa *et al.*, 2012; Lalo, U. *et al.*, 2018), potentially via the MSK1-dependent phosphorylation of CREB, an evolutionarily-conserved transcription factor regulating the expression of genes affecting memory formation. Using a mutant mouse expressing a kinase-inactive form of MSK1 (MSK1 KD), we have been investigating the role MSK1 plays in modulating the cognitive, synaptic, anatomical and genomic responses to environmental enrichment.

Methods: 3D neuron-reconstruction, RNA-sequencing and single-cell patch-clamp electrophysiological recordings from the hippocampal CA1 region of mice reared in standard housing and enriched environment housing were used to characterise the spectrum of changes from the transcriptomic to the cellular level.

Approach for statistical analysis: RNAseq analysis has been performed using standard DESeq2 workflows mediated by R. Electrophysiology analysis has been carried out using 2-way ANOVA comparisons between groups and non-parametric comparisons of empirical cumulative density functions. 3D neuron-reconstruction will be assessed using 2-way ANOVA between groups based on measures of dendritic complexity and using Scholl analysis.

Results and conclusions: RNAseq results indicate that over 50% of 3-month environmental enrichment-dependent effects are MSK1 mediated, and the extent to which they impact upon synaptic transmission and neuronal structure are being investigated.. Combining these methods gives an insight into the genomic, molecular and cellular underpinnings of MSK1-dependent memory formation.

Corrêa, S.A.L., *et al.* (2012). "MSK1 Regulates Homeostatic and Experience-Dependent Synaptic Plasticity". *The Journal of Neuroscience*, 32, 13039-13051.

Lalo, U. *et al.* (2018) "Role for Astroglia-Derived BDNF and MSK1 in Homeostatic Synaptic Plasticity", *Neuroglia*, 1, 381-394

Poster number: PM043 (SP)

Theme: Learning and memory

Infantile Amnesia and The Memory Engram

Authors: Ms Sarah D. Power¹, Dr Clara Ortega-de San Luis¹, Ms Lydia C. Marks¹, Dr James D. O'Leary¹, Prof Tomás J. Ryan^{1,2}

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Infantile amnesia, the developmental loss of memories formed in early childhood (prior to 2–4 years), affects 100 % of humans. Although behavioural neuroscience has already demonstrated that rodents display infantile amnesia, little is known about the basic neurobiology of the phenomenon. This project aims to probe the question of how memories are stored in the brain throughout development, by integrating recently developed engram labelling technology with various rodent models of infantile amnesia.

Infant mice (P17) display forgetting in various paradigms of learning including contextual fear conditioning (CFC) and novel object recognition (NOR). To determine whether the engram cells activated at the time of encoding are also active during recall, we quantified the number of *c-fos* positive cells overlapping with ChR2-EYFP positive cells as a measure of engram reactivation. We characterized engram cell activity during recall trials at developmental stages prior to, and after, forgetting in infant mice. Recently we found that optogenetic stimulation of ChR2-EYFP expressing engram neurons in the DG and CA1, labelled during encoding of a fear memory in infancy, is sufficient for recall of the fear memory. These data demonstrate that memory engrams retain information following infantile amnesia and that when these cells are reactivated by blue light in a context different from the original one used for the conditioning, these animals display freezing behaviour, giving evidence of fear memory recall. Further, we investigated the capability of memory reinstatement of forgotten infant memories using updating paradigms and optogenetic stimulation. Standard parametric statistical tests will be employed where appropriate.

This experimental framework will allow for the potential retrieval of seemingly lost-memories from early childhood, as well as a deeper understanding of how long-term memories are stored as an enduring and stable biological change.

Poster number: PM044 (SP)

Theme: Learning and memory

Divergent synaptic plasticity at parvalbumin and somatostatin inhibitory synapses within the CA1 region of the hippocampus

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Introduction: The hippocampus hosts a vast diversity of inhibitory interneurons whose inhibition of excitatory cells are an integral part of the complex hippocampal network function. With often opposing roles, elucidating the function of specific interneurons is critical to understanding these processes. One aspect of network inhibition that is unclear is the capacity of inhibitory connections to undergo synaptic plasticity to either increase or decrease the 'strength' of inhibition. Parvalbumin (PV) and somatostatin (SST) expressing interneurons have distinct roles within the hippocampal network achieved via their diverse morphology and axonal projections (Pelkey *et al.* 2017). With these distinct roles in network activity, alterations in synaptic inhibition at these synapses may have profound impacts on the hippocampal network. However, the requirements for these synapses to undergo plasticity and the network consequence of altering the level of inhibition at distinct inhibitory synapses remains unclear.

Methods: Using a combination of patch-clamp electrophysiology and optogenetics we compare inhibitory synaptic plasticity induction at specific inhibitory synapses onto excitatory CA1 pyramidal neurons (Pyr) in brain slices of mice.

Approach for statistical analysis: Electrophysiological data was analysed using custom Matlab scripts with statistical analysis consisting of paired t-tests between control and test, plasticity pathways. Significance assigned if $p < 0.05$.

Results and conclusion: We find that high frequency interneuron firing at PV-Pyr and SST-Pyr synapses leads to long term depression (iLTD) and long term potentiation (iLTP) of inhibitory responses, respectively. Both forms of plasticity are independent of glutamatergic activity but do require postsynaptic depolarisation. Additional experiments have shown that this requirement can be met via postsynaptic action potential firing, with both PV and SST synapses showing discrete spike timing plasticity windows brought about via an unknown mechanism but dependent on postsynaptic calcium.

Ongoing experiments and computational modelling will aim to explore a potential mechanism by which plasticity at these two interneuron populations can regulate hippocampal network function during certain behavioural states.

Pelkey KA, Chittajallu R, Craig M, Tricoire L, Wester JC, McBain CJ (2017) Hippocampal GABAergic Inhibitory Interneurons. *Physiol Rev* 97:1619-1747

Poster number: PM045 (SP)

Theme: Learning and memory

Hippocampal processing of ambiguous aversive cues

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Introduction: The hippocampus is required for spatial and episodic memory but not simple Pavlovian conditioning. Consequently, the hippocampus is thought to be necessary for contextual conditioning but not for conditioning to discrete stimuli (CS). Here we investigated the role of the hippocampus in processing ambiguous discrete auditory cues.

Methods: In experiment 1, we trained mice with hippocampal lesions and sham-lesioned controls to discriminate between three distinct auditory cues: one cue predicted footshock on all trials (CS+); a second cue predicted the absence of footshock (CS-); and a third cue predicted footshock on 20% of trials, and was therefore ambiguous (CSa). In experiment 2, in a separate group of mice each implanted with 12 tetrodes into the hippocampus, we recorded multiple single-unit activity from the dentate gyrus, CA1 and CA3 regions during the recall of unambiguous and ambiguous fear cues.

Analysis approach: In experiment 1, we measure the freezing responses of mice during cue presentations and analyzed these using a factorial analysis of variance. In experiment 2, we analyzed the temporal patterns of co-firing in the spike trains, and compared the degree of correlation between these patterns during different cue presentations.

Results and conclusions: In experiment 1, we found that sham-lesioned mice exhibited equivalently high levels of fear to the CS+ and CSa and minimal fear to the CS-. In contrast, hippocampal lesioned mice exhibited high levels of fear to the CS+ but minimal fear to the CS- and CSa. This suggests that the hippocampus is necessary for processing discrete ambiguous cues, but not discrete unambiguous cues. In experiment 2, we found that dentate granule cells exhibited a representation of the ambiguous CSa that was significantly more strongly correlated with the CS+ representation than the CS- representation. Our data suggest that hippocampal ensembles can support the processing of discrete cues by making predictions based on partial or ambiguous input.

Poster number: PM046 (SP)

Theme: Learning and memory

Network abnormalities rather than hippocampal atrophy predict remote memory impairment in hippocampal amnesia

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Introduction: Hippocampal amnesia occupies a central place in memory neuroscience, yet its neural underpinnings are hotly debated. Several frameworks address the foundations of remote memory, generating competing predictions about the extent of retrograde amnesia following hippocampal and extra-hippocampal damage. Since network-wide disruption is well-documented in other diseases with focal damage, we hypothesized that hippocampal damage is followed by abnormalities within the extended hippocampal system, and that those predict retrograde amnesia more reliably than hippocampal volumes.

Methods: We assessed our hypothesis in a large cohort of patients (n=38) with a previous history of autoimmune limbic encephalitis, a syndrome that typically causes focal hippocampal damage. We conducted neuropsychological assessment, structural MRI and resting-state fMRI in these patients and in age-/sex-matched healthy controls (n=41) to investigate the relationship of retrograde amnesia with structural/functional abnormalities.

Approach for statistical analysis: The Holm-Bonferroni sequential method of correction for multiple testing was employed for comparisons between controls and patients in neuropsychological test scores, as well as for correlations between patients' scores and the mean values of clusters reflecting structural/functional abnormalities. For voxel-based whole-brain analyses (structural MRI and resting-state fMRI), FWE-correction ($p < 0.05$) was applied for cluster size or at voxel peak-level ($p < 0.001$ unc.). Mediation analyses involved patients' hippocampal volumes as independent variables, values of structural/functional abnormalities in extra-hippocampal structures as mediator variables, and their remote autobiographical memory scores as dependent variables.

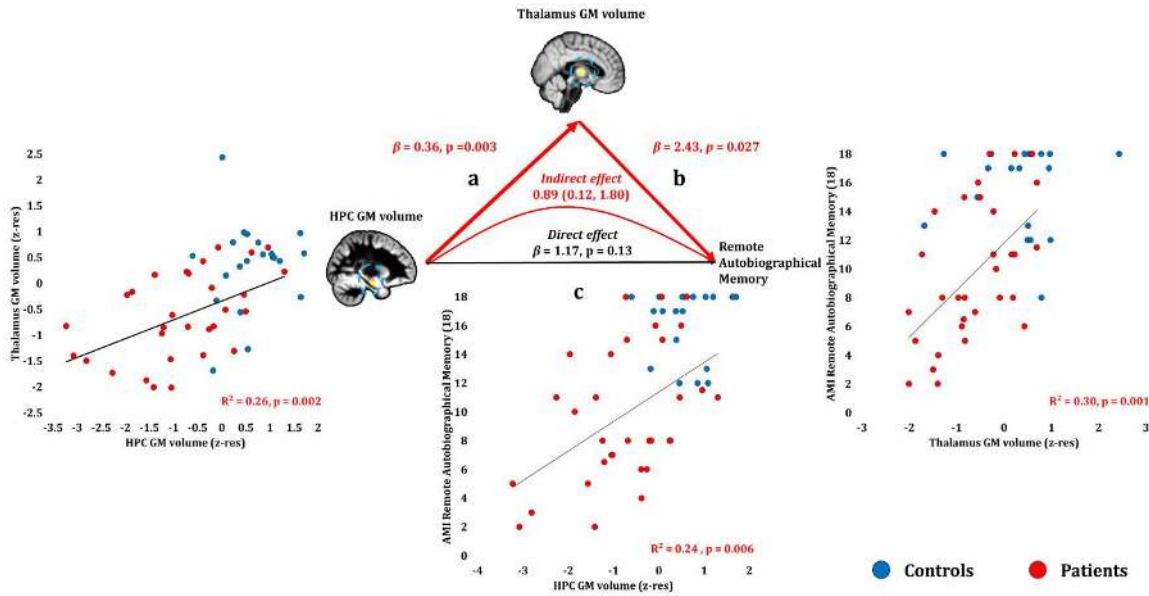


Figure 1: a: mean GM volume of the two HPC clusters correlated with the mean GM volume of the three thalamic clusters across patients; b: remote autobiographical memory scores correlated across patients with the mean GM volume of the three thalamic clusters; the mediation analysis demonstrates that this effect held when the correlation of thalamic GM volume with the mean GM volume of the HPC clusters was accounted for; c: mean GM volume of the HPC clusters correlated with remote autobiographical memory scores; the mediation analysis demonstrated that this relationship did not hold over: and above the correlation of the mean GM volume of the thalamic clusters with the HPC clusters; there was thus no direct effect of reduced HPC GM volume on remote autobiographical memory (within parenthesis: 95% confidence intervals); GM volumes from VBM clusters are residualized against age, sex, and TIV across participants; remote autobiographical memory scores are the sums of the AMI scores for autobiographical memories for childhood and early adulthood (max = 18). AMI: Autobiographical Memory Interview; GM: grey matter; HPC: hippocampus; TIV: total intracranial volume; VBM: voxel-based morphometry.

Results and Conclusions: Patients showed impaired remote autobiographical memory and anterograde amnesia, but spared remote personal semantic memory, executive, language, visuospatial and motor functions. Their cohort showed hippocampal atrophy that was focal within the medial temporal lobe. However, whole-brain voxel-based comparisons with healthy controls also disclosed thalamic volume reduction, along with reduced inter-hippocampal and cortico-hippocampal resting-state functional connectivity and reduced low-frequency oscillations in the posteromedial cortex. Remote autobiographical memory scores correlated with hippocampal volumes, yet the effects of hippocampal atrophy were fully mediated by patients’ correlative reduction in thalamic volumes (fig 1). Our findings highlight the importance of examining the abnormalities in the extended hippocampal system following focal hippocampal damage. Accounting for those may help resolve inconsistencies in the literature.

Poster number: PM047 (SP)

Theme: Learning and memory

Neuromodulation of Synaptic Plasticity

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Introduction: Spike timing-dependent plasticity (STDP) is a physiologically relevant form of Hebbian learning, in which near coincident pre- and postsynaptic firing induces plasticity: Long term potentiation (LTP) is induced when the presynaptic spike precedes postsynaptic firing, and long term depression (LTD) when postsynaptic firing precedes the presynaptic spike (Bi and Poo, 1998). However, these plasticity rules are profoundly influenced by neuromodulators (Seol et al., 2007), which can affect memories and behavioural outcome. Studies from our lab have shown that modulatory input that arrives even after plasticity induction can change plasticity rules; the application of dopamine after the induction converts LTD into LTP (Brzosko et al., 2015). This suggests that during the induction of plasticity, a synaptic molecular tag is set, through which modulatory signals can act. In this study we investigate the underlying molecular mechanism.

Methods: Whole-cell patch-clamp recordings were performed on acute hippocampal CA1 pyramidal neurons using Schaffer collateral stimulation. After a baseline period, STDP was induced by repeated pairings of EPSPs and single postsynaptic action potentials and EPSPs were monitored for at least 40 min after the pairing protocol. This protocol was combined with 2-photon imaging for simultaneous detection of calcium transients.

Approach for statistical analysis: Statistical comparisons were made using one-sample two-tailed or paired two-tailed Student's *t*-test, with a significance level of $\alpha = 0.05$.

Results: We show that calcium permeable AMPA receptors are required for the dopamine-induced conversion of LTD into LTP. This is mediated via signalling through the calcium-sensitive adenylate cyclases (AC) 1/8. Alternatively, synaptic stimulation could be replaced by a postsynaptic burst 10 min after the induction protocol, which was sufficient to convert LTD into LTP in the presence of dopamine.

References

GQ Bi, MM Poo (1998) *The Journal of Neuroscience* 18: 10464–10472.

Brzosko Z, Schultz W and Paulsen O (2015) *eLife* 4: e09685.

Seol GH, Ziburkus J, Huang S, Song L, Kim IT, Takamiya K, Hugarir RL, Lee HK and Kirkwood A (2007) *Neuron* 55: 919–929.

Poster number: PM048 (SP)

Theme: Methods and techniques

Structural connectivity and its association with blood flow after two hours in a hypoxic environment

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Introduction: Regional alterations in cerebral blood flow (CBF) occurs under hypoxic conditions, for example when at altitude (Ainslie, Hoiland, & Bailey, 2016). Using blood perfusion data Lawley, et al., (2016) demonstrated that acute hypoxia led to increases of CBF in frontal areas, and unexpected reductions in the posterior cingulate, and precuneus. It is unclear how these transient regional modifications affect information flow in structural networks at the global and local level.

Methods: Data previously collected (Lawley, Macdonald, Oliver, & Mullins 2016) was used in this study. For all participants ($n=11$) high resolution T1 weighted, diffusion weighted, and arterial spin labelled images were acquired using a 3T scanner in two conditions: normoxia and two hours in hypoxia. ExploreDTI (Leemans et al., 2009), was used to reconstruct white matter pathways. The Automated Anatomical Labelling (AAL) Atlas was used to parcellate cortical and subcortical areas into 90 regions (Tzourio-Mazoyer, et al., 2002). White matter trajectories were mapped between parcellated brain regions to form structural brain networks. Graph theory measures assessed alterations in global and local information flow between normoxia and hypoxia. Associations between structural and functional measures in hypoxia were assessed by correlating local measures with CBF data.

Approach for Statistical Analysis: Global-efficiency and characteristic-path-length were calculated for the whole brain. Nodal-degree and betweenness-centrality were calculated for the ROI: precuneus, and posterior cingulate. Between group differences in global and local brain measures were assessed using *t*-tests, and *Wilcoxon signed-ranks*. Permutation tests assessed associations between local connectivity measures and CBF in the ROI.

Results and Conclusions: There was no difference in the global or local structural connectivity of the brain between normoxia and hypoxia. Moreover, there were no associations between reductions of CBF in hypoxia and measures of local structural connectivity in the ROI. This suggests that in hypoxia there was no difference in the ability of the

brain to transmit information around the structural network, despite reductions in CBF. Brain function is generally considered to be mediated by white matter connections (Sotiropoulos, & Zalesky, 2017), therefore a reduction in functional measures without a commensurate reduction in structural connectivity measures was unexpected.

	t statistic	Degrees of freedom (df)	Significance (p)	Effect size (d)
Global Measure				
Characteristic Path Length	-0.459	10	0.656	0.145
Local Measure				
Nodal Degree				
Posterior Cingulate left hemisphere	1.117	10	0.290	0.353
Posterior Cingulate right hemisphere	1.166	10	0.271	0.353
Precuneus left hemisphere	1.098	10	0.298	0.347
Precuneus right hemisphere	-0.829	10	0.427	-0.260
	z statistic (Wilcoxon)		Significance (p)	Effect size (d)
Global Measure				
Global Efficiency	-0.267		0.790	-0.052
Local measure				
Betweenness Centrality				
Posterior Cingulate left hemisphere	-1.646		0.100	-0.322
Posterior Cingulate right hemisphere	-0.890		0.373	-0.175
Precuneus left hemisphere	-1.245		0.213	-0.244
Precuneus right hemisphere	-0.089		0.929	-0.017

Table 1. Global measures computed for the whole brain, and local measures computed for the regions of interest: posterior cingulate and precuneus



Figure 1. ExploreDTI was used to visualize the nodes of the network between conditions (normoxia left, hypoxia right). Each node is weighted based on its value of nodal degree, retrieved from the FA weighted connectivity matrix.

Poster number: PM049 (PP)

Theme: Methods and techniques

Sampling around the clock: the bioRHYTHM pilot study

Authors: Dr Thomas Upton¹, Professor Stafford Lightman¹
¹University of Bristol, Bristol, United Kingdom

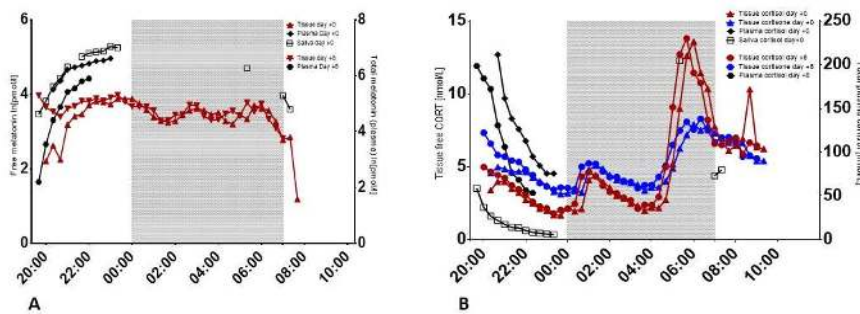
Introduction: Rhythms characterise the metabolism of all living things. Superimposition of rhythms of different periods creates a dynamic environment that is coordinated by an endogenous clock machinery to maintain healthy homeostasis.

It is our belief that, given the complexity of the systems involved, it is inappropriate and insufficient to extrapolate information about the state of an organism based on single time point measurements of single analytes.

We propose that simultaneous, longitudinal assessment of multiple internal processes, measured during normal daily activity, will provide a richer, more meaningful understanding of the internal biological state.

Pilot experimental work indicates:

1. Automated microdialysis detects robust, dynamic rhythms of circadian hormones in human subcutaneous tissue,
3. Rhythms in temperature and cardiac output can be determined with high accuracy using non-invasive 'wearable' technology (Smarr, Burnett, Mesri, Pister, & Kriegsfeld, 2016).



Simultaneous subcutaneous free melatonin (A) and cortisol (B) rhythms detected by automated ambulatory microdialysis in a healthy volunteer. Concentrations strongly correlate with saliva and plasma samples. Unpublished pilot data.

Methods: Healthy participants aged 18-38 will complete 48-hour ambulatory microdialysis sampling sessions. During each session, information will be collected in the following ways:

- continuous measurement of free tissue concentrations of melatonin and cortisol (U-RHYTHM microdialysis sampling device)
- continuous interstitial glucose monitoring (CGMS; FreeStyle Libre or similar subcutaneous sensor)
- ambient light exposure (CamNtech MotionWatch or similar)
- actigraphy, skin temperature, skin conductance, and heart rate (CamNtech watch, Oura ring)
- meta data in the form of self-reported sleep, physical activity and meal information

Analysis approach: Tissue concentrations of hormones will be analysed in the microdialysis samples using liquid chromatography-mass spectrometry. Concentration changes in subcutaneous fluid samples across different periods and times of the day will be analysed using appropriate statistical methods, e.g. two-way ANOVA.

To assess rhythmicity, techniques such as cosinor-based rhythmometry methods will be applied. Data collected from the wearable devices will be analysed using mathematical algorithms that explore relationships between endogenous physiological rhythms (e.g. hormone levels in subcutaneous fluid) and dynamic data collected by the peripheral sensor devices.

Reference

Smarr, B. L., Burnett, D. C., Mesri, S. M., Pister, K. S. J., & Kriegsfeld, L. J. (2016). A Wearable Sensor System with Circadian Rhythm Stability Estimation for Prototyping Biomedical Studies. *IEEE Transactions on Affective Computing*, 7(3), 220–230.

Poster number: PM050 (SP)

Theme: Methods and techniques

Spontaneous neuronal activity co-culture assay using ipsc derived astrocytes and cortical neurons

Authors: Censo Biotechnologies Daniel Tams¹, Mrs Lauren Hindhaugh¹, Mrs Susana Alcantara², Dr Tim Dale², Dr Del Trezise², Mr Ashley Barnes¹

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Introduction: Complex neuronal assays that exploit state of the art iPSC differentiation protocols and assay technologies will provide drug discovery scientists with the opportunity to assess disease progression in a live cell-temporal dependant way. Understanding how neuronal networks form under normal and pathological conditions will allow researchers to define disease relevant assays windows using complex biological function.

Method: Censo's proprietary differentiation method was used to create pure, human excitatory cortical neurons from healthy and diseased donors. Astrocytes were differentiated from healthy human iPSC-derived neural progenitor cells using a commercially available differentiation reagent. Both cell types were cryopreserved in assay ready vials prior to co-culture.

Spontaneous neuronal activity was measured using the IncuCyte® S3 for Neuroscience. Neurons and astrocytes were plated onto Laminin in a 96 well plate and transfected with IncuCyte® NeuroBurst Orange Reagent, astrocytes were mitotically inhibited post transfection. Fluorescent images were recorded at 3 fps for 3 minutes every 24 hours and media was changed every 2-3 days.

Results

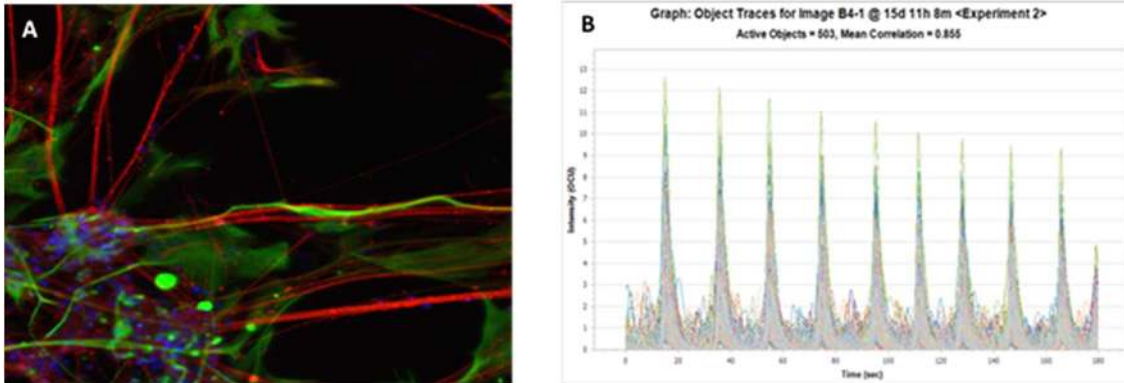


Figure 3 Spontaneous neuronal activity. Co-culture of neurons and astrocytes (A) Neurons (Red), Astrocytes (Green). Synchronised burst activity traces (B). Burst intensity for each traced neurite is shown as a single line. Synchronised bursting can be observed when the correlation of the individual bursts increases and individual traces are over-laid. Here we will present data on the application of this technology to drug discovery including applying compound treatments to complex multicellular systems and assessing the functional role of disease causing mutations. We show how network formation changes over time and that compound treatment can be used to manipulate the system.

Conclusion: Human iPSC derived cortical neurons and astrocytes were used in conjunction with the IncuCyte[®] S3 for Neuroscience to assess the human model of neuronal network formation.

Poster number: PM051 (SP)

Theme: Methods and techniques

Optogenetics: HT4 cells can be stably transfected using AAV to express Opsin from *carbydea rastonii* in order to create light activation of the cAMP pathway

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Optogenetics refers to the method of gene transfer of opsins into an excitable cell like the neuron and using light to modulate behaviour of the cell in a living animal. The method is a paradigm shift in neurobiology, as it allows us to observe and modulate neurons individually in living animals. The method has hitherto used microbial opsins (Type I) that open ion channels along with specialised light delivery techniques in cells in culture and in transgenic animals expressing these opsins. Type II opsins on the other hand stimulate unique G-protein coupled pathways. JellyOp from the box jelly fish (*carbydea rastonii*) is a type II opsin that was recently shown to activate the GαS-cAMP pathway. It was also shown, that JellyOp can be expressed in cell lines using non-viral delivery methods, and that it causes increase of cAMP levels to light stimulation at an intensity of >1μW/sqcm, which is many orders of magnitude less than that required to stimulate cells transfected with microbial opsins.

We used JellyOP in a unique recombinant AAV construct to express the opsin in cells derived from the mouse hippocampal cell line (HT4 cells). After transfection of HT4 cells, we did a light stimulation experiment. The transfected cells were exposed to interrupted light stimulation of 10s pulses for a period of 10 minutes. Non-transfected cells and cells not exposed to light throughout the experiment were used as controls. We then estimated the levels of cAMP-dependent kinase (PKA) levels on light exposure.

Our results show for the first time, that transfection of HT4 cells using a recombinant AAV2 vector, carrying a transgene construct of the opsin from *carbydea rastonii* is feasible and sufficient to cause robust expression. pVASP expression levels were equivocal, but a small trend is noted ($p=0.2$).

Poster number: PM052 (SP)

Theme: Methods and techniques

Deciphering the gut feeling: identifying neuronal networks underlying gut brain communication

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In recent years, different lines of evidence have shown that the microbes inhabiting the gut can communicate with the brain. Alterations to, or the lack of gut bacteria, has been shown to affect molecular, anatomical and behavioural parameters, which have been linked to physiological and psychological disease. However, the mechanisms underlying these effects have not been identified thus far.

In this study we used targeted recombination in active populations (TRAP) to express MCherry in a subset of neurons activated by vagus nerve signalling. Genetically modified animals harbouring the Cre-lox tool allowed inducible expression of Cre under the *Fos* promoter. *Fos* is an immediate early gene that is commonly expressed in response to neuronal activation. By virally delivering the gene of interest (MCherry) to the target brain region, a very specific subset of neurons expressed this gene following neuronal activation. Cholecystokinin (CCK), a gut peptide that is released upon food intake, was recruited to induce neuronal activation via the vagus nerve and associated brain regions. Following a resting period to allow gene expression to trace the signal propagation pathway, animals were perfused and the brain harvested for analysis of regions of the brainstem.

Activation of neurons in the hypoglossal nucleus, and to a lesser extent the nucleus tractus solitarius, was observed following CCK stimulation. The data is comparable to seeing *Fos* expression in these brain regions in response to CCK injection. The results indicate the capability of TRAP utilisation to further investigate neuronal networks underlying vagus nerve related gut-brain communication. It is our aim to extend this technology to analyse the activation patterns of live biotherapeutics to investigate the neuronal networks underlying microbiota gut-brain communication and the mechanisms involved.

Poster number: PM053 (SP)

Theme: Methods and techniques

Stereomate: a tissue clearing and automated image analysis methodology for detailed quantitative assessment of CNS elements

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Introduction: With the recent resurgence of tissue clearing methods in neuroscience comes the arduous task of assessing large 3D datasets. Extracting the semantic meaning of these complex images is currently hindered by a lack of automation in the assessment of these datasets.

Methods: We have developed a tissue clearing methodology, compatible with immunofluorescence, and specifically designed to facilitate high-resolution confocal imaging deep within tissue blocks (500um+).

We further present StereoMate, which applies stereological analysis to image stacks. StereoMate first provides a range of image pre-processing techniques, including image deconvolution and filtering, facilitating automated image thresholding techniques to segment image structures.

StereoMate then analyses these in an ROI dependent fashion using a novel di-sector probe; the ROI Di-Sector. This assigns biological objects to user-defined, biologically relevant ROIs, which also act as a novel stereological Optical Di-Sector probe. Each ROI returns an object map, and quantitative data can be derived at the pixel, object and ROI level.

To assess this methodology, we have used the spinal cord as our model system, and peripheral nerve injury as our perturbation of CNS structures.

Approach for statistical analysis: For hypothesis testing, one-way ANOVA was used to assess microglial cell numbers post nerve injury, and two-way ANOVA (with spinal cord lamina in the second dimension) used to assess PSD95 puncta number across lamina post nerve injury. Furthermore, exploratory data analysis of these datasets will be presented on the poster.

Results and conclusions: To validate the methodology, we tested two hypotheses for which evidence has previously been demonstrated.

First, we labelled spinal cord tissue 21 days post peripheral nerve injury and sham tissue for the microglial marker Iba1, and identified an up-regulation of microglial cell numbers 21 days post peripheral nerve injury ($p < 0.001$, OneWay ANOVA, Tukey post-hoc, $n=5$).

Second, we labelled nerve injured and sham tissue with PSD95, to mark asymmetric excitatory postsynaptic structures, there was a significant reduction in PSD95+ puncta seen in lamina III ($p < 0.01$, two-way ANOVA, Bonferroni post hoc, $n=5$).

We conclude that StereoMate is an effective tool for extracting and quantitatively assessing CNS structures in three dimensions, and that the rich multivariate datasets collected bring statistical data mining possibilities to histological data.

Poster number: PM054 (SP)

Theme: Methods and techniques

Transcranial Magnetic Stimulation (TMS) as a clinical tool: The test-retest reliability of TMS measures in individuals early after stroke and in healthy adults across the lifespan

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Transcranial magnetic stimulation (TMS) is increasingly suggested for use in neurorehabilitation to predict recovery, to evaluate the efficacy of an intervention and as a probe to give details of the excitability of the motor system. As a result the reliability of TMS derived measures in a clinical and older population is needed. This study investigated the test-retest reliability of MEP characteristics in younger and older neurologically-intact adults, and individuals early after stroke.

Two identical data collection sessions separated by one to three days for people with stroke and five to seven days for neurologically-intact adults. MEP characteristics were: motor threshold; amplitude; latency; silent period; and recruitment curve slope. Muscles investigated were: biceps brachii (BB); extensor carpi radialis (ECR); and abductor pollicis brevis (APB). Test-retest reliability was calculated using the intra-class correlation coefficient (ICC) and limits-of-agreement (LOA).

Participants were 51 neurologically-intact adults, and 30 individuals with acute stroke a mean of 38.6 (SD 19.8) days after stroke. Test-retest reliability was variable. In people with stroke ICC (95% confidence intervals) values ranged from: 0 (0, 0.35) for recruitment curve slope paretic ECR to 0.88, (0.75, 0.95) for MEP amplitude in paretic APB. LOA ranged from: -13.89 (-107.43 to 79.65) for silent period non-paretic ECR to -0.05 (-2.67 to 2.56) for latency paretic

APB. In neurologically-intact adults ICCs ranged from: 0 (0, 0.05) for non-dominant limb ECR recruitment curve slope to 0.87 (0.52, 0.96) for resting motor threshold non-dominant BB. The LOA ranged from: -0.13 (-2.06 to 1.80) for latency non-dominant limb BB to -3.90 (-72.92 to 65.12) for silent period non-dominant limb APB.

This is the first study to assess multiple MEP characteristics of three upper limb muscles both proximal and distal in individuals early after stroke and in neurologically-intact younger and older adults. The findings indicate variability in reliability of TMS measurement. ECR appears to have highest and most consistent ICC values (healthy and stroke), there is wider confidence intervals in older and stroke participants while Motor threshold was most reliable measure. Caution needs to be applied when using TMS as a clinical assessment tool and consideration given to target muscle/TMS measure.

Poster number: PM055 (SP)

Theme: Methods and techniques

The Neuroscience of Driving: A magnetoencephalographic study

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Traditional behavioral probes for neuroscience are often limited in their ability to predict real-world functional performance. For example: driving is a ubiquitous, high-risk and complex behavior requiring integrated functioning across visual, motor and cognitive systems, yet we know very little of the neural mechanisms underlying this rich behavior. We used an ecologically valid simulated driving task of graduated complexity with simultaneous magnetoencephalographic (MEG) recording to probe oscillatory activity.

For this pilot study, typically developing young drivers (aged 20-24 years) were recruited to perform a number of tasks using an MEG-compatible simulator that elicited motor and visual responses (i.e., braking or steering in response to cues such as traffic lights), as well as on-going visuo-motor integration and frontal cognitive processing. Neuromagnetic data was recorded continuously during the tasks using a whole cortex 275-channel MEG system (CTF International), sampling at 1200Hz per channel with 3rd order gradiometer environmental noise reduction. Volumetric MRI (conducted with a 3T Siemens Prisma™ MR scanner) was used both for MEG source localization, and grey and white matter ROI voxel segmentation and quantification.

Visual alpha-band, motor beta-band and frontal gamma-/theta-band responses were localized to stimulus-onset and motor-response epochs, using differential Synthetic Aperture Magnetometry (SAM) beamformer methods (Gaetz et al., 2010; 2013). Time-frequency plots from the peak locations were analyzed for frequency, power, latency and duration, and grand average difference waves were calculated from the MEG source localization data.

This paradigm was successfully piloted, without significant artifact. Preliminary results reveal localized brain regions of motor and sensorimotor cortex activity, as well as theta power increases in the frontal lobe as task demand increased. This new paradigm allows us to not only examine the neural mechanisms underlying driving skill and error, but also probe integrated brain function in different populations using a more ecologically-relevant complex task.

Gaetz, W., Macdonald, M., Cheyne, D., Snead, OC. (2010). Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement beta rebound. *NeuroImage*, 51:792–807.

Gaetz, W., Liu, C., Zhu, H., Bloy, L., & Roberts, T. P. L. (2013). Evidence for a motor gamma-band network governing response interference. *NeuroImage*, 74, 10.1016/j.neuroimage.2013.02.013.

<http://doi.org/10.1016/j.neuroimage.2013.02.013>

Poster number: PM056 (SP)**Theme:** Methods and techniques**Development of a bioprinting based model of neuroinflammation using human iPSC derived neurons and glia****Authors:** Mr Gareth Chapman¹, Mr. Thomas Richardson², Dr. Mathew Hockley¹, Ms. Tanya Singh¹, Ms. Sharna Lunn¹, Dr. Adam Perriman², Dr. Yasir Syed¹¹Cardiff University, Cardiff, United Kingdom, ²Bristol Univeristy, Bristol, United Kingdom

Introduction: Neuroinflammation forms a key role in the pathogenesis of many neuronal disorders including both neurodegenerative and psychiatric disorders. The study of neuroinflammation using human induced pluripotent stem cell (hiPSC) derived neuronal lineages has traditionally been limited to simplistic co-culture-based paradigms. While these systems have given us a simplistic understanding of the interactions between the cells types these systems do not account for the complex intercellular interactions that are critical for the proper functioning of these cells. Therefore, recent work has mainly focussed on the development of 3D model systems which more faithfully recapitulate the complexity seen in *in vivo* models. However, these models are often severely limited by the lack of reproducibility therefore preventing their use in any high through-put modalities. Bioprinting proposes a novel solution to these problems as it offers a highly reproducible output which introduces some of the complexity seen in more complex 3D cell models.

Methods: We have used hiPSC derived astrocytes, neurons and microglia generated from development pattern approaches to model interactions between these cells in a 3D printed system. Bioprinting was carried out using an extrusion-based methodology and alginate based bioink.

Approach for Statistical Analysis: All analysis is based on imaging where each condition comprises of 3 biological replicates each comprised of 3 technical replicates. Images where analysed using a mix of commercially available and proprietary software and the results where analysed using Student's T-Tests comparing the biological replicates in each case.

Results and Conclusions: We have demonstrated that alginate based bioinks must include extra cellular matrix (ECM) components for the long-term survival of neuronal lineage cells. These components may be added as supplements to the bioink or the alginate can be functionalised using critical peptides found within the ECM proteins. Furthermore, we have shown that hiPSC derived neurons are highly sensitive to the stresses of bioprinting and therefore this must be accounted for when bioprinting with multiple cell types. This system provides a highly reproducible platform which can be used to examine the interactions between astrocytes, microglia and neurons and can be used as a high through-put screening platform for neuroinflammatory drugs.

Poster number: PM057 (SP)**Theme:** Methods and techniques**Establishing the marine invertebrate *Pleurobrachia pileus* as a model organism in neuroscience****Authors:** Ms Amy Courtney¹, Ms Amy Hassett¹, Mr. Ross O'Carroll¹, Mr. George O.T. Mercet¹, Dr. Mark Pickering¹¹School of Medicine, University College Dublin, Ireland

Introduction: While modern neuroscience research is dominated by a small number of model organisms, exploiting the greater diversity of neurobiology can allow key scientific questions to be asked. *Pleurobrachia pileus* is representative of marine invertebrate phylum ctenophora. They possesses a decentralised neuronal network beneath the epithelial layer. Behavioural responses are similar across all animals, despite the large range of body

sizes observed (from 1mm to 20mm in length) therefore as the animal size changes, the nerve net must undergo restructuring and remodelling while maintaining function.

Methods: To permit long term studies we developed a custom built aquarium system with automated feeding. To categorise behaviours, aquarium videos were acquired at the start and end of a 12 hour light-dark cycle. An ethogram was manually annotated for 5 animals within each video. To investigate nerve net structure, anti-tyrosylated α -tubulin immunofluorescence imaging of fixed whole mount tissue preparations was carried out using a custom-built automated scanning epifluorescent microscope and analysed using a novel semi-automated Matlab script.

Approach for statistical analysis: The overall approach used in this study is to establish a baseline statistical profile of both behaviour and nervous system morphology in *P pileus*. We calculated the median percentage of time spent exhibiting each behaviour in 20 animals. For the nerve net, we calculated the distribution of polygon size, circularity, orientation, and neurite density, as well as branch angle and number.

Results and conclusions: To date, we have maintained ~100 animals collected in the Irish Sea for at least four months in our aquarium system. We identified and characterised 6 behavioural categories which elude to the richness and variability in their behavioural repertoire. The behaviours and time spent in each state are (median; range); drifting (81.0%; 24.0-98.6%), feeding (1.6%; 0-9.5%), tentacle resetting (8.8%; 0-14.4%), swimming up (0%; 0-2.2%), swimming down (0%; 0-74.0%) and escape swimming (0%; 0-9.1%). We have characterised nerve net morphology across animals of varying sizes to elucidate the fundamental properties of the network. This organism may represent a useful model system to investigate the basic principles of structure/function relationships in neural circuits.

Poster number: PM058 (PP)

Theme: Methods and techniques

Getting the best from your mouse: reward preference, behavioural tracking methods and memory performance in C57BL6/J mice

Authors: Ms Abigail Hatcher Davies¹, Mr Jonas Rybnicek¹, Dr Fiona McLean¹, Dr Rosamund Langston¹

¹University Of Dundee, Dundee, United Kingdom

Introduction: Novel object recognition (NOR) is a behavioural task commonly used in mice to assess memory. Typically one trial per day is run and, due to the variable nature of spontaneous exploration tasks, long testing periods or (more commonly) large numbers of animals are required for statistically significant results. Recently a team at Durham University in collaboration with Campden Instruments developed an automated semi-operant apparatus for testing multiple consecutive NOR trials, with the aims of reducing handling stress and behavioural noise caused by multiple separate testing episodes and reducing animal numbers (Chan et al, 2018).

Methods: We beta-tested a version of this apparatus to compare it to traditional open field manual testing boxes, find the best way to incentivise mice with liquid reward and investigate different methods of scoring the behavioural data.

Mice were tested on NOR in both manual and automated continual trials apparatus using a counterbalanced within-subjects design. Mice completed 4 "traditional" trials which were administered once per day and 12-16 automated trials which were completed in 1-2 separate sessions. Prior to the start of memory testing a taste preference test was carried out in a separate mouse cohort to identify preferred reward. Soy milk and almond milk were strongly preferred by mice, significantly more than strawberry or chocolate milk, 10% sucrose or Ribena.

Mice performed at a similar level in the NOR task in both the open field testing boxes and the Campden Instruments automated apparatus, indicating that the Campden Instruments automated apparatus is an appropriate apparatus for testing short term object recognition memory in mice. The consecutive nature of the trials in the automated

apparatus provides a higher amount of memory interference which may explain why performance is not better than with the traditional method despite the larger number of trials.

Approach for Statistical analysis:

Data analysis is underway to compare variability data scored by a human observer blinded to novel object identity to multiple types of behavioural tracking software and a machine-learning algorithm (Mathis et al, 2018). The findings should help reduce variability not just in the behaviour of the mouse but also in the observer.

Poster number: PM059 (SP)

Theme: Methods and techniques

Discovery of a series of novel leelamine metabolites in rat tissue using liquid chromatography and tandem mass spectrometry

Authors: Mr. Brendan Harhen^{1,3,4}, Dr. Alvaro Llorente-Berzal^{1,3,4}, Dr. Howard Fearnhead¹, Dr. Michelle Roche^{2,3,4}, Prof. David Finn^{1,3,4}

¹Pharmacology and Therapeutics, National University of Ireland, University Road, Galway, Ireland., ²Physiology Anatomy, School of Medicine, National University of Ireland, University Road, Galway, Ireland., ³NCBES Galway Neuroscience Centre, National University of Ireland, University Road, Galway, Ireland., ⁴Centre for Pain Research, National University of Ireland, University Road, Galway, Ireland

Introduction: Leelamine is a diterpene molecule which exhibits cannabinoid-like pharmacological activity and has therapeutic potential in melanoma treatment. Metabolism of pharmacological agents may influence their efficacy. In mice, leelamine was reported to be oxidatively metabolised into one major metabolite. The aim of this study was to determine leelamine metabolism in rat tissue.

Methods: Male Sprague Dawley rats received a single acute i.p. injection of leelamine (25mg/kg) or vehicle (n=7 per group) and behaviour in the tetrad test for cannabinoid activity was assessed. Subsequently, the animals were euthanised at 30, 60 or 120 mins post-injection, and various tissues were harvested and stored for further bioanalysis. Liver sample aliquots were homogenised in ice cold acetonitrile and the supernatants were clarified by centrifugation. Samples were analysed by LC/MS operated in full scan mode scanning 200-1000m/z using positive and negative ion electrospray ionisation modes.

Analysis approach: The livers of 2 test rats were compared to 2 control rats from each time cohort using qualitative LC/MS.

Results and conclusions: Intense peaks were observed in the liver of leelamine-treated rats that were not observed in control rats. Signals at m/z 286 (leelamine), 302(leelamine+16) and 318 (leelamine+32) were observed respectively suggesting monooxygenated (m/z 302) and dioxygenated (m/z 318) leelamine. *Ex vivo* leelamine standard was chemically unmodified. Moreover, these putative polar metabolites had earlier retention times than leelamine. Tandem mass spectrometry of m/z 286, 302 and 318 yielded similar fragmentation patterns and fragment ion series except that the fragment ion m/z series increased by 16 and 32 respectively. Another major signal at m/z 284 was observed in leelamine-treated rats. This suggested an alternative metabolic pathway for leelamine in rats through a separate desaturation process. Tandem mass spectrometry of m/z 284 yielded an almost identical fragmentation pattern to leelamine except that the fragment ion m/z series decreased by 2 m/z. Metabolites were detected at high intensity relative to the leelamine signal indicating rapid leelamine metabolism. Leelamine is metabolised *in vivo*, by divergent oxidation and desaturation pathways.

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Poster number: PM060 (SP)**Theme:** Methods and techniques**A persistent homology-based method to classify neuron morphologies and predict neurodegeneration****Authors:** Mr. Luke Ziolkowski¹, Dr. Carl Hammarsten², Dr Jordan McCall¹¹Washington University in Saint Louis, Saint Louis, United States, ²Lafayette College, Easton, United States

Introduction: The morphology of a cell can have an intricate relationship with how it functions. Specifically, in the neuron, biochemical and electrophysiological properties affect and are affected by the shape, size, and complexity of dendrites, the soma, and the axon. Neurons are often divided into separate cell types based on their differing morphology, and various conditions and diseases can also cause these differences.

Methods: We generated three approaches to quantify neuronal morphology: two using a topological data analysis method known as persistent homology and one using a traditional Sholl analysis. Using 2-dimensional point cloud data acquired from the Allen Cell Types Database and NeuroMorpho.org (A), we used these approaches to calculate three separate morphological metrics for each cell.

Approach for statistical analysis: We then used support vector machines trained with these metrics to classify cells into their respective cell type group, or to predict a neurodegenerative condition.

Results and conclusions: These metrics were able to accurately distinguish between certain cell types, but failed to discriminate between others (B – EC metric is generated from persistent homological approach). Two of the metrics also had a significant ability to predict neurodegeneration. Although persistent homology appears to have an advantage in classifying data by including more information than Sholl analysis, any predictive superiority requires further investigation. Current efforts are aimed at applying these metrics in dynamic cell imaging paradigms such as calcium and voltage imaging.

Poster number: PM061 (SP)**Theme:** Methods and techniques**Age related performance and sources of variability in rat spontaneous novelty detection tasks****Authors:** Miss Sophie Drysdale¹, Miss Abi Hatcher-Davies¹, Dr Rosamund Langston¹¹Dundee Neuroscience, Systems Medicine, Ninewells Hospital & Medical School, University of Dundee, Dundee, United Kingdom

Introduction: Spontaneous novel object recognition (NOR) is a commonly used behavioural task in laboratory rodents to assess memory, demonstrated by preference for novel stimuli. Typically one trial per day is run (resulting in a single data point for each animal tested) and, due to the variable nature of spontaneous exploration tasks, long testing periods or (more commonly) large numbers of animals are required for statistically significant results. Recently a team at Durham University in collaboration with Campden Instruments developed an automated apparatus for testing multiple consecutive NOR trials, with the aims of reducing handling stress and behavioral noise caused by multiple separate testing episodes and reduce animal numbers (Chan et al, 2018).

Methods: We beta-tested a version of this apparatus to investigate whether it could be used successfully in rats of varying ages to test not only the basic NOR task but more complex recognition memory tasks involving the locations and contexts of different stimuli within the apparatus (Ameen-Ali et al, 2012; Seel et al, 2018).

Rats aged from 6 weeks to 2 years were habituated to the testing apparatus and then given 16 memory tests where multiple features of the environment must be combined and remembered in order to detect the novel configuration of stimuli in the test (Eacott & Norman, 2004).

Results and Conclusion: All age groups of rats performed at a similar level in the NOR task, indicating that the Campden Instruments automated testing box is an appropriate apparatus for testing short term object recognition in rats aged 6 weeks to 2 years.

All age groups exhibited highly variable performance in the place, context and episodic memory tasks. Since there was not a clear relationship between age and performance, we investigated other factors which may produce variability in these data. Sex, age, bodyweight and parentage were investigated but none showed strong correlations with memory performance and therefore none were identified as the main source of variability in these data.

Future work will address time of day, temperature and animal facility routines as possible causes of variability and overall poor performance in the more sensitive place, context and episodic spontaneous recognition memory tasks.

Poster number: PM062 (SP)

Theme: Methods and techniques

Combined defects in cytoplasmic dynein and TBK1 modulate protein degradation pathways

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Introduction: Formation of cytoplasmic aggregates and mislocalisation of disease-associated proteins are pathological hallmarks of amyotrophic lateral sclerosis (ALS). Autophagy is the major intracellular degradative pathway involved in the clearance of protein aggregates, damaged organelles and stress granules. Decreased function of cytoplasmic dynein, the motor protein required for retrograde transport, impairs autophagic clearance of aggregate-prone proteins. Moreover, the serine/threonine-protein kinase TANK Binding Kinase 1 (TBK1) phosphorylates autophagic adaptors such as p62 and optineurin. Variations in TBK1 have been implicated both as a risk factor and as a cause of ALS.

In this study, we seek to test the hypothesis that reduced cytoplasmic dynein function combined with certain variations in TBK1 lead to impaired degradation of ALS-associated protein aggregate and consequently neuronal cell death.

Methods: Autophagic flux was monitored through estimating levels of LC3II and p62 by western blot analysis in primary mouse embryonic fibroblasts (MEFs) and murine neuroblastoma (Neuro2A) cells. For induction of autophagy, cells were cultured in serum free medium and then treated with BX795 or ciliobrevin to inhibit TBK1 or cytoplasmic dynein, respectively.

Results and conclusions: After inducing autophagy and TBK1 inhibition in MEFs, levels of the autophagosomal marker LC3II increased but the levels of p62, a marker of ubiquitinated proteins, decreased. Moreover, following dynein and TBK1 inhibition in serum-starved Neuro2A cell, level of p62 decreased but these inhibitions increased LC3II levels. We observed a similar pattern of LC3II and p62 levels in MEFs harbouring a p.F580Y mutation in cytoplasmic dynein heavy chain 1 (Dync1h1) and in Neuro2A cells after dynein and TBK1 inhibition.

These data suggest that reduced functions of cytoplasmic dynein and TBK1 decrease efficiency of autophagy but might stimulate degradation of misfolded proteins through the activation of proteasome system. Current work is now focused on these findings, analysing the clearance of protein aggregates in cells with reduced dynein and TBK1 functions, after proteasome inhibition.

Poster number: PM063 (SP)

Theme: Methods and techniques

An Automated Cell Distribution Analysis Method for Cell Counting Across Whole Brain Microscopy Data

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Introduction: Current methods for three-dimensional whole tissue volume imaging at single cell resolution include light-sheet microscopy and block-face imaging. These techniques offer the potential to quantify the three-dimensional distribution of important anatomical structures. However, manually generating quantitative results from these extensive datasets is time intensive and impractical. Therefore, we have developed an automated cell quantification pipeline, following serial two-photon whole brain microscopy. In future, we hope to compare the distribution of specific cell types across the entire mouse brain in order to identify age-related changes in neuronal density.

Methods: Following serial two-photon whole brain microscopy we performed segmentation of the whole brain dataset using the Allen Brain Atlas. This enabled the impartial identification of thousands of anatomical regions of interest. A targeted cell counting approach within these specific structures of interest was performed in order to reduce processing time and keep the pipeline computationally light.

Approach for Statistical Analysis: Cell counting was achieved by applying a threshold derived using the circularity of objects in the image. Potential cell-like objects identified by the thresholding technique were fed into a convolution neural network classifier which has been pre-trained on thousands of manually identified cell and non-cell objects. The classifier is used to confirm the correct detection of a cell.

Results and conclusions: We demonstrate the validity of our automated cell counting approach following serial two-photon tomography of brains obtained from Sox14^{gfp/gfp} and Sox14^{gfp/+} mice in order to map Sox14 interneuron distributions in both thalamic and hypothalamic brain regions.

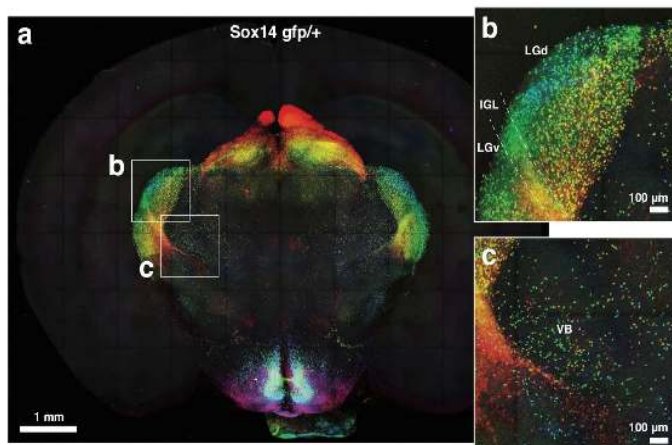


Figure 4. Depth-coded single cell-resolution projection across 2.3mm thick coronal volume of a Sox14^{gfp/+} mouse brain (a) showing enlarged views of the dorsal lateral geniculate nucleus (b) and the ventrobasal complex (c).

Poster number: PM064 (SP)**Theme:** Methods and techniques**Ultrasonic modulation of higher order visual pathways in humans**

Authors: Verena Braun¹, Joseph Blackmore², Michele Veldsman³, Robin O. Cleveland², Christopher R. Butler¹
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Introduction: Transcranial ultrasonic stimulation (TUS) is an emerging non-invasive brain stimulation method where low-intensity ultrasound is delivered safely through the skull to the brain. TUS has been used to target primary sensory regions of the human brain but its effect on higher-order and deeper cortical areas has not been studied. Moreover, concerns have recently arisen that TUS effects may be driven by auditory confounds. We investigated whether TUS can modulate higher-order visual processing and tested for auditory confounds.

Methods: Magnetic resonance imaging was used to map skull anatomy and functional regions of interest for each participant (n=19). Segmented imaging datasets formed the basis of 3D ultrasound simulations to determine transducer placements and source amplitudes. Thermal simulations ensured that temperature rises were <0.5 °C at the target and <3 °C in the skull. To test for unspecific auditory activation, TUS (500 kHz, 300 ms 50% duty cycle bursts) was applied to primary visual areas and participants were asked to distinguish stimulation from non-stimulation trials. We further tested whether TUS can modulate higher-order visual processing, by applying TUS to areas involved in motion processing during a motion detection task. EEG data were collected throughout.

Approach for statistical analysis: Auditory confounds were assessed on a behavioural as well as electrophysiological level. Event-related potentials were examined for auditory activation and stimulation detection rates are reported as d' values. Changes in motion detection performance were assessed by comparing hit rates during stimulation trials to hit rates during trials in which TUS was not applied.

Results and conclusions: We identified behavioural and electrophysiological evidence that TUS elicits an auditory signal which enables participants to distinguish stimulation and non-stimulation trials. This signal can, however, be effectively masked by playing an auditory stimulus at the pulse repetition frequency. Future studies using TUS must ensure that auditory confounds are controlled for. Nevertheless, once an auditory mask was applied, TUS to pathways involved in motion processing led to decreased motion detection rates showing that TUS can be used in humans to modulate activity in higher-order visual pathways in a task-specific and anatomically precise manner.

Poster number: PM065 (SP)**Theme:** Methods and techniques**Dynamics of spinal cord injury in vivo using two-photon microscopy**

Authors: Ms Barbora Svobodova^{1,2}, Dr Ondrej Zelenka^{1,3}, Dr Ondrej Novak^{1,2}, Dr Pavla Jendelova^{1,2}
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Spinal cord injury (SCI) is a devastating clinical condition with profound and irreversible impact on patient's quality of life, with no effective treatments available. Better comprehension of both primary and secondary mechanisms involved in SCI is a critical prerequisite for any development of new therapeutic interventions. However, standard experimental approaches mostly used for studying SCI lack temporal resolution necessary for understanding its inherently dynamic aspects. Therefore, basic successive mechanisms of SCI are still poorly understood. Using

repeated intravital two-photon imaging, we studied dynamic reactions of genetically-defined cell types following SCI. We implanted a custom-made imaging chamber, performed laminectomy and covered it with a spinal cord window. Thus, we obtained permanent optical access to the dorsal spinal cord for weeks up to months. Transgenic mouse strains were used to visualize spinal cord neurons and glial cells. One week after the window implantation, we did a laser-induced SCI with transection of axons in the dorsal column. Time-lapse imaging enabled us to repeatedly observe and evaluate the morphological changes after SCI. Individual axons and cells were precisely reidentified and tracked between individual consecutive imaging sessions. We observed heterogeneously asynchronous, spatially intermingled morphological changes and their continuous transitions between diverse states including axonal swelling and dieback, formation of retraction bulbs or spheroids, often with a subsequent fragmentation. In a subset of mice we transplanted GFP-labeled mesenchymal stem cells, tracked the grafted cells in vivo and observed the changes of their morphology. This methodology can be useful for real-time assessment of new therapeutic strategies.

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Poster number: PM066 (SP)

Theme: Methods and techniques

Advanced gait analysis detects subtle movement impairments in MPTP-treated mice

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Introduction: At the earlier stages of Parkinson's disease (PD) progression changes in the nigrostriatal system cause only subtle motor symptoms. Preventing the disease progression beyond the early symptomatic stage is an important objective of PD therapy and therefore it is important to have means to detect very early clinical signs of motor deficiency in animal models of PD. A widely used approach for modelling the nigrostriatal system deficiency in animals is administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is selectively toxic to dopamine neurons of the substantia nigra (SNpc). Between many administration protocols used in mice, a sub-chronic administration of the drug followed by a recovery period causes partially compensated nigrostriatal pathology that does not compromise mouse performance in conventional motor behaviour tests. A method capable to detect subtle changes in the motor function of these mice will be a valuable tool for detecting very early signs of the nigrostriatal pathology in other mouse models of PD and selecting early symptomatic animals in preclinical trials.

Methods: 12-week old C57BL/6J males received either a daily i.p. injection of 30 mg/kg MPTP (20 mice) or a vehicle (16 mice) for five consecutive days. Three weeks after the last injection animals' balance and coordination were assessed using the inverted grid and vertical pole tests, and the Noldus CatWalk gait analysis system, and dorsal striatum biopsies collected for analysis of dopamine and its metabolites levels by HPLC with electrochemical detection.

Approach for statistical analysis: GraphPad Prism software was used to calculate means±SEM and evaluative statistical significance of differences between animal groups by Student's t-test.

Results and conclusions: Consistently with the previous reports, three weeks after subchronic MPTP administration the striatal dopamine content was reduced but the remaining level (63.9±3.37%) was sufficiently high to retain normal animal balance and coordination in the inverted grid and vertical pole tests. However, of 187 parameters detected by the CatWalk system 63 were significantly different between two groups of animals, suggesting that the CatWalk gait analysis is a powerful tool for detection of the otherwise undetectable signs of an impaired.

Poster number: PM067 (SP)**Theme:** Neurodegenerative disorders & ageing**Role of cellular prion protein in tau-mediated inhibition of synaptic long-term depression in vivo****Authors:** Dr Tomas Ondrejcek¹, Dr Neng-Wei Hu¹, Dr Grant Corbett², Dr Graham Fraser³, Dr Michael Perkinson³, Dr Andrew Billinton³, Prof Dominic Walsh², Prof Michael Rowan¹¹*Department of Pharmacology & Therapeutics and Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland,*²*Laboratory for Neurodegenerative Research, Ann Romney Center for Neurologic Diseases, Brigham & Women's Hospital, and Harvard Medical School, Boston, USA, ³Neuroscience, IMED Biotech Unit, AstraZeneca, Cambridge, UK*

Introduction: The early stages of Alzheimer's disease are associated with synaptic damage prior to loss of neurons in vulnerable brain regions such as hippocampus. Synaptic long-term potentiation (LTP) has been shown to be disrupted by certain soluble aggregated forms of two key proteins, A β and tau. Much less, however, is known about how long-term depression (LTD), an alternative mechanism for the storage of memory, is affected by tau.

Methods: Here we investigated the effect of different tau species on synaptic plasticity at CA3-to-CA1 synapses in the rat hippocampus *in vivo*.

Approach for statistical analysis: Differences in the magnitude of LTD and LTP between experimental groups were analyzed using repeated measures two-way ANOVA followed by appropriate post hoc tests.

Results and conclusions: Intracerebroventricular injections of soluble tau aggregates (StAs), but not monomers or fibrils of human recombinant tau increased the threshold for LTD induction. StA-mediated inhibition of LTD was prevented by antibodies binding cellular prion protein (PrP). We found that blockade of the putative PrP co-receptor mGlu5R did not prevent the StA-mediated disruption of synaptic plasticity. A selective antagonist of GluN2B subunit-containing NMDA receptors reduced inhibition of LTD, but not LTP, by StAs. We also investigated the interaction between soluble aggregates of A β and tau to disrupt synaptic plasticity. Intriguingly, A β and tau appeared to act synergistically to inhibit LTP, while the ability of soluble A β to facilitate the induction of LTD was fully prevented by StAs. Collectively, the present findings support PrP-targeting strategies as a means to reduce the synaptotoxicity of soluble species of tau.

Poster number: PM068 (SP)**Theme:** Neurodegenerative disorders & ageing**An agent that restores protein synthesis, ISRIB, prevents A β -facilitated hippocampal LTD in the live rat****Authors:** Dr Nengwei Hu^{1,2}, Professor Michael Rowan¹¹*Department of Pharmacology & Therapeutics and Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland,*²*Department of Physiology and Neurobiology, Zhengzhou University School of Medicine, Zhengzhou, China*

Synaptic long-term depression (LTD) is believed to underlie critical mnemonic processes in the adult hippocampus and the promotion of LTD mechanisms by synaptotoxic soluble oligomers of amyloid- β (A β) has been proposed to underlie synaptic dysfunction in Alzheimer's disease (AD). Translational dysregulation in AD due to aberrant eIF2 is well documented. It's still unclear if the deficits in translational control are involved in the promotion of LTD mechanisms mediated by AD brain A β . Here we examined the effects of the small molecule ISRIB, which restores translation downstream of eIF2, on AD brain A β -facilitated LTD in the dorsal hippocampus *in vivo*.

EPSPs were recorded in the CA1 area of urethane-anaesthetized adult male Wistar rats. Control LTD was induced by 900 pulses (LFS-900) and A β -facilitated LTD by 300 pulses (LFS-300) at 1Hz. Agents were injected via a cannula implanted in the lateral ventricle.

Two-way ANOVA with repeated measures with Sidak's multiple comparison test was used. A value of $P < 0.05$ was considered statistically significant.

We found that: (i) The protein synthesis inhibitor emetine blocked the late, but not the early, phase of control LTD induced by LFS-900. (ii) In contrast, LFS-300 induced robust and persistent LTD in A β -injected rats both in the absence and presence of emetine. (iii) Systemic injection of ISRIB did not affect control LTD induced by LFS-900. (iv) In A β -injected animals pretreated with ISRIB LFS-300 induced an initial depression that gradually decayed back to baseline level at 3h. The present data indicate that under physiological conditions *in vivo* the induction of stable LTD requires protein synthesis, consistent with an important role of LTD in Learning and memory. In contrast, A β -facilitated LTD was inducible under translational dysregulation conditions, consistent with a role of disrupted protein-synthesis in synaptic dysfunction in early AD. A chemical inhibitor of the integrated stress response, ISRIB, prevents A β -facilitated LTD, most likely via restoring normal protein synthesis. Although the relative contributions of accelerated assembly, enhanced stability, or allosteric to ISRIB action remain to be resolved (Zyryanova et al., Science, 2018), our findings lend support to further investigating its potential promise as a novel therapy for early AD.

Poster number: PM069 (PP)

Theme: Neurodegenerative disorders & ageing

Development of a novel rat model of Parkinson's disease induced using AAV-mediated α -synuclein overexpression combined with FN075-mediated α -synuclein aggregation

Authors: Ms. Rachel Kelly¹, Ms. Silvia Cabre¹, Ms. Veronica Alamilla¹, Dr. Andrew G. Cairns², Dr. Jörgen Ådén², Prof. Fredrik Almqvist², Dr. Alexis Bemelmans³, Dr. Emmanuel Brouillet³, Dr. Declan McKernan¹, Dr. Eilis Dowd¹

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Introduction: It is widely considered that the most valid animal models of Parkinson's disease (PD) to have emerged in recent years are those induced by viral overexpression of human alpha-synuclein variants in the rat brain. These models are associated with alpha-synuclein overexpression and aggregation leading to nigrostriatal neuronal dystrophy/degeneration with associated motor decline. However, these models are limited by their slowly developing pathology and high degree of variability. We have recently developed a novel peptidomimetic small molecule (FN075) that is capable of promoting alpha-synuclein oligomerisation and progressive fibril formation¹ and inducing nigrostriatal degeneration after intra-nigral injection in mice². Therefore, in this study, we seek to determine if combining viral-mediated overexpression of alpha-synuclein with FN075-mediated aggregation of alpha-synuclein results in a more rapidly developing and consistent model of PD when compared with either approach alone.

Methods: To test this hypothesis, 40 female Sprague-Dawley rats will be given unilateral intra-nigral injections of AAV- α -synuclein (AAV₆ pseudotype, A53T variant, PGK promoter) or AAV-GFP as a control. Four weeks later, the rats will be given unilateral intra-nigral injections (at the same site) of FN075 (1.9 μ g in 4 μ l) or vehicle as a control to yield 4 experimental groups: AAV-GFP & vehicle, AAV-GFP & FN075, AAV- α -synuclein & vehicle, and AAV- α -synuclein & FN075. The impact of the single and combined treatments on motor function will be assessed using a battery of lateralised tests of spontaneous motor function (Stepping, Whisker and Corridor tests) at regular intervals until sacrifice 6-8 weeks later. After sacrifice, immunohistochemical analyses will be used to assess alpha-synuclein expression and aggregation, as well as nigrostriatal degeneration (tyrosine hydroxylase staining) and neuroinflammation (microgliosis (OX-42 staining) and astrocytosis (GFAP staining)).

Approach for statistical analysis: A randomised and blinded study design will be used to compare treatment groups. Assuming data will exhibit homogeneity of variance and normal distribution (verified using Levene's and Shapiro-

Wilk's tests, respectively), all data will be analysed using ANOVA (one-way, two-way or repeated measures as appropriate).

References:

1. Cegelski L et al., 2009. Nat Chem Biol. 5:913-9.
2. Chermenina M et al 2015, NPJ Parkinson's disease; 1: 15024.

Poster number: PM070 (SP)

Theme: Neurodegenerative disorders & ageing

Brain-predicted age difference as an objective measure of cognitive function

Authors: Rory Boyle¹, Lee Jollans¹, Dr Laura M Rueda-Delgado¹, Rossella Rizzo², Ezgi Fide³, Prof Görsev G Yener^{3,4,5}, Dr Daniel Carey⁶, Prof Ian H Robertson^{1,7}, Prof Derya Durusu Emek-Savaş^{3,7,8}, Prof Yaakov Stern⁹, Prof Rose Anne Kenny^{6,10}, Prof Robert Whelan^{1,7}

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Introduction: Brain-predicted age difference (brainPAD) can identify individuals who are at risk of unhealthy ageing at an early stage in the lifespan. BrainPAD is calculated by subtracting an individual's chronological age from their 'brain' age, which is estimated from a machine learning analysis of neuroimaging data. Higher brainPADs indicate 'older' brains and are associated with increased mortality risk and poorer physical ageing [1]. However, it remains to be seen whether brainPAD can identify individuals at risk of cognitive decline. To validate brainPAD as a cognitive ageing biomarker, the specific relationship between brainPAD and cognitive function must be established in older adults.

Methods: Voxelwise grey matter density values were extracted from 1,359 pre-processed T1-weighted open-access MRI scans, resulting in a 1,359 (scan) x 54,869 (voxels) matrix. This matrix was used as the input data in an Elastic Net machine learning regression model, with 10-fold cross validation, in order to predict the outcome variable, chronological age. This model significantly predicted age ($r = 0.88$, $p < 0.0001$). The brain voxels most responsible for 'older' brains were located within areas vulnerable to age-related grey matter volumetric decline: the temporal lobe, thalamus, precentral gyrus, and hippocampus.

Approach for statistical analysis: The 'learned' coefficients from the machine learning model were then applied to T1 MRIs in three external datasets (TILDA, DEU, CR/RANN) in order to estimate 'brain age'. Brain-predicted age was externally validated in each dataset (TILDA: $r = 0.63$; DEU: $r = 0.78$; COLU: $r = 0.87$, all significant at $p < 0.0001$). BrainPAD scores were then calculated for the three datasets and Spearman's rank correlations were conducted to investigate the associations between brainPAD and specific domains of cognitive function.

Results and conclusions: Across multiple datasets, brainPAD was reliably correlated with measures of processing speed, visual attention, and cognitive flexibility; semantic verbal fluency; and general cognitive status. These results provide firm evidence of associations between increased brainPAD and reduced cognitive function and consequently support the use of brainPAD as a cognitive ageing biomarker.

[1] Cole, J.H. et al (2018) *Mol. Psychiatry*

Poster number: PM071 (SP)

Theme: Neurodegenerative disorders & ageing

Impaired long-term depression in APP-overexpressing rats in vivo. Role for metabotropic glutamate receptor 5

Authors: Dr Igor Klyubin¹, Dr Yingjie Qi¹, Dr Nen-Wei Hu¹, Prof Michael Rowan¹

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Introduction: We previously reported an A β -mediated age-dependent inhibition of long-term potentiation in the McGill-R-Thy1-APP transgenic rat model of Alzheimer's disease amyloidosis (Qi *et al.*, *Acta Neuropath. Commun.*, 2014). Here, we investigated the effect of APP overexpression on long-term depression (LTD).

Methods: *In vivo* experiments were carried out on acutely urethane-anaesthetized 5-6 month-old pre-plaque male rats. Electrically evoked field excitatory postsynaptic potentials were measured at CA3 to CA1 synapses in the right dorsal hippocampus. To induced LTD, we applied electrical 1 Hz low frequency stimulation (LFS) (Hu *et al.*, *Nat. Commun.*, 2014).

Approach for statistical analysis: One-way ANOVA followed by Bonferroni's multiple comparison test was used to compare the magnitude of LTD between multiple groups. Paired and unpaired Student's t-tests were used to compare within one group and between two groups, respectively.

Results and conclusions: 1 Hz LFS induced robust LTD in wild-type animals (58 \pm 8%, n=6, p<0.05, compared with pre-LFS baseline). In contrast, no significant LTD was observed in transgenic littermates (108 \pm 11%, n=7, p>0.05, compared with pre-LFS baseline, p<0.05, compared with wild-type animals). Interestingly, repeated systemic treatment with metabotropic glutamate receptor 5 antagonist basimglurant (2 mg/kg, i.p. for three consecutive days) fully reversed the LTD deficit in transgenic animals (68 \pm 8%, n=5, p<0.05, compared with pre-LFS baseline, p>0.05, compared with wild-type animals). Thus, targeting mGluR5 is an attractive strategy to abrogate not only the LTP deficit (Zhang *et al.*, *Neuropharmacology*, 2017) but also the LTD impairment. The finding that, in addition to LTP induction, LTD is also disrupted in pre-plaque transgenic rats indicates that the dynamic range of synaptic plasticity available in the CA1 area is greatly reduced very early in Alzheimer's disease. Supported by the Health Research Board and Science Foundation Ireland.

Poster number: PM072 (SP)

Theme: Neurodegenerative disorders & ageing

Altered alpha-tubulin post-translational modification (PTM) expression in the cerebrospinal fluid (CSF) of Parkinson's disease (PD) patients

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Introduction: Parkinson's disease (PD) is the most common motor neurodegenerative disorder in the world, affecting 1% of the population over the age of 60. All available treatments are symptomatic and, at the time of diagnosis, most patients have had a substantial permanent loss of dopaminergic neurons in the substantia nigra. Currently there are no biomarkers which can diagnose PD before the motor symptoms present. Microtubule dynamics are fundamental for neuronal survival, synaptic function and remodelling, including formation and maintenance of axons, dendrites and dendritic spines. Growing evidence, including post-mortem Alzheimer's disease (AD) studies [1] and

preclinical/clinical PD studies [2,3], suggest a role for α -tubulin post-translational modifications (PTMS; markers of microtubule dynamics) in the pathogenesis and treatment of neurodegenerative disorders. Here, we investigated for the first time the expression of α -PTMS in the plasma and cerebrospinal fluid (CSF) of healthy controls compared to PD patients.

Methods: 64 plasma samples (32 control, 32 PD) and 64 CSF samples (32 control, 32 PD) were obtained from the BioFIND study. This is an observational clinical study designed to discover and verify biomarkers of PD, sponsored by the Michael J Fox Foundation for Parkinson's Research with support from the National Institute of Neurological Disorders and Stroke (NINDS). The plasma and CSF samples were analysed by infrared Western Blot to quantify the plasma and CSF α -tubulin PTMs.

Approach for statistical analysis: The infrared Western Blot signals were expressed as percentage control. The data were then analysed using unpaired *t*-test and two-way ANOVA followed by Fishers LSD.

Results and conclusions: A significant decrease in the expression of the tyrosinated/detyrosinated α -tubulin ratio was identified in the CSF of PD patients when compared to controls. This is indicative of less dynamic microtubules in the PD patients. Thus, the cycle of tyrosination/detyrosination of α -tubulin in the CSF could represent a potential biomarker of disease as well as an innovative therapeutic target for development of new drugs.

References

- [1] Zhang et al., (2015) *Translational Neurodegeneration* 4(9): <https://doi.org/10.1186/s40035-015-0030-4>.
 [2] Cartelli et al., (2012) *PLOS ONE* 7(8): 10.1371/annotation/6db7193b-913a-42f2-aa7c-139d6e15142a.
 [3] Cartelli et al., (2013) *Sci Rep.* 3:1837: doi: 10.1038/srep01837.

Poster number: PM073 (SP)

Theme: Neurodegenerative disorders & ageing

Persistent modulation of hippocampal LTP and LTD by exogenous corticosterone in a rat model of Alzheimer's disease amyloidosis: in vivo longitudinal studies

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Previously we reported that transgenic (TG) rats overexpressing mutant human APP (McGill-R-Thy1-APP) develop an A β -dependent deficit in synaptic LTP induced by standard conditioning stimulation (200 Hz-HFS) as early as 3-4 months of age, whereas there was no deficit in LTP induced by a strong conditioning stimulation protocol (400 Hz-HFS) (Qi et al., *Acta Neuropath. Comm.*, 2014). Here we performed a longitudinal study to examine the effect of the stress hormone corticosterone (Cort) on LTP and LTD induction.

Electrically evoked field EPSPs were recorded in stratum radiatum of CA3 to CA1 synapses in the dorsal hippocampus of chronically implanted adult freely behaving male rats.

Whereas single subcutaneous injection of Cort at a dose of 10mg/kg had no effect on LTP induced by 400Hz-HFS in either wild type or pre-plaque TG littermates (5 months old), 3 injections of the same dose of Cort over 3 days inhibited LTP in both groups. Remarkably, longitudinal studies of these latter rats revealed that whereas LTP in TG was still strongly inhibited, 400Hz-HFS induced robust LTP in WT rats both at 1 and 2 months post-treatment. Moreover, application of 900 pulses at 1Hz induced LTD at this time period in Cort-treated TG rats but not in control TG rats. In contrast, treatment of 5 months old WT or TG littermates with half this dose of Cort (5mg/kg, s.c. for 3 days) did not inhibit LTP or facilitate LTD up to 2-3 months post-treatment. Finally, to test whether Cort could accelerate the deficit in LTP induced by 200Hz-HFS, 3-month-old TG rats were treated for 3 days with Cort (10mg/kg, s.c.). The onset of the LTP deficit in these rats did not appear to be different from that found in control TG rats.

In conclusion, although Cort persistently inhibited LTP and facilitated LTD in older pre-plaque TG rats, Cort did not accelerate the deficit in LTP induced by 200Hz-HFS in young TG rats. This age-dependent increased vulnerability to persistent disruption of synaptic plasticity by brief elevated Cort exposure in TG rats may mediate corticosteroid-triggered exacerbation of early Alzheimer's disease.

Poster number: PM074 (SP)

Theme: Neurodegenerative disorders & ageing

Diet with walnuts decrease amyloid beta-protein production by affecting the activities of secretases in transgenic mouse model of Alzheimer's disease

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Introduction: Amyloid beta-protein (A β) is the major protein of amyloid deposits in the brain of patients with Alzheimer's disease (AD). Extensive evidence suggests neurotoxic effects of A β , and the role of oxidative stress and inflammation in AD. Walnuts are rich in components with antioxidant and anti-inflammatory properties. Previous studies have shown that walnut extract inhibits A β fibrillization, solubilizes its fibrils, and has protective effects against A β -induced oxidative stress and cell death. In the Tg2576 transgenic mouse model of AD (AD-tg), we have reported that dietary supplementation of walnuts (a) improves the memory, learning skills, anxiety and motor coordination; and (b) decreases free radical levels and oxidative damage, and increases antioxidant status. In this study, we examined the effects of walnuts in the diet on the processing of amyloid precursor protein (APP) in AD-tg mice. APP is processed by non-amyloidogenic and amyloidogenic pathways. In non-amyloidogenic pathway, APP is cleaved by α -secretase. In amyloidogenic pathway, APP is cleaved by β -secretase with subsequent cleavage by γ -secretase, thus releasing A β .

Methods: From the age of 4 months, the experimental groups of AD-tg mice were fed diets containing 6% (T6) or 9% walnuts (T9) (equivalent to 1 or 1.5 oz, daily intake of walnuts in humans) for 5, 10 or 15 months. The control groups, i.e., AD-tg (T0) and wild-type mice (Wt), were fed a diet without walnuts. The diets for the experimental and control mice were comparable in total calories and the contents of protein, carbohydrate and fat. These mice at different ages (4, 9, 14 and 19 months) were examined for the activities of α , β and γ secretases in the liver.

Results and Conclusions: T0 mice showed a significant age-dependent decrease in α -secretase activity and increase in β - and γ -secretase activities compared to Wt mice. The activities of secretases were significantly restored in AD-tg mice on diets with 6% or 9% walnuts. Long-term supplementation with walnuts in the diet for 10 or 15 months was more effective in modulating the activities of these enzymes. These results suggest that dietary supplementation with walnuts may lead to decreased processing of APP to A β , thereby reducing amyloid burden in AD.

Poster number: PM075 (PP)

Theme: Neurodegenerative disorders & ageing

Investigating the role of glial tau in Alzheimer's disease using drosophila

Authors: Ms Lucy Minkley¹, Dr Oyinkan Adesakin¹

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Alzheimer's disease (AD) is characterised by the presence of extracellular amyloid plaques and intracellular tangles of hyperphosphorylated Tau. Accumulation of Tau occurs in both neurons and in glia, but in contrast to neurons, less is known about the role glial Tau plays in AD. In this project, we will investigate the role of Tau in glia, using the fruit fly *Drosophila melanogaster*.

Drosophila have a relatively complex nervous system with several distinct glial cell types. These have strong homology to those seen in humans, and perform specific functions: including astrocytes which contact synapses, cortex glia which provide trophic support to neuronal cell bodies, wrapping glia which ensheath axons, and perineurial and subperineurial glia which together make up the blood brain barrier. It is not clear to what extent the different glial cell types contribute to AD toxicity, and if a specific glia cell type is more vulnerable to Tau toxicity. To tackle these questions, we have expressed human Tau in each of the glia cell types in the fruit flies using the *Drosophila* GAL4/UAS system, and performed behavioural assays to assess their functional health. Our preliminary data suggest that certain glial populations are more vulnerable to Tau toxicity.

Post-translational modifications of Tau, such as phosphorylation and acetylation, mediate tangle formation and toxicity. Identification of post-translational modification enzymes that influence Tau toxicity in glia would help to characterise cell-specific pathways by which Tau contributes to AD. We will perform genetic screens of candidate post-translational modification enzymes in *Drosophila* expressing Tau, to identify potential modifiers of Tau toxicity in glia, by using a combination of behavioural and molecular assays. The assays will be carried with appropriate numbers of flies and biological repeats in order to carry out statistical analyses.

In summary, the data from this project will enable us to identify a role for glial Tau in AD pathogenesis, determine whether any of the candidate enzymes specifically influence Tau toxicity in glia, and thus identify potential therapeutic targets or/and biomarkers for AD.

Poster number: PM076 (SP)

Theme: Neurodegenerative disorders & ageing

Potential of an injectable IL-10 rich collagen hydrogel for cell transplantation in Parkinson's disease

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Introduction: The main limitation of fetal cell therapy for Parkinson's disease is the poor graft survival upon transplantation. We have shown that neurotrophin-loaded collagen hydrogels can enhance the survival of the grafted cells^{1,2}. Here, we hypothesise that site-specific delivery of anti-inflammatory factors using injectable biomaterial scaffolds can target the elevated inflammatory response present after cell transplantation and therefore increase graft survival. The aim was to assess if the collagen hydrogel could retain IL-10 and if IL-10 had any beneficial effects on cell survival, re-innervation and the host immune response in a rat Parkinson's disease model.

Methods: Male Sprague Dawley rats were given an intra-striatal delivery of 1000 ng of IL-10 alone or encapsulated in collagen hydrogels. Polymerisation, biocompatibility, biodegradability and IL-10 retention were assessed using immunohistochemistry. In another study, Parkinsonian rats (6-hydroxydopamin-lesioned) were injected with primary dopaminergic cells (400,000 cells from E14 rat embryos) with or without IL-10 (1000 ng) within or without a collagen hydrogel. Rats were sacrificed 12 weeks post-transplantation and assessed using immunohistochemistry for graft survival, re-innervation and host immune response.

Approach for statistical analysis: A randomised and blinded experimental approach was used. All data were analysed using one-way ANOVA, with post hoc Bonferroni test.

Results and conclusions: The loading of IL-10 within the collagen hydrogel resulted in significant retention of the anti-inflammatory cytokine in the striatum, and reduced the host microglial response at the site of administration at early time-points. Despite these beneficial effects, in the longer-term study, IL-10 did not improve dopaminergic neuron survival, re-innervation or function. Therefore, this suggests that anti-inflammatory intervention at the site of

transplantation is not sufficient in its own to enhance the survival of primary dopaminergic grafts. Further studies should investigate the effects of anti-inflammatory intervention with other neurotrophic factors to determine if there is a synergistic effect of the two approaches on cell survival.

References:

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Acknowledgements:

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Poster number: PM077 (SP)

Theme: Neurodegenerative disorders & ageing

Effects of the ketone body 3-hydroxybutyrate on neuronal Bioenergetics during excitotoxic stress

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Introduction: Protective effects of ketone bodies in the setting of epilepsy treatment in patients have been described, yet their mechanism of action is not understood. Glutamate is the main excitatory neurotransmitter in the CNS and excessively released during seizures. Overactivation of glutamate receptors promotes neuronal dysfunction and death through glutamate excitotoxicity. Neuronal excitation and glutamate toxicity can be substantially modulated by alterations in the energy substrates. The main purpose of this study is to analyse the effects of the metabolic switch imposed by ketogenic substrates on glutamate-mediated Ca²⁺ signalling and mitochondrial bioenergetics in ambient and 5% O₂.

Methods: We conducted single-cell imaging using LSM-5 Live and LSM-710 confocal microscopes, High Content Screening analysis using fluorescence and bright field imaging, western-blotting, and bioenergetics assays using the Seahorse-96XF Analyser in primary mouse hippocampal and cortical neuron cultures.

Approach for statistical analysis: Primary analysis was performed by one-way ANOVA followed by Bonferroni multiple-significance-test correction.

Results and conclusions: Spontaneous cytosolic Ca²⁺ peaks were observed in mature cortical and in hippocampal neurons in 21% and 5% O₂. Under basal conditions, glucose injection induced a fast ATP production by increasing glycolysis in association with OXPHOS inhibition. In contrast, injection of the ketone body 3-hydroxybutyrate promoted a strong increase in mitochondrial respiration. Cortical neurons growing in 5% O₂ presented significantly lower basal respiration, and higher coupling efficiency and maximal uncoupled respiration compared to neurons growing in ambient O₂. Upon glutamate stimulation, cytosolic Ca²⁺ levels and Ca²⁺-dependent activation of mitochondrial respiration were stronger with 3-hydroxybutyrate than with glucose. Furthermore, at low oxygen, glutamate-induced stimulation of respiration was enhanced and more sustained, and maximal uncoupled respiration inhibition was partially prevented compared to ambient O₂. Interestingly, glutamate-induced activation of mitochondrial respiration was independent of Malate-Aspartate shuttle (MAS) activity in the presence of 3-hydroxybutyrate but not with glucose, as concluded from the strong OXPHOS activation after the inhibition of the shuttle using aminooxyacetic acid. In 5% oxygen, this effect was further enhanced.

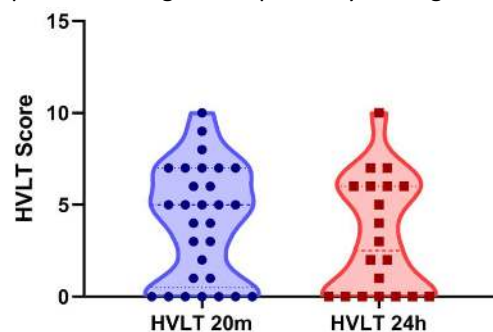
In conclusion, 3-hydroxybutyrate preserved mitochondrial bioenergetics on excitotoxic stress independently of MAS activity, and more efficiently in neurons growing in 5% O₂ than ambient O₂.

Poster number: PM078 (SP)**Theme:** Neurodegenerative disorders & ageing**Long-term memory as a predictor of cognitive decline in patients with amnesic mild cognitive impairment: a pilot study****Authors:** Ms Esther Saunders-Jennings¹, Mr Alfie Wearn¹, Dr Michael J. Knight¹, Ms Serena Dillon¹, Ms Demitra Tsivos¹, Ms Hanna Isotalus¹, Dr Bryony McCann¹, Dr Risto A. Kauppinen¹, Dr Elizabeth J. Coulthard^{1,2}¹University of Bristol, Bristol, United Kingdom, ²Neurology, Southmead Hospital, Bristol, United Kingdom

Accelerated forgetting may be an important indicator of incipient Alzheimer's disease. To probe accelerated forgetting, memory must be tested over a longer period than the 30-minute delay typically used in diagnostic tests. Previous studies suggest that performance after a 7-day delay can distinguish those with a diagnosis of amnesic mild cognitive impairment (aMCI) from healthy controls, better than performance at 30-minutes (Walsh et al., 2014). Here we present data from a pilot study investigating whether a 24-hour delay in memory testing could be as useful as longer delays. We hypothesise that 24-hour Hopkins Verbal Learning Test-Revised (HVLT-R) scores will predict change in general cognitive ability (Montreal Cognitive Assessment; MoCA) of those with aMCI, better than 20-minute HVLT-R scores and that volume and integrity of the hippocampus will predict performance on long-term memory tasks.

From a group of 30 aMCI participants, 15 participants had both baseline and one-year follow up data, including cognitive testing (HVLT-R, MoCA) and a 3T structural MRI scan, including a multi-echo sequence to measure quantitative T2 relaxometry. Brain volume was assessed using ASHS (Automatic Segmentation of Hippocampal Subfields). Based on recently published data (Knight et al., 2018), novel measures of tissue integrity were quantified by T2 relaxometry. Correlational analysis was performed using Pearson's *r*.

Neither 20-minute nor 24-hour HVLT-R significantly correlated with decline in MoCA or hippocampal volume change over the year. Unsurprisingly, 20-minute performance ($M=4.03$, $SD=3.11$) was higher than 24-hour performance ($M=3.25$, $SD=3.16$). Upon visual inspection of the data, 24-hour performance was bimodal. When split on the median, 24-hour performance shows high-performing individuals with aMCI ($M=6$, $SD=1.89$) and those who are low-performing ($M=0.5$, $SD=0.85$). This will be investigated further to observe whether this is a meaningful method of distinguishing individuals with aMCI. Further investigation of the utility of T2 quantitation are also to be carried out. This pilot study shows the feasibility of the research. Conclusions are limited by a small sample size and short follow-up period. Ongoing research is investigating this further in a larger sample, using longer delays (7 and 28 days), to probe the diagnostic specificity of long-term memory consolidation.

**Poster number: PM079 (PP)****Theme:** Neurodegenerative disorders & ageing**Using EEG frequency tagging to assess cognition in dementia****Authors:** Mr Volkan Nurdal¹, Dr George Stothart¹

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Dementia is one of the society's greatest health challenges, projected to affect a million people in the UK alone by 2025 (Prince *et al.*, 2014), with Alzheimer's Disease (AD) being the most common cause. Currently, AD is diagnosed too late to effectively intervene, with research suggesting neuropathology may have been present for up to 20 years prior to diagnosis. Current diagnostic techniques (neuropsychological assessment and structural brain imaging) are clearly ineffective in detecting the earliest stages of the disease. This lack of early diagnosis leads to irreversible neurodegeneration and may be a major factor in the last 20 years of pharmaceutical industry failure to develop a disease modifying therapy.

Recently a new electroencephalography (EEG) technique, Fast-Periodic-Visual-Stimulation (FPVS), has enabled reliable assessment of cognitive performance in single subjects in as little as 1-minute recording time, due to its very high signal to noise ratio. The technique uses frequency tagging to tag standard and oddball stimuli in a so-called FPVS-oddball paradigm and was first demonstrated by Heinrich *et al.* (2009), then extensively developed by Rossion *et al.* (2014-2016). To date, this technique has been mostly used in studies of face processing and recognition. Stothart *et al.* (2017) demonstrated the adaptability of the FPVS-oddball paradigm to measure conceptual processes by objectively measuring semantic categorisation, via the presence or absence of an oddball response, at the individual subject level in under 2-minutes recording time, without the subject responding in any way.

FPVS technique can be adapted to measure a range of cognitive processes. Currently, we are focusing on developing, adapting and refining the FPVS technique to examine the neural correlates of cognitive functions (e.g. short-term memory, prospective memory) in young adults. The following studies will investigate these processes in older adults and AD patients, with the long-term aim of developing it as a diagnostic tool.

We will be using EEG to record the brain activity of healthy young adults. Examples of stimulus presentation and EEG response measured in an FPVS-oddball paradigm are illustrated in Figure 1.

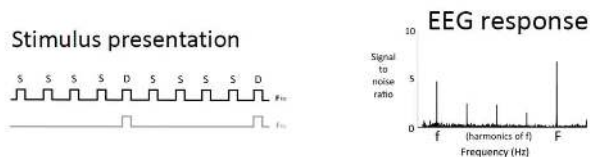


Figure 1: The diagram on the left illustrates an example train of stimuli presented in an FPVS-oddball paradigm. The graph on the right illustrates an example EEG response obtained from the aforementioned stimuli.

Cluster permutation testing will be used to identify regions of interest where oddball responses are the strongest.

Poster number: PM080 (SP)

Theme: Neurodegenerative disorders & ageing

Neurotoxic effects of acrylamide on dopaminergic neurons in primary mesencephalic cell culture

Authors: Professor Ismaeel Bin-jaliah¹, Professor Khaled Radad¹, Professor Mubarak Al-Shraim¹, Professor Rudolf Moldzio², Professor Wolf-Dieter Rausch²

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Introduction: Acrylamide (ACR) is a synthetic monomer with a wide range of industrial applications. ACR formation during processing of food containing carbohydrates and proteins at high temperatures had withdrawn a high concern worldwide and had persuaded researchers to investigate its potential risk to human health. The loss of dopaminergic neurons in the substantia nigra is a recognized neuropathological characteristic of Parkinson's disease, which is too an appealing universal neurodegenerative disease. In this study, we investigated whether ACR adversely affects the dopaminergic neurons in primary mesencephalic cell culture.

Method: Primary mesencephalic cell cultures were prepared from embryonic mouse mesencephala at gestational day 14, where the embryos were collected under aseptic condition in Dulbecco's phosphate buffered saline then the mesencephala were excised and the cultures were prepared. On the ninth day in vitro (9th DIV), two sets of cultures were treated with different concentrations of acrylamide (0.001 mM, 0.01 mM, 0.1 mM, 1 mM, and 2 mM) for either 24 hr or 48 hr. At the end of each treatment, culture media were utilized for measuring lactate dehydrogenase. The cultured cells were stained immunocytochemically against tyrosine hydroxylase and neuronal nuclear antigen (NeuN).

Approach for statistical analysis: Data for each parameter were obtained from three experimental repeats. Comparisons were made using ANOVA and post-hoc Duncan's. The p value < 0.05 was considered as statistically significant.

Results and conclusions: Acrylamide significantly reduced the neuronal survival and neurites number of dopaminergic neurons. In the 48 hr treated cultures compared to untreated controls, ACR significantly reduced neurons number by 47.1 % and 60.7 %, and neurites number of survived neurons by 38.3 % and 53.1 %, at 1 mM and 2 mM concentrations, respectively. Additionally, ACR at 2 mM significantly increased lactate dehydrogenase by 130.4 %. It decreased NeuN immunoreactivity by 15.9 % and 18.1 % at 1 mM and 2 mM, respectively. In conclusion, our present study shows that acrylamide reduced the total neuronal cells and adversely affects dopaminergic neurons in primary mesencephalic cell culture. Indeed, further mechanistic studies are recommended.

Poster number: PM081 (SP)

Theme: Neurodegenerative disorders & ageing

Mitochondrial distribution in substantia nigra neurons: Implications for degeneration in Parkinson's disease

Authors: Dr Amy Reeve¹, Dr John Grady², Dr Eve Cosgrave¹, Miss Emma Bennison¹, Dr Chun Chen¹, Miss Nishani Jeyapalan¹, Mrs Philippa Hepplewhite¹, Dr Chris Morris³

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Introduction: The correct distribution of mitochondria is essential for the provision of ATP to regions of the neuron which are particularly energy demanding e.g the synapse. Mitochondrial dysfunction within the cell bodies of substantia nigra neurons has been well documented in both ageing and Parkinson's disease. However an investigation of the presence of such changes in distal parts of the neuron was warranted. This is especially important since the loss of these neurons in Parkinson's disease is associated with loss of synapses within the striatum, which may precede neuronal loss. We investigated whether mitochondrial changes previously reported within substantia nigra neurons were also seen within the synapses and axons of these neurons.

Methods: Using high resolution quantitative fluorescent immunohistochemistry we determined mitochondrial density within remaining dopaminergic axons and synapses, and quantified deficiencies of mitochondrial Complex I and Complex IV in these compartments.

Results and conclusions: In Parkinson's disease mitochondrial populations were increased within axons and the mitochondria expressed higher levels of key electron transport chain proteins compared to controls. Furthermore we observed synapses which were devoid of mitochondrial proteins in all groups, with a significant reduction in the number of these 'empty' synapses in Parkinson's disease. This suggests that neurons may attempt to maintain mitochondrial populations within remaining axons and synapses in Parkinson's disease to facilitate continued neural transmission in the presence of neurodegeneration, potentially increasing oxidative damage. This compensatory event may represent a novel target for future restorative therapies in Parkinson's disease.

This work was supported by Parkinson's UK (F-1401)

Poster number: PM082 (SP)

Theme: Neurodegenerative disorders & ageing

Viral mediated neuroinflammatory priming exacerbates α -synuclein aggregate-induced neuroinflammation and degeneration: Implications for viral etiology in Parkinson's disease

Authors: Dr Declan Mckernan¹, Dr Laura Olsen¹, Dr Andrew Cairns², Dr Jorgen Aden², Ms Silvia Cabre¹, Ms Veronica Alamilla¹, Dr Niamh Moriarty¹, Prof Fredrik Almqvist², Dr Eilis Dowd¹

¹Nui Galway, Galway, Ireland, ²Umea University, Umea, Sweden

Background: Although the etiology of idiopathic Parkinson's disease (PD) remains unknown, evidence suggests that PD may manifest after a lifetime of environmental exposures, including viral infection¹, interacting with underlying genetics.

Aim: The aim of this study was to determine the effect of viral priming (using the synthetic dsRNA viral mimetic Poly I:C) on α -synuclein aggregate-induced neuropathology (induced by the small peptidomimetic FN0752,3) in vivo in rats.

Methods: Thirty-two male Sprague-Dawley rats received unilateral intra-nigral injection of Poly I:C (30 μ g) or vehicle, followed two weeks later by a subsequent unilateral intra-nigral injection of FN075 (1.93 μ g) or vehicle. The effect of viral-like priming was assessed using immunostaining for filamentous α -synuclein, dopaminergic degeneration, and neuroinflammatory markers. Motor behaviour was measured every two weeks after FN075 injection.

Results: Relative to the vehicle or single exposure, viral-like priming in combination with α -synuclein aggregation led to significant motor impairment, which was underpinned by the significant exacerbation of neuroinflammation and dopaminergic neuronal death in the substantia nigra.

Conclusions: This study has demonstrated that viral mediated neuroinflammatory priming can dramatically enhance the consequences of α -synuclein aggregate formation in the nigrostriatal pathway, lending further support to the growing evidence that suggests viral infections are involved in PD etiology.

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Acknowledgments:

NUIG College of Medicine, Nursing, and Health Sciences

Poster number: PM083 (SP)**Theme:** Neurodegenerative disorders & ageing**Difference in the reaction of the electrode-tissue interface to chronically implanted active and inactive deep brain stimulation electrodes****Authors:** Dr Judith Evers^{1,2}, Dr. Hanne Jahns³, Joseph Brady³, Professor Madeleine Lowery^{1,2}¹*School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland*, ²*CÚRAM Centre for Research in Medical Devices, Galway, Ireland*, ³*School of Veterinary Medicine, University College Dublin, Dublin, Ireland*

Introduction: Efficacy of implanted stimulation and recording electrodes in deep brain stimulation (DBS) and brain machine interfaces degrades over time due to changes at the electrode-tissue interface including impedance, neuroinflammation and glial scarring. However, the exact mechanisms involved, in particular the influence of current or voltage applied during active stimulation, are not fully established. The aim of this study was to investigate the electrode-tissue interface in chronically implanted stimulation electrodes and compare changes with and without the application of current stimulation. DBS of the subthalamic nucleus (STN), an established treatment for Parkinson's Disease, was chosen as a model.

Methods: Experiments were approved by the UCD Animal Research Ethics Committee and licenced by the Health Products Regulatory Authority of Ireland. Bipolar concentric electrodes were implanted in the STN of 8 male Wistar rats (400g). 4 rats received DBS (130Hz, 100µA, 60s, 4 hours/day) and 4 received no stimulation for 8 weeks. Impedance spectroscopy was performed ≥3 times/week. Brains were fixed by cardiac perfusion with 10% neutral buffered formalin and 5µm sections were labelled for astrocytes (GFAP), neurofilament and microglia (Iba-1) by immunohistochemistry.

Approach for statistical analysis: Impedance data was compared using a two-way repeated-measures ANOVA and histological data was assessed by a pathologist.

Results and conclusions: Baseline impedance at 1kHz was 19.8kΩ±4.1kΩ. After rapid changes in the first 2 weeks, impedance was significantly lower in the stimulation group: 53.2kΩ±2.0kΩ (control group) and 24.8kΩ±1.7kΩ (DBS group). The astrocyte and microglia reaction around the electrode was influenced by electrode movement, but when comparing results from firmly implanted electrodes, there was a mild increase in the number of astrocytes surrounding stimulated electrodes versus non-stimulated. Neurofilament staining revealed indicators of axonal injury in 2/4 stimulated rat brains while no evidence of axonal injury was observed in brains without stimulation. The preliminary data showed an effect of stimulation on the surrounding parenchyma and the electrode-tissue-interface beyond the foreign body response in addition to reduced electrical impedance in the stimulation group. The exact mechanisms need to be elucidated further but these changes are likely to impact stimulation and recording and may, therefore, contribute to changes in efficacy of interventions with time.

Poster number: PM084 (SP)**Theme:** Neurodegenerative disorders & ageing**Longitudinal trajectories of social and cognitive activities and their relationship with brain structure and function****Authors:** Ms Melis Anatürk^{1,2}, Dr Sana Suri³, Dr Enikő Zsoldos¹, Dr Nicola Filippini^{1,2}, Ms Abda Mahmood¹, Dr Archana Singh-Manoux^{4,5}, Dr Mika Kivimäki⁴, Dr Clare Mackay^{1,3}, Dr Klaus Ebmeier¹, Dr Claire Sexton^{1,3,6}¹*Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JX*, ²*Wellcome Centre for Integrative Neuroimaging, Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK*, ³*Wellcome Centre for Integrative*

Neuroimaging, Oxford Centre for Human Brain Activity, University of Oxford, Warneford Hospital, Oxford, OX3 7JX, UK, ⁴Department of Epidemiology and Public Health, University College London, London, WC1E 6BT, UK, ⁵Inserm U1153, Epidemiology of Ageing and Neurodegenerative diseases, Université Paris-Descartes, France, ⁶Global Brain Health Institute, Memory and Aging Center, University of California, San Francisco, San Francisco, California 94158 USA,

Introduction: Epidemiological and neuroimaging studies converge to suggest that a socially and cognitively active lifestyle may contribute to maintaining cognitive health in old age. However, studies that examine activity-brain relationships typically rely on a cross-sectional design, meaning that longitudinal *change* in activity patterns, and their relationship with underlying brain structure, is not well characterised.

Methods: In a sample of 561 members of the Whitehall II Imaging Sub-Study (mean age at baseline = 53.1 years \pm 4.9, range = 46 – 68), we investigated whether social and cognitive activity trajectories correlated with brain structure and cognition. Participants self-reported their activity levels 5 times over a sixteen-year period and subsequently underwent a 3T MRI scan and tests of executive function, memory and processing speed.

Approach for statistical analysis: Latent growth curve modelling (LGCM) was used to identify the mean trajectory of activities followed by our sample, as well as derive estimates of each individual's trajectory over time. We evaluated these activity trajectories (i.e. intercept and change parameters) as predictors of grey matter volume, white matter microstructure and cognition, in a set of linear regressions.

Results and conclusions: A quadratic LGCM (compared to an intercept-only and linear LGCM) best described how activity levels changed between mid-life to late-life. We observed that more frequent participation in social and cognitive activities was related to higher levels of executive function and memory performance. Additionally, activity trajectories following an 'inverted U' shape were related to lower executive functioning. No relationship was, however, found between activities and MRI measures of brain structure. Overall, our study suggests that maintaining high levels of social and intellectual activity in adulthood may help to promote cognitive health in late life. This study additionally offers a novel approach to characterizing leisure activity-brain associations.

Poster number: PM085 (SP)

Theme: Neurodegenerative disorders & ageing

The neurophysiological effects of early tauopathy in the RTG4510 mouse model of dementia

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Introduction: Pathological accumulation of tau has been associated with several dementia-spectrum disorders, including Alzheimer's Disease, collectively known as tauopathies. These disorders display a progressive, age-associated neurodegeneration with associated cognitive impairment. Pathological tau has been implicated in altering synaptic function (Jackson et al, 2017), neuronal excitability (Crimins et al, 2012) and network activity (Menkes-Caspi et al, 2015), in cortical brain circuits prior to neurodegeneration and symptomatic onset. Therefore, we aim to provide mechanistic insight into the relationship between tau pathology, morphological and functional changes in early, pre-degenerative stages of the disease using the well characterised rTg4510 (TG) model of tauopathy.

Methods: *In vitro* and *in vivo* whole-cell patch clamp electrophysiological recordings were used to assess synaptic function, intrinsic properties and network state in putative pyramidal neurons in layer 2/3 of the somatosensory cortex. Specifically, spontaneous and evoked currents and action potential properties were recorded. Recorded neurons were filled with biocytin and Alexa dye, imaged using 2-photon microscopy and morphologically reconstructed post-hoc.

Approach for statistical analysis: *In vitro* recordings were excluded if the access resistance was greater than 40 M Ω . Sample distributions were checked for normality (Shapiro Wilk test), and parametric (Student's t-test) or non-parametric tests (Mann-Whitney U test) were used as appropriate. $P < 0.05$ was used to define statistical significance.

Results and conclusions: Interestingly, NMDA:AMPA ratios of evoked synaptic currents were decreased in TG mice compared to WT controls (WT 0.75 +/- 0.1, TG 0.56 +/- 0.1, $p = 0.03$). Intrinsic electrophysiological properties were generally unchanged between genotypes with capacitance (WT 73.2 pF +/- 10.3, TG 53.8 pF +/- 5.1, $p = 0.05$) and resting membrane potential (WT -74.6 mV +/- 3.4, TG -67.5 mV +/- 2.2, $p = 0.04$) being significantly different. TG neurons exhibited increased dendritic branching in proximal regions to the soma, unrelated to changes in total dendrite length or area covered. Network measures, including up down states, were examined using *in vivo* recordings.

Changes in NMDA-receptor mediated glutamatergic synaptic transmission may be an early cause of neuronal dysfunction in tauopathies, suggesting NMDA receptor modulators may be a potential therapeutic target.

Poster number: PM086 (SP)

Theme: Neurodegenerative disorders & ageing

Reduced astrocyte beclin 1 impairs the retromer complex and receptor-mediated phagocytosis

Authors: Dr Kurt Lucin¹, Ms Yuberki Delgadillo¹, Ms Evelyn Lemus¹

¹*Eastern Connecticut State University, Willimantic, United States*

Introduction: Phagocytosis plays an important role in maintaining brain homeostasis and when impaired can result in the accumulation of unwanted cellular material. While microglia are traditionally considered the phagocytes of the brain, astrocytes are also capable of phagocytosis and are the most numerous cell in the brain. In Alzheimer's disease (AD), astrocytes can be found surrounding β -amyloid (A β) plaques yet seem unable to eliminate these deposits, suggesting phagocytosis may be impaired in AD. Mechanisms that might diminish astrocyte phagocytosis in AD are currently unclear. Here, we demonstrate that the autophagy protein beclin 1, which is reduced in AD, plays a role in regulating astrocyte phagocytosis.

Methods: An astrocyte cell line (C6 cells) was used to study astrocyte function. Beclin 1 protein levels were reduced using an shRNA lentivirus and compared to a scrambled shRNA control lentivirus. Protein levels were quantified using western blot. Phagocytosis was quantified using latex beads and by manually counting cells with internalized beads.

Approach for statistical analysis: Statistical differences were determined by using a student's T-test or a one-way ANOVA for multiple comparisons.

Results and conclusions: We show that reducing beclin 1 in C6 astrocytes impairs phagocytosis of latex beads. Reduced beclin 1 levels are accompanied by decreased expression of the retromer, a protein complex involved in receptor trafficking. Reducing beclin 1 also results in diminished expression of SR-B1, a phagocytic scavenger receptor known to bind A β . These findings suggest a link between the protein beclin 1, receptor trafficking, and receptor-mediated phagocytosis. Therefore, enhancing beclin 1 in astrocytes may provide a novel approach for the treatment of AD.

Poster number: PM087 (SP)

Theme: Neurodegenerative disorders & ageing

Chronic neurodegeneration induces Type I interferon synthesis via STING, shaping microglial phenotype and accelerating disease progression

Authors: Dr Arshed Nazmi¹, Dr Robert H. Field¹, Dr Eadaoin W. Griffin¹, Dr Orla Haugh¹, Dr Edel Hennessy¹, Dr Donal Cox¹, Ms Renata Reis¹, Dr Lucas Tortorelli¹, Dr Carol L. Murray¹, Dr Ana Belen Lopez-Rodriguez¹, Dr Lei Jin², Prof. Ed C Lavelle¹, Dr Aisling Dunne¹, Dr Colm Cunningham¹

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Introduction: Type I interferons are the principal anti-viral molecules of the innate immune system and can be made by most cell types, including CNS cells. IFN-I has been implicated in neuroinflammation during neurodegeneration but its mechanism of induction and its consequences remain unclear. In the current study we assessed expression of IFN-I in murine prion disease (ME7) and examined the contribution of the IFN-I receptor IFNAR1 to disease progression.

Methods: Behavioural and motor co-ordination testing were performed in all mice strains used. FACS was employed for the isolation microglia and astrocytes from single cell suspension of mice brains. Changes in protein expression was analysed using Immunohistochemistry and western blotting.

Approach for statistical analysis: Different statistical analysis will be used depending on the experimental design. Two-way ANOVA with disease and strain as between subject's factors, Repeated measures ANOVA for behavioural tests, T-test, Survival time (days) was assessed by Kaplan-Meier log rank survival analysis.

Results and Conclusion: The data indicate a robust IFN β response, specifically in microglia with evidence of IFN-dependent genes in both microglia and astrocytes. This IFN-I response was absent in STING^{-/-} mice. Microglia showed increased numbers and activated morphology independent of genotype but transcriptional signatures indicated an IFNAR1-dependent neuroinflammatory phenotype. Isolation of microglia and astrocytes demonstrated disease-associated microglial induction of TNF- α , TGF β 1 and of phagolysosomal system transcripts including cathepsins, CD68, C1qa, C3 and TREM2 that were diminished in IFNAR1 and STING deficient mice. Microglial increases in activated Cathepsin D and CD68 were significantly reduced in IFNAR1^{-/-} mice, particularly in white matter, and increases in COX-1 expression and prostaglandin synthesis were significantly mitigated. Disease progressed more slowly in IFNAR1^{-/-} mice, with diminished synaptic and neuronal loss and delayed onset of neurological signs and death but without effect on proteinase K-resistant PrP levels. Therefore, STING-dependent IFN-I influences microglial phenotype and, although this may occur secondary to early disease, this neuroinflammation influences neurodegenerative progression. These data expand our mechanistic understanding type I interferon induction and its impact on microglial function during chronic neurodegeneration.

References:

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Poster number: PM088 (SP)**Theme:** Neurodegenerative disorders & ageing**The role of endogenous cellular prion protein in brain synaptic function****Authors:** Ms Aeen Ebrahim Amini^{1,3}, Mr John Georgiou¹, Mr Changiz Taghibiglou², Mr Graham Collingridge^{1,3}¹*Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada*, ²*Department of Pharmacology, University of Saskatchewan, Saskatchewan, Canada*, ³*Department of Physiology, University of Toronto, Toronto, Canada*

Introduction: One of the major neurotransmitter receptors in the brain are α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA_Rs) which are involved in glutamate-based neuronal communication. The composition, distribution and number of AMPA_Rs can modulate synapse strength, which is known as synaptic plasticity. Defects in synaptic plasticity may be responsible for many brain disorders including Alzheimer's disease (AD). It has been shown that beta-amyloid oligomers bind the endogenous cellular prion protein (PrP^C), a cell-surface glycoprotein with many physiological functions such as cellular differentiation, adhesion and control of cell morphology. On the other hand, it has been shown that PrP^C interacts with the GluA2 subunit of AMPA_Rs. However, the role of PrP^C in synapse function remains poorly understood.

Methods: We used electrophysiological techniques to explore the function of PrP^C at Schaffer collateral-CA1 synapses in the hippocampus, a region critical for Learning and memory and preferentially affected in AD. We measured field Excitatory Postsynaptic Potential (fEPSP) to compare paired-pulse facilitation, input/output, and long-term potentiation (LTP) in C57BL/6J wild type mice with C57BL/6J-PrnP knockout (KO) mice.

Approach for statistical analysis: We used student's t-Test and two-way ANOVA to statistically analyze LTP and input/output, respectively.

Results and conclusions: Preliminary data showed that KO mice had enhanced LTP when triggered with a threshold theta-burst stimulation induction protocol. KO mice had unaffected paired-pulse facilitation, but reduced basal synaptic transmission. Ongoing investigations will confirm these initial findings and examine the underlying mechanism of enhanced LTP in the PrP^C KO mice.

Poster number: PM089 (SP)**Theme:** Neurodegenerative disorders & ageing**The accumulation of autophagic vacuoles in the Alzheimer's disease brain is not caused by impaired lysosomal digestion****Authors:** Mr. Anirudh Jaisimha³, Dr. Shane Hegarty³, Prof. Dominic Walsh^{1,2}, Dr. Barry Boland^{1,3}¹*Laboratory for Neurodegenerative Research, School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin, Belfield, Ireland*, ²*Laboratory for Neurodegenerative Research, Ann Romney Centre for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, U.S.A.*, ³*Dept. of Pharmacology and Therapeutics, University College Cork, Cork, Ireland*

Introduction: The accumulation of autophagic vacuoles (AVs) is a hallmark of degenerating neurons in Alzheimer's disease (AD). The central aim of this study was to determine if this pathology is caused by defective lysosomal proteolysis or inefficient delivery of AVs to late endosomes/lysosomes. Our objectives were to identify specific biomarker profiles that differentiate underlying causes of impaired autophagic flux, and compare them with profiles obtained from post-mortem human brain tissue of control and AD patients.

Methods: *In vitro*: Pharmacological models of impaired autophagic flux were induced in rat primary cortical neurons at DIV14: (1) Impaired lysosomal digestion (leupeptin and cathepsin L and B inhibition), (2) Lysosomal deacidification (chloroquine and bafilomycin), (3) Impaired delivery of AVs to lysosomes (U18666A) and (4) Lysosomal rupture (Glycyl-L-phenylalanine 2-naphthylamide (GPN). The expression of LC3-II, p62, amyloid precursor protein (APP) and its C-terminal fragments (APP-CTFs) and cathepsin D (pro- and active forms) were examined by western immunoblot. Lyotracker Red was used to assess lysosomal membrane integrity and acidification. *In vivo*: RIPA-extracted lysates from post-mortem human brain tissue (medial temporal gyrus) at different Braak stages (Control, Stage 0; and AD, Stages I-VI).

Statistical Analysis: Significance was assessed using one-way ANOVA followed by Tukey's post-hoc test.

Results/Conclusions: AD brain samples had increased expression of LC3-II and p62 from Braak Stage II onwards, indicative of impaired autophagic flux. In primary cortical neurons, inhibition of cathepsins L and B caused an accumulation of APP-CTFs, with preferential increases in two non-canonical truncated CTFs (CTF-6 and CTF-7). The absence of CTF-7 in neurons treated with chloroquine, bafilomycin or U18666A suggests CTF-6 and -7 are transient by-products of lysosomal digestion. This was further supported by the elimination of CTF-6 and -7 in lysosome-enriched subcellular fractions from neurons treated with the lysosomal rupturing agent, GPN. Expression profiles of APP-CTFs and active cathepsin D were unaltered across all AD brain samples, suggesting impaired lysosomal proteolysis does not underlie AV accumulation in the AD brain. Future analysis of novel lysosomal APP-CTFs (-6 and -7) described in this study could be used to assist in defining the underlying nature of impaired autophagic flux in other neurodegenerative diseases.

Poster number: PM090 (SP)

Theme: Neurodegenerative disorders & ageing

Absence of the NLRP3 inflammasome improves microglial phagocytic and migratory activity - implications for Alzheimer's disease

Authors: Dr Roisin McManus^{1,2}, Ms Angelika Griep^{1,2}, Prof. Michael Heneka^{1,2}

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This laboratory has previously demonstrated an important role for the inflammasome in the progression of Alzheimer's disease (AD). NLRP3 inflammasome activation was found in post-mortem tissue from individuals with AD (Heneka et al., 2013) and importantly this effect was also observed in AD transgenic mice expressing amyloid precursor protein (APP) and presenilin 1 (PS1; APP/PS1 mice). However, APP/PS1 mice deficient for NLRP3 or caspase-1 were protected from AD-pathology, with decreased neuroinflammation and improved spatial memory in comparison with control APP/PS1 mice.

This current study is part of a larger European InCure consortium, examining innate immune signaling and inflammasome activity in microglia by RNA sequencing and comparing these results with functional readouts, in a range of neurodegenerative diseases. Our study focuses on AD and to investigate this, we established a model of amyloid β (A β)-induced microglial activation *in vitro* by preparing microglia from the brains of postnatal 1-day old wildtype and NLRP3^{-/-} mice. Importantly we asked whether the A β -induced response *in vitro* was comparable with the response observed in APP/PS1 mice *in vivo* by examining APP/PS1 and APP/PS1.NLRP3^{-/-} mice at 4, 6 and 12 months.

It was observed that A β induced the production of IL-1 β in wildtype cells only, increased expression of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and cleaved caspase-1. These changes were mirrored *in vivo* starting from 6 months in APP/PS1 mice only. Release of IL-1 β was not detectable in NLRP3^{-/-} cells or mice. We found that *in vivo* APP/PS1.NLRP3^{-/-} mice were protected from A β -deposition at all ages and this

was associated with increased microglial phagocytosis in comparison with APP/PS1 mice. Similarly, we observed that *in vitro* NLRP3^{-/-} microglia had enhanced phagocytic activity, used altered mechanisms to degrade A β , and had increased migration to A β than their wildtype counterparts.

Microglia were prepared *in vitro* and *ex vivo* for RNA sequencing analysis. These results will uncover the A β -induced gene network, and specifically highlight any protective events occurring in the absence of inflammasome activity. Identification of these network hubs and checkpoints will help establish new diagnostic biomarkers and gain insights into the prevention and early treatment of AD.

Poster number: PM091 (SP)

Theme: Neurodegenerative disorders & ageing

PINK1 constitutively activates Akt via regulation of essential PI(3,4,5)P₃ lipid dynamics: implications for targeting Akt defects in Parkinson's disease.

Authors: Ms Rachel M. Furlong^{1,2}, Dr Andrew Lindsay¹, Dr Karen Anderson³, Prof. Phillip T. Hawkins³, Prof. Aideen M. Sullivan², Prof. Cora O'Neill¹

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Introduction: PI3-kinase/Akt signalling is central to cell survival, metabolism, protein and lipid homeostasis, and is impaired in Parkinson's disease (PD). Akt activation is reduced in the PD brain, and by many PD-causing genes, including PINK1. However, mechanisms underlying PINK1's function in PI3-kinase/Akt signalling remain unclear. This study aimed to delineate the mechanisms by which PINK1 regulates Akt signalling, in order to determine the role of PINK1 in the altered Akt signalling that occurs in PD.

Methods: Immortalised mouse embryonic fibroblast lines (MEFs) derived from PINK1^{+/+} or PINK1^{-/-} mice, and PINK1^{-/-} MEFs expressing human PINK1 or triple-kinase-dead PINK1, were employed and analysed by western immunoblotting, immunofluorescence, and mass spectrometry.

Approach for statistical analysis: Data are expressed as means \pm standard error of the mean (SEM). Statistical analysis was carried out using one way ANOVA, followed by post-hoc Tukey test.

Results and Conclusions: Our results reveal for the first time that PINK1 constitutively activates Akt in a PINK1-kinase dependent manner, in the absence of growth factors. Additionally, PINK1 enhances Akt activation in normal growth medium, by increasing Akt phosphorylation at Ser473 and Thr308 residues. Rapid and transient agonist-induced production of PI(3,4,5)P₃ at the plasma membrane is essential for initiation of Akt signalling, recruiting inactive cytosolic Akt to the plasma membrane. We present new evidence that PINK1 kinase activity significantly accelerates the localisation of GFP-Akt-PH and PI(3,4,5)P₃ to the plasma membrane in immediate response to IGF-1. We show that PINK1 deletion can modulate PIP₂ and PIP₃ levels under certain conditions and that His- tagged PINK1 colocalises with PI(3,4,5)P₃ in normal growth medium. PI(3,4,5)P₃ is important for long-term agonist-induced activation of Akt within endomembrane compartments. Importantly, we demonstrate that PINK1 significantly enhances a time- and PINK1 kinase activity-dependent increase in localisation of PI(3,4,5)P₃ to the Golgi in response to sustained IGF-1 stimulation.

We provide new mechanistic insights revealing that failure in Akt signalling in key PD genetic models occurs at the level of PI(3,4,5)P₃ production at plasma and endomembranes, the most vital step in Akt activation. This draws attention to the importance of phospholipid dynamics in targeting defective Akt signalling in PD.

Poster number: PM092 (SP)**Theme:** Neurodegenerative disorders & ageing**Investigating the role of urea transporters in the brain during health and disease****Authors:** Ms Farhana Pinki^{1,2}, Dr Gavin Stewart¹, Dr Derek Costello²¹*School of Biology & Environmental Science, University College Dublin, Dublin, Ireland*, ²*School of Biomolecular & Biomedical Science, University College Dublin, Dublin, Ireland*

Introduction: Alzheimer's disease (AD) is the most common form of dementia worldwide. Current treatment strategies show limited effectiveness; highlighting the importance of understanding disease mechanisms to identify novel therapeutic targets. Urea was once viewed simply as a waste product, but is now known to have a complex regulatory system in the body. Although largely secreted by the kidneys, urea can be found in high concentrations throughout the body, including the brain. Recent reports have indicated increased levels of brain urea in models of neurodegenerative disease such as AD. However little investigation has been made to date into the mechanisms of urea transport within the brain, and its potential role in disease pathogenesis. The current study proposes to examine urea transport mechanisms in the brain, and to understand its role in AD. We propose that regulation of urea transport in the brain may provide a therapeutic strategy for alleviating AD pathology, and other neuroinflammatory conditions.

Methods: We will use a combination of PCR and Western immunoblot analysis to examine the expression of urea transporters UT-A, UT-B1 and UT-B2 in the brain. We will compare expression in mammalian brain to that in peripheral tissues, such as gut and bladder in which the expression and function of urea transporters has been well-established. A region-specific examination will be carried out in cortex, hippocampus and hypothalamus from rodents, and cell-specific expression will be determined in cultured astrocytes, microglia and neurons. Further analysis will be carried out to examine changes in urea concentrations and transporter expression in cells under control conditions and in the presence of inflammatory stimuli including lipopolysaccharide and amyloid- β . These will be compared with changes in brain tissue from aged rodents, and from the APP/PS1 δ e9 mouse model of AD.

Analysis: Statistical analysis will determine differences in the expression of urea transporters between brain regions and across cell-types (ANOVA). Additional analysis will examine changes in transporter expression and urea concentration in the presence and absence of inflammatory stimuli (one- or two-way ANOVA, as appropriate). Finally, we will compare whether expression of urea transporters in the brain is significantly impacted by age or inflammatory-related disease.

Poster number: PM093 (SP)**Theme:** Neurodegenerative disorders & ageing**Gait, cognition and MRI outcomes in older adults: baseline findings from the react MRI sub-study****Authors:** Ms Naiara Demnitz¹, Ms Poppy Seager¹, Dr. Afroditi Stathi², Dr. Janet Withall³, Prof. Helen Dawes⁴, Dr. Patrick Esser⁴, Prof. Klaus Ebmeier¹, Prof. Heidi Johansen-Berg¹, Dr. Claire Sexton^{1,5}¹*University Of Oxford, Oxford, United Kingdom*, ²*University of Birmingham, Birmingham, United Kingdom*, ³*University of Bath, Bath, United Kingdom*, ⁴*Oxford Brookes University, Oxford, United Kingdom*, ⁵*University of California San Francisco, San Francisco, United States*

Introduction: We have previously shown an association between gait and cognition in older adults, but less is known about the neural correlates of poor gait. Using the baseline data from the Retirement in Action (REACT) study, a community-based physical activity intervention, the aim of this study was to examine the association between spatial-temporal gait parameters and brain structure and function in older community-dwellers.

Method: Eighty-one older adults (mean age 76 ± 6.8 years, 63% women) underwent brain MRI scans and assessments of gait, executive function and memory. Total grey matter, white matter hyperintensities and hippocampal volumes were quantified using automated software. Walking speed, cadence and stride length were measured over a 10 meter walk at self-selected pace, using an inertial measurement unit. A computerised test of spatial and visual memory was used to measure relational memory and executive function was assessed through the Flanker and 2-back tasks. Partial correlations were used to determine the associations between gait, cognition and hippocampal measures, controlling for age, gender and BMI.

Results: Hippocampal volume and white matter hyperintensities were not associated with any gait parameter (all $p > 0.05$). After adjusting for age, gender and BMI, gait speed was positively correlated with performance on the 2-back task ($r = 0.24$, $p = 0.016$), but not memory. Cadence and stride length were not related to measures of cognition.

Discussion: In contrast to previous reports, we did not find evidence of an association between spatial-temporal indices of gait and MRI outcomes. On the other hand, the observed association between gait and a measure of executive function, but not memory, is consistent with previous reports indicating a stronger association between gait and executive function than between gait and other cognitive domains.

Poster number: PM094 (PP)

Theme: Neurodegenerative disorders & ageing

Pathology-specific mutation and GABA_A influence hyperphosphorylated tau localization in murine stem cell-derived isocortical neurons

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Introduction: Microtubule associated protein TAU stabilizes the neuronal cytoskeleton via helical filament adhesion, a process tightly regulated by several kinases and phosphatases. In neurodegenerative tauopathies, MAPT phosphorylation becomes aberrant and monomers assemble into insoluble, seemingly-randomized aggregates as a function of hyperphosphorylation; this exact mechanism is elusive. Recent findings suggest that excitatory signal conduction may lead to MAPT aggregate propagation thereby increasing pathological TAU expression¹. Our project investigates disease-relevant, molecularly phenomenological aspects of TAU aggregation via *in vitro* isocortical neuron models derived from mouse embryonic stem cells (mESCs). We assert that MAPT mutations will change the dynamics of compartmentalization *in vitro* and may imply susceptibility of phosphorylated-TAU microtubule-dissociation in tauopathies. Future experiments will investigate channelrhodopsin-mediated effects on TAU phosphorylation with respect to mutagenized MAPT.

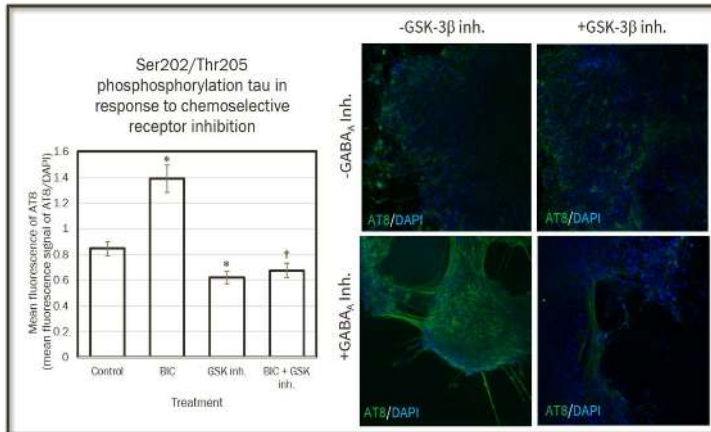
Methods: In brief, mESCs are differentiated to mature, isocortical neurons and maintained 30 days *in vitro* (DIV) before conducting inhibitor-mediated experiments (n=3). Progenitor samples will be incubated at DIV 10 with respective viruses harboring transgenes of MAPT isoform D (P301L, P301S, ΔK280, non-mutated). On DIV30, samples will be treated with 20 μM bicuculline, 1 μM tetrodotoxin, or media alone for 48 hours. After fixation, cells will be treated overnight with anti-PHF tau AT8 (1:200, ms) and anti-MAP2 (1:6000, ch) followed by corresponding secondary antibodies and DAPI. Samples will be mounted and assayed as z-stacks (15-20 slices, ~1 μm per slice) utilizing a Leica SP2 confocal microscope.

Statistical analysis: Images will be analyzed utilizing in-house designed, semi-supervised ImageJ and Matlab batch-processing macros. ImageJ macros perform slice-by-slice pixel intensity measurements of all channels and particle counting of AT8⁺ channels. Matlab macro performs Spearman's Rho correlations between corresponding AT8⁺ and

MAP2⁺ slices. AT8 pixel intensities are normalized against DAPI pixel intensities (AT8/DAPI) and resulting data will be analysed using multiple ANOVA followed by pairwise multiple comparisons.

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Preliminary data; wild type neurons (DIV30, n=3) 48-hour treatments with 20 μ M bicuculine (BIC), 10 μ M CHIR99201(GSK inh.), and 20 μ M bicuculine + 10 μ M CHIR99201. * = p-val<0.05 compared to control, †=p-val<0.05 compared to bicuculine

Poster number: PM095 (SP)

Theme: Neurodegenerative disorders & ageing

Machine learning approach to classification of Parkinson's disease patients based on EEG microstates

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Introduction: Extensive development of machine learning techniques with applications in neuroscience over the last decade has resulted in growing need for data. Processing large amounts of data with pattern recognition methods has proven to lead to new insights in clinical neuroscience. The primary goal of our study is the development of a database containing EEG records, which will be suitable for benchmark analysis with the use of the state-of-art machine learning techniques. Of special interest is the examination of rest-state EEG with microstate analysis to identify biomarkers of pathological conditions. However, fewer studies tried to complete EEG microstates with machine learning. In our study, we propose to combine these techniques to enhance EEG analysis.

Methods: To this end, we selected 45 EEG recordings in elder subjects, the age span 48-75. Recordings were obtained from 25 normal controls, 10 recordings - from subjects diagnosed as non-demented Parkinson's disease patients (PDN) and 10 - from Parkinson's disease patients with dementia (PDD). 1-minute recordings were processed using eLoreta software with filtering in 8-13 Hz (alpha) and 4-13 Hz (alpha-theta) range. 4 microstates for each frequency range were considered based on literature review for rest-state EEG studies. Microstates were computed separately for each subject.

Analysis approach: The extracted microstates were used to build a linear support vector machine (SVM) model. The existing data were split in 7:3 ratio for training and validation set, appropriately.

Results and conclusion: The accuracy for distinguishing between control, PDN and PDD groups did not exceed 56%. However, the accuracy of prediction of the pathology type with the control group excluded exceeded 75%, thereby showing the sensitivity of the proposed method to specific pathological conditions. Neither selection of electrode subset nor selection of specific frequency range did affect the SVM performance. Thus, using microstate analysis with SVM based machine learning approach to pattern recognition may be useful for detection of specific pathological conditions.

Acknowledgments

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Poster number: PM096 (SP)

Theme: Neurodegenerative disorders & ageing

The effect of inflammatory microglial factors and apolipoprotein e genotype on astrocytes in a human induced pluripotent stem cell-derived in vitro model of Alzheimer's disease

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Introduction: Apolipoprotein E (ApoE) genotype is a major risk factor for late-onset Alzheimer's disease (AD), with the E4 allele contributing to a 3- to 4-fold increased risk in developing AD (Jendresen *et al.*, 2017). Emerging evidence supports a neuro-injurious role of astrocytes in AD, with astrocytes developing a reactive phenotype when exposed to inflammatory microglial factors (Liddelow *et al.*, 2017). Human induced pluripotent stem cells (iPSC) may be derived from human somatic cells and subsequently patterned into numerous cell types making them an ever more popular method of disease modelling. Following this, the aim of this study was to derive astrocytes from human iPSC with the ApoE E3E3 and E4E4 genotypes in order to investigate the effect of ApoE genotype on astrocyte reactivity and subsequently their effect on iPSC-derived neurons.

Methods: Human iPSC homozygous for ApoE3 and ApoE4 were patterned towards a neural fate using dual SMAD inhibition (Chambers *et al.*, 2009) to produce neural progenitor cells (NPC). Subsequently, astrocytes were derived using epidermal growth and human leukemia inhibitory factors (Serio *et al.*, 2013) to produce mature astrocytes after 90 days. Astrocytes were characterised by immunostaining for astrocyte markers, then stimulated with IL-1 α , TNF α and C1q (Liddelow *et al.*, 2017) to induce reactivity and a reactivity profile was generated via ELISA and qPCR analysis. NPC were matured and treated with astrocyte conditioned media (ACM), stained for β -tubulin and quantified by cell counting.

Approach for statistical analysis: Statistical analysis was carried out using GraphPad Prism 7.0. One-way ANOVA with Tukey post hoc was used for analysing data within ApoE genotypes, and a two-way ANOVA with Bonferroni post hoc used to analyse and compare data between ApoE genotypes.

Results and conclusions: iPSC-derived astrocytes are positive for astrocyte markers GFAP, S100 β , Connexin-43 and EAAT1 confirming cell fate. Stimulation with microglial factors resulted in increased IL-6, RANTES and GM-CSF secretion, as well as increased expression of genes associated with reactivity including *IL6*, *ICAM1*, *LCN2* and *SERPINA3*. ACM from reactive astrocytes diminishes neuronal health indicated by a significantly decreased number of neuronal clusters in culture.

In conclusion, the ability to produce reactive astrocytes derived from genotyped human cells *in vitro* provides a powerful model for researching the mechanisms underlying the detrimental role of astrocytes and the effect of ApoE genotype in AD.

Poster number: PM097 (SP)

Theme: Neurodegenerative disorders & ageing

Acute transient cognitive dysfunction and acute brain injury induced by systemic inflammation occur by dissociable IL-1-dependent mechanisms

Authors: Dr Donal T. Skelly^{1,3}, Dr Eadaoin W. Griffin¹, Dr Carol L. Murray¹, Dr Sarah Harney², Mr Conor O'Boyle¹, Dr Edel Hennessy¹, Dr Marc-Andre Dansereau¹, Dr Arshed Nazmi¹, Dr Lucas Tortorelli¹, Professor J. Nicholas Rawlins⁴, Professor David Bannerman⁴, Dr Colm Cunningham¹

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Introduction: Systemic inflammation can cause delirium, especially in the context of neurodegeneration. Delirium also contributes to long-term cognitive decline, implying that systemic inflammatory events also induce brain injury. It is unclear whether acute cognitive dysfunction and brain injury occur by overlapping or discrete mechanisms.

Methods: The effect of systemic challenge (intraperitoneally) with LPS, IL-1 β and TNF- α on C57BL/6 and IL-1R1^{-/-} mice was studied in the presence and absence of ME7 disease, which was used as a model of neurodegeneration. IL-1RA and dexamethasone were used as adjunctive challenges. Working memory was assessed with food-rewarded and escape from water T-maze tasks. Contextual and auditory fear conditioning tasks were also used. The time course of systemic and CNS inflammatory markers were studied using ELISA and quantitative PCR. We applied IL-1 β directly to *ex vivo* hippocampal slices and performed whole-cell patch clamp recordings from CA1 pyramidal cells. Immunohistochemistry for apoptotic cells was performed.

Approach for statistical analysis: Behavioural data were compared by repeated measures ANOVA with Bonferroni *post hoc* tests. Molecular, electrophysiology and TUNEL data were analysed by two-way ANOVA, followed by Bonferroni *post hoc* tests.

Results and conclusions: In normal mice, systemic LPS impaired long-term memory consolidation but not working memory. However, in mice with ME7 disease, systemic LPS induced working memory deficits. Systemic IL-1RA was protective against, and systemic IL-1 β replicated, these deficits. Dexamethasone, which abrogated systemic cytokines, protected against these deficits, without blocking brain IL-1 β synthesis. Direct application of IL-1 β to *ex vivo* hippocampal slices induced non-synaptic depolarisation and irreversible loss of membrane potential in diseased CA1 neurons, and systemic LPS increased apoptosis in the degenerating brain, both in an IL-1R1-dependent fashion. In summary, LPS induced working memory dysfunction via circulating IL-1 β but direct hippocampal action of IL-1 β caused neuronal dysfunction and, potentially, neuronal death. Thus, the memory deficits and brain injury in the degenerating brain, caused by LPS, occur by dissociable IL-1-dependent processes.

The fact that reversible cognitive deficits, resembling delirium, and acute brain injury, contributing to long-term cognitive impairment, are mechanistically dissociable has implications for the management of cognitive dysfunction during acute illness.

Poster number: PM098 (SP)**Theme:** Neurodegenerative disorders & ageing**Are visual hallucinations in Parkinson's disease a result of hypoperfusion of visual processing areas in the occipital cortex?****Authors:** Dr Lindsey Sinclair¹, Mr Jake Brenton¹, Dr Alan King Lun Liu², Mr Robert MacLachlan¹, Prof Steve Gentleman², Prof Seth Love¹¹University Of Bristol, Bristol, United Kingdom, ²Imperial College London, London, United Kingdom

Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder, in which patients frequently suffer from dementia. Up to 1/3 of patients with PD experience visual hallucinations (VH), which can be very distressing.

Neuroimaging studies suggest that perfusion is reduced in the occipital lobe in those with VH but as Lewy bodies are sparse in this region they cannot explain the hallucinations. Recent work suggested that decreased cholinergic input may directly lead to the decreased perfusion.

We hypothesised that individuals with Parkinson's disease and visual hallucinations have biochemical evidence of reduced microvascular perfusion and reduced cholinergic activity in areas of the brain which process visual images.

Methods: We obtained tissue from BA18 & BA19 for a well characterised cohort matched for age, gender and post mortem interval. It comprised 11 individuals PD - VH, 9 individuals PD +VH, 16 individuals PDD + VH, and 25 controls. Von Willebrand factor, vascular endothelial growth factor, MAG:PLP1 ratio (a measure of tissue oxygenation relative to metabolic demand), AChE, BChE and α -synuclein were quantified by ELISA.

Approach for Statistical Analysis: The MAG:PLP ratio was the primary outcome. Parametric statistical tests were used, unless it was not possible to normalise variables. Non parametric tests e.g. Kruskal Wallis test were then used. Where the Dunn test was used, Bonferroni correction was applied. A threshold for α of 0.05 was used throughout.

Results and Conclusions: The groups were well matched for age, but the controls had a slightly longer post-mortem interval (additional 12 hours, $p=0.014$). There was no evidence of chronic hypoperfusion in PD ($F=0.7184$, $p=0.54$). Dorsal AChE concentration was reduced in individuals with PD and VH in both BA18 ($\beta = -0.17\text{ng/ml}$, $p=0.001$) and BA19 ($\beta = -0.13\text{ng/ml}$, $p=0.029$). In ventral BA19 AChE concentration was decreased ($X^2=7.0$, $p=0.03$) and BChE concentration was increased ($X^2=11.5$, $p=0.003$) in individuals with PD and visual hallucinations. There was no relationship between AChE concentration and PD disease duration or insoluble α -synuclein concentration. Our results do not support chronic hypoperfusion of visual processing areas in the occipital cortex as a cause of VH in those with PD. The cholinergic data require further investigation by the additional measurement of ChAT.

Poster number: PM099 (SP)**Theme:** Neuroendocrinology and autonomic systems**Using genetic manipulations to understand the role of RFRP-3 in the regulation of reproduction****Authors:** Dr Caroline Ancel¹, Ms Mathilda Plate¹, Ms Megan Inglis¹, Professor Greg Anderson¹¹University Of Otago, Dunedin, New Zealand

In 2000, gonadotrophin-inhibitory hormone was discovered in birds and shown to inhibit gonadotrophin secretion. The mammalian ortholog was concurrently discovered in humans and rats and termed RFamide-related peptide-3 (RFRP-3). Recent results have shown that the effects of centrally-administered RFRP-3 on gonadotrophin secretion are sex- and cycle stage-dependent in mice (Ancel et al., 2017). Indeed, intracerebroventricular injections of RFRP-3

stimulated LH secretion in males, and inhibited LH secretion in females at the time of the preovulatory LH surge. In addition, the stimulatory effect observed in males was shown to be mediated in part by GPR54, the receptor for Kisspeptins, suggesting the involvement of other pathways. In order to further our understanding of the ways in which RFRP neurons modulate the reproductive axis, we have developed a novel transgenic mouse line. Using a Cre-loxP conditional transgenic method, we knocked the receptor for RFRP-3 (GPR147) out of GnRH neurons and analysed puberty onset in these mice. While the absence of GPR147 on GnRH neurons advanced puberty onset in male mice, it resulted in a delay in female puberty, once again indicating a sex-specific role of the RFRP system in the regulation of the reproductive function. Current work is aimed at dissecting the potential involvement of GnRH neurons in the pathways mediating RFRP-3 effects on LH secretion in mice carrying a deletion of GPR147 in GnRH neurons. Both male and female mice received intracerebroventricular injections of RFRP-3 and LH levels were subsequently assayed in tail-tip blood samples. Taken together, these new tools provide us with the possibility to advance our understanding of the structure and the functions of the RFRP neuronal system in mice.

Poster number: PM100 (SP)

Theme: Neuroendocrinology and autonomic systems

Suprachiasmatic Vasopressin Neurons Alter the Activity of Preoptic Kisspeptin Neurons in Female Mice

Authors: Mr Bradley Jamieson¹, Mr Gregory Boucher¹, Associate Professor Rebecca Campbell¹, Dr Richard Piet¹

¹*Centre for Neuroendocrinology & Department of Physiology, University Of Otago, Dunedin, New Zealand*

Introduction: Kisspeptin neurons in the preoptic area (POA) of the hypothalamus drive the activity of gonadotropin-releasing hormone neurons to generate the surge secretion of gonadotropins that ultimately triggers ovulation. The central circadian clock in the suprachiasmatic nucleus (SCN) times the preovulatory surge, ensuring coordination of ovulation and sex behaviour. In particular, SCN neurons are thought to project to, and control the activity of, POA kisspeptin neurons to initiate the surge. Here, we aimed to determine whether SCN arginine vasopressin (AVP)-expressing neurons innervate POA kisspeptin neurons, and to examine the functional impact this may have on kisspeptin neuron electrical activity.

Methods: Mice expressing cre recombinase (CRE) in AVP neurons were injected with a viral vector carrying either a CRE-dependent mCherry or a CRE-dependent channelrhodopsin (ChR2). mCherry-injected mice were processed for immunohistochemistry (IHC) to examine innervation of POA kisspeptin neurons by SCN AVP neurons. Brain slices from ChR2-injected mice were obtained and either whole-cell or on-cell patch clamp electrophysiological recordings of kisspeptin neurons undertaken.

Approach for statistical analysis: IHC images were analysed using the image J software. Kisspeptin neuron electrical activity was analysed across time using a one-way ANOVA. Specific time points were compared using Student's t-test.

Results and conclusions: We found a dense projection from SCN AVP neurons to POA kisspeptin neurons and close fibre appositions at the kisspeptin neuron somata. This suggests that SCN AVP neurons may establish putative synaptic inputs onto kisspeptin neurons. Despite this, in the majority of kisspeptin neurons (93%) we recorded from, blue-light stimulation did not evoke postsynaptic currents (n = 4 mice), indicating that SCN AVP neurons do not communicate with kisspeptin neurons using fast amino acid neurotransmitters. However, in approximately half of kisspeptin neurons, high frequency stimulation (one minute at 20 Hz) of SCN AVP axons results in a significant (p < 0.05, n = 7) increase in action potential firing, which was delayed and long lasting consistent with the release of a neuropeptide. Together, our results reveal both anatomically and functionally a microcircuit between SCN AVP neurons and POA kisspeptin neurons, through which the SCN may time the preovulatory surge.

Poster number: PM101 (SP)**Theme:** Neuroendocrinology and autonomic systems**Effect of the TRPV1 channel blocker SB-366791 on isolated vasopressin neurons from non-pregnant and late-pregnant rats****Authors:** Dr Alexander Seymour¹, Professor Charles Bourque², Professor Colin Brown¹¹*Brain Health Research Centre, Centre for Neuroendocrinology and Department of Physiology, Biomedical Sciences School, University of Otago, Dunedin, New Zealand*, ²*Centre for Research in Neuroscience, Research Institute of the McGill University Health Centre, Montreal, Canada*

Introduction: During pregnancy there is a reduction in plasma osmolality, resulting in fluid retention for fetal blood supply and to prepare the mother for lactation. Reduced plasma osmolality results from a decreased threshold for arginine-vasopressin (AVP) release; however the mechanisms governing this change in threshold are unknown. Recently, a variant of the transient receptor potential vanilloid-1 (TRPV1) channel (Δ N-TRPV1) has been shown to regulate osmotic-induced changes in AVP neuronal firing rate (and hence AVP release). Here, we recorded from isolated AVP neurons to determine whether changes in Δ N-TRPV1 enhances AVP neuronal excitability to decrease the osmotic threshold for AVP release during pregnancy.

Methods: Female non-pregnant or late-pregnant (day 18-21 gestation) AVP-eGFP transgenic rats were decapitated, brains removed, and 1 mm³ blocks of tissue containing the supraoptic nucleus were extracted. A blood sample was taken and plasma osmolality was measured using freezing point depression osmometry. Blocks were incubated in buffer containing protease, washed, titrated, and the resulting cell suspension was plated on petri dishes. AVP neurons (identified via presence of cytoplasmic GFP) were patched and current clamp recordings were obtained at 295 mOsmol kg⁻¹. Voltage steps were used to characterise the current-voltage relationship and gap-free recording was used to monitor firing rate and membrane potential during baseline recording, and during application of the TRPV1 blocker SB-366791.

Approach for statistical analysis: Plasma osmolality was analysed using a two-tailed Student's t-test. All other analyses were performed using Two-way Analysis of Variance. $P < 0.05$ was considered significant.

Results and conclusions: Plasma osmolality was significantly lower in late-pregnant rats compared to non-pregnant rats ($P < 0.001$). SB-366791 did not affect the firing rate ($P = 0.55$ effect of drug; $P = 0.78$ effect of reproductive status; $P = 0.14$ interaction), membrane potential ($P = 0.40$ effect of drug; $P = 0.18$ effect of reproductive status; $P = 0.96$ interaction) or voltage-current relationship in either non-pregnant or late-pregnant rats. These data suggest that Δ N-TRPV1 channels do not affect electrical properties of isolated AVP neurons from non-pregnant and late-pregnant rats at an osmolality typically observed in the non-pregnant state.

Poster number: PM102 (SP)**Theme:** Neuroendocrinology and autonomic systems**Mapping o-linked glycosylation in the brain during pregnancy****Authors:** Dr Rachael Augustine¹, Dr Zsuzsanna Barad¹, Rachel Wallace¹, Dr Jeff Erickson¹, Professor Colin Brown¹¹*Department of Physiology, University Of Otago, Dunedin, New Zealand*

Introduction: During pregnancy, maternal metabolism changes to support the developing fetus and to prepare for lactation. Among the many maternal changes that occur is an increase in circulating glucose levels, which in many cases cannot be fully offset by increased insulin production, leading to hyperglycemia and even gestational diabetes. Glucose can affect cell function by O-linked N-acetylglucosamine (O-GlcNAc) modification of proteins, but it is

unknown whether this process plays a physiological role in the central regulation of metabolism in pregnancy. Food intake and energy balance are regulated by various neuron populations in hypothalamic arcuate nucleus (Arc), paraventricular nucleus (PVN) and ventromedial hypothalamus (VMN).

Methods: Immunohistochemistry for O-GlcNAc modification was carried out in sections of hypothalamus from virgin and late-pregnant mice, to determine whether, and where, O-GlcNAc modification occurred. Sections were photographed using an Olympus microscope and were analyzed using FIJI image processing software to count the number of O-GlcNAc positive cells in regions of interest.

Statistical Analysis: Means \pm SEM were compared between non-pregnant and pregnant mice using unpaired student t-tests. $P < 0.05$ was considered significant.

Results and conclusions: There were regional differences in the distribution of O-GlcNAc modifications in the hypothalamus. Preliminary results showed a non-significant trend towards an increase in O-GlcNAc in the PVN, Arc and VMN. Further research is being carried out using a mouse model of gestational diabetes to investigate O-GlcNAc modifications in a state of hyperglycemia and glucose intolerance.

Poster number: PM103 (SP)

Theme: Neuroendocrinology and autonomic systems

Sub-chronic synthetic glucocorticoid treatment is associated with deficits in NMDA receptor-dependent LTP

Authors: Mr Matthew Claydon¹, Dr Zuner Bortolotto¹, Dr Becky Conway-Campbell¹, Professor Stafford Lightman¹
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Introduction: The aim of this project is to investigate how disruption of physiologically occurring circadian and ultradian glucocorticoid (GC) rhythms interacts with synaptic plasticity processes in the brain. Interruption of the normal pulsatile nature of GC action is associated with pathophysiology such as inflammation, early life stress¹ and depression². It is unclear, though, whether disruptions to GC pulsing are merely symptomatic or causal. Although relatively little research has been conducted addressing GC rhythms in plasticity, they are thought to be important in maintaining hippocampal stability and readiness to undergo plastic changes. However, the effect on plasticity and memory processes incurred by changes in these oscillations has not been addressed adequately in the literature. Synthetic GCs, like methylprednisolone (MPL), are widely used in a clinical setting for their powerful anti-inflammatory effects³⁻⁵. Compared with corticosterone and hydrocortisone, the natural glucocorticoid receptor (GR) ligands, these synthetic GCs have been shown to cause prolonged GR activation in both cell lines⁶ and discrete brain regions (unpublished data). Sub-chronic treatment (3-5 days) in rodents has been shown to disrupt ultradian and circadian patterns of GR mediated gene transcription, activity profiles and body temperature⁷⁻⁹. Moreover, there have been reported associations between long-term treatment with synthetic GCs and cognitive dysfunction in humans¹⁰.

Furthermore, sub-chronic MPL treatment in rodents has also been shown to induce deficits in object recognition and object location memory tasks (unpublished data), though this is not mechanistically understood. We therefore aim to investigate the effects of sub-chronic treatment with MPL on hippocampal synaptic function.

Methods: *In vitro* field electrophysiology conducted on hippocampal slices from adult male Lister hooded rats.

Approach for statistical analysis: t-tests for assessing significant differences between conditions at certain time points

Results and conclusions: We present a deficit in LTP induced by a mild, NMDA receptor dependent protocol, in rats treated for 3-5 days with methylprednisolone (Fig 1). MPL treatment results in prolonged and repeated GR activation

analogous to the effects of chronic stress exposure on GR activity. Consistent with our methylprednisolone data, chronic stress has been reported to elicit reduced potential for LTP and increased tendencies for the induction of LTD in inputs to dorsal CA1¹¹⁻¹⁴.

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Poster number: PM104 (SP)

Theme: Neuroendocrinology and autonomic systems

Changes in the pattern of circulating cortisol differentially modulate daily mood oscillations and the resting state networks of the human brain

Authors: Dr Konstantinos Kalafatakis¹, Dr Georgina Russell¹, Dr Meryem Grabski², Dr Stuart Ferguson³, Mrs Nicky Marchant¹, Mrs Jamini Thakrar¹, Professor Catherine J. Harmer⁴, Professor Marcus R. Munafò¹, Ms Aileen Wilson¹, Dr Jonathan C. Brooks¹, Mr Patrick Murphy¹, Dr Ngoc J. Thai¹, Professor Stafford L. Lightman¹

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Introduction: Preclinical evidence indicates that dynamic oscillations of glucocorticoids play an important regulatory role in the mammalian body, especially the brain [1, 2]. In this context, this study was designed to test whether glucocorticoid rhythmicity is important for regulating mood and resting state networks of the human brain.

Methods: Fifteen healthy, male, right-handed individuals participated in an interventional, double-blinded, placebo-controlled, three-way crossover study. All procedures were in accordance to the principles of the Research Governance Framework for Health and Social Care and the declaration of Helsinki. Endogenous glucocorticoid biosynthesis was pharmacologically suppressed and coupled with a different mode of hydrocortisone replacement therapy per study arm; either a subcutaneous pulsatile hydrocortisone infusion, approximating the normal ultradian and circadian rhythm, or a subcutaneous continuous hydrocortisone infusion, completely eliminating the ultradian rhythm, or *per os* treatment, creating a suboptimal combination of both rhythms. In all replacement strategies, the total amount of hydrocortisone was 20 mg/day [3, 4]. Individuals participated in a resting state functional neuroimaging experiment and were engaged with multiple ecological momentary assessments on their positive and negative affective state, and the levels of perceived fatigue.

Analysis Approach: Functional neuroimaging data were analysed using FSL software (www.fmrib.ox.ac.uk, University of Oxford) [5], and behavioural data were analysed using STATA[®] release 14.

Results and conclusions: Ratings of vigor, ability to concentrate and self-perceived fatigue were markedly different between treatment groups. Moreover, the circadian pattern of mood oscillations differed in a treatment group-dependent manner. Dual regression analysis also revealed glucocorticoid rhythm-related changes in the functional connectivity within resting state networks of the human brain. Moreover, seed-based functional connectivity analysis highlighted a differential interplay of major nodes of the corticolimbic system with the default mode, salience and the executive control networks.

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Poster number: PM105 (PP)

Theme: Neuroendocrinology and autonomic systems

The Facilitating Effect of Oxytocin on Sexually Conditioned Partner Preference in the Female Rat

Authors: Mr Conall Eoghan Mac Cionnaith¹, Mr Eamonn Gomez-Perales¹, Ms Rebecca Cernik¹, Ms Marjolaine Rivest-Beauregard¹, Ms Alice Lemay¹, Ms Lisa Thomasse¹, Dr Wayne Brake¹, Dr James Pfaus¹

¹*Concordia University, Montreal, Canada*

Introduction: A growing body of evidence shows important roles of Pavlovian learning in sexual partner selection. Female rats who repeatedly copulate with almond scented males selectively solicit, and preferentially receive the scented male's ejaculations, relative to an unscented male. In female prairie voles, partner preference formation is blocked by the administration of an oxytocin receptor antagonist and is facilitated by oxytocin. Previous studies examining sexually conditioned partner preference in the female rat have typically required ten conditioning trials prior to partner preference emerging. The aim of this study is to examine whether oxytocin facilitates faster formation of sexually conditioned partner preference in female rats.

Methods: Hormonally-primed ovariectomised Long-Evans female rats (N=72) will be given either one, five, or ten sexual conditioning trials with an almond scented male prior to an open-field partner preference test. Females will be injected intraperitoneally with either 20µg of oxytocin or saline one minute before conditioning trials (n=12). In the partner preference test, an almond scented and an unscented male will be tethered to opposite corners of the open field, allowing the female to copulate preferentially with either male. Partner preference tests will be recorded and then scored by a blinded observer for 1) solicitations made toward the scented and unscented males, 2) ejaculations received by the female from each male, and 3) the female's choice for first solicitation and ejaculation.

Approach for statistical analysis: Each behaviour will be analysed with a 3x2x2 three-way mixed ANOVA. We hypothesise a three-way interaction between drug treatment, number of conditioning trials, and the type of male (scented vs unscented). Specifically, females given one and five conditioning trials with oxytocin will solicit and receive more ejaculations from the scented male compared to the unscented male, and this effect will not be present in the saline treated groups. At ten trials we expect no differences in solicitations made toward and ejaculations received from the scented male between the oxytocin and saline treated females. The choice for first ejaculation and solicitation will be analysed using χ^2 tests. Sample size was calculated to achieve 90% power with a medium effect size.

Poster number: PM106 (SP)

Theme: Neuroendocrinology and autonomic systems

Adiposity is an important mediator of FGF21 responsiveness in the Siberian hamster

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Administration of a single pharmacological dose of FGF21 to obese mice is sufficient to decrease plasma glucose levels, whilst chronic administration of FGF21 increases energy expenditure, resulting in weight loss. Both adipose tissue and the CNS have been proposed to be important sites of action for FGF21, however their relative roles in mediating the effects of FGF21 remain unclear. Using a natural model of adiposity, the Siberian hamster, we determined the effects of chronic FGF21 on energy homeostasis, glucose and lipid uptake. In hamsters maintained in long day lengths to induce adiposity, chronic administration of FGF21 reduced body weight, a consequence of reduced food intake and increased energy expenditure. Furthermore, FGF21 treatment increased glucose uptake in brown and white adipose tissue only, as assessed in PET scan studies of 18F-deoxyglucose uptake. This was a direct effect of treatment as demonstrated (a) in a pair-fed group, which achieved similar weight loss via caloric restriction and demonstrated glucose uptake comparable to vehicle treated controls, and (b) in primary adipocyte cultures, where glucose uptake increased in response to treatment with FGF21. In hamsters maintained in short day lengths (for 8 weeks) that induces an intermediate state of hypophagia and abdominal fat catabolism, the effects of chronic FGF21 treatment on body weight, food intake and regional glucose uptake were attenuated, whilst the effect on energy expenditure was absent. In addition, at the nadir of the seasonal body weight cycle, 12 weeks post exposure to short day lengths, all effects of FGF21 treatment were absent, suggesting that adiposity, is key to governing FGF21 responsiveness in this animal model. Indeed, FGF21's obligate co-receptor β -klotho was significantly reduced not only in the adipose tissue of short day exposed animals, but also in long day animals treated with FGF21 and the pair-fed group. These data provide important insights into the mechanism of FGF21 action and identify the important contribution of adipose tissue to the metabolic and homeostatic effects of FGF21.

Poster number: PM107 (SP)**Theme:** Neuroendocrinology and autonomic systems**Kisspeptin - A Novel Clinical Test of Hypothalamic Function in Men with Hypogonadotrophic Hypogonadism****Authors:** Dr Maria Phylactou¹, Dr Ali Abbara¹, Dr Pei Chia Eng¹, Dr Sophie Clarke¹, Dr Edouard Mills¹, Dr Muralidhara Koteshwara¹, Dr Germaine Chia¹, Dr Lisa Yang¹, Dr Pratibha Machenahalli¹, Mrs Deborah Papadopoulou¹, Dr Chioma Izzi-Engbeaya¹, Dr Channa Jayasena¹, Dr Alexander Comninos¹, Professor Waljit Dhillon¹¹Imperial College, London, United Kingdom

Introduction: Hypogonadotrophic Hypogonadism is characterised by hypogonadism in the context of low / inappropriately normal gonadotrophin levels. Congenital HH (CHH) occurs due to defective hypothalamic GnRH neuronal migration (e.g. Kallman's syndrome), or secretion. However, no direct test of hypothalamic GnRH neuronal function currently exists. Kisspeptin is a neuropeptide that stimulates endogenous hypothalamic GnRH release. Thus, we investigated whether kisspeptin could be used to interrogate hypothalamic function in men with CHH.

Methods: Men with CHH (low testosterone, low LH/FSH, normal MRI pituitary / baseline pituitary function, absent puberty, unprimed by pulsatile GnRH; n=4) and healthy eugonadal men (n=20) received an intravenous bolus of GnRH (100mcg), or kisspeptin-54 (6.4nmol/kg), on two study visits ≥ 1 week apart. Serum gonadotrophins were measured every 15mins for 6hrs following injection.

Analysis Approach: Increases in serum gonadotrophins from baseline following GnRH / kisspeptin in eugonadal men and CHH were compared by unpaired t test.

Results: Mean increase in serum LH from baseline was 8.2 ± 3.8 iU/L in eugonadal men and 0.12 ± 0.13 iU/L in CHH ($P=0.0003$) following kisspeptin administration. All eugonadal men had an LH increase >1.5 iU/L, whereas all men with CHH had an LH increase <1.5 iU/L following kisspeptin. In contrast, mean increase in serum LH from baseline following GnRH was 6.2 ± 3.2 iU/L in eugonadal men and 2.2 ± 3.8 iU/L in CHH ($P=0.062$). Therefore, whilst the kisspeptin-induced LH increase effectively discriminated men with HH from eugonadal men (area under ROC 1.0), GnRH-induced LH increase was less discriminatory (area under ROC 0.82). In eugonadal men, the maximal increase in LH following kisspeptin significantly predicted the maximal increase in LH following GnRH (univariate linear regression, $r^2=0.45$; $P=0.0013$), however this relationship was lost in men with HH ($r^2=0.03$; $P=0.83$).

Conclusions: Collectively, these data confirm that a novel kisspeptin test of hypothalamic GnRH function can better discriminate men with CHH from eugonadal men than currently available investigations (such as GnRH test). Therefore, a kisspeptin test could offer significant clinical benefit for the accurate diagnosis and management of patients with hypogonadism.

Poster number: PM108 (PP)**Theme:** Neuroendocrinology and autonomic systems**GABA_B receptors in subpopulations of enteric neuronal and enteroendocrine cells in the proximal small intestine are regulated by subtype-specific kctd auxiliary subunits****Authors:** Dr Inês Guerra Mollet¹, Prof. Paula Macedo^{1,2,3}¹CEDOC - Chronic Diseases Research Centre, NMS - NOVA Medical School, 1150-082 Lisbon, Portugal, ²Departamento de Ciências Médicas, Universidade de Aveiro, 3810-193 Aveiro, Portugal, ³Associação Protetora dos Diabéticos de Portugal – Education Research Centre (APDP – ERC), 1250-189 Lisbon, Portugal

Introduction: It has been postulated that disrupted signalling in the proximal small intestine could be central to the aetiology of type 2 diabetes. Within the gut wall complex signalling takes place involving enteroendocrine cells and networks of distinct layered enteric plexi. To explore the hypothesis of imbalance between autonomic excitatory and inhibitory neurochemistry in the proximal small intestine in diabetes we propose to examine the expression of the metabotropic GABAB receptors which constitute part of the main inhibitory neurotransmission system in neuronal cells. GABAB receptors have been described in the brain as large complexes composed of heteromeric GABBR1 and GABBR2 receptor subunits and auxiliary KCTD homo-tetrameric subunits. The KCTD subunits modulate the properties of the GABAB core receptor by increasing GABA agonist potency thus enhancing desensitization in a KCTD-subtype-specific manner. Although the expression of GABAB receptors has been reported in the gut their association with KCTD-subtypes in this tissue is lacking.

Methods: Diet induced pre-diabetes was modelled in an initial set of five C57BL/6 male mice placed on high fat diet for 12 weeks along with five control male mice on normal chow diet. Weight and fasting blood glucose was monitored at the start and before sacrifice. The complete small intestine including duodenum, jejunum and ileum was collected after overnight fasting and fixed in 4% PFA. Tissue cryosections will be investigated by IHC/IF and laser scanning confocal microscopy for the distribution and co-localisation of GABBR1 and GABBR2 receptors and three KCTD subtypes (KCTD8, KCTD12 and KCTD16). Preliminary results in control mice show subpopulations of cells staining for GABBR1 and GABBR2 receptor subunits in crypts, villi, submucosal or myenteric layers that co-localise with each of the KCTD subunits suggesting KCTD sub-type specific regulation in both neuronal and enteroendocrine cells. Work is on-going to consolidate tissue distribution, co-localisation by proximity ligation assay, identification of specific cell types, and ex-vivo agonist responses of GABA_B receptors in gut samples.

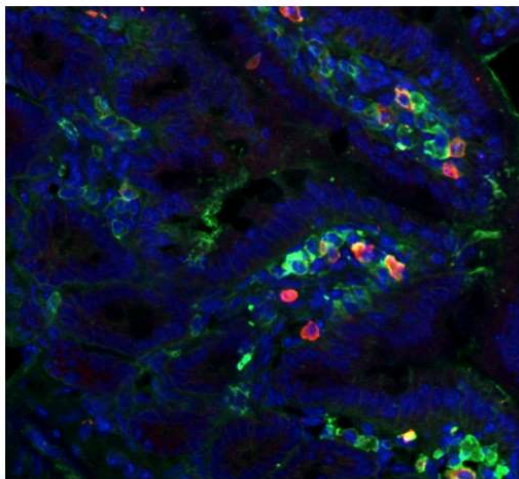


Fig. 1 – Co-localisation of immunofluorescent signal for GABBR1 (Red) receptors and KCTD8 (Green) auxiliary subunits in a subpopulation of cells located in villi of jejunum of 11 week old C57BL/6 male mouse in 12um cryosection. (Novus-Biologicals GABBR1 #H00002550-M01 (1:10); KCTD8 NBP1-86327 (1:10); Alexa Fluor 594 anti-mouse IgG #A21203 (1:500); Alexa Fluor 488 anti-rabbit IgG #A21206 (1:1000)).

Analysis approach: Statistical significance of distribution, co-localisation and agonist responses will be calculated from 10 measurements on each sequential 1cm-long ex-vivo section or cryosection along the small intestine.

Funding: British Society for Neuroendocrinology – Project Support Grant

Poster number: PM109 (SP)**Theme:** Neuroendocrinology and autonomic systems**Transcriptome Profiling of Hypothalamic Kisspeptin Neurons****Authors:** Mr Stephen M Manchishi¹, Professor William H Colledge¹¹*Department of Physiology, Development and Neuroscience, University Of Cambridge, Cambridge, United Kingdom*

Introduction: Kisspeptin, a peptide product of the *Kiss1* gene, is a critical player in reproductive function, particularly as the major upstream neuroendocrine regulator of Hypothalamic-Pituitary-Gonadal (HPG), is crucial for GnRH release. In mice, two distinct populations of *Kiss1* expressing neurons are predominant in areas of the hypothalamus implicated in the neuroendocrine regulation of gonadotropin secretion; the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV). The two populations are heterogenous within and between nuclei populations. To further understand their unique physiological significance, the transcriptome profiles of *kiss1* neurons from the middle and caudal ARC and AVPV in mice was compared.

Methods: Brains of adult transgenic heterozygous *Kiss1*/tdTomato female mice in oestrous were rapidly extracted in ice-cold oxygenated artificial cerebrospinal fluid, vibratome sectioned at 300µm intervals to obtain AVPV, rostral and caudal ARC coronal sections. Micro-punches were collected from AVPV, rostral and caudal ARC nuclei and dissociated in papain solution. tdTomato-positive cells from the resulting cell suspension were individually collected using glass micropipette under an inverted fluorescence microscope with a red fluorescence protein filter. A pool of 10 – 15 cells from each region was transferred to a separate PCR tube containing 9.5µL of PBS with 10% recombinant RNase inhibitor and immediately frozen at -80°C until processed for cDNA synthesis, amplification and sequencing.

Approach for statistical analysis: Reads were mapped using STAR v2.5.2a. EnsemblMus_musculus.GRCm38 reference genome was used to do the mapping of reads, using the annotated transcripts from the ensemblMus_musculus.GRCm38.84.gtf file. Differential Gene Expression Analysis was done using the counted reads and the R package, edgeR, for pairwise comparisons. Principal Component Analysis (PCA) plots and heatmaps were plotted based on normalised and variance-stabilized transformed counts.

Results and conclusions: A large amount of samples were inter-mixing between groups. The 'all samples' PCA plot showed clear clustering of the AVPV samples and both the ARC samples in a cluster together, indicating considerable differences between AVPV and ARC groups, which was also seen when considering the pairwise comparison of groups individually. The Caudal and Rostral ARC appear to be more similar as the differences were not statistically significant.

Poster number: PM110 (SP)**Theme:** Neuroendocrinology and autonomic systems**The Y2R in the vagus nerve regulates satiety and mediates the effects of PYY3-36 on food intake****Authors:** Ms Aldara Martin Alonso¹, Dr Simon C. Cork¹, Professor Herbert Herzog², Professor Stephen R. Bloom¹, Professor Kevin G. Murphy¹, Dr Victoria Salem¹¹*Section of Investigative Medicine, Division for Diabetes, Endocrinology and Metabolism, Department of Medicine, Imperial College London, London, United Kingdom*, ²*Neuroscience Division, Garvan Institute of Medical Research, Sydney, Australia*

Introduction: The gut hormone peptide YY 3-36 (PYY₃₋₃₆) is released postprandially from intestinal L cells and produces potent anorectic effects in both rodents and humans, making it a promising anti-obesity agent. To facilitate the design of such PYY₃₋₃₆-based agents, it is necessary to understand its mechanisms of action. Its receptor, the Y2

receptor (Y2R), is expressed in various appetite-regulating brain regions, including the vagus nerve, the major neural link between the gut and the brain. However, it is unclear if the vagus nerve is necessary for the anorectic effects of PYY₃₋₃₆. We hypothesised that administration of low dose PYY₃₋₃₆ reduces food intake by activating vagal afferent signalling and does not require direct access to central appetite/nausea-altering pathways to have an effect.

Methods: We generated an afferent vagus nerve-specific Y₂R deficient mouse model by delivering an adeno-associated virus (AAV) that drives Cre recombinase into the nodose ganglion (NG) of Y₂R^{loxP/loxP} mice. Wild type litter mates injected with AAV-GFP (green fluorescent protein) were used as controls.

Results and Conclusions: Quantification of Y2R mRNA expression in the NG demonstrated significant knockdown (KD) in AAV-Cre-injected mice compared with controls. Since the NG contain only the cell bodies of afferent vagal fibres, this is to our knowledge the first example of superselective Y2R vagal deafferentation, confirmed by the preserved response to exogenous CCK in both control and Y2R KD groups. Intraperitoneal injection of 3µg/kg PYY₃₋₃₆ resulted in a significant decrease in food intake in control mice, but not in Y2R KD mice. Stimulation of endogenous PYY₃₋₃₆ release through acute administration of a mixed-nutrient meal resulted in significantly higher 24 hour food intake in Y2R KD mice compared with controls. These results suggest that vagal Y2R mediate the effects of endogenous and low dose exogenous PYY₃₋₃₆ on food intake.

Poster number: PM111 (PP)

Theme: Neuroendocrinology and autonomic systems

Investigating the synaptic densities on gnRH neuron using expansion microscopy

Authors: Dr Shel-Hwa YEO¹, Professor A.E HERBISON¹

¹*Centre for Neuroendocrinology, Department of Physiology, University of Otago, Dunedin, New Zealand*

Introduction: Expansion microscopy (ExM) technology is able to resolve the current optical diffraction-limit of light microscopy which makes it impossible to visualize synapses or synaptic proteins. This technology utilizes a chemical process to physically expand tissues isotropically, enabling 3-dimension nanoscale resolution imaging applicable to diffraction-limited confocal microscopes. Here, we describe the application of the ExM technique in examining GnRH neuronal morphology and pre-synaptic proteins.

Methods: Adult GnRH-GFP female mice at oestrus, proestrus and dioestrus stages were transcardially perfused and brain slices of 60 µm thickness were collected from the preoptic area region. The slices were immunostained for GFP and synaptophysin, a marker for presynaptic proteins, prior to the expansion procedure. Nikon A1R upright confocal microscope equipped with a long working distance water-immersing lens (25X Numerical Aperture 1.1; Working Distance 2 mm) was used to image the expanded slices in wide-field settings. The expansion factor of the brain slices was assessed by measuring the perimeter of GnRH neuronal nuclei before and after expansion. A 4.2 expansion factor was achieved. The expanded slices demonstrated a clear GnRH neuronal morphology, with visible structures like dendritic spines, stubs and filopodia. Montages of Z-stack images were able to trace up to 71.4 µm (physical size post-expansion 300 µm /4.2) of the primary or secondary dendrites. To evaluate the density of the synaptic inputs on GnRH neuronal dendrites, the number of synaptophysin-immunoreactive puncta was counted. This work establishes the initial use of ExM to evaluate the GnRH neuron in mice. Further assessment of the synaptic inputs on proximal and distal sites of GnRH neurons will be undertaken to examine whether differences in specific neurotransmitter input correlate with varying levels of pulsatile gonadotropin secretion in mouse model.

Approach for Statistical Analysis: All image analyses will be undertaken using ImageJ and relevant plugins such as RG2B and SynapCountJ. Differences in synaptic density at different stages of oestrous cycle will be assessed using a repeated-measures ANOVA. To confirm that the sample size is sufficient to support the data, observed power will be calculated in ANOVA analyses.

Poster number: PM112 (PP)**Theme:** Neuroendocrinology and autonomic systems**Investigating Stress Related Neural Circuitry with Stem Cell Derived Visceral Motor Neurons****Authors:** Ms Stephanie Hynes¹, Professor Anthony Graham, Dr Ivo Lieberam¹Centre for Developmental Neurobiology, King's College London, London, United Kingdom, ²Centre for Stem Cells and Regenerative Medicine, King's College London, London, United Kingdom

The fight-or-flight response is the physiological reaction in response to a perceived threat and is executed by the sympathetic nervous system via the release of hormones, such as adrenaline. The stress response originates from the CNS, which send signals to the preganglionic sympathetic neurons (PGCs), which are visceral motor neurons situated in the thoracic spinal cord. PGCs are either connected to postganglionic sympathetic neurons, which in turn relay the signal to the target organ, or directly project to the adrenal medulla to innervate neuroendocrine chromaffin cells (CACs). CACs are responsible for the synthesis and release of noradrenaline and adrenaline into circulation to regulate organ and body homeostasis. This system can be affected in diseases, such as familial dysautonomia.

My project is to model the specification of PGCs, and their subsequent synapse formation with CACs in mouse embryonic stem cells (mESCs) and primary mouse tissue. I am using an mESC cervical motor neuron protocol (Wichterle et al, 2002), which has been modified to produce motor neurons with a thoracic identity using a Tet-on gene expression system for *HoxC9* and *FoxP1*. I then plan to combine the PGCs *in vitro* with primary mouse chromaffin cells in compartmentalised cell culture devices, where I will study the synapse formation and perform functional image analysis to measure synaptic activity.

The differentiated mESCs have been seen to exhibit early markers of PGCs, and their identity is further being validated using *in vivo* grafting experiments into chick embryos, to study their projections to target cells. In addition to this, primary mouse chromaffin cells have successfully been isolated from adult mouse adrenal glands. I have gathered data using Immunofluorescence, automated cell counting, qPCR.

These results demonstrate the ability to produce neurons expressing early PGC markers and a source of target CACs. This is the first step towards exploring PGC synapse formation in an *in vitro* system, which could potentially be used as a disease model for conditions such as familial dysautonomia.

Wichterle H, Lieberam I, Porter JA, Jessell TM. (2002). Directed differentiation of embryonic stem cells into motor neurons. *Cell Press*. 110 (3), 385-97.

Poster number: PM113 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Exploring the function and interactions of UCH-L1.****Authors:** Ms Siobhan Bennett¹, Professor Jeremy Henley¹University Of Bristol, Bristol, United Kingdom

Introduction: Ubiquitin C-terminal hydrolase L1 (UCH-L1) is a neuronal specific a cysteine hydrolase comprising up to 5% of total neuronal protein in the brain. Although classed as a deubiquitinating enzyme (DUB), the specific functions of UCH-L1 remain elusive. Loss of UCH-L1 leads to axonal die back, ataxia and death of mouse models. Moreover, UCH-L1 mutations have been linked to Alzheimer's and Parkinson's Diseases. The aims of this project are to: i) define

the proteins that interact with UCH-L1; ii) identify its mechanisms of action iii) determine its role(s) in neuronal stress responses.

Methods: We first made shRNA constructs to knockdown (KD) UCH-L1 in primary cultured hippocampal and cortical neurons. We then performed a TMT Mass Spectrometry screen of wildtype and UCH-L1 knockdown cultures to identify how the proteome differed. Selected candidate proteins from the proteomic screen were verified by Western blotting in WT and KD neurons. To define if the changes in protein abundance were mediated via interaction with UCH-L1, either directly or in protein complexes, we performed immunoprecipitation experiments.

Approach for statistical analysis: The proteomics was performed on one set of WT and UCH-L1 KD cortical cultures. All Western blot experiments were performed at least 3 times on separate cultures from different litters.

Results and conclusions: From the proteomics we ranked proteins that had multiple hits and were either up- or downregulated by more than 20%. Proteins that were increased included the GTPase family members dynamin 1, 2 and 3, and the mitochondrial proteins Fis1 and MFN2. Proteins that were markedly decreased were the deSUMOylating enzyme SENP3, Actin and CAMK1. Surprisingly, Western blotting revealed that, in direct contrast to the proteomics, the neuron-enriched dynamin 1 and 3 are significantly reduced in UCH-L1 KD neurons. Moreover, we have shown that UCH-L1 can interact with dynamin 3. These results suggest that levels of dynamin 1 and 3 are controlled UCH-L1 and are intriguing because they are important for clathrin mediated endocytosis. We are now defining how UCH-L1 affects the stability of dynamin 1 and 3 and investigating the effect of UCH-L1 KD on neurotransmitter release and AMPAR surface expression.

Poster number: PM114 (SP)

Theme: Neuronal, glial and cellular mechanisms

Functions of the LNX family of ubiquitin ligases in the brain: proteomic and gene knockout analyses reveal interactions with presynaptic proteins and a role in regulating anxiety-related behaviours

Authors: Ms Joan Lenihan¹, Dr Orthis Saha¹, Dr Victoria Heimer-McGinn¹, Dr John Cryan¹, Dr Paul Young¹

¹University College Cork, Cork, Ireland

Introduction: Ligand of NUMB Protein X1 and X2 (LNX1 and LNX2) are E3 ubiquitin ligases, named for their ability to interact with and promote the degradation of the cell fate determinant protein NUMB. On this basis they can potentially modulate NUMB/NOTCH signalling. However, LNX1/2 proteins can bind, via their four PDZ domains, to many other proteins besides NUMB, suggesting additional roles for these proteins in the brain. However, the physiological relevance of these interactions remains unclear, and our understanding of mammalian LNX protein function in vivo is limited.

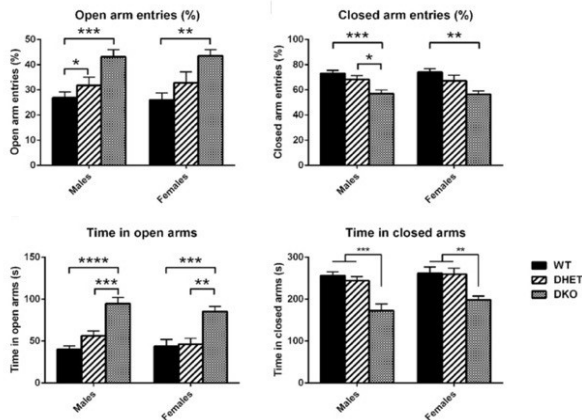
Methods: LNX1 and LNX2 interactomes were characterised by affinity purification and mass spectrometry. Mice lacking both LNX1 and LNX2 expression in the brain were generated and subjected to behavioural and other analyses.

Approach for statistical analysis: Experimental data were analysed by one-way or two-way ANOVA and Bonferroni post hoc tests.

Results and conclusions: Proteomic analysis identified and/or confirmed interactions of LNX1 and LNX2 with proteins known to have presynaptic and neuronal signalling functions, including the presynaptic active zone constituents ERC1, ERC2 and liprin- α 1, as well as FCHSD2 (nervous wreck homologue) and SRGAP2. We show that liprin- α 1, KLHL11, KIF7 and ERC2 are substrates for ubiquitination by LNX1. Surprisingly, the neuronally-expressed LNX1p70 isoform, that lacks the catalytic RING domain, was found to promote ubiquitination of liprin- α 1 and KLHL11. We

propose a model whereby LNX1p70 may function as a scaffold to promote ubiquitination of its ligands through other E3-ligases in its interactome (e.g. MID2/TRIM1 and TRIM27).

Mice lacking both LNX1 and LNX2 expression in the brain are healthy, exhibit unaltered levels of NUMB protein and do not display neuroanatomical defects indicative of aberrant NUMB function. Behavioural analysis of these double knockout mice revealed decreased anxiety-related behaviour, as assessed in the open field and elevated plus maze paradigms. By contrast, no major defects in learning, motor or sensory function were observed. Taken together our data suggest that neuronal LNX-interacting proteins other than NUMB may contribute to the anxiolytic phenotype observed.



Decreased anxiety-related behaviour in LNX knockout mice. Wild type (WT) and LNX1/LNX2 double heterozygous (DHET) and double knockout (DKO) mice were tested in the elevated plus maze. Increased entries into, and time spent in the open versus the closed arms of the maze by DKO animals is indicative of reduced anxiety-like behaviour.

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Poster number: PM115 (SP)

Theme: Neuronal, glial and cellular mechanisms

Serotonergic modulation of the ventral pallidum by 5HT1A, 5HT5A, 5HT7 AND 5HT2C receptors.

Authors: Mr Martin Clark¹, Dr Enrico Bracci¹

¹The University of Sheffield, Sheffield, United Kingdom

Introduction: Serotonin's involvement in reward processing is controversial. The large number of serotonin receptor sub-types and their individual and unique contributions have been difficult to dissect out, yet understanding how specific serotonin receptor sub-types contribute to its effects on areas associated with reward processing is an essential step.

Methods: The current study used multi-electrode arrays and acute slice preparations to examine the effects of serotonin on ventral pallidum (VP) neurons.

Approach for statistical analysis: extracellular recordings were spike sorted using template matching and principal components analysis, Consecutive inter-spike intervals were then compared over periods of 1200 seconds for each treatment condition using a student's t test.

Results and conclusions: Our data suggests that excitatory responses to serotonin application are pre-synaptic in origin as blocking synaptic transmission with low-calcium aCSF abolished these responses. Our data also suggests that 5HT1a, 5HT5a and 5HT7 receptors contribute to this effect, potentially forming an oligomeric complex, as 5HT1a antagonists completely abolished excitatory responses to serotonin application, while 5HT5a and 5HT7 only reduced the magnitude of excitatory responses to serotonin. 5HT2c receptors were the only serotonin receptor sub-type tested that elicited inhibitory responses to serotonin application in the VP. These findings, combined with our previous data outlining the mechanisms underpinning dopamine's effects in the VP, provide key information, which will allow future research to fully examine the interplay between serotonin and dopamine in the VP. Investigation of dopamine and serotonin's interaction may provide vital insights into our understanding of the VP's involvement in reward processing. It may also contribute to our understanding of how drugs of abuse, such as cocaine, may hijack these mechanisms in the VP resulting in sensitization to drugs of abuse.

Poster number: PM116 (SP)

Theme: Neuronal, glial and cellular mechanisms

Cytokine-induced inflamed mixed glial in-vitro model to study inflammatory and glycan responses associated with spinal cord injury

Authors: Mr Vaibhav Patil¹, Ms Carla Winter¹, Dr Siobhan McMahon^{1,2}, Dr Michelle Kilcoyne^{1,3}, Prof. Abhay Pandit¹
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Introduction: Spinal cord injury (SCI) causes severe primary mechanical injury followed by more complex secondary trauma characterised by inflammation and glial scar formation¹. An inflammation triggered at the site of injury elicits astrocytes and microglial activation which evokes induction of pro-inflammatory cytokines and oxidative stress that exacerbate injury². The role of glycans has been explored in SC regeneration³. However, most *in-vitro* studies of glial cells do not account for the complexity of inflammatory cascade and the role of glycans in inflammation. Therefore, we have developed a clinically relevant cytokine-induced inflamed mixed glial culture (MGC) *in-vitro* model to study acute and chronic phase of inflammation and associated glycan modulation.

Methods: MGCs were prepared from spinal cords isolated by hydraulic extrusion technique from three-day-old post-natal rats. MGCs were treated with TNF- α , IL-1 β and IL-6 in various combinations for 24 hrs (acute) and 21 days (chronic). Lectin staining was performed to identify any altered expression pattern of mammalian glycosylation. Proteome profile array was conducted to assess the expression of various cytokines during inflammation. Seahorse XFp Cell Mito Stress (Agilent Technologies, Inc.) assay was performed to evaluate the mitochondrial function, which further validated using JC-1 dye by flow cytometry.

Statistical Analysis: Data was analysed using GraphPad Prism 6 (GraphPad software, Inc.). Group analysis was done by one-way ANOVA followed by *post hoc* Tukey or student-*t* test. Differences were considered significant if $p < 0.05$.

Results and Conclusions: Cytokine combination/s treatment induced acute and chronic-like inflammatory conditions in MGC, as NF κ B-p65, MAPK-p38 and neuroinflammatory pathways as well as cell surface sialylation and fucosylation were differentially regulated (Figure 1). Inflammation triggered in MGC caused mitochondrial respiration impairment.

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Poster number: PM117 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Spontaneously opening GABA_A receptors decrease excitability and tune coincidence detection in hippocampal granule cells****Authors:** Mr Nathanael O'Neill¹, Dr Sergiy Sylantyev¹¹*Center for Clinical Brain Sciences University Of Edinburgh, Edinburgh, United Kingdom*

Introduction: Background on spontaneously opening GABA_ARs: The principal mode of inhibitory neurotransmission in the adult central nervous system is activation of synaptic and extrasynaptic GABA_A receptors by GABA.

However, some GABA_A receptors can open spontaneously, in the complete absence of GABA (s-GABA_ARs). In dentate gyrus granule cells (DGCs) these GABA-independent receptor openings give rise to tonic inhibitory currents.

s-GABA_ARs are resistant to block by competitive antagonists (e.g. SR-95531) – but can be blocked by open-channel blockers (e.g. picrotoxin).

Rationale: Almost nothing is known about the functional role or pharmacology of s-GABA_ARs.

Aim: Provide a functional characterisation of s-GABA_AR mediated tonic inhibition in DGCs.

Methods: Parasagittal hippocampal slices from 3-week old S.Dawley rats for *in vitro* whole-cell voltage and current clamp recordings.

Approach for statistical analysis: Input of s-GABA_ARs measured as the difference between responses in the presence of SR-95531 only vs SR-95531 + picrotoxin. Statistical comparisons were made using paired and unpaired Student's t-test. Data = Mean ± SEM.

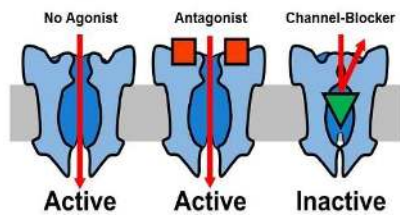
Results and conclusions:

1. GABA-independent s-GABA_ARs mediate tonic inhibition in DGCs.
2. s-GABA_ARs have a pharmacology similar to synaptic GABA_A receptors (sensitive to Zolpidem and Midazolam) and, therefore, likely contain γ subunits.
3. Outwardly rectifying s-GABA_AR current reduces membrane resistance, decreases excitability and increases the rheobase; but does not alter resting membrane potential.

4. Blocking s-GABA_ARs narrows the temporal window for successful coincidence detection but does not alter LTP amplitude.

Spontaneously Opening GABA_A Receptors

GABA_A Receptors can open without GABA



GABA-independent s-GABA_ARs provide the majority of inhibitory charge in the Dentate Gyrus

↓ Membrane resistance, ↓ Excitability, ↑ Rheobase, ↑ Signalling fidelity

Similar pharmacology to synaptic GABA_A receptors (Zolpidem + Midazolam sensitive)

Poster number: PM118 (SP)

Theme: Neuronal, glial and cellular mechanisms

Computational analysis of AGO-Seq profiling reveals disease-stage specific microRNA editing in experimental epilepsy

Authors: Mr Kelvin Lau E How¹, Dr Gary Brennan¹, Dr Ngoc Thanh Nguyen¹, Prof. David Henshall¹

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Introduction: Adenosine deaminase acting on RNA (ADAR) is a well-characterized RNA editing mechanism in mammals that primarily edits adenosine residues to inosine in double stranded RNA. Dysregulation of ADAR editing has been implicated in various neurological diseases, including recently epilepsy. It is unknown, however, whether this RNA editing extends to noncoding RNAs. There is now extensive evidence that small noncoding RNAs called microRNAs contribute to the cascade of molecular and cellular changes that accompany epilepsy development following brain injuries and seizures. Since microRNA precursors are substrates for ADAR in normal and diseased brain, we profiled A-I microRNA editing in experimental epilepsy to characterise this RNA modification.

Methods: MicroRNA expression data were generated following Argonaute sequencing of microRNAs present in the hippocampus of mice (intra-amygdala Kainic-Acid model) at different time points - 24 hours (pre-epileptic) and 2 weeks (chronically epileptic). Data were cleaned and submitted to Chimira, a web-server based platform to analyze modifications details in small RNA-seq data.

Approach for Statistical Analysis: Binomial cumulative distribution was used to identify significant edited sites within mature microRNAs. Only miRNA sites which were significantly edited in at least one group were included in further analysis to see if they differentially edited ($p < 0.1$) between the control and treatment groups using the two-tailed t-test.

Results and conclusion: We observed a significantly lower level of editing at position 6 of microRNAs at the 24-hour time point whereas there was significantly higher editing at position 7 of microRNAs at the later time-point, compared to the respective controls. Statistical analysis identified 5 differentially edited microRNAs – miR-378c (position 16), -421-3p (position 14) in the 24-hour's group, and let-7b (position 8), -3099-3p (position 7), and -376a (position 4) in 2-week mice. These data suggest that miRNAs undergo specific differential ADAR editing during epileptogenesis and in chronic epilepsy. Future studies will be needed to establish whether this is a cause or consequence of epilepsy and whether this is a potential therapeutic target to re-shape the protein expression landscape in epilepsy.

Poster number: PM119 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Differential effects of chronic neuroinflammation on adult and adolescent hippocampal neurogenesis****Authors:** Ms Lauren C. Pawley¹, Mr Andrew J. McGovern¹, Dr James D. O'Leary¹, Dr Cara M. Heuston¹, Prof John F. Cryan¹, Dr Olivia F. O'Leary¹, Dr Yvonne M. Nolan¹¹University College Cork, Cork, Ireland

Introduction: Adolescence is a critical period of development associated with plasticity-driven organisation of neural circuits in the hippocampus. Hippocampal neurogenesis is a form of brain plasticity where new neurons are generated throughout the lifespan. It is a key process for Learning and memory and emotional regulation. Elevated levels of the pro-inflammatory cytokine interleukin-1 β (IL-1 β) are implicated in memory and stress-related disorders. Acutely elevated levels of hippocampal IL-1 β has been shown to reduce hippocampal neurogenesis. However, the effect of chronic exposure of IL-1 β on hippocampal neurogenesis hasn't been fully interrogated, nor have potential differences in the effect of inflammation during adulthood and adolescence, a time of increased vulnerability.

Methods: A lentivirus causing overexpression of IL-1 β was injected into the hippocampus of adult or adolescent rats and allowed to overexpress IL-1 β for six weeks to ensure chronic neuroinflammation. Virus validation and confirmation of IL-1 β overexpression was confirmed by immunohistochemistry. The number of DCX+ cells in the DG of the hippocampus was measured as a marker of neurogenesis. The length of DCX neurites and the number of neurite branch points were measured as an index of neurite complexity (n=3-4).

Approach for statistical analysis: A two-tailed t-test was carried out and an alpha level of 0.05 was criterion for statistical significance.

Results and conclusions: Hippocampal IL-1 β overexpression decreased neurogenesis irrespective of whether the IL-1 β was injected during adulthood or adolescence. However, the magnitude of IL-1 β -induced reductions in neurogenesis was greater when administered during adolescence suggesting that the adolescent brain might be more vulnerable than the adult brain to neurogenesis-impairing effects of IL-1 β . Conversely, IL-1 β overexpression in adulthood but not adolescence decreased the neurite length of these newly-born neurons. This suggests that the newly-born neurons that remain after IL-1 β in adolescence might somehow compensate for greater reductions in neurogenesis by increasing their neurite length. Together, these findings indicate that chronically increased IL-1 β impairs hippocampal neurogenesis in both adulthood and adolescence but to different extends on neuronal complexity. Understanding the consequences of chronic hippocampal inflammation at different time points in the lifespan may help to develop therapeutics for disorders associated with memory and stress.

This work was supported by Science Foundation Ireland (SFI/IA/1537)

Poster number: PM120 (SP)**Theme:** Neuronal, glial and cellular mechanisms**The dynamic regulation of PICK1 bar domain dimerisation****Authors:** Ms Georgiana Stan¹, Dr Jonathan Hanley¹¹University of Bristol, Bristol, United Kingdom

Introduction: Synaptic plasticity is the cellular mechanism that underlies the modification of neural circuits during Learning and memory processes. Long term depression (LTD) represents a reduction in synaptic strength brought about by reducing the number of AMPARs at synapses. PICK1-mediated endocytosis of GluA2-containing AMPA receptors is an integral component of NMDA-induced LTD (Fiuza et al., J Cell Biol, 2017; Terashima et al., Neuron,

2008). Via its BAR domain, PICK1 forms dimers that bind curved membranes, and can also form higher order oligomers (Karlsen et al., Structure, 2015). We are investigating whether PICK1 dimerisation or oligomerisation is dynamically regulated by relevant stimuli, such as NMDAR stimulation in neurons. More specifically, we are interested in how PICK1 dimerisation/oligomerisation is regulated through subcellular localisation, signalling pathways and other protein-protein or protein-lipid interactions.

Methods: We are using purified proteins to investigate the properties of PICK1 dimerisation in a reduced system. HEK293 and primary neuronal cell cultures transfected with PICK1 WT and mutant constructs followed by crosslinking under various conditions are employed to determine the regulation behind PICK1 dimerisation within a cellular environment. In addition, we are using FLIM-FRET microscopy to define the dynamics and localisation of PICK1-PICK1 interactions in neurons in response to plasticity stimuli.

Results and Conclusion: Our results suggest that PICK1 self-association is dynamically regulated in an activity-dependent manner, as shown by FLIM-FRET imaging. We report signalling factors that influence PICK1 dimerisation, and the regions of PICK1 that are responsible for this regulation. Preliminary data also suggest that lipid binding is important for PICK1 self-association. Ongoing work is investigating the importance of regulating PICK1 dimerisation in synaptic plasticity. In conclusion, our work suggests that PICK1 self-association is tightly regulated indicating a functional relevance for its dimerisation/oligomerisation in neurons.

Poster number: PM121 (SP)

Theme: Neuronal, glial and cellular mechanisms

The effects of ghrelin-GHSR signalling on neuronal autophagy

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Introduction: The orexigenic hormone ghrelin, which is upregulated during calorie restriction or fasting, has demonstrated neuroprotective and neurogenic effects in rodent models. The cellular autophagy pathway is also upregulated during fasting. Autophagy is a catabolic process where cytoplasmic content is sequestered in a vesicular organelle called an autophagosome and degraded following lysosomal fusion. Loss of autophagy in rodent models causes neurodegeneration, while dysfunctional autophagy has been observed in neurodegenerative human post-mortem tissue. Here, we investigate whether ghrelin modulates autophagy in the adult mouse brain and determine whether ghrelin peptides influence neuronal autophagic flux *in vitro*.

Methods: To assess the effect of ghrelin signalling on autophagy *in vivo*, coronal brain sections from Ghrelin-, GOAT- (Ghrelin-O-acyl transferase) and GHSR- (Growth Hormone Secretagogue Receptor) knockout (KO) mice, as well as Wild-Type (WT) controls, were immunostained with an antibody against the autophagy protein, Beclin-1. To assess the effects of ghrelin signalling on autophagy *in vitro*, autophagic flux was assessed using the Cyto ID assay (Enzo Life Sciences) or LC3-II Western blotting in the presence or absence of lysosomal inhibition. The neuronal SN4741 cell line was used as an *in vitro* model as these cells express GHSR.

Approach for statistical analysis: Beclin-1 expression between WT and KO control brains was assessed using an unpaired Student's *t*-test. The effect of ghrelin peptides on autophagic flux *in vitro* was assessed using one-way ANOVA and Dunnett's multiple comparison test.

Results and conclusions: While both ghrelin-KO and GOAT-KO mice displayed no significant change in hippocampal Beclin-1 expression, GHSR-KO mice showed a significant decrease in Beclin-1 expression in the dentate gyrus ($p=0.0018$ vs WT) and CA1 ($p=0.0009$ vs WT) of the hippocampus. On the other hand, *in vitro* data demonstrated that

ghrelin peptides (acyl-ghrelin, unacylated-ghrelin, L692-585) significantly downregulated autophagic flux ($p < 0.0001$) in the presence of lysosomal inhibition. These data indicate that ghrelin-GHSR regulates neuronal autophagy. Further studies are on-going to characterise ghrelin-induced neuronal autophagy and to determine whether it mediates the neuroprotective and neurogenic actions of ghrelin.

Poster number: PM122 (SP)

Theme: Neuronal, glial and cellular mechanisms

Colony stimulating factor 1 receptor (CSF1R) regulation of autophagy in microglial cells

Authors: Ms Sadia Islam¹, Dr James Murray¹, Dr Colm Cunningham¹

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Microglial cells and inflammation are implicated in the aetiology of Alzheimer's disease (AD). Therefore, manipulating microglial cell function may be of therapeutic benefit. Microglial cells express the CSF1R, while, the CSF1R antagonist, GW2580, inhibits microglial proliferation and prevents AD-like disease progression. CSF1 stimulation of macrophages activates Akt/PKB and mTORC1 signalling and inhibition of mTORC1 promotes autophagy in multiple cell types. Therefore, this pathway is likely conserved in microglia and may regulate microglial cell autophagy, through mTORC1.

We show that CSF1 treatment of adult murine immortalised microglial (iMG) cells activated mTORC1 signalling, with peak phosphorylation of Akt and S6K1 observed at 10 mins, also promoting cell proliferation over 48 hours. To mimic a nutrient stress, amino acid starvation of iMG cells induced macroautophagy, characterised by the loss of p62/SQSTM1 and of LC3B-II expression, which are hallmarks of autophagy induction. During bioenergetic stress, phosphoglycerate kinase 1 (PGK1), a key enzyme in glycolysis, mediates phosphorylation of the critical autophagy regulatory protein, Beclin1, at Ser30 to promote increased autophagic activity to support ATP generation by glycolysis. However, following amino acid deprivation, phosphorylation of Beclin1 at Ser30 was attenuated in iMG cells. While glucose starvation did not induce autophagy in iMG cells, suggesting that novel regulatory mechanism(s) may exist in microglial cells that allow them to respond to their nutrient environment. To assess whether mTORC1 was involved in regulation of iMG cell autophagy, downstream of the CSF1R, iMG cells were treated with the inhibitors rapamycin (mTORC1-specific) and KU-0063794 (pan-mTORC1/2), but neither drug was able to induce autophagy. Taken together, these data demonstrate that unlike classical macrophage signalling, the CSF1R and mTORC1 signalling are uncoupled from the control of autophagy, at least in the iMG microglial cell model. This may have significance for the understanding of CSF1R antagonists as therapeutic agents in the treatment of AD.

Poster number: PM123 (PP)

Theme: Neuronal, glial and cellular mechanisms

Effects of antidepressants on PEDF secretion from astrocytes and neuronal complexity

Authors: Ms Claire McGrory^{1,2}, Dr Karen Ryan^{1,2}, Professor Declan McLoughlin^{1,2}

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Introduction: Pigment epithelium-derived factor (PEDF) is a 50-kDA glycoprotein of the serine protease inhibitor family that is expressed in both the CNS and periphery. PEDF protects neuronal growth in high stress conditions, possibly playing a role in brain disorders^{1,2}. We have previously reported that PEDF protein is increased in blood plasma in medicated depressed patients compared to healthy controls and increased further by a course of electroconvulsive therapy (ECT)⁴, suggesting that PEDF is involved in depression biology and molecular response to

ECT. We therefore wanted to investigate the effect of antidepressants drugs on PEDF in primary neuronal/glial cultures.

Methods: Primary neuronal/glial cells will be isolated from 1-3 day old male rat pups. Throughout experiments cells will be tested for PEDF mRNA expression using qRT-PCR and protein levels using western blotting/ELISA. We have already found that *PEDF* mRNA expression occurs in astrocytes while neurons express the PEDF receptor. Astrocytes will be treated with a selected dose (based on viability data) of the SSRI fluoxetine and tricyclic imipramine over a time course of 30min-24hr. If PEDF secretion from astrocytes is increased, neurons will be incubated with antidepressant-treated conditioned media from astrocytes for 24hr with/without a PEDF-receptor inhibitor. If PEDF is involved in antidepressant-induced neuronal complexity we will try to establish what signalling pathways are involved using various inhibitors.

Approach to statistical analysis: Statistical analysis will be carried out on GraphPad Prism5. An n of 6 will be used for experiments. Depending on normality, data will be analysed with a parametric/non-parametric Student t tests or a parametric one-way analysis of variance (ANOVA)/Kruskal-Wallis non-parametric ANOVA. Post-hoc testing will be performed where appropriate. $P > 0.05$ will be deemed statistically significant.

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Poster number: PM124 (PP)

Theme: Novel treatments & translational neuroscience

The role of retinoids in the treatment of glioma

Authors: Ms Patricia Flynn¹, Dr Collette Hand², Dr Niamh Bermingham³, Dr Michael Jansen³, Dr Andre Toulouse¹
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Introduction: CNS tumours have an incidence of 8:100,000 in Ireland. 80% of primary brain tumours develop as gliomas and can be classified into 4 prognostic categories (Grade I to Grade IV). Adult diffuse infiltrating gliomas, in particular grade IV glioblastoma, are difficult to treat as resection is difficult and adjuvant therapy (radiotherapy/chemotherapy) may retard but does not cure disease resulting in disproportionate morbidity and mortality given tumour incidence and prevalence. Treatment challenges include the toxicity and limited ability of systemically administered agents to access brain tissue and the presence of undifferentiated cancer stem cells (CSC) at the core of the tumour.

Retinoids, synthetic analogues of retinoic acid, are potent differentiation agents that have garnered attention as a potential adjuvant therapy to stimulate the terminal differentiation of glioma CSC and reduce growth of tumour cells. Retinoid signalling culminates in activation of three nuclear receptors (retinoic acid receptors RARa, RARb and RARg) that stimulate the expression of target genes. Each RAR codes for four to seven functional isoforms differing in their N-terminal active domain. While evidence shows that retinoid action in glioma cell lines is partly mediated by RARa and RARg, RARb has been described as a potential tumour suppressive gene in a multitude of other tumour types. Little data is available to assess the potential role of the RARs in glioma.

Considering the potential therapeutic benefit of retinoids and the mixed functions of RAR isoforms, we wish to determine their expression status in gliomas of various histological grades and in normal brain tissue. We

hypothesize that low grade gliomas/normal tissue will have preserved expression of tumour suppressive RAR isoforms while high grade tumours and CSCs will express isoforms associated with invasiveness and high proliferative rates.

Methods: Using published microarray data, we have identified 1200 glioma and control samples for which expression data can be obtained. Normalized expression values will be obtained for each gene and averaged according to histological type, prognostic and survival time.

Statistical analysis: For each gene, the average expression value will be determined for each category. ANOVA with post-hoc comparison and correlations will be performed between groups.

Poster number: PM125 (SP)

Theme: Neuronal, glial and cellular mechanisms

Does histone deacetylase-6 inhibition affect glial activation in a cell-specific manner?

Authors: Dr Aedin Minogue¹, Pamela Moorhouse¹, Daire Healy¹, Hannah Cahill¹

¹Trinity College Dublin, Dublin, Ireland

Histone deacetylases (HDACs) are a family of proteins that deacetylate lysine residues on histones as well as several other nuclear, cytoplasmic and mitochondrial proteins. While some classes of HDACs are primarily localised in the nucleus, others can translocate between the nucleus and the cytoplasm. Inhibitors of HDACs display anti-inflammatory properties and consequently, have been suggested as possible therapeutic targets for several diseases where neuroinflammation is evident. However, targeting specific HDACs may provide a more successful outcome since HDACs have roles in a variety of cellular processes. Recently, enhanced expression of HDAC6 has been reported in neurons in AD brain post-mortem though no evidence has been presented for glial expression. The aim of this study was to assess the effects of HDAC6 inhibition on glial activation in response to inflammatory stimuli. Microglial-derived cytokines interleukin-1 (IL-1)- α and tumour necrosis factor (TNF) α have been shown to be capable of inducing phenotypes (termed A1 and A2) in astrocytes akin to those described for microglia (Liddel et al., 2017). Consequently, IL-1 α /TNF α or lipopolysaccharide (LPS) were used to induce inflammatory activity in glia and the effect of HDAC6 assessed using the HDAC6-specific inhibitor, tubastatin A.

To validate the results, data was collected from both primary cells and the mouse astrocyte cell line C8-D1A exposed to inflammatory stimuli in the presence/absence of the HDAC6 inhibitor, tubastatin A. Each experiment was performed 3 times in triplicate. Statistical analyses were carried using two-way ANOVA and Student's t-test where applicable.

The LPS-induced release of IL-6 and MCP-1 was attenuated by co-incubation with tubastatin A in microglia but not in astrocytes indicating a differential effect of HDAC6 inhibition. Astrocytes were incubated in the presence of the microglia-derived cytokines IL-1 α and TNF α to drive them towards a pro-inflammatory (A1) state. IL-6 and MCP-1 release were enhanced from IL-1 α /TNF α -exposed, in comparison to vehicle-treated astrocytes while IGF-1 release was reduced. In this instance, inhibition of HDAC6 exacerbated the cytokine-stimulated release of IL-6 from astrocytes while having no effect on MCP-1 or IGF-1. These data indicate that HDAC6 may play cell-specific roles in the CNS which require greater investigation for assessment of potential therapeutic value.

Poster number: PM126 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Genome-wide in vivo mapping of neural cell type specific microRNAs in epilepsy reveals determinants of cellular phenotype and contribution to disease****Authors:** Dr Gary Brennan^{1,2}, Dr Thomas Hill^{1,2}, Ms Elizabeth Brindley¹, Dr Cristina Reschke^{1,2}, Ms Asia Batool¹, Dr Mairéad Diviney¹, Professor David Henshall^{1,2}¹Royal College Of Surgeons Ireland, Dublin, Ireland, ²FutureNeuro Research Centre, Royal College of Surgeons Ireland, Ireland

Introduction: Defined cellular populations contribute to disease in specific ways. Omic-based profiling of individual cell types in healthy and control brain is required to define the role of individual cell types in disease. Recently it has emerged that microRNAs (small non-coding RNAs) are involved in the development of acquired temporal lobe epilepsy. How they shape the neuronal and microglial response to an epilepsy-inciting event is unclear. To address this we now generate an inducible transgenic reporter mouse which allows genome-wide profiling of the miRnome from both neurons and microglia in healthy and epileptic mice.

Methods: A transgenic mouse line homozygous for a FLAG-tagged-Ago2 gene (*Rosa-Stop^{fl/fl}-Flag-Ago2*) were crossed with two different inducible cre-recombinase mouse lines, one with a *Cx3cr1* microglial specific promoter and one with a *Thy1* neuronal promoter producing two specific genotypes *Cx3cr1-cre^{tg/tg};Rosa-Stop^{fl/fl}-Flag-Ago2*, *Thy1-cre^{tg/+};Rosa-Stop^{fl/fl}-Flag-Ago2* respectively. Upon the administration of tamoxifen these mice then express Flag-tagged Ago2 in either microglia or neurons. Epilepsy was induced by injecting kainic acid directly to the amygdala of adult mice, a sham injection of PBS was administered to generate control animals. Hippocampus was harvested from epileptogenic animals (24h post KA) and chronically epileptic animals (2 weeks post KA) and from time matched control animals. Immunoprecipitation for Flag followed by RNA isolation was performed to isolate Ago2-bound miRNAs from neurons or microglia. Sequencing libraries were generated from immunoprecipitated miRNAs and from total cellular miRNA and sequenced on an Illumina miSeq.

Approach for statistical analysis: Count based miRNA expression data was generated by mapping to mouse miRBase. Principal component analysis (PCA) was used to reveal simplified dynamics within the data and identify clustering of samples. Differential miRNA expression between groups was analysed by using Bayesian moderations and an adjusted p-value set at 5%.

Results and Conclusions: Tamoxifen treatment successfully induced cell-specific expression of Flag-Ago2. Initial characterisation by RIP-PCR identified neuronal enriched miRNAs in Cre-*Thy1* mice and microglial enriched miRNAs in Cre-*Cx3cr1* mice. Neurons and microglia have unique miRNA profiles which are differentially regulated in epilepsy. This study provides the first comprehensive microRNA map in brain and identifies unique cell-specific miRNA regulation in epilepsy.

Poster number: PM127 (SP)**Theme:** Neuronal, glial and cellular mechanisms**The search for functional OGR1 in neurons; how does our brain detect acidic microenvironments?****Authors:** Ms Audrey Bradford¹, Dr. Andrew Irving¹¹Conway Institute, University College Dublin, Dublin, Ireland

Introduction: OGR1 is a ubiquitously expressed GPCR known to detect acidic microenvironments. In recent publications, OGR1 has been linked to many pathological conditions including cancer, inflammation and hypoxia. At

the mRNA level, OGR1 is thought to be neuronally expressed both centrally and peripherally, and in the immortal neuroblastoma cell line SH-SY5Y.

This project aims to characterise OGR1-mediated signalling in a recombinant expression system and to better elucidate OGR1 function in neurons.

Methods: HEK 293AD cells were transiently transfected with recombinant HA-tagged OGR1 (species; rat). Gq signalling in cells was demonstrated by live-cell FURA-2 based microfluorimetry. Cells were treated with acidic buffer treatment (physiological buffer pH 6.4). The same methodology was applied to primary neuronal cells; cerebellar, cortical and hippocampal, and differentiated SH-SY5Y cells (IGF-1 differentiation protocol).

Approach for statistical analysis: Single-cell analysis was carried out for all live-cell calcium data with equal numbers of cells being taken from three independent experiments (e.g. n = 30 from 3 independent experiments; 10 cells from each experiment). Peak responses were measured from intracellular calcium traces using Origin software and data was graphed as mean plus/minus SEM using Prism.

Results and conclusions: OGR1-mediated proton-sensitive calcium transients were reproducible, Gq-dependent (YM-254890-sensitive) and required calcium release from intracellular stores (thapsigargin-sensitive). This data characterises calcium transients further downstream of already published OGR1-mediated IP₃ signalling. Despite being reported to express endogenous OGR1, proton-sensitive calcium signalling was not detected in SH-SY5Y cells including SH-SY5Y cells exposed to IGF-1 differentiation. Similar, results were found in primary neuronal cells (cerebellar, cortical and hippocampal).

The results described here show that the HEK HA-OGR1 overexpression system provides a valuable model for investigating this novel receptor. OGR1-mediated calcium transients are reproducible and dependent on the Gq-pathway. In addition to this, cerebellar, cortical and hippocampal neurons did not show any indication of proton-sensitive calcium signalling (pH 6.4) under resting conditions. Future work will investigate whether OGR1 is functionally expressed in these cells.

Poster number: PM128 (SP)

Theme: Neuronal, glial and cellular mechanisms

Integrated network analysis of MIRNA dysregulation in epileptogenesis

Authors: Diana Smirnovova¹, Dr Sebastian Bauer^{2,3}, Stefan Haunsberger¹, Dr Felix Rosenow^{2,3}, Dr Morten Trillingsgaard Veno⁴, Prof Jorgen Kjems⁴, Prof Jochen H. M. Prehn¹, Dr Niamh M. C. Connolly¹

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Introduction: miRNAs are short strands of RNA involved in post-transcriptional regulation of gene expression, and miRNA dysregulation has been implicated in the pathogenesis of epilepsy. Identifying the functional impact of such dysregulation is far from straight-forward, with many studies limited to subjective selection of miRNAs and/or their gene targets.

Methods: Using miRNA Ago2 RNA-Seq data from the hippocampus of rats exposed to perforant path stimulation, we performed Weighted Gene Co-expression Network Analysis (WGCNA) to identify clusters of co-regulated miRNAs that are differentially expressed at early and late stages of the epileptogenic phase in this animal model. To investigate the functional role of these miRNA clusters, we developed an unbiased, systems-level approach to prioritise miRNA-gene target interactions (MTIs) and facilitate focussed functional and pathway enrichment analyses.

Approach for statistical analysis: Differential expression analyses (LIMMA, EDGER), and WGCNA were performed using R v3.5.1. MTI prioritisation and functional analysis of targets were performed using in-house developed pipelines in R and Julia v0.6.2. Pathway enrichment analysis was performed using in-house developed pipelines that utilise Reactome Pathway Database.

Results and conclusions: While some miRNAs and their associated miRNA clusters were differentially co-regulated throughout the epileptogenic phase (e.g. miR-17-92 cluster, miR-142-5p), others were present only at early or late stages. This suggests persistent but varying miRNA-mediated regulation during epileptogenesis and highlights the potential to discriminate these stages and target therapy accordingly. Identification and prioritisation of the gene targets of these miRNA clusters, and associated pathway analysis, identified multiple epilepsy-related genes (e.g. PTEN, SMAD proteins) and pathways that could critically affect different phases of the epileptogenesis process. Together, our approaches can be used to thoroughly characterise miRNA dysregulation and its functional impact in epileptogenesis.

Poster number: PM129 (PP)

Theme: Neuronal, glial and cellular mechanisms

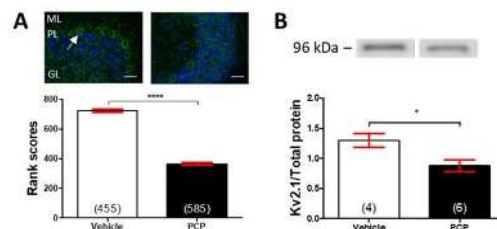
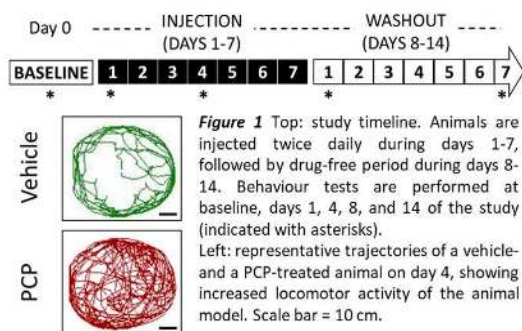
Investigating the regulation of a voltage-gated potassium channel in the cerebellum of a pharmacological mouse model of schizophrenia

Authors: Mr Lukasz Lagojda¹, Dr Lan Zhu¹

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Introduction: Schizophrenia is a debilitating neurodevelopmental disorder affecting 1% of the global population. The glutamate hypothesis poses that the *N*-methyl-D-aspartate receptor (NMDAR) hypofunction is the key player in the development of different domains of schizophrenia symptoms. Phencyclidine (PCP) is a non-competitive NMDAR antagonist, which is widely used to generate animal models of schizophrenia¹. The cerebellum has long been known for its motor related functions. Recently, an increasing body of evidence associates cerebellar structural and functional abnormalities with schizophrenia². Voltage-gated potassium channels (Kv) play intricate roles in neuronal excitability and firing frequency. The Kv2.1 is a type of Kv which has been shown to regulate the excitability of neurons in the brain. Limited evidence suggests that the Kv2.1 gene is a schizophrenia vulnerability risk gene and the dysregulation of Kv2.1 in the brain is associated with schizophrenia^{3,4,5}.

This study aims to: 1) characterise the cellular and subcellular expression of Kv2.1 in the cerebellum; 2) investigate the regulation of Kv2.1 in a PCP mouse model of schizophrenia. Our preliminary data shows that Kv2.1 is expressed in the cerebellar Purkinje cells and granule cells and its expression is significantly downregulated in the cerebellum of the PCP mouse model (Figure 2).



Methods: Adolescent male mice from the same litters were randomly allocated into two groups, which received (i.p.) PCP (5mg/kg) and saline (0.9%), respectively (Figure 1). Animal locomotor activity and novel object recognition tests were performed before, during and after the treatment. After the last behavioural test, cerebellar samples were collected for immunohistochemistry, Western blotting and RT-qPCR.

Approach to statistical analysis: Two-way mixed ANOVA, with treatment groups (vehicle and PCP) as the between-subjects independent variable, and time points as the within-subjects independent variable, was employed for behavioural analysis.

Independent t-test or non-parametric alternative will be used to compare the Kv2.1 protein expression and mRNA transcripts between two groups in immunohistochemistry and Western blotting experiments, and in RT-qPCR experiment, respectively.

¹Jones *et al.* (2011) *BJP*; 164:1162-1194

²Andreasen and Pierson (2008) *Biol psychiatry*; 64:81-88

³Smolin *et al.* (2012) *Int J Neuropsychopharmacol*; 15:869-882

⁴SWG of PGC. (2014) *Nature*; 511:421-427

⁵Peltola *et al.* (2016) *Schizophrenia Bulletin*; 42:191-201

Poster number: PM130 (SP)

Theme: Neuronal, glial and cellular mechanisms

Long-term plasticity in hippocampal neurogliaform interneurons

Authors: Dr Marion Mercier¹, Dr Vincent Magloire¹, Dr Jonathan Cornford¹, Professor Dimitri Kullmann¹

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Introduction: Long-term potentiation (LTP) of excitatory transmission onto hippocampal principal cells plays an important role in memory encoding. Within stratum radiatum, LTP at Schaffer collateral-CA1 pyramidal cell synapses is balanced by a complementary increase in the recruitment of feed-forward inhibitory interneurons (Lamsa *et al.*, 2005). CA1 pyramidal cells also exhibit LTP at their distal synapses located in stratum lacunosum moleculare (SLM), which receive excitatory input from entorhinal cortex layer III (ECIII). Whilst this pathway recruits strong feed-forward inhibition, mediated largely by neurogliaform (NGF) interneurons, it is not known whether ECIII synapses onto SLM interneurons can also be potentiated.

Methods: Whole-cell recordings were performed in SLM interneurons in hippocampal slices from wild-type mice, or neuron-derived neurotrophic factor (NDNF+) cells in slices from *Ndnf-Cre* mice (Tasic *et al.*, 2016). Responses were evoked by electrical stimulation, or optogenetic stimulation of EC or thalamic fibers.

Approach for statistical analysis: Paired or un-paired t-tests, and one way ANOVAs were used as appropriate.

Results and conclusions: A low-frequency stimulation pairing protocol induced pathway-specific, NMDA receptor-dependent LTP in SLM interneurons. This form of LTP could also be induced by selective optogenetic stimulation of EC fibers, but not of fibers from the nucleus reuniens of the thalamus, which also sends excitatory projections to SLM. Interestingly, a spike-timing-dependent-plasticity (STDP) protocol also induced LTP in SLM interneurons, but this was neither pathway-specific nor NMDA receptor-dependent; instead, it was blocked by the calcium chelator BAPTA, or combined application of the R-, T- and L-type Ca²⁺ channel blockers Ni²⁺ and nimodipine. This suggests that Ca²⁺ influx through voltage-gated calcium channels during backpropagating action potentials is sufficient for LTP induction in these cells. Finally, using the *Ndnf-Cre* mouse line, recently developed and shown to target NGF cells in

cortex LI, we found that it also selectively targets hippocampal NGF cells, and confirmed that LTP is expressed in this subset of SLM interneurons.

Lamsa, K. et al. (2005). Hebbian LTP in feed-forward inhibitory interneurons and the temporal fidelity of input discrimination. *Nature Neuroscience* 8: 916-924.

Tasic, B. et al. (2016) Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nature Neuroscience* 19: 335-346.

Poster number: PM131 (SP)

Theme: Neuronal, glial and cellular mechanisms

Cyclooxygenase-2 expression in the brain following ischemic stroke and its effects on glial cells

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Introduction: Ischemic stroke affects an estimated 23,000 people per annum in Ireland. Despite significant advancements in treatment, prevention and supportive care, it still remains a significant problem and economic burden. The pathophysiology of ischemic brain injury is complex, with neuronal injury being heavily impacted by an excessive inflammatory response, which is mediated in part by glial cells. Glial cells (microglia and astrocytes) become activated following ischemia and can produce an array of harmful mediators exacerbating the ischemic damage. Cyclooxygenase-2 (COX-2) is a rate-limiting enzyme in the production of prostaglandins from arachidonic acid. Prostaglandin E₂ (PGE₂) has been shown to be a key component in the initiation and propagation phases of inflammatory processes in the brain. Inhibition of COX-2 either pharmacologically or genetically has been demonstrated to decrease neuronal injury after cerebral ischemia, however how COX-2 affects glial cell activity is currently unknown.

Methods: Left middle cerebral artery occlusion (4hr) was induced in male Sprague Dawley rats (n=3/4 per group) followed by either 2hr full reperfusion or no reperfusion. In sham-operated animals, surgery was performed but insertion of the occluder was omitted. Following surgery, rats were sacrificed, brains were perfusion fixed and harvested, sectioned (30µm thickness) and stained with antibodies specific to COX-2, microglia (IBA-1) and astrocytes (GFAP) for immunofluorescent analysis.

Approach for statistical analysis: Statistical significance was assessed by 2-way ANOVA with Tukey's post-hoc analysis.

Results and conclusions: Our data demonstrates that ischemic stroke followed by either full or no reperfusion causes significant increases in COX-2 expression in the core of the lesion compared to the un-lesioned and sham controls. There were significant increases in both the lesioned core and penumbra for microglia area per cell body (µm²) and microglia volume per cell body (µm³) in the ipsilateral hemisphere when compared to the un-lesioned hemisphere and sham controls. There were no significant changes in astrocyte morphology in the core or penumbra. In conclusion, COX-2 is upregulated in the ischemic hemisphere and is not co-localised with microglia or astrocytes. It is plausible that this increase in COX-2 contributes to changes in microglia morphology observed following ischemic stroke.

Poster number: PM132 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Ligands for the putative cannabinoid receptor, gpr55, modulate bv2 microglial cell migration, phagocytosis and the neuronal caspase-3 activation evoked by a β .****Authors:** Ms Orla Haugh¹, Dr. Andrew Irving², Prof. Veronica Campbell¹¹Trinity College Dublin, Dublin, Ireland, ²University College Dublin, Dublin, Ireland

Introduction: The orphan G-protein coupled receptor, GPR55, is widely expressed throughout the body, including in the neurons and glia of the brain. It is responsive to cannabinoids, however its endogenous agonist is believed to be L- α -lysophosphatidylinositol (LPI). To date, there has been limited research into the role of GPR55 in central immune processes. This makes research into GPR55 as a potential therapeutic target attractive, particularly in relation to neuroinflammatory conditions such as Alzheimer's disease (AD). The present study examined the role of GPR55 in central immune processes using a rat cortical culture model and the BV2 microglial cell line.

Methods: Cultured primary cortical cells obtained from neonatal rats and BV2 microglia were immunolabelled for GPR55. They were treated with the endogenous agonist for GPR55, LPI (10 μ M), or the novel and selective GPR55 agonist N-((4-(N-Phenylsulfamoyl)phenyl)carbamothioyl)-[1,1'-biphenyl]-4-carboxamide (N-PCC; 1 μ M). The cells were pre-treated with the selective GPR55 antagonist, CID16020046 (20 μ M), to determine agonist selectivity. LPI- and N-PCC-induced effects on BV2 microglial function were assessed using a chemotactic migration assay; and a fluorescent latex bead phagocytosis assay. Cortical neuron apoptosis in response to the pathological hallmark of AD, A β , was assessed using active caspase-3 immunocytochemistry.

Approach for statistical analysis: Data are reported as the mean \pm S.E.M. of the number of experiments indicated in each case. A One- or Two-way ANOVA was performed followed by a post-hoc test if results were significant. P<0.05 was considered significant. All statistical analyses were performed using GraphPad Prism software (Version 5.0).

Results and Conclusions: It was found that GPR55 was expressed in cortical neurons and microglia, as well as in BV2 microglia. LPI attenuated BV2 microglial migration in response to A β -primed neuronal medium. In contrast, N-PCC increased BV2 cell migration and phagocytic ability. Both LPI and N-PCC protected neurons against A β -evoked active caspase-3 induction.

To the best of our knowledge, this is the first study to show that GPR55 ligands modulate A β -evoked microglial cell migration and neuronal apoptosis. This implicates GPR55 in having a regulatory role in processes relevant to pathological conditions such as AD, rendering the receptor an attractive therapeutic target.

Poster number: PM133 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Novel rat monoclonal antibody against murine p2ry12 for specific detection and isolation of microglia****Authors:** Thurka Poobalasingam, Dr Anna Cartier¹, Dr Lasse Dissing-Olesen², Dr Hong Zhang¹, Dr Juan Moyron-Quiroz¹, Dr Kenya Cohane¹, Dr Sara Sampietro¹, Dr Miguel Tam¹, Dr Beth Stevens², Dr Peggy Taylor¹¹BioLegend, 9727 Pacific Heights Blvd, San Diego, United States, ²Children's Hospital Boston, 300 Longwood Avenue, Center for Life Sciences 12th Floor, Boston, United States

Introduction: Microglia are the brain and spinal cord-resident macrophages that function as sentinels in maintaining central nervous system homeostasis. Dysregulation of these sentinels has been associated with neuropsychiatric and neurodegenerative disorders. A major limitation in understanding microglial contribution to cellular processes and their role in disease has been the lack of tools to specifically distinguish these cells from other myeloid cells. In an

effort to produce a novel, microglia-specific tool, we have generated a rat monoclonal antibody against murine Purinergic Receptor P2Y₁₂ (P2RY₁₂), a highly selective marker for microglial cells that enables immunostaining in histological sections as well as isolation of these cells by flow cytometry and magnetic nanobeads.

Methods: The specificity of the P2RY₁₂ antibody was validated in single cell homogenates from various different organs including the brain, spinal cord, spleen, liver, and lungs which were analyzed by flow cytometry. Phenotype of corresponding tissue resident macrophages i.e. microglia, splenic macrophages, Kupffer cells, and alveolar macrophages, was confirmed by their CD11b and CD45 expression. Additionally, immunohistochemistry was used to further validate the antibody in tissue sections from these organs. Furthermore, we validated the utility of the P2Y₁₂ antibody for use in combination with BioLegend's MojoSort™ magnetic cell separation system, to isolate microglia with high purity and yield.

Analysis Approach: Cells were isolated from 7-day old C57BL/6 mouse brains using biotinylated P2RY₁₂ antibody, followed by incubation with streptavidin nanobeads. Isolated cells were co-stained with CX3CR1 and CD11b as general markers for microglia and flow cytometric quantification demonstrated a purity of microglia above 99%. Ongoing experiments address LPS-induced alterations in microglial morphology, an inflammatory stimulus known to downregulate P2RY₁₂ and to induce amoeboid morphology in microglia.

Results and conclusions: With our studies we demonstrate the specificity, versatility, and utility of a novel and unique rat anti-mouse P2RY₁₂ antibody that will facilitate research in microglia and their role in the CNS.

Poster number: PM134 (SP)

Theme: Neuronal, glial and cellular mechanisms

Investigating the pathogenic mechanisms of progressive myoclonic epilepsy with ataxia

Authors: Ms Jenna Carpenter^{1,2}, Miss Jana Heneine¹, Dr Marisol Sampedro Castaneda¹, Dr Roman Praschberger¹, Dr James Jepson¹, Dr Roope Mannikko¹, Dr Gabriele Lignani¹, Professor Stephanie Schorge²

¹UCL Queen Square Institute of Neurology, London, United Kingdom, ²UCL School of Pharmacy, London, United Kingdom

Introduction: Progressive myoclonic epilepsy (PME) is a rare and severe genetic epilepsy syndrome that accounts for 1% of all epilepsies. The syndrome is characterised by core symptoms of myoclonus (involuntary muscle jerks), epilepsy and progressive neurological dysfunction (dementia or ataxia). Here we aimed to characterize the neuronal effects of mutations recently identified in KCNC1 (K_v3.1, p.Arg320His) and Golgi SNARE receptor complex member 2 (GOSR2, p.Gly144Trp) that have been shown to cause PME with ataxia.

Methods: Transfection and lentiviral-mediated transgene delivery were used to express WT and mutant K_v3.1b channels in cortical neuronal cultures prepared from C57BL/6 neonatal mice. Whole-cell current clamp recordings were carried out at 32°C, at 14-16 DIV, in order to assess the impact of mutant K_v3.1b channel expression on interneuronal firing. In parallel, two-electrode voltage clamp experiments were performed in *X. laevis* oocytes expressing K_v3.1b alpha pore mutants, in order to investigate the presence of a pathogenic, H⁺-carried, gating-pore current in K_v3.1b p.R320H.

Whole-cell voltage-clamp recordings of miniature excitatory post-synaptic currents (mEPSCs) were carried out in cortical neuronal cultures transduced with lentiviruses delivering GOSR2 transgenes, at 14-16 DIV. In addition, immunoblots for selected presynaptic proteins were carried out using neuronal lysates prepared from cortical cultures expressing GOSR2 transgenes.

Approach for statistical analysis: For two categorical groups, means were compared using Student's two-tailed *t*-test. To compare three categorical groups, we used One-Way ANOVA followed by Bonferroni post-hoc multi-comparison

test. To analyze two groups and two independent variables we used two-way repeated measures ANOVA, followed by Bonferroni post-hoc multi-comparison test.

Results and conclusions: We observed morphological defects and alterations in high frequency firing for interneurons expressing $K_v3.1b$ p.R320H. We excluded gating-pore currents through the voltage-sensor domain of $K_v3.1b$, as a potential mechanism of pathogenicity. For PME caused by mutation in *GOSR2*, we found that early secretory pathway deficits induced by overexpression of *GOSR2* p.G144W, resulted in a significant reduction in spontaneous neurotransmitter release at glutamatergic synapses, via a presynaptic mechanism. Overall, this data contributes to a greater mechanistic understanding of PME with ataxia with implications for other forms of PME caused by different gene mutations.

Poster number: PM135 (SP)

Theme: Neuronal, glial and cellular mechanisms

Unique roles of neuronal microRNAs in mRNA transport and synaptic connectivity

Authors: Ms Karishma Joshi¹, Professor Ruth Luthi-Carter¹

¹*University Of Leicester, Leicester, United Kingdom*

Introduction: microRNAs (miRNAs) are small non-coding regulators of mRNA expression, generally via mRNA degradation. However, our previous work indicates that neurons may use a different miRNA regulatory regime in which miRNAs co-exist with their targets. These include miRNA135b and miRNA137, which regulate the fractions of their target mRNAs on translating ribosomes (Jovičić, 2011). We hypothesise that these neuronal miRNAs sequester their targets in specialised, translationally silent sub-compartments. Polymorphisms in miRNA genes have been associated with human psychiatric disorders, including miRNA137 in schizophrenia and miRNA135b in depression (Issler et al., 2014, Kos et al., 2016). We aim to elucidate the roles of these miRNAs in regulating neuronal function, connectivity and plasticity.

Methods: Primary E16 rat cortical neurons were subjected to lentiviral-mediated miRNA overexpression. Sucrose density fractionation, RT-qPCR and western blotting evaluated sub-compartmentalisation of miRNAs, their mRNA targets and various RNA binding proteins (RBPs). Combined fluorescence in-situ hybridisation and immunocytochemistry (FISH/ICC) and RBP immunoprecipitation (IP) followed by RT-qPCR were used to evaluate miRNA-mRNA-RBP co-localisation. The relationships of miRNA expression and target protein levels were assessed via western blotting.

Approach for statistical analysis: Two-group comparisons were drawn using two-tailed Student's t-test (threshold 95%).

Results and conclusions: Both miRNAs and their mRNA targets were detected in dense sub-cellular fractions. miRNA135b overexpression led to increased mRNA target levels without affecting target protein levels. Interestingly, miRNA137 overexpression resulted in a significant increase of Syt1 protein ($p < 0.01$), in contrast to previous studies (Siegert et al., 2015). The sucrose gradient distributions of RBPs MOV10 and SMN overlapped with those of the miRNAs. MOV10 and SMN were also co-detected with miRNAs and their targets in combined FISH/ICC experiments. Likewise, MOV10 IP pulled down both miRNA135b and miRNA137, and miRNA135b was significantly enriched by SMN IP. These results support the view that stable miRNA-mRNA-RBP complexes play specialised roles in neuronal mRNA transport and/or signal-dependent translation, thus regulating unique cellular features, including neuronal polarity, connectivity and plasticity.

References:

Issler, O. et al. (2014) *Neuron* 83, 344-360.

Jovičić, A. (2011) Ph.D thesis 5237, EPFL.
Kos, A. *et al.* (2016) *Neuroscientist*, 22, 440-446.
Siegert, S. *et al.* (2015) *Nat Neurosci* 18, 1008-1016.

Poster number: PM136 (SP)**Theme:** Neuronal, glial and cellular mechanisms**Role of NMDA receptors in modulating synaptic release and plasticity at dorsal cochlear nucleus multisensory synapses****Authors:** Ms Masa Svent¹, Prof Nicholas Hartell¹, Dr Martine Hamann¹¹*University of Leicester, Leicester, United Kingdom*

Introduction: Recent studies have shown that acoustic over-exposure leads to gap-detection deficits in a rodent model, and leads to a saturation of long-term potentiation (LTP) at dorsal cochlear nucleus (DCN) multisensory synapses (Tagoe *et al.*, 2017), which occurs due to NMDA receptor (NMDAR) activation. The aim of this study is to investigate the presynaptic role of NMDARs in modulating synaptic release and plasticity at those synapses.

Methods: Whole-cell recordings of fusiform cells were performed in CBA mouse brain slices containing the DCN. Excitatory postsynaptic currents (EPSCs) were evoked by stimulating parallel fibres in the DCN molecular layer. Miniature EPSCs (mEPSCs) were recorded in the presence of tetrodotoxin (1 μ M). LTP was induced using high-frequency stimulation (HFS, 100 Hz, 1 s), combined with depolarisation (-30 mV), applied twice at a 20 s interval. Low frequency stimulation (LFS, 2 Hz, 10 min) protocol was also used to prevent or reverse LTP. Calcium imaging at presynaptic terminals was performed in SyGCaMP2-mCherry-expressing transgenic mice.

Approach for statistical analysis: Miniature and evoked EPSCs were analysed using paired t-tests, ANOVA multiple comparison and Kolmogorov-Smirnov tests. Calcium imaging data were analysed using paired t-tests and two-way ANOVA tests.

Results and conclusion: Perfusion of NMDA (500 nM) increased the frequency of mEPSCs in 6 out of 13 fusiform cells and increased the basal fluorescence associated to presynaptic calcium levels in 4 slices, indicating that NMDAR activation modulates spontaneous, calcium-dependent release at DCN multisensory synapses. HFS of parallel fibres induced EPSC LTP, which was prevented or reversed by LFS or blocking NMDARs with D-AP5 (50 μ M). This suggests that NMDAR activation is involved in the process of LTP, while the blocking of NMDARs triggers depotentiation. In conclusion, blocking NMDARs at DCN multisensory synapses could be used to reverse the effect on LTP saturation and gap detection deficits observed after acoustic over-exposure.

ReferenceTagoe, T., Deeping, D. & Hamann, M. (2017) *Exp Neurol*, 292, 1-10**Poster number: PM137 (SP)****Theme:** Novel treatments & translational neuroscience**Xenon prevents late-onset traumatic brain injury-related cognitive impairment and improves survival following traumatic brain injury in mice****Authors:** Dr Rita Campos-Pires^{1,2,3}, Mr Tobias Hirnet⁴, Ms Flavia Valeo¹, Dr Bee Eng Ong¹, Ms Joanna Saville¹, Dr Konstantin Radyushkin⁵, Dr Christopher Edge^{6,7}, Professor Nicholas Franks⁶, Dr Serge Thal⁴, Dr Robert Dickinson^{1,2}

¹Department of Surgery & Cancer, Imperial College London, London, United Kingdom, ²Royal British Legion Centre for Blast Injury Studies, Department of Bioengineering, Imperial College London, London, United Kingdom, ³Charing Cross Hospital, London, United Kingdom, ⁴Department of Anesthesiology, Medical Centre of Johannes Gutenberg University, Mainz, Germany, ⁵Mouse Behavioural Outcome Unit, Johannes Gutenberg University, Mainz, Germany, ⁶Department of Life Sciences, Imperial College London, London, United Kingdom, ⁷Royal Berkshire Hospital, Reading, United Kingdom

Introduction: TBI is a complex and dynamic process that results in long-term neurodegeneration, and disability, leading to reduction in life-expectancy. Currently, TBI treatment is mainly supportive and no specific neuroprotective drugs are available. Xenon is neuroprotective in a number of models of brain ischemia. Here we evaluate the neuroprotective efficacy of the noble gas xenon on long-term cognitive, histological and survival outcomes, in a well-established animal model of TBI.

Methods and Analysis: Young adult male C57BL/6 mice (n=72) received a right parietal controlled cortical impact as described previously.¹ Sham animals underwent an identical procedure, but no craniotomy or impact were performed. Animals were randomly assigned to control (75%N₂:25%O₂) and xenon-treatment groups (75%Xe:25%O₂). Neurological outcome score (NS) was assessed at 24 hours, and a contextual fear conditioning (CFC) test was done 2 weeks and 20 months after injury. Histological outcomes were analyzed at 24 hours (contusion volume) and 20 months (contusion volume, GFAP expression, neuronal and microglial cell count). Survival was assessed in a cohort (n=50) kept for 20 months after injury. Outcomes were measured by researchers blinded to treatment. P-values of less than 0.05 were taken to indicate significance.

Results and Conclusion: Xenon significantly (p<0.05) reduced secondary injury development and improved neurological score (p<0.001) at 24 hours. None of the groups exhibited memory deficits at 2 weeks. However, at 20 months, the control TBI group developed significant (p<0.05) memory deficits when compared to sham animals. Strikingly, the memory deficit was absent in xenon-treated animals. We found a significant increase in GFAP stained area in ipsilateral & contralateral hypothalami (p<0.01 & p<0.05, respectively) and ipsilateral retrosplenial cortex (p<0.01) in control animals when compared with sham animals, at 20 months. Xenon treatment prevented or reduced these increases. Control TBI animals had higher mortality than sham animals from 6 months after injury. Survival in the xenon-treated animals was significantly improved (p<0.05) up to 12 months after injury compared to the control TBI group. These findings support the idea that xenon treatment may offer long-term neuroprotection and improved outcome in TBI patients.

¹ Campos-Pires *et al*, 2015, Critical Care Medicine, v43 p149.

Poster number: PM138 (SP)

Theme: Novel treatments & translational neuroscience

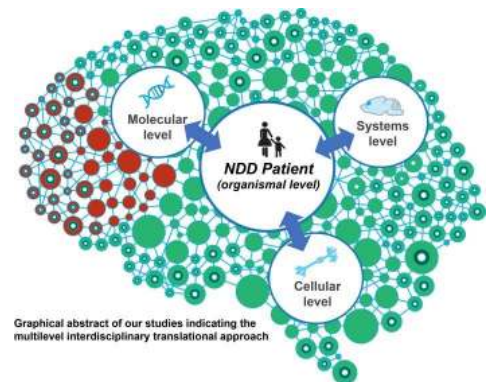
Integrating biological and neuropsychiatric underpinnings of neurodevelopmental disorders in order to design novel treatment strategies

Authors: Dr SM Kolk¹, Dr JS Witteveen¹, Dr MH Willemsen², Dr TC Dombroski¹, Dr L van Dongen², Dr NH van Bakel¹, Dr WM Nillesen², Dr JA van Hulten¹, Dr EJ Jansen¹, Dr D Verkaik², Dr HE Veenstra-Knol³, Dr CM van Ravenswaaij-Arts³, Dr JS Wassink-Ruiter³, Dr M Vincent⁴, Dr A David⁴, Dr C Le Caignec^{4,5}, Dr J Schieving⁶, Dr C Gilissen², Dr N Foulds^{7,8}, Dr P Rump³, Dr T Strom^{9,10}, Dr K Cremer¹¹, Dr AM Zink¹¹, Dr H Engels¹¹, Dr SA de Munnik², Dr JE Visser^{1,6,12}, Dr HG Brunner², Dr GJ Martens¹, Dr R Pfundt², Dr T Kleefstra²

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Médicale, Nantes, France, ⁵Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, INSERM UMRS 957, Nantes, France, ⁶Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, Netherlands, ⁷Wessex Clinical Genetics Services, University Hospital Southampton National Health Service Foundation Trust, Princess Anne Hospital, Southampton, UK, ⁸Department of Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK, ⁹Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany, ¹⁰Institute of Human Genetics, Technische Universität München, Munich, Germany, ¹¹Institute of Human Genetics, University of Bonn, Bonn, Germany, ¹²Department of Neurology, Amphia Hospital Breda, Breda, Netherlands

Introduction: Mendelian neurodevelopmental disorders (NDDs) are caused by mutated genes that often have a large effect on the disease risk. The occurrence of psychiatric and cognitive symptoms in NDDs indicates that abnormal development of the prefrontal cortex (PFC), which controls key cognitive functions, may be a key feature of NDDs. To investigate this hypothesis, we focus on the *Witteveen-Kolk Syndrome* (WitKoS, OMIM 613406), caused by heterozygous *SIN3A* mutations, a gene encoding a transcriptional repressor and MeCP2 interactor¹. We hypothesize that the initial PFC developmental defect gives rise to subsequent problems in establishing appropriate inputs onto developing PFC neurons, eventually leading to hypo/hyperconnectivity with other brain areas.



Methods: In our studies, we 1) assessed PFC-related (psycho)pathology *in* WitKoS patients, 2) characterized the spatio-temporal aspects of PFC development in WitKoS using human brain organoids and mouse models (in utero electroporation) and 3) delineated the molecular basis of WitKoS-related psychopathology.

Approach for statistical analysis: For the various types of analyses we used standard and validated statistical approaches as described in our Nature Genetics paper¹. Our preliminary developmental and neuropsychiatric studies of WitKoS patients suggest a high susceptibility to specific age-related PFC-associated psychopathology including psychoses and depression. *In vivo* functional knockdown of Sin3a led to reduced prefrontal neurogenesis and altered neuronal identity in the developing PFC. A better understanding of the neurocognitive processes on one site and the biological mechanisms on the other, will open doors to investigate new therapeutic interventions and improve care for NDDs patients.

¹Witteveen JS, Willemsen MH, Dombroski TC, ... Kleefstra T, Kolk SM. (2016) Haploinsufficiency of MeCP2-interacting transcriptional co-repressor SIN3A causes mild intellectual disability by affecting the development of cortical integrity. Nature Genetics 48(8):877-87. doi: 10.1038/ng.3619

Poster number: PM139 (PP)

Theme: Novel treatments & translational neuroscience

Investigating the cellular and molecular mechanisms underlying neural synchronisation-induced amyloid clearance for Alzheimer's disease

Authors: Dr Eilis Dowd¹, Dr Niamh Moriarty¹, Ms Christina Ryan^{1,2}, Mr Cameron Keighron^{1,2}, Mr Barry McDermott³, Dr Marggie Jones³, Dr Martin O'Halloran³, Dr Leo Quinlan²

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Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder characterised by extracellular deposits of beta-amyloid and intracellular neurofibrillary tau tangles. Current pharmacotherapies for AD simply address neurotransmitter deficiencies to temporarily alleviate cognitive symptoms, and there remains a major unmet clinical need to develop disease-modifying therapies that can slow disease progression.

Alterations in electroencephalogram gamma wave oscillations have been observed in Alzheimer's patients, but the relationship between this and disease pathology is unclear. Intriguingly, one recent report (Iaccarino et al., 2016; *Nature*. 540:230-235) demonstrated that gamma wave entrainment, induced by a non-invasive 40Hz flickering light, reduced amyloid deposition, plaque load and hyperphosphorylated tau in Alzheimer's models. Although the decrease in plaque load was associated with increased microglial phagocytic activity, the mechanisms underlying these effects are unknown. Given the potential of this non-invasive therapeutic modality for Alzheimer's disease, it is crucial that further studies are completed to assess its underlying mechanisms at a cellular and molecular level.

Therefore, the aim of this study is to develop an *ex vivo* model system for 40Hz electrical stimulation-induced neural synchronisation in primary neural cultures, and to assess the cellular and molecular events linking 40Hz-induced neural synchronisation, microglial activation and amyloid clearance.

Methods: To do so, primary neural cultures dissociated from the developing hippocampus and cortex will be subjected to 40Hz electrical stimulation. Optimisation of stimulation parameters such as modality (voltage or current controlled), amplitude, duration, wave pattern and duty-cycle will be assessed. Once the optimal parameters for synchronisation are established (confirmed using raster plots), cultures will be seeded with aggregated beta-amyloid, and various cellular and molecular measures of microglial activation and amyloid clearance will be measured (i.e. morphological changes using microscopy, neuroinflammatory markers using qPCR, cytokine release using ELISA, amyloid clearance using ELISA and amyloid uptake using dual-immunofluorescence).

Approach for statistical analysis: A randomised and blinded study design will be used to compare stimulation parameters, stimulated vs. unstimulated groups, and amyloid seeded vs. unseeded groups. Assuming data will exhibit homogeneity of variance and normal distribution (verified using Levene's and Shapiro-Wilk's tests, respectively), all data will be analysed using ANOVA (one-way, two-way or repeated measures as appropriate).

Poster number: PM140 (SP)

Theme: Novel treatments & translational neuroscience

Gonadotrophin rise following kisspeptin analogue (MVT-602) is increased in women with hypothalamic amenorrhoea compared to healthy women

Authors: Dr Pei Chia Eng¹, Dr Ali Abbara¹, Dr Maria Phylactou¹, Dr Sophie A Clarke¹, Dr Lisa Yang¹, Dr Edouard GA Mills¹, Dr Manish Modi¹, Miss Deborah Papadopoulou¹, Dr Isabella Plumtre¹, Dr Tia Hunjan¹, Miss Kate Purugganan¹, Miss Lisa Webber¹, Mr Rehan Salim¹, Dr Alexander N Comninos¹, Professor Waljit Dhillon¹
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Introduction: Hypothalamic amenorrhoea (HA) is a condition characterised by reduced GnRH pulsatility due to low body weight, excessive exercise, or psychological stress, causing anovulatory infertility. Kisspeptin is a neuropeptide that is known to be a key regulator of hypothalamic GnRH function. Hypothalamic kisspeptin expression is reduced, and kisspeptin receptor expression increased, in a rodent model of HA. Kisspeptin analogue (MVT-602) is a modified form of kisspeptin with a longer half-life compared to native kisspeptin-54 (1.5-2.2h vs 0.5h). We investigated the hormonal response to MVT-602 in women with HA to evaluate its potential future utility in the treatment of anovulatory infertility.

Methods: A previous dose-finding study during the follicular phase of healthy women determined that no further increase in gonadotrophin rise was observed at doses of MVT-602 higher than 0.03nmol/kg. We therefore compared the gonadotrophin rise following a subcutaneous bolus of MVT-602 at a dose of 0.03nmol/kg in 6 women with HA with 9 healthy women studied during the follicular phase of their menstrual cycle (day 1-4). Serum gonadotrophin and oestradiol levels were monitored every 30mins for 24hrs. Mean±SD is presented, and groups were compared by unpaired t test.

Results: The maximal rise in LH following MVT-602, was >2-fold greater in women with HA compared to healthy women in the follicular phase (maximal change in LH: HA 18.3±11.0iU/L, follicular phase 7.4±2.7iU/L; P=0.01). The time to peak LH was expedited in women with HA (time to first peak: HA 380±53mins, follicular phase 1067±415mins; P=0.002). Serum FSH rise was also augmented by >4-fold in women with HA (maximal change in FSH: HA 10.0±4.4iU/L, follicular phase 2.2±1.6iU/L; P=0.0003). Maximal rise in oestradiol was higher in women with HA (700pmol/L) when compared with healthy women (297pmol/L; P=0.03).

Conclusion: In women with HA, the rise in gonadotrophins following MVT-602 is more pronounced and occurs sooner than in healthy women. The augmented and sustained rise in oestradiol highlights the potential for MVT-602 to be used as an ovulation induction agent in women with anovulatory HA. Therefore, further research is indicated to evaluate repeated administration of MVT-602 as a novel therapeutic approach to restore fertility in HA.

Poster number: PM141 (PP)

Theme: Novel treatments & translational neuroscience

Evaluating the antidepressant-like effects of a novel 5-HT₄ agonist on emotional cognition biomarkers of depression in treatment resistant depression

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Introduction: For a significant number of patients with depression, current antidepressants – such as selective-serotonin uptake inhibitors (SSRIs) - are ineffective. However, evidence from animal models suggests that 5HT₄ agonism may be able to effectively augment SSRI treatment.

To explore the potential antidepressant augmentation effect of PF-04995274 - a novel, highly-selective 5-HT₄ receptor partial agonist developed by Pfizer – we will use an experimental medicine model developed by our group. Our previous work has found that citalopram – an SSRI – produces early changes in emotional processing which are critical to subsequent clinical outcomes. Therefore, we will assess whether 7 day administration of PF-04995274 (in addition to ongoing SSRI treatment) produces similar changes; results indicating antidepressant-like effects, expressed as an increase in accurate perception and memory of positive versus negative stimuli, would support future assessment of 5HT₄ agonists for treatment of resistant-depression.

Methods: Depressed patients, who have failed to respond to current SSRI treatment, will be randomized (double-blind) to PF-04995274 (15mg) or placebo, for 7 days. On day 7, a battery of tasks measuring different aspects of emotional processing (perception, memory, attention and physiological reactivity) will be conducted, alongside other measures of cognition including auditory verbal learning and instrumental learning. Our primary outcome is the Facial Expression Recognition Task (FERT), in which participants must identify the emotion expressed by faces presented on screen (happiness, fear, anger, disgust, sadness, surprise).

Approach for statistical analysis: Before unblinding, we will meet with a statistician to determine which variables will be included as covariates and finalise secondary analysis plans. Python and R programming will be used to analyse behavioural data, with scripts shared openly for enhanced reproducibility. Demographic and baseline measures will

be analysed using independent t-tests or Mann-Whitney tests, depending on the data normality. All other measures will be analysed using a repeated measures ANOVA with significant interactions followed up using simple main effect analyses.

For example, we will use a mixed model repeated-measures ANOVA, with emotion and group as factors, to analyse positive vs negative facial expression recognition accuracy in the FERT, and identify whether there is a treatment difference across emotions.

Poster number: PM142 (PP)

Theme: Novel treatments & translational neuroscience

Super-resolution imaging to uncover microRNA control of astrocytes in epilepsy

Authors: Dr Janosch Heller¹, Dr Ingmar Schoen¹, Prof David Henshall¹

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Introduction: More than 70 million people worldwide (6 million in Europe) are affected by epilepsy, of whom at least 30% do not respond to commonly available antiepileptic drugs. A universal hallmark of epileptic tissue is astrocyte dysfunction which has not received much attention as a therapeutic target. Astrocytes play an active role in shaping and maintaining neuronal circuits through their role in extracellular potassium buffering as well as their secretion and clearance of neurotransmitters. Molecular signal exchange between astrocytes and synapses occurs in a highly heterogeneous microenvironment. In previous work we successfully employed super-resolution microscopy to decipher the intimate nanoscale relationship between astrocytic processes and glutamatergic synapses. The research described here builds on those earlier studies and emerging data showing that the molecular machinery for microRNAs is present locally, within astrocyte processes. As we have shown earlier, microRNA function is widely disrupted in the epileptic brain and targeting microRNAs in neurons alleviates seizures in epilepsy. Therefore, we propose a novel strategy for seizure-suppressive or disease-modifying actions that specifically target astrocytes to prevent excessive network excitation and thus seizure generation.

Methods: We will employ immunohistochemistry of hippocampal brain tissue followed by super-resolution single molecule localisation microscopy (SMLM). Super-resolution microscopy can circumvent the optical diffraction limit and offers ease of use and flexibility not seen in electron microscopy. This imaging technique will allow us to visualise astrocyte processes and microRNAs in rodent and human brain. We will then target candidate microRNAs to influence astrocyte morphology, and increase local translation of neurotransmitter and ion channels in astrocytic processes. In turn, this allows the clearing of excess glutamate and potassium from the synaptic cleft and hence prevents synchronous neuronal discharges that generate seizures.

Approach for statistical analysis: We intend to use t-test to assess the level of significance between two groups and to use ANOVA in experiments with more than two groups.

Poster number: PM143 (SP)**Theme:** Novel treatments & translational neuroscience**Context-specific anticonvulsive and anti-epileptogenic effects of P2Y₁ antagonism during acute seizures and epilepsy in mice****Authors:** Dr Tobias Engel¹, Dr Mariana Alves¹¹Royal College of Surgeons in Ireland, Dublin, Ireland

Introduction: Drug resistance remains a clinical challenge in epilepsy with ~30% of patients not responding to current pharmacological treatments. Targeting neuroinflammation has attracted much attention, however, what drives inflammatory processes during epilepsy is incomplete understood. Adenosine triphosphate (ATP), usually present at low extracellular concentrations in the brain, is released from cells during pathological processes such as cell death, inflammation and increased neuronal activity to act as neurotransmitter, activating specific purinergic receptors termed P2 receptors thereby driving inflammatory processes in the brain. P2 receptors are further subdivided into fast-acting ionotropic P2X channels consisting of seven subtypes (P2X₁₋₇) and slower-acting metabotropic P2Y receptors including eight subtypes (P2Y_{1,2,4,6,11,12,13,14}). Whereas P2X receptors have been widely described during epilepsy, demonstrating a functional contribution of these receptors to disease progression, in particular for the P2X₇ receptor subtype, P2Y receptors have received much less attention. Recent studies, however, also suggest a prominent role of P2Y receptors during seizure generation and possibly epilepsy development.

Methods: Using two mouse models of status epilepticus (intraamygdala kainic acid and intraperitoneal pilocarpine-induced status epilepticus), P2Y₁-deficient mice and P2Y₁ agonists and antagonists we demonstrate context-specific anticonvulsive and anti-epileptogenic potential of P2Y₁-targeting. Statistical analysis of data was performed using Graph Pad Prism 5 and STATVIEW using ANOVA and Student's t-test as appropriate. Significance was accepted at p<0.05.

Results and Conclusions: While under physiological conditions P2Y₁ activation is protective, under pathological inflammatory conditions, P2Y₁ activation drives seizure pathology and epilepsy development with P2Y₁ antagonism reducing seizure severity and brain damage, delaying the development of epilepsy and suppressing epileptic seizures. Our data provides for the first time evidence that drugs targeting P2Y₁ may be useful in the treatment of drug refractory status epilepticus and epilepsy.

Poster number: PM144 (SP)**Theme:** Novel treatments & translational neuroscience**Chronic oral g115 reduces immobility in the forced swim test without altering BDNF signaling or hippocampal neurogenesis****Authors:** Prof R Andrew Tasker^{1,2}, Mr Dylan Terstege¹, Ms Debra MacDonald¹¹Department of Biomedical Sciences, UPEI, Charlottetown, Canada, ²Translational Neuropsychiatry Unit, Aarhus University, Risskov, Denmark

Introduction: Current drug therapies for depression are unsuitable for many patients due to lack of efficacy or side effects so many patients are turning to natural products. Panax ginseng has long been used for depression in traditional Asian medicine. Purified ginsenosides are reported to reduce depressive behaviours in animal models; an effect that often correlates with increases in depression-induced reductions in BDNF signaling and neurogenesis. These data imply a causal relationship that has not yet been established. Our objective was to determine if chronic consumption of the ginsenoside mixture G115 would alter depressive-like behaviours, BDNF signaling and neurogenesis in normal (non-depressed) rats.

Methods: Male SD rats (225-250 g; N=30) were acclimated over 3 days to voluntarily consume a 10% sucrose solution within a predetermined time. Rats that met criterion were then randomly assigned to either control (n=13) or G115 (n=14) groups and fed either G115 in sucrose, or vehicle, twice daily for 14 days plus 4 testing days. Rats were tested in an open field (OF), elevated plus maze (EPM), Forced swim pre-test and Forced Swim Test (FST) on successive days. After euthanasia brain tissue was dissected and either flash frozen for Western blot analysis of BDNF and TrkB expression or formalin fixed for dual immunohistochemistry of doublecortin (DCX) and NeuN.

Approach for statistical analysis: All experiments were conducted and analysed experimenter-blind. Behaviours were scored from video recordings. Data were imported into SPSS (v.23) and compared using Student's t-test.

Results and conclusions: Rats chronically consuming G115 had significantly reduced immobility time ($p=0.002$) and increased latency to immobility ($p=0.016$) with a corresponding increase in both struggling ($p=0.031$) and swimming ($p=0.034$) time in the FST. No significant differences between groups were found in measures of locomotor (OF) or anxiety (OF; EPM) behaviour eliminating these as confounding factors. BDNF and TrkB expression in prefrontal cortex and hippocampus was not different between groups, nor were DCX positive cell counts in hippocampal regions. We conclude that oral G115 reduces depressive-like behaviours in rats but is not causally related to changes in either BDNF signaling or hippocampal neurogenesis in normal rats.

Poster number: PM145 (SP)

Theme: Novel treatments & translational neuroscience

Argonaute-2 sequencing of rodent temporal lobe epilepsy models identifies multiple microRNA targets for seizure suppression

Authors: Gareth Morris^{1,2,3}, Morten Veno⁴, Cristina Reschke^{1,3}, Sebastian Bauer^{5,6}, Yan Yan⁴, Tobias Engel¹, Eva Jimenez-Mateos¹, Vamshi Vangoor⁷, Beatrice Salvetti⁸, Federico Del Gallo⁸, Amaya Sanz Rodriguez^{1,3}, Juha Muilu⁹, Paolo F Fabene⁸, Jereon Pasterkamp⁷, Jochen HM Prehn¹, Stephanie Schorge², Felix Rosenow^{5,6}, Jorgen Kjems⁴, David C Henshall^{1,3}

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Introduction: MicroRNAs are short noncoding RNAs that shape the gene expression landscape, including during the pathogenesis of temporal lobe epilepsy. *In vivo* deployment of oligonucleotide inhibitors, termed antagomirs, has been successful in demonstrating functional roles for several microRNAs in epilepsy models. It is unknown, however, what portion of brain-expressed microRNAs are functionally engaged or whether additional microRNAs may be targets for seizure control.

Methods: Here we sequenced Argonaute 2-loaded microRNAs in the hippocampus from three different animal models, in two species and across multiple time-points, to identify unique and shared functional microRNA changes in experimental epilepsy. We used this to rationally inform target microRNAs for seizure suppression and tested this using the antisense oligonucleotides (antagomirs) in the mouse intra-amygdala kainate model of epilepsy. Finally, we used electrophysiological techniques to probe the mechanistic effects of these antagomirs in naïve rodent brain.

Approach for statistical analysis: For *in vivo* antagomir screening and *ex vivo* biophysics, data were tested for normality using a Kolmogorov-Smirnov test. Data were analysed with the appropriate statistical test (detailed in individual figure legends). α was set at 0.05, unless corrected for multiple comparisons as detailed in the figure legends.

Results and conclusions: We identified over 400 Argonaute 2-loaded microRNAs in each model and found levels of almost half changed in epilepsy. We selected microRNAs that were commonly upregulated in all three animal models and performed a systematic antagomir screen which identified anti-seizure phenotypes upon inhibition of miR-10a-5p, miR-21-5p and miR-142-5p. We assessed effects of these antagomirs on network, synaptic and biophysical properties of rodent hippocampi and identified mechanisms using a target capture sequencing assay. Together, these studies provide a comprehensive cataloguing of the functional microRNA in the hippocampus and a pipeline of new targets for seizure control in experimental epilepsy.

Poster number: PM146 (SP)

Theme: Novel treatments & translational neuroscience

Blood Adenosine Concentration as a Novel Diagnostic for Seizures and Epilepsy

Authors: Doctor Edward Beamer¹, Doctor Hany ElNaggar^{1,2}, Professor Norman Delanty², Professor David Henshall¹, Mister Austin Lacey^{1,2}, Professor Nicholas Dale³, Doctor Mariana Alves¹, Doctor Tobias Engel¹

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A simple method for diagnosing seizures and epilepsy using the detection of biomarkers from blood offers advantages over currently available methods. Principally: lower cost, less necessary expertise, potential for detecting seizures retrospectively, and fast results. Criteria for a clinically useful biomarker include sensitivity, specificity, minimal invasiveness, ease of analysis and robustness to artefacts. We used an enzyme-based detection system, which can reliably measure concentrations of adenosine in the blood. This method involves the immediate analysis of a small amount of fresh blood (finger prick), with results obtained within 5 minutes. In an intra-amygdala kainic acid mouse model of status epilepticus, blood adenosine concentrations increased, 40 minutes following kainic acid injection and remained elevated for 4 hours following seizure termination with lorazepam. Concentrations of adenosine in the blood correlated with the severity of seizures, as indicated by the total power of EEG ($R^2 = 0.4892$, $p < 0.0001$) and with markers of neuronal death in the CA3 region of the hippocampus three days following injection ($R^2 = 0.2805$, $p = 0.0006$). Data obtained from the epilepsy monitoring unit, Beaumont Hospital, indicate that baseline (>24h seizure free) blood adenosine concentrations are elevated in epilepsy patients compared with controls ($t_{34} = 2.907$, $p = 0.0064$) and that blood adenosine increases sharply immediately following generalized tonic-clonic seizures. Further, patients with non-epileptic attack disorder showed blood adenosine concentrations no different from controls. These results indicate that blood adenosine concentrations are elevated following seizures in both mice and patients, and that in epilepsy patients; blood adenosine is both chronically elevated and acutely elevated following seizures.

Poster number: PM147 (SP)

Theme: Novel treatments & translational neuroscience

Finding Alzheimer's Early: Blood-based MicroRNA biomarkers tracking the Prodromal stages of Alzheimer's Disease

Authors: Mr Aidan Kenny¹, Dr Eva Jimenez-Mateos¹, Dr Miguel Calero², Dr Alberto Rabona², Dr Miguel Fernández-Blázquez², Dr Miguel Medina^{2,3}, Dr Tobias Engel¹

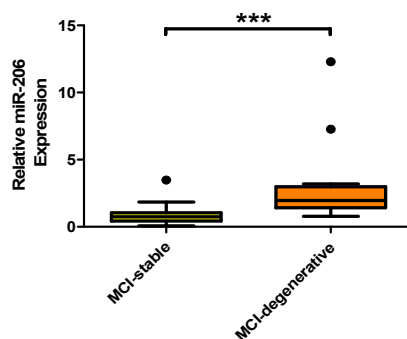
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Introduction: Non-invasive and practical biomarkers for earlier stages of Alzheimer's disease (AD) are a critical requirement for the development of effective treatments. Multiple neurodegenerative processes and irreversible damage present at the clinically diagnosable stages of AD make any attempts at targeting any single mechanism driving the development of the disease futile at advanced stages where AD pathology has wreaked havoc for up to 20 years. Diagnosing prodromal AD in patients with mild cognitive impairment (MCI) is a key target. For this purpose microRNA (miRNA) molecules and their distinct changes in expression present in plasma of MCI and clinical AD subjects was investigated.

Methods: subjects were recruited within the Vallecas Project (CIEN foundation) and annually evaluated and blood sampled for 6 years. OpenArray (OA) Analysis was performed on blood plasma from 60 subjects, control, MCI and AD. Potential miRNA biomarkers identified within the OpenArray were validated by individual RT-qPCR in 90 subjects. Validated miRNA were stratified based on MCI subject neuropsychological outcomes (Δ MMSE, FCSRT). A cohort of 4 groups of 6 subjects were analysed for tracking at 3 timepoints tracking progression of biomarkers with disease pathogenesis.

Approach for statistical analysis: OA outcomes were normalised to Gross mean normalisation (GMN) strategy and analysed by $\Delta\Delta$ CT relative to Control with cut off of significant change set at >2 and <0.5 relative expression. RT-qPCR validation was normalised to stably expressed endogenous miRNA (identified in OA) and quantified by $\Delta\Delta$ CT analysis relative to Control, measures of statistical analysis were tested by Kurskal-Wallis with Dunn's Post-hoc test, and Mann-Whitney.

Results and conclusions: OA identified 61/12 miRNAs up/down in AD and 8/36 in MCI. From the OA analysis miR-206, Let-7b and miR-135a were selected for validation by RT-qPCR. MiR-206 and Let-7b showed significant changes from control. MCI stratification of miR-206 by neuropsychological outcomes showed significant changes between stable MCI and cognitively deteriorating MCI (graph). Longitudinal analysis of miR-206 showed unchanged expression within stable mci over the 3 timepoints while control converting to dementia showed significant increase. MiR-206 and Let-7b show promise as biomarker to utilised in enriching MCI cohorts for prodromal AD



Poster number: PM148 (PP)

Theme: Novel treatments & translational neuroscience

Can the endocannabinoid receptor system reduce neuronal inflammation in arthritis?

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Introduction: Rheumatoid arthritis (RA) is an autoinflammatory condition characterised by painful and chronically inflamed joints. Dysregulation of the immune system leads to elevated concentrations of proinflammatory cytokines

which contribute to disease pathogenesis and neuropathic pain. The endocannabinoid receptor system (ES) is primarily found in the immune and nervous systems and is known to have potential as a therapeutic target. Cannabidiol (CBD) is a natural compound, with few adverse effects that target the ES. CBD is a non-psychoactive phytocannabinoid that possesses analgesic, neuroprotective and anti-inflammatory effects. It could serve as an effective treatment to suppress inflammation and pain simultaneously in RA. The mechanisms that underpin the relationship between inflammation, pain signalling and the ES are poorly understood. Here, we propose a study of the analgesic potential of CBD using *in vitro* and *in silico* methods.

Methods: A pathway map and predictive model of RA pathophysiology. was generated from primary literature using the CellDesigner and COPASI software tools. Human iPSC derived sensory neuron and neuroblastoma cell line will be cultured and lipopolysaccharide (LPS) used to induce an inflammatory challenge. CBD will be administered at a range of doses in order to study its anti-inflammatory potential. Initially, LPS doses will be optimised in neuronal culture experiments. Next, a series of CBD dose-response experiments will be conducted to quantify any changes in intracellular or extracellular cytokine expression by Real-Time PCR and ELISA, respectively. This data will be used to calibrate ours *in silico* pathway maps and models. Ultimately this pathway model will also be used to provide preclinical evidence of CBD's effects beyond neuronal cells.

Approach for statistical analysis: Statistical analysis package SPSS (version 24) will be used to analyse the different treatment doses in challenged and control cells. One-way ANOVA will be used initially, followed by paired student T-test (two tail distribution) to establish if there is a statistically significant difference between treatment and control replicates.

Poster number: PM149 (SP)

Theme: Novel treatments & translational neuroscience

FKBP5 inhibition increases hippocampal neurogenesis and neuronal outgrowth

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Introduction: Stress is a risk factor for several psychiatric disorders including depression but the neurobiology underlying stress susceptibility is not yet understood. However, polymorphisms in the gene encoding FK506-binding protein 51 (FKBP5) have been linked to susceptibility to stress-related psychiatric disorders but whether this protein can be targeted for their treatment remains unknown. Chronic stress reduces hippocampal postnatal neurogenesis (the production of new neurons), an effect prevented by chronic antidepressant treatment. Antidepressants can also prevent stress-induced neuronal atrophy (reductions in the complexity and length of neurites) in the hippocampus. The aim of this study was to investigate whether pharmacological inhibition of FKBP5 positively influence neurite outgrowth and hippocampal neurogenesis and thus may have antidepressant-like effects in the brain.

Methods: Primary hippocampal neuronal cultures (E18; C57/BL6) were treated with increasing concentrations of a highly selective FKBP5 inhibitor for 48 hrs. Hippocampal neural progenitor cells (NPCs) (P28 male Sprague Dawley) were isolated and allowed to proliferate as neurospheres for 4 days. NPCs were then dissociated and cultured under differentiation conditions for 7 days in the presence of the inhibitor. Cells were fixed and stained with anti β III tubulin, a neuronal marker and the percentage of neurons, neurite branching and neurite length were analysed.

Approach for statistical analysis: One-way ANOVA or Kruskal-wallis tests were carried out depending on normality and homoscedasticity criteria. The significance threshold was set at $p = 0.05$. Each analysis was followed by a post hoc test, Tukey or Dunns.

Results and conclusions: In primary hippocampal neuronal cultures, the FKBP5 inhibitor (250, 500, 1000 nM) increased neurite outgrowth and branch points. Interestingly, the concentration of FKBP5 inhibitor that produced maximal effects (500 nM) had a greater effect than brain-derived growth factor (BDNF; 40 ng/mL). In postnatal hippocampal neurospheres, the highest tested dose of the FKBP5 inhibitor (100 nM) increased neurogenesis (the number of β III tubulin positive cells) and also increased branching complexity and neurite length of these differentiated neurons. In conclusion, FKBP5 inhibition increases neurogenesis and neuronal complexity thus suggesting that further research on FKBP5 as a novel pharmacological target for treatment of depression.

Poster number: PM150 (PP)

Theme: Novel treatments & translational neuroscience

Trial designs for delivery of novel therapies for neurodegeneration: the trident trial

Authors: Dr Cheney Drew^{1,2}, Dr Feras Sharouf², Dr Lucy Brookes-Howell¹, Dr Philip Pallmann¹, Mrs Astrid Burrell, Dr Bernadette Sewell³, Dr Dave Gillespie¹, Prof Kerry Hood¹, Prof Monica Busse^{1,2}, Prof Liam Gray², Prof Anne Rosser²
¹Centre for Trials Research, Cardiff University, Cardiff, United Kingdom, ²Brain Repair And Intracranial Neurotherapeutics (BRAIN) Unit, Cardiff University, Cardiff, United Kingdom, ³Swansea University, Swansea, United Kingdom

Introduction: Huntington's Disease is a progressive neurodegenerative disorder characterised by a triad of motor, cognitive and psychiatric symptoms. It is incurable and currently there are no available disease-modifying therapies that slow or halt disease progression. There is relatively focal and specific loss of striatal medium spiny neurons (MSNs), which makes HD suitable for cell replacement therapy (CRT), a process involving the transplant of donor cells to replace those lost due to disease.

Methods: TRIDENT is a Phase I, Trial within Cohort (TWiC) study designed to assess safety and feasibility of transplanting foetal cells into the striatum of people with HD. 18 to 30 participants will be enrolled in the study and a sub-cohort will be screened for suitability for CRT. Up to 5 eligible participants will be randomly selected to undergo CRT where 12-22 million foetal cells will be transplanted uni-laterally. The Trial Steering Committee will independently review safety outcomes at the 4-week primary end-point before conducting each subsequent surgery. All participants will undergo a detailed battery of clinical and functional assessment at baseline, 6 and 12 months. Surgery will be performed 1 month after baseline and CRT participants will undergo regular clinical follow-up for at least 12 months.

Evaluation of trial processes will also be undertaken. CRT participants and their carers will be interviewed approximately one month before and after surgery. Non-transplanted participants will also be interviewed. Additionally, staff delivering the intervention and those involved in the clinical care of participants will be interviewed and surgical procedures will be video recorded.

Analysis Approach:

Quantitative Data

TRIDENT is a feasibility study and as such no formal statistical hypothesis testing will be carried out. Exploratory evaluation of outcomes will be carried out to explore plausible trial designs for subsequent randomised controlled trials aimed at evaluating efficacy of CRT.

Qualitative data

Participant interviews will be analysed using a framework approach to incorporate thematic and case analysis. Video data of the surgery will be analysed to identify fidelity markers which will involve documenting and describing movements, instruments and actions to provide a stepwise account of the procedure.

Trial Status: Open to recruitment ISRCTN:52651778

Poster number: PM151 (SP)

Theme: Novel treatments & translational neuroscience

Towards proteomic differentiation of mental health disorders

Authors: Dr Coral, R Lapsley¹, Dr Steven Watterson¹, Dr John Brady², Professor Anthony, J Bjourson¹, Dr Elaine, K Murray¹

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Introduction: Alterations in the inflammatory response have been studied extensively in connection with psychiatric disorders including depression and schizophrenia (1). A small number of pro-inflammatory cytokines have been consistently reported, however the immune response is complex, involving both innate (inflammatory) and adaptive processes. The aim of this study was to conduct an initial proteomic analyses to examine a broad spectrum of cardiac and immune-related proteins from individuals with depression, schizophrenia and healthy controls to determine differences in protein levels between cohorts.

Methods: Proteins in peripheral plasma samples were characterised with the O-Link proximity extension assay using the cardiovascular II and III, immune response and the inflammation panels to determine difference in protein concentrations between cohorts; depression (n=15), schizophrenic patients (n=21) and healthy controls (n=16).

Analysis approach: A one-way between groups analysis of variance ANOVA was conducted to explore the relationship between the different mental health disorders and protein levels, and Gene Ontology information for the differentially expressed proteins were explored. Additional analysis of the protein values determined a single score, for each participant, based on a combination of individual cytokine measurements to classify each participant into the correct cohort.

Results and Conclusions: The comparison of depression and healthy cases revealed significant differential abundance in the relative expression of 22 proteins between the depression and healthy groups, 7 downregulated and 15 upregulated across the four panels. Those upregulated proteins were enriched for inflammatory processes, and have been previously linked to chronic inflammatory conditions. Between schizophrenia and healthy controls, there were 143 proteins differently expressed, and similar to depression the upregulated proteins showed significant enrichment for inflammation. Finally, 99 proteins were found to be differentially expressed between depression and schizophrenia cases. A combined score of a selection of the top ranked differentially expressed proteins showed robust sensitivity and specificity to distinguish between the healthy and depression cases. Despite modest numbers in this preliminary investigation exploratory statistical analysis uncovered a number of significantly altered proteins that will be validated in larger sample numbers. These results indicate that a panel of inflammatory proteins could have clinical utility in screening for depression, and in differentiating between psychiatric disorders.

References:

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Poster number: PM152 (SP)**Theme:** Novel treatments & translational neuroscience**Molecular mechanisms of miRNA biofluid transport in epilepsy****Authors:** Ms Elizabeth Brindley¹, Dr Gary P Brennan¹, Dr Mairead Diviney¹, Dr Thomas Hill¹, Dr Cristina Ruedell Reschke¹, Dr Catherine Mooney², Dr Ngoc Nguyen¹, Aasia Batool¹, Elena Langa¹, Karen Conboy¹, Prof David C Henshall¹¹Royal College Of Surgeons, Co Dublin, Ireland, ²University College Dublin, Co Dublin, Ireland

Introduction: Diagnosing epilepsy is difficult and expensive; therefore a molecular biomarker to aid with diagnosis would be major advance in the field. MiRNAs are small non-coding RNAs, ubiquitously expressed in the brain. MiRNAs are detected in plasma bound to the Ago2 protein, which increases their stability in circulation. We profiled Ago2-bound miRNA from plasma of epileptic patients and a mouse model of epileptogenesis, with the aim to increase the sensitivity of biomarker discovery and investigate the mechanism of miRNA transfer from blood to brain in epilepsy.

Methods: Using small RNAseq the Ago2-bound-RNA pool isolated from plasma of mice during epileptogenesis were characterised. Furthermore, bound-pools of RNA isolated from plasma of control, epilepsy and PNES patients were investigated. Finally, by generating two transgenic rodent lines, expressing Ago2 in a brain-cell-type-specific manner, an empirical link between miRNA and cellular origin was established.

Statistics: Sequencing reads were mapped against miRbase v21. Counts and quality control checks were performed using the Chimera software. MiRNAs were determined to be differentially expressed if log₂ fold changes were ± 1.2 with a p-value of <0.05. When comparing epilepsy controls samples in the validation cohort, t-test were performed. Differential expression was determined using the aforementioned log₂ fold change differences and p-values.

Results and conclusions: The profile of Ago2-miRNA pool differed significantly to the total circulating plasma indicating a selective mechanism of brain-specific miRNAs in epilepsy. In addition, a number of brain-enriched miRNA were detected in the plasma of epilepsy patients when compared to control. The findings of this study suggest that by focusing on the molecular carriage mechanism and cellular origins of miRNA, the sensitivity and specificity of molecular biomarkers of epilepsy is enhanced.

Poster number: PM153 (SP)**Theme:** Novel treatments & translational neuroscience**Partial recovery of proprioception in rats with dorsal root injury following human olfactory bulb cell transplantation****Authors:** Dr Daqing Li¹, Dr Andrew Collins¹, Ms Modinat Liadi¹, Dr Pawel Tabakow², Dr Wojciech Fortuna², Professor Geoffrey Raisman¹, Professor Ying Li¹¹Spinal Repair Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, London, United Kingdom, ²Department of Neurosurgery, Wroclaw Medical University, Wroclaw, Poland

Introduction: Olfactory ensheathing cells (OECs) are specialised glial cells which can be obtained from either olfactory bulb or olfactory mucosa tissue. Transplantation of OECs has been shown to be effective in a number of different experimental CNS injury models.

Methods: We transplanted human olfactory bulb OECs (hOECs) mixed with collagen into a unilateral transection of four dorsal roots (C6-T1) in a rat model. By mixing with collagen, we could maximise the limited numbers of hOEC

from an olfactory bulb biopsy and optimise cavity-filling. Cyclosporine was administered daily to prevent immune rejection. Forelimb proprioception was assessed weekly in a vertical climb task.

Approach for statistical analysis: Results are expressed as means \pm SEM, with statistical comparison between groups made using a one-way analysis of variance (ANOVA), to determine F-ratio significance. Post hoc analysis was with Bonferroni multiple comparisons and IBM SPSS Statistics 22.0 software was used. Details of animal numbers are given below each graph.

Results and conclusions: Transplanted cells were seen at both short and long-term after surgery; many were concentrated within the lesion cavity but others were found with elongated processes in the overlying connective tissue. There were some fibres in the injury area associated with transplanted cells which were immunostained for neurofilament and TUJ1. Half of the rats receiving hOEC transplants showed some functional improvement over six weeks of the study whilst the other half did not and performed similarly to 'injured only' rats. We believe this preliminary study is the first to transplant human olfactory bulb cells into a rat model of dorsal root injury; by refining each component part of the procedure, we can continue to maximise the repair potential of OECs in a clinical setting.

Poster number: PM154 (PP)

Theme: Psychiatry and mental health

An investigation into the safety and anti-depressant efficacy of otc herbal products for anxiety

Authors: Mr. Tomasz Szank¹, Dr Gary Stack¹, Dr Therese Montgomery¹

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Introduction: 6 % of the Irish population are believed to be suffering from depression, whilst 800,000 deaths are reported annually worldwide ^{3,4} Depression will therefore be the largest contributor to disease burden by 2030 and there is an urgent need to develop improved treatments. Current pharmacotherapies are based upon the monoamine theory of depression, originally formulated over 50 years ago. However, conventional antidepressants can induce unpleasant side-effects, resulting in low patient compliance and a high failure response rate³. Herbal extracts of the medicinal plant *Rhodiola rosea* have been used traditionally to treat anxiety, stress and depression with few reported side effects, yet little is known as to the mechanism of action ^{1,2,3}. The primary goal of this research is to determine the safety & potential anti-depressant efficacy of the *Rhodiola rosea* bioactive compounds, salidroside and rosavins on neuronal cell lines.

Methods: Cytotoxic and/or neuroprotective effects will be examined *in-vitro* using the MTT and Trypan Blue assays in SHSY5Y cells. Monoamine transporter activity will be assessed using [³H] transporter substrates.

Approach for statistical analysis: Data will represent the mean \pm SEM of three independent observations performed in triplicate. Statistical analysis will be performed using unpaired T-tests and/or One-way analysis of variance (ANOVA) with an appropriate post-hoc test.

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Poster number: PM155 (SP)**Theme:** Psychiatry and mental health**Basic auditory processing in adolescents and adults with 22q11.2 Deletion Syndrome and its association with cognitive profile and psychotic symptomatology****Authors:** Dr Ana Francisco¹, Dr John Foxe^{1,2,3}, Douwe Horsthuis¹, Dr Sophie Molholm^{1,2,3}¹*Department of Pediatrics, Albert Einstein College of Medicine, Bronx, USA*, ²*Department of Neuroscience, Rose F. Kennedy Center, Albert Einstein College of Medicine, Bronx, USA*, ³*Department of Neuroscience, The Ernest J. Del Monde Institute for Neuroscience, School of Medicine and Dentistry, University of Rochester, Rochester, USA*

Background: 22q11.2DS is characterized by increased vulnerability for developmental delays, cognitive deficits, and neuropsychiatric symptoms, with up to 30% of these individuals developing schizophrenia. The deletion's impact on brain activity is not yet well understood. In schizophrenia, auditory neural circuits are impaired, with clear differences in the auditory evoked potential (AEP) and in the mismatch negativity (MMN; index of auditory sensory memory). We asked whether the AEP/MMN in 22q11.2DS would be similarly affected and investigated how these responses related to IQ, working memory, and psychotic symptoms.

Methods: Eighteen individuals with 22q11.2DS (14-35 years old) and 18 neurotypical age-matched controls participated. The Wechsler intelligence scales provided IQ and working memory scores; the SCID was used to assess psychiatric symptomatology. A duration oddball paradigm was employed during which standard tones of 100 ms (1000 Hz, ~70 dB) were interspersed with deviant tones of 180ms, while high density EEG was recorded.

Results: The 22q11.2DS group was characterized by significantly lower IQ and working memory scores than controls, and higher psychotic symptoms. The duration-MMN was intact in both groups, although the 22q11.2DS group showed significantly larger AEPs and MMNs. Analyses taking individual differences into consideration revealed increased variability within the 22q11.2DS group, and a correlation between working memory and MMN (mostly driven by the 22q11.2DS group), such that the better the working memory scores, the greater the MMN. Within the 22q11.2DS group, the number of psychotic symptoms correlated with MMN amplitude (the more symptoms, the smaller the MMN) and working memory (more symptoms, lower working memory scores).

Conclusions: These results are consistent with a highly variable phenotype in 22q11.2DS and stress the need for subgrouping within 22q11.2DS. Further, differing from the typically decreased duration-MMN in idiopathic schizophrenia, in 22q11.2DS the duration-MMN was instead larger than in controls; and better cognitive functioning was associated with larger MMNs and less severe psychotic symptoms. One possibility is that better working memory is a protective factor for psychosis in 22q11.2DS. These data point to potential neural and cognitive biomarkers predictive of the risk for developing schizophrenia in 22q11.2DS.

Poster number: PM156 (SP)**Theme:** Psychiatry and mental health**Shank3 KO mice do not respond to the synaptic changes observed after traumatic brain injury****Authors:** Ms Carolina Urrutia Ruiz¹, Ms Silvia Cursano¹, Dr. Tobias M. Boeckers¹¹*Institute for Anatomy and Cell Biology, Ulm University, Albert Einstein Allee 11, 89081 Ulm, Germany, Ulm, Germany*

Introduction: Traumatic brain injury (TBI) might lead to psychiatric disturbances, most presumably associated with neuronal loss and/or an altered reconstitution of the synaptic connections that could lead to an imbalance between synaptic inhibition-excitation. At excitatory synapses, Shank proteins are large scaffolding proteins present at postsynaptic density (PSD), being considered to be “master organizer” of the PSD. Significant neurological and psychiatric conditions, such as ASD, have been attributed to mutations or loss of a copy of the Shank3 gene. This study is aimed to analyse changes of synaptic contacts in response to TBI and in the context of an additional Shank3 loss.

Methods: TBI was performed in WT and Shank3-KO mice. After 5, 10 and 18 days the dendritic spines excitatory synapses and neuronal loss were analysed. The expression of the stress-related hormone Corticotropin-Releasing-Hormone (CRH) peptide was also assessed. Finally, behavioural analysis was performed to analyse motor, cognitive and social interactions.

Approach for statistical analysis: Two or Three-ways ANOVA was performed for comparing the WT and Shank3-KO mice regarding different time points and the ipsilateral and contralateral side of the injury. A $P < 0.05$ was considered statistically significant.

Results and conclusions: TBI-WT mice presented less excitatory synapse and dendritic spines within the hippocampus that did not recover within the post injury time points assessed. Loss of neurons was not detected. However, Shank3-KO animals, despite presenting a lower basal level of dendritic spines and excitatory synapses, presented no major loss of synapses or dendritic spines. Hippocampal CRH expression was highly upregulated in TBI-WT but not in TBI-Shank3-KO animals, indicating an altered stress response in Shank3-KO mice. In the open field arena, TBI-WT mice tended to have no anxious or disoriented behaviour, TBI-Shank3-KO did not present any changes. Both strains, showed, however, an enhanced learning of fear in a fear conditioning paradigm after TBI. No changes were presented in social behaviour. Therefore, re-arrangements of the synaptic morphology and behavioural changes after TBI are altered in mice that are Shank3-deficient, indicating that SHANK3-KO mice differently respond to a traumatic brain injury paradigm.

Poster number: PM157 (PP)**Theme:** Psychiatry and mental health**Affective Cognition in Depression & Schizophrenia: Contributions of Familial and Environmental Risk****Authors:** Ms Franziska Goer¹, Dr. Richard Drake¹, Prof Joanna Neill¹, Prof Rebecca Elliott¹¹*University Of Manchester, Manchester, United Kingdom*

Despite the immense cost to individuals and society, current treatments for mental illnesses such as schizophrenia and depression primarily target symptom reduction over improvements in social functioning. While antidepressants and antipsychotics often generate symptom reduction, they have less effect on affective (emotion-laden) cognition or quality of life (Green et al., 2012). There is a clear need for an improved understanding of mechanisms contributing to poor functional outcomes in these disorders so that these may be targeted in novel treatments.

While depression and schizophrenia are associated with extensive cold (non-affective) cognitive deficits, studies suggest deficits in hot (affective) cognition may be a better predictor of functional outcomes (Roiser, Elliott, & Sahakian, 2012). A central question is whether affective cognition deficits observed in schizophrenia and depression are driven by acute symptoms or rather contribute to these symptoms as a causal factor.

Initial evidence supports the latter hypothesis, but more research is needed to establish whether affective cognition abnormalities are critical markers of high-risk states (e.g. history of early life stress [ELS] or first-degree relatives [FDRs] of individuals with serious mental illness). Moreover, the possible link to functional outcomes must be assessed in order to develop novel treatments and personalised interventions that aim to improve quality of life in patients as well as reducing symptoms.

The current study will address these aims by systematically assessing affective cognition, using the novel standardized EMOTICOM test battery, in individuals with schizophrenia and depression. Additionally, participants with ELS and FDRs of schizophrenia patients will be recruited to assess the relative contribution of familial and environmental risk to affective cognition abnormalities. An extensive assessment of cold cognition (using the well-established CANTAB test battery) will allow for a nuanced control of non-affective cognitive deficits. Social functioning and quality of life measures will be collected during the initial assessment and 12-month follow-up to investigate possible relationships between affective cognition and functional outcomes.

Neuropsychological task data will be analysed using multivariate techniques in SPSS. Multiple regression approaches will be used to assess the contributions of symptoms, familial, and environmental risk to affective cognition abnormalities, controlling for demographic factors and cold cognition.

Poster number: PM158 (SP)

Theme: Psychiatry and mental health

Effects of maternal prebiotic intake on anxiety-like behaviour and the blood metabolome in offspring

Authors: Ms Jennifer Hebert¹, Mr. Daniel Radford-Smith², Dr. Fay Probert³, Professor Daniel C Anthony³, Professor Philip WJ Burnet¹

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Introduction: The perinatal period is critical for brain development. In adult mice, the prebiotic Bimuno[®] galactooligosaccharide (BGOS) reduced anxiety and altered levels of NMDA receptor subunits.^{1,2} Furthermore, maternal BGOS supplementation reduced anxious/depressive-like behaviours and central NMDA receptor subunit expression in offspring (unpublished data). Here, we investigated whether these behavioural changes were due to prenatal or postnatal factors. We also analysed the blood metabolome to identify potential mechanisms.

Methods: Pregnant CD1 mouse dams were randomly assigned to receive normal drinking water or water supplemented with BGOS. Half of the litters were cross-fostered at birth to a mother of the opposite treatment group. At postnatal days 22-23, pups were tested in the open field test (OFT) and light-dark box (LDB). Blood plasma was then isolated for ¹H NMR-based metabolomics.

Approach for statistical analysis:

Behaviour: A two-way ANOVA was used, followed by Bonferroni post-hoc tests.

Plasma ¹H NMR: Integrals of 0.02 ppm-width bins from the plasma ¹H NMR spectra were imported into R software. Orthogonal partial least squares discrimination analysis (OPLS-DA) was performed with 10-fold external cross-validation to generate predictive models and identify the metabolites driving group differences.

Results and conclusions: Both prenatal and postnatal BGOS increased exploratory behaviour in the OFT, while postnatal BGOS alone reduced anxiety and exploration in the LDB. These data suggest that maternal prebiotic feeding may not have influenced offspring anxiety *in utero*, given that pups not exposed to BGOS during gestation

also displayed improved behaviours when fostered/suckled by BGOS-fed dams. The OPLS-DA model of the ¹H NMR data was able to discriminate between plasma from BGOS and control pups. The 10-fold cross-validation procedure confirmed that the accuracy of this separation was significantly better than random chance. Further analysis of metabolites may reveal mechanisms driving the behavioural changes.

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Savignac, H. M. *et al.* Prebiotic administration normalizes lipopolysaccharide (LPS)-induced anxiety and cortical 5-HT_{2A} receptor and IL1- β levels in male mice. *Brain. Behav. Immun.* 52, 120–131 (2016).

Poster number: PM159 (SP)

Theme: Psychiatry and mental health

Cannabidiol modulation of recall related functional connectivity in psychosis

Authors: Ms Aisling O'Neill^{1,2}, Dr Robin Wilson¹, Ms Grace Blest-Hopley¹, Mr Luciano Annibale¹, Dr Vincent Giampietro¹, Prof Andrea Mechelli¹, Dr Sagnik Bhattacharyya¹

¹King's College London, London, United Kingdom, ²Royal College of Surgeons in Ireland, Dublin, Ireland

Introduction: Recent preclinical and clinical evidence suggests that cannabidiol (CBD), an extract of the cannabis plant, may have some antipsychotic efficacy in established psychosis. Furthermore, in healthy individuals, CBD has also been shown to counter the psychosis like effects of delta 9-tetrahydrocannabinol (Δ 9-THC), the main psychoactive extract of cannabis, on the neural substrates implicated in both psychosis and memory function. However, the acute effect of CBD on these same neurocognitive mechanisms has not yet been investigated in individuals with psychosis.

Methods and Analysis: In the current study, 15 psychosis patients were studied on separate days at least one week apart, to investigate the effects of a single dose of orally administered CBD (600mg) compared to a matched placebo, using a double-blind, randomized, placebo-controlled, repeated-measures, within-subject cross-over design. Participants were scanned using a block design fMRI paradigm, while performing a verbal paired associate learning task. 13 psychosis patients completed both study days. 19 healthy controls (HC) were also scanned using the same fMRI paradigm under identical conditions, but without any drug administration. Data were analysed using a psychophysiological interaction approach and non-parametric ANOVAs, to explore the context dependent functional connectivity (FC) of three key seed regions (left hippocampus, left middle frontal gyrus, and right parahippocampal gyrus). Analyses were performed using the XBAM v4.1 software, and the SPSS software.

Results: Effects of CBD on mediotemporal and prefrontal recall related FC were the primary outcomes of interest. No significant performance differences were observed between patients and the HC group during recall. However, patients under the placebo condition displayed significantly increased mediotemporal–prefrontal, and prefrontal–striatal FC, compared to the HC group. Acute administration of CBD partially normalised this hyperconnectivity in the psychosis patients, such that the FC of these regions in the patient group under CBD condition was less than in the same group under placebo condition, and greater than that of the HC group.

Conclusions: These findings further implicate disruptions of the fronto-temporal and fronto-striatal neural circuits in the pathophysiology of psychosis, and suggest that normalization of the FC of these key regions may underlie the antipsychotic effect of CBD in psychosis.

Poster number: PM160 (PP)**Theme:** Psychiatry and mental health**Examining multisensory processing of social and non-social information in relation to the degree of trait anxiety in a non-clinical sample****Authors:** Miss Naomi Heffer¹, Mr Crescent Jicol¹, Dr Anke Karl², Dr Chris Ashwin¹, Dr Karin Petrini¹¹*Department of Psychology, University Of Bath, Bath, United Kingdom,* ²*Mood Disorders Centre, University of Exeter, Exeter, United Kingdom*

Introduction: The ability to regulate affective states and interact with others may be influenced by an individual's capacity to efficiently process multisensory socio-emotional cues. Despite evidence of altered multisensory processes in individuals with socio-emotional deficits (e.g. autism), there are few studies examining multisensory processes in relation to the level of anxiety traits. Research using nonclinical individuals with low vs. high trait anxiety reported that multisensory processing of faces and voices is modulated by the degree of anxiety, such that there is greater weighting of the modality where negative information is being presented, even when information from this modality is not relevant to the task. The present study aims to extend this research using a similar study design with faces-voices, but also including bodily stimuli and non-social stimuli, to determine whether anxiety-related differences in multisensory processes are specific to integration of particular socio-emotional signals or whether there is a more domain-general deficit.

Methods: Non-clinical adults with varying levels of trait anxiety will categorise visual, auditory and audio-visual stimuli as happy or sad. Faces-voices will be used to replicate the finding that individuals with higher anxiety are less able to recognise the emotion conveyed by individual cues when presented with incongruent multisensory information. Body motion-voice stimuli will be used to determine whether this effect extends to other types of social stimuli, and flash-bleep stimuli to determine whether this extends to non-social stimuli. We aim to show whether there are differences between lower and higher trait anxiety in how cue modality and congruency of cues in audio-visual displays affect sensory modulation.

Approach for statistical analysis: Participants will be split into two groups based on whether their trait anxiety score falls above or below the median for the whole sample. The DVs will be accuracies and reaction times, and ANOVA's will be used to analyse the data with anxiety (lower/higher) as a between-participants factor and emotion (angry/happy), modality (visual, audio or audio-visual), congruency for bimodal stimuli (congruent/incongruent) and stimulus (face-voice, body motion-voice, non-social) as within-participant factors. We expect to see between-group differences for all stimuli, but most acutely for the social stimuli, due to the social deficits present in anxiety.

Poster number: PM161 (SP)**Theme:** Psychiatry and mental health**Sex hormone levels and responses to intranasal oxytocin in autistic and neurotypical women****Authors:** Ms Tanya L Procyshyn¹, MV Lombardo^{1,2}, M-C Lai^{1,3,4}, Bonnie Auyeung^{1,5}, SK Crockford^{1,6}, JB Deakin^{7,8}, S Soubramanian^{7,9}, A Sule⁷, Simon Baron-Cohen¹, Richard AI Bethlehem¹¹*Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom,*²*Department of Psychology, Centre for Applied Neuroscience, University of Cyprus, Nicosia, Cyprus,* ³*Department of Psychiatry, Centre for Addiction and Mental Health and The Hospital for Sick Children, Toronto, Canada,* ⁴*Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan,* ⁵*Department of Psychology, University of Edinburgh, Edinburgh, UK,* ⁶*Theoretical and Applied Linguistics, University of Cambridge, Cambridge, UK,* ⁷*Department of Psychiatry, University of Cambridge, Cambridge, UK,* ⁸*Cambridgeshire and*

Peterborough NHS Foundation Trust, Cambridge, UK, ⁹Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK

Introduction: Oxytocin may be of therapeutic use for enhancing social functioning in autism. Given recent evidence that (i) response to oxytocin treatment may depend on baseline hormone levels and (ii) oxytocin may alter short-term production of other socially-relevant hormones, further investigation of the relationships among endogenous hormone levels and oxytocin is warranted.

Methods: As part of a larger fMRI experiment with a cross-over design [1], saliva samples were collected from 47 women (age 18–50) at three timepoints: (1) baseline, (2) after intranasal administration of placebo or 24 IU oxytocin, and (3) at the end of scanning (approximately 2 hours after administration). Participants comprised 16 women with autism-spectrum conditions (ASC group) and 31 neurotypical women (NT group). Salivary estradiol and testosterone were quantified by ELISA. Baseline hormone levels were calculated as the mean of the two pre-administration values. Post-administration changes in estradiol and testosterone were calculated as percent change relative to individual baseline.

Approach for statistical analysis: Welch's t-test was used to compare hormone levels between groups. Pre- to post-administration changes in hormone levels were analysed by ANOVA (Group (ASC or NT) x Drug Condition (oxytocin or placebo)).

Results and conclusions: Baseline estradiol and testosterone levels did not differ significantly between groups, but percentage change (time 1 vs. time 3) did. For estradiol, the mean change was +12% for the ASC group and -9.9% for the NT group (Tukey HSD, $p = 0.01$) for combined drug conditions. For testosterone, mean change was +7.8% for the ASC group and -14.6% for the NT group for combined drug conditions (Tukey HSD, $p = 0.001$). Under the oxytocin condition, percentage change testosterone showed an even larger between-group difference (+14.4% for the ASC group vs. -15.5% for the NT group, Tukey HSD, $p = 0.013$). These findings suggest a difference in endogenous sex steroid response to oxytocin between neurotypical and autistic women. Next, we plan to analyse resting state fMRI data under oxytocin and placebo conditions in combination with salivary hormone data.

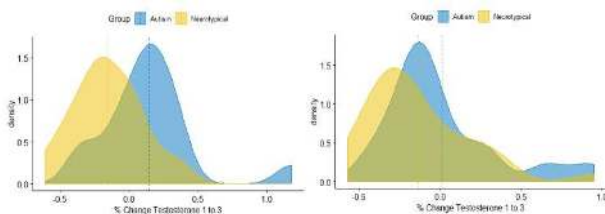


Figure 1. Density plots of percentage change testosterone from time 1 (baseline) to 3 (approx. 2 hours after administration) under Oxytocin (left panel) and Placebo (right panel) conditions between autistic and neurotypical females. The dashed lines indicate the group-specific means.

1. Bethlehem, RAI et al. Intranasal oxytocin enhances intrinsic corticostriatal functional connectivity in women. *Transl. Psychiatry* 7, (2017).

Poster number: PM162 (SP)**Theme:** Psychiatry and mental health**Relational memory in a mouse model of schizophrenia****Authors:** Ms Margarida Trigo^{1,2}, Dr John Gigg¹, Prof Joanna Neill¹, Dr Jill Silverman³¹The University of Manchester, Manchester, United Kingdom, ²The University of Dundee, Dundee, United Kingdom,³UC Davis MIND Institute, Sacramento, United States of America

The subchronic phencyclidine (scPCP) rodent model is currently one of the best animal models for the negative symptoms and cognitive deficits of schizophrenia. One of these deficits is in relational memory, memory for relationships, which can be tested through the transitive inference test. This task has recently been adapted for the Bussey-Saksida touchscreen operant chamber using C57 mice. These touchscreens are analogous to diagnostic tools used in the clinic and are, therefore, highly translational. Due to their recent development, however, performance between sexes has not yet been analyzed. Furthermore, the scPCP mouse model has not been tested for relational memory, impeding development of new therapies for such deficits. We, therefore, first compared touchscreen operant performance in male and female C57 mice. Here we find for the first time that males and females C57 mice show equivalent cognitive performance in visual discrimination, reversal and recall tasks. However, males were not able to perform novel object recognition, used to assess scPCP phenotype. We chose, therefore, female mice to investigate transitive inference capacity in the scPCP model. Female C57 mice after subchronic dosing of vehicle (0.9% saline) or PCP (10mg/Kg daily for 10 days, 4 days washout) showed that both groups were able to learn the premise pairs and infer the easier A>E discrimination. However, neither group could use transitivity by choosing B over D in the transitive inference test. Our results demonstrate that, since both genders performed at comparable levels in the visual discrimination, reversal and recall tasks, relevant results could be obtained by using only one gender, sparing the need for a larger number of animals. As the transitive inference results using the scPCP model were inconclusive, further study is required to determine relational memory deficits in the scPCP and other animal models of schizophrenia in order to identify the model that best captures this cognitive deficit as seen in patients.

Poster number: PM163 (PP)**Theme:** Psychiatry and mental health**Evaluating the antidepressant-like effects of a novel 5-HT₄ agonist on neuroimaging measures of emotional processing in unmedicated depression****Authors:** Dr Jessica Scaife¹, Dr Amy Gillespie¹, Dr Cassandra Gould van Praag¹, Dr Wendy Howard¹, Dr Beata Godlewska¹, Dr Angharad de Cates¹, Prof Philip Cowen¹, Dr Susannah Murphy¹, Prof Catherine Harmer¹¹Oxford University, Department Of Psychiatry, Warneford Hospital OX37JX, Oxford, United Kingdom

Introduction: Current antidepressants – such as selective-serotonin uptake inhibitors (SSRIs) - can take 4-6 weeks to produce clinical benefits and are not effective in all patients. Evidence from animal models of depression suggests that specifically targeting the 5HT₄ receptor may lead to faster clinical improvement.

We will explore the potential antidepressant effect of PF-04995274, a novel, highly-selective 5-HT₄ receptor partial agonist developed by Pfizer, using an experimental medicine model developed by our group. Our previous work has found that escitalopram – an SSRI – produces early changes in fMRI activity during emotional processing tasks, and that these changes at one week predict subsequent clinical response[1]. Therefore, we will assess whether 7 day administration of PF-04995274 produces similar changes; results indicating antidepressant-like effects, expressed as reduction in neural activity to fearful versus happy facial expressions, would support future assessment of 5HT₄ agonists for treatment of depression.

Methods: Un-medicated depressed patients will be randomized (double-blind) to PF-04995274 (15mg), citalopram (20mg; positive control) or placebo, for 7 days. On day 6 of drug/placebo administration, 3T MRI data will be acquired comprising structural, functional (emotional and cognitive task), multi-echo resting state (rs-fMRI) and perfusion (arterial spin labelling, ASL) measures. Physiological and eye-tracking measures will be recorded. The primary functional measure is a well-validated gender discrimination task involving rapid presentation of fearful and happy faces in a block design, evoking passive emotional processing.

Approach for statistical analysis: Before unblinding, we will meet with a statistician to determine which variables will be included as covariates and finalise secondary analysis plans. MRI analysis will follow fmri prep pre-processing and GLM analysis of task effects using FSL, with amygdala and hippocampal regions of interest (Harvard-Oxford Cortical Structural Atlas) and co-variates of interest identified in behavioural analysis. Rs-fMRI will employ tedana denoising and independent component analysis to identify drug-related changes in resting state networks. ASL analysis will be used to identify and control for differences in brain activity related to perfusion.

[1] Godlewska, B. et al (2016). Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational psychiatry*, 6(11), e957.

Poster number: PM164 (PP)

Theme: Psychiatry and mental health

Clustering analysis for the identification of subgroups of major depressive disorder (MDD).

Authors: Ms Caitlin Devine¹, Dr Coral R. Lapsley¹, Dr Margaret McLafferty², Professor Siobhan O'Neill², Professor T. M. McGinnity³, Professor Anthony J. Bjourson¹, Dr Elaine K. Murray¹

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Introduction: Major Depressive Disorder (MDD) is a heterogenous psychiatric disorder characterised by a wide range of complex symptoms such as low mood, anhedonia and feelings of worthlessness. The pathophysiology and aetiology of depression are not fully understood so there exists a great need for discovery of biomarkers that could be used for identification of at-risk individuals and diagnosis.

It is believed that the interaction of a multitude of factors leads to depression including genetic, environmental, biological and behavioural factors (Wright, Stern and Phelan, 2012).

The aim of this study is, using computational approaches, to examine and analyse large data sets which include high quality phenotypic data and biological markers to identify subgroups of individuals with depression who display similar features.

Materials & methods: This study will be carried out using data from the Ulster University Student Wellbeing Study (SWS). Data was collected during registration week 2015 and participation involved completing an online survey and providing a saliva sample collected using the Oragene OG-500 kit. Of the 1646 students who provided a sample, 739 completed the survey.

Clustering analysis will be carried out on the phenotypic data from the SWS to determine the presence of subtypes of depression based on phenotypic traits. Clustering will be carried out on R Studio, with the silhouette function being used to determine the optimal number of clusters. Following clustering, a summary function will be used to interpret the clusters and detail the most relevant features of each (Martin, 2016).

Approach for statistical methods: Various clustering algorithms will be explored, including k-means, k-modes, expectation maximum, and the random-swap algorithm which has been proven to identify the correct clusters with

high probability and in some instances it has outperformed k-means in result quality (Franti, Virtajoki and Hautamaki, 2008).

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Poster number: PM165 (SP)

Theme: Psychiatry and mental health

The psychedelic 5-MEO-DMT alters anxiety and depression behaviours in cocaine-experienced animals

Authors: Mr Josiah O'Sullivan¹, Prof Keith J Murphy¹

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Introduction: The epidemic of drug addiction is a huge personal and social burden. Long-term exposure to drugs of abuse causes functional changes in behavioural control and cognitive systems that will work against efforts to remain abstinent due to diminished self-control capacity (Garavan, Kaufman and Hester 2008, Anderson et al. 2004). Chronic abuse of addictive substances produces a molecular-dependence where marked and enduring changes in gene and protein expression programmes underpin aspects of initial withdrawal and more long-lasting maladaptations that explain deficits in cognitive function, mood, anxiety and stress control. These deficits represent a substantial determinant of relapse risk.

Psychedelic drugs produce strong subjective effects including changes in thought, mood, and perception. There is a growing body of evidence supporting the use of psychedelic drugs in treating various affective disorders. Beneficial effects have been reported in clinical trials of various serotonergic (5-HT) psychedelics in the treatment of major depressive disorder, end-of-life anxiety and addiction (Nichols 2016). However, little is understood regarding the mechanism through which these drugs are mediating their benefits. For this study we used the 5-HT targeting psychedelic, 5-methoxy-N,N-dimethyltryptamine (5-Meo). 5-Meo is an agonist at 5-HT-1A, 5-HT-2A and 5-HT-2C receptors.

Methods and statistical analysis: Our study aimed to investigate changes in anxiety and depression behaviours induced by repeated cocaine exposure and the effect of an acute 5-Meo treatment on those behavioural abnormalities. Wistar rats were administered cocaine (15 and 20mg/kg i.p.) for 14 days and then received a single administration of 5-Meo (10 or 20mg/kg). The animals were then tested in the open field, elevated X maze and forced swim test to measure anxiety and depression-like behaviours respectively. Where appropriate, data was analysed by two-way ANOVA with Bonferroni's post hoc test

Results and conclusion: We previously found 5-Meo can reverse the majority of measured molecular changes induced by the repeated cocaine administration across multiple brain structures. We now report 5-Meo mediated context-dependent changes in behaviour, decreasing immobility in the forced swim test in cocaine-experienced animals. Both drug-independent and substance-induced depression are large risk factors driving relapse to drug use (Samet et al. 2013). 5-Meo decreased despair-like behaviour in cocaine-experienced animals suggesting it may have utility treating affective disorders and drug addiction.

Poster number: PM166 (SP)

Theme: Psychiatry and mental health

Translating Active Avoidance: A Novel Investigation of the Neurocognitive Bases of Active Coping in Female Adolescents with Depressive Symptoms

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Introduction: Globally, depression is the leading cause of illness in youth, and is twice as common in females. Identifying features that differentiate adolescents vulnerable to depressive symptoms (DS) from those who are resilient will help us understand who becomes depressed, when, and why. Abundant evidence from humans and murine models link active coping to stress resilience and passive coping to internalizing symptoms. To date, assessment of coping in humans has relied on self-report instruments. Here, we apply an innovative translation of the Sidman avoidance paradigm, which assays active coping (i.e., active avoidance) in animals, to assess the neurocognitive bases of coping and its relation to depression in adolescence.

Methods: 54 female adolescents (*M* age =16.36, range =13-20) were recruited from the community. Participants completed the Active Coping task (ACT) and measures of executive function (EF) and IQ. Resting-state functional MRI (rs-fMRI) data was acquired using an EPI sequence on a 3T scanner.

Analysis Approach: We used a series of multiple regression analyses to examine: 1) whether ACT performance differentiated adolescents experiencing DS from those who were not, and 2) whether cognitive resources influenced the ACT-DS relationship. Analyses of rs-fMRI data will examine the relationship between ACT and regulatory circuits connecting the amygdala and medial and lateral prefrontal cortex.

Results and conclusions: ACT significantly predicted DS across the full sample. When measures of cognitive ability were entered into the model, the observed ACT-DS relationship did not remain significant. However, within an “affected” subgroup of participants experiencing significant DS (i.e., BDI >16, n =27), ACT continued to predict DS even when EF and IQ were added to the model, demonstrating that ACT was not simply explained by cognitive resources. We predict that individual differences in ACT will be related to the strength of regulatory connections between amygdala and medial and lateral prefrontal cortex. Considering low treatment efficacy in adolescent depression, our research demonstrates the potential of translational and objective assays of coping to reveal novel targets for intervention. Such efforts are crucial if we are to develop novel treatments to tackle the puzzle that is adolescent depression.

Poster number: PM167 (SP)

Theme: Sensory and motor systems

Daddy-long-legs and enhanced walking speed

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Introduction: The body works as a fundamental reference for visuo-perceptual tasks in spatial surroundings (Van der Hoort, 2011). In fact, modifying the body representation with illusions through the use of virtual reality can indirectly

affect the perception of the dimension and distance of objects in space (Banakou et al., 2013). Here, we used a full body illusion to verify the hypothesis that the altered body representation influences locomotion.

Methods: We induced the full body illusion in 41 healthy participants by using two videos showing a pair of artificial legs of two possible lengths (Standard/Long), in two possible orientations (Anatomical/Non-anatomical), stimulated by a visible stick; while watching the videos, participants received an equivalent tactile stimulation. After watching the video, participants performed an Imagery Walking Task in a virtual environment. In this task, participants saw a pylon at four different distances (6, 12, 18, 24m) for five seconds, and were asked to imagine walking to the pylon 's location. We measured the time they spent in reaching the target location.

Approach for statistical analysis: To verify our hypothesis, we calculated a misestimation score based on the participants walking speed $[(\text{estimated time} - \text{actual time})/\text{actual time} * 100]$. We run a Linear Mixed Model (LMM) three-way ANOVA on this measure, considering legs' lengths, legs' orientation, and pylon's locations as within-subject fixed effect factors.

Results and conclusions: We found an overall underestimation of the walking time, with significant interactions between legs' length and legs' orientation $[F(1,2533) = 7.12, p \leq .05]$ and between legs' length and pylon's distance $[F(3,2533) = 2.94, p \leq .05]$, confirming that participants imagined walking shorter distances after watching the videos with the longer legs compared to the standard ones. This difference decreased when the pylon was displayed farther. These findings provide evidence that the Full Body Illusion influenced participants' perceived walking distance.

Poster number: PM168 (SP)

Theme: Sensory and motor systems

Insect steering framework: Translation from Orientation Decisions to Motor Commands

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Introduction: The Lateral Accessory Lobe (LAL), a homologous structure among many insect species, has been mostly studied regarding pheromone tracking in silkworms (Iwano 2010) and phonotaxis in crickets (Zorovic 2013). The outputs of the LAL have been shown to correlate with the observed motor activity regarding these specific behaviours. In these studies, the local neurons have been shown being sensitive to inputs from various other modalities than focused on. Lesion studies have shown, that the LAL is crucial for an insect's ability to steer correctly (Harley 2011). Other studies have shown, that the LAL is a source for steering behaviours, what a mapping of the descending pathways towards the motor centres revealed (Namiki 2018).

Methods: Literature review with the focus on multimodal integration and the translation of orientation decisions into motor commands.

Results and future work: A general framework how orientation decisions can be translated into steering commands: Multiple sensory processing areas of different modalities communicate approach/aversion signals to the LAL and are optimally integrated

Depending on the sensory availability, either searching behaviours or direct steering behaviours are generated These behaviours are fed into the motor centre and are also communicated back to the sensory processing areas as an efference copy

Based on this framework, the LAL network (based on current literature) will be investigated as a computational neural network, as well as an algorithmical model to investigate the relation of sensory input to motor output in a virtual environment.

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Poster number: PM169 (SP)

Theme: Sensory and motor systems

Using neurally-informed models to characterise age-related changes in human perceptual decision making

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Introduction: Ageing impacts performance on a wide range of cognitive tasks and computational modelling studies have suggested that these changes are at least partly attributable to age-related effects on decision making. However, the degree to which these models accurately reflect changes to the underlying neural computations remains unclear. The recent isolation of brain signals that trace the evolving decision process provides new opportunities for testing and refining predictions arising from these models.

Methods: Younger (N=39) and older (N=42) participants performed motion discrimination and contrast-change detection tasks, while we recorded 64-channel EEG. This approach allowed us to isolate two functionally distinct categories of decision signals: effector-selective beta-band activity that represents the translation of sensory evidence into a specific motor plan, and a domain-general signal found in the event-related potential, termed the centroparietal positivity, that exhibits the same accumulation properties irrespective of the type of response. We compared the dynamics of these neural signatures of decision formation to key parameter values derived from fitting a drift diffusion model to the behavioural data.

Approach for statistical analysis: Two-tailed, between-subjects t-tests and ANOVAs (or nonparametric equivalents) were conducted to assess the statistical significance of age-related effects on behaviour and neurophysiology. Bayesian statistics were conducted to quantify the relative likelihood of the data under the null versus the alternative hypothesis.

Results and conclusions: Our results indicate marked discrepancies between the age-related effects on the model output and neural data. Most notably, while the model predicted higher decision boundaries in older age for both tasks, the neural data indicated no such differences. To reconcile the model and neural findings, we constrained certain model parameters to match our neurophysiological observations. In addition to providing more parsimonious accounts of behaviour, the resultant models furnished novel predictions regarding other features of the neural data which were empirically validated. These included a slower rate of evidence accumulation amongst older adults during motion discrimination and a beneficial reduction in between-trial variability in accumulation rates in both tasks, which was linked to more consistent attentional engagement. Our findings highlight how combining human brain signal measurements with computational modelling can yield unique insights into group differences in neural mechanisms for decision making.

Poster number: PM170 (SP)

Theme: Sensory and motor systems

Neural phase synchronization underlies visual imagery of faces

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Introduction: Mental imagery is the process through which we retrieve and recombine information from our memory to elicit the subjective impression of “seeing with the mind’s eye”. Many studies using imaging and neurophysiological techniques have shown several similarities in brain activity between visual imagery and visual perception. For example, researchers have found that the vividness of a visual mental image is correlated, first, with the degree of activity in early visual cortex relative to whole brain activity, and secondly, with the degree of overlap between imagery and perception, especially in inferior parietal, premotor cortex, and over the whole visual cortex. Other studies have looked at memory retrieval as a core feature of mental imagery given the overlap of cognitive and neural resources shared between the two. Here we characterize the brain dynamics of visual imagery of faces by using EEG phase-synchrony analysis.

Methods: Participants had to imagine familiar famous faces after being prompted by a name cue. Target faces were imagined inside an oval. The stimuli employed were previously validated.

Approach for statistical analysis: We quantified phase locking between pairs of electrodes to measure dynamical interactions among electrodes oscillating in the same frequency band. A cluster-based nonparametric statistical framework was used throughout the analysis of the power and wPLI (weighted phase lag index) time-frequency charts. Time-frequency windows of interest were compared in pairs of experimental conditions. This procedure compared corresponding temporal points in the subject-wise averages using one-tailed dependent (for within-subject comparisons) or independent (for between-subject comparisons) samples *t*-tests

Results and conclusions: We found that internal generation of visually imagined faces is associated with long-range phase synchronization in gamma frequency band between frontal and parietal electrodes and theta frequency band between frontal electrodes. These results suggest that fronto-parietal gamma phase synchronization may be related to the endogenous binding of facial visual features transiently sustained in memory (memory retrieval of faces), whereas the interhemispheric frontal-theta synchrony might be encoding the memory reactivation of face stimuli (binding of facial features) (see Figure 1).

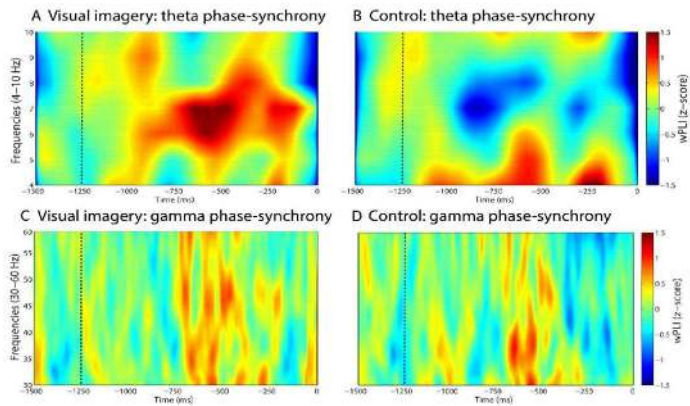


Figure 1. **A and B.** Theta phase-synchrony between frontal and parietal electrodes. wPLI (4-10 Hz) for visual imagery (**A**) and control (**B**) conditions. A cluster-based permutation test comparing visual imagery and control conditions was performed. A significant difference between conditions was found ($p = 0.019$, visual imagery minus control) in the theta band (4-7 Hz). Only interhemispheric fronto-frontal pairs of channels were considered for the analysis. **C and D.** Gamma phase-synchrony between frontal and parietal electrodes. Gamma wPLI (30-60 Hz) for visual imagery (**C**) and control (**D**) conditions. A cluster-based permutation test comparing visual imagery and control conditions was performed. A significant difference between conditions was found ($p = 0.019$, visual imagery minus control). All the values in the figure are expressed in standard deviations in reference to the baseline (-1500 to -1250 ms). Trial length (-1500 ms) is relative to response time (0 ms).

Poster number: PM171 (SP)

Theme: Sensory and motor systems

Cross-modal perception in synaesthetes during Art and Music practices

Authors: Dr Svetlana Rudenko¹, Dr Richard Roche², Dr John Dingliana¹

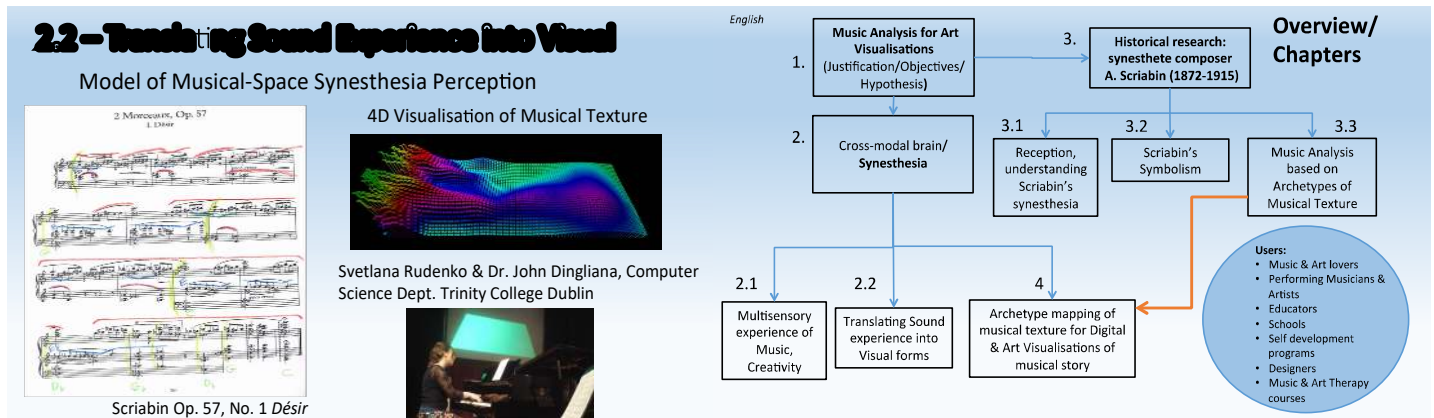
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Introduction: Synaesthesia is a relatively rare condition characterised by cross-communication between the sense modalities wherein a sensory experience in one modality (e.g. an auditory stimulus) automatically elicits a concurrent perceptual experience in another (e.g. a visual percept). Some synaesthetes utilise these cross-modal pairings for creative purposes, as in the case of Vincent van Gogh, Wassily Kandinsky and Olivier Messiaen, all of whom appear to exhibit chromesthesia, where sounds are converted to colours.

Methods: Interviews

Approach to Statistical Analysis: Here we report the contents of interviews with three synaesthete artists who all experience auditory stimulation in the form of visual experiences. Each of the three describe the nature of their synaesthetic experience and the process by which they produce their artistic output in response to specific musical compositions.

Results and Conclusions: We highlight some examples of sensory transposition by artists, including visualisation of musical texture as a 4D digital model of musical-space synaesthesia perception. We discuss what these cases reveal about the nature of synaesthesia, as well as how visual digital applications may benefit from considering aspects of multisensory design.



Poster number: PM172 (SP)

Theme: Sensory and motor systems

Differential effect of kappa opioid receptor modulation in the wistar-kyoto rat model of hyperalgesia associated with negative affective state

Authors: Mehnaz Ferdousi^{1,3}, Patricia Calcagno^{1,2,3}, Sonali Aggarwal^{1,2,3}, Connie Sanchez⁴, Karen Smith⁴, John Kelly^{1,3}, Michelle Roche^{2,3}, David Finn^{1,3}

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Introduction: The role of the endogenous opioid system in pain-negative affect interactions and the influence of genetic background is poorly understood. The Wistar-Kyoto (WKY) rat, a genetic model of anxiety and depression, displays a hyperalgesic phenotype, compared with Sprague-Dawley (SD) counterparts. We showed earlier that WKY rats exhibit higher expression of the gene encoding kappa opioid receptor (KOP) in the amygdala and lower expression of the KOP- and dynorphin-encoding genes in the cerebral cortex, compared to SD rats. KOP antagonism produces anxiolytic and antidepressant-like effects in WKY rats versus SD counterparts. Here, we compared the effects of systemic administration of U50488 (KOP agonist) and DIPPA (KOP antagonist) on nociceptive responses to thermal and inflammatory stimuli and anxiety/depression-related behaviours in WKY versus SD rats.

Methods: Adult male WKY and SD rats (n=8/group) were allocated to groups across two experiments using a within-subject design. Experiment 1 investigated the effects of U50488 (1, 2.5, and 5mg/kg, s.c.) or DIPPA (2.5 and 5mg/kg, s.c.) in hot plate (HP), elevated plus maze (EPM), open field, and forced swim tests. Experiment 2 investigated the effects of U50488 (1 or 2.5mg/kg, s.c.) and DIPPA (2.5mg/kg, s.c.), alone or in combination, in the formalin test.

Approach for statistical analysis: Data were analysed using repeated measures or two-way ANOVA followed by SNK *post hoc* or Kruskal Wallis H-test followed by Mann-Whitney U-test ($p < 0.05$ significant).

Results and conclusions: In the HP test, the minimal effective dose of U50488 was 2.5 and 5mg/kg in SD and WKY rats, respectively. In the EPM, DIPPA at 5mg/kg increased the open arm entry in WKY, but not SD rats. U50488 significantly reduced formalin-evoked nociceptive behaviour in SD, but not in WKY, rats, an effect not attenuated by

DIPPA. DIPPA, administered alone, was antinociceptive in SD, but not in WKY rats, in both HP and formalin tests. These data indicate WKY rats are hypo-responsive to KOP modulation in tests of thermal and inflammatory pain, suggesting an altered expression/functionality of KOP may underlie the hyperalgesic phenotype of WKY rats. The data also provide further evidence for anxiolytic effects of KOP antagonism in WKY versus SD rats.

Poster number: PM173 (SP)

Theme: Sensory and motor systems

Behavioural characterisation of the spared nerve injury model of neuropathic pain in male and female sprague-dawley rats

Authors: Ms Laura Boullon^{1,2}, Prof David P. Finn^{1,2}, Dr Alvaro Llorente-Berzal^{1,2}

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Introduction: Neuropathic pain is pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system. Central sensitisation after nerve injury induces pain response in the presence of non-noxious stimuli, a phenomenon called allodynia. Moreover, chronic neuropathic pain is associated with depressed mood in humans and depression-like behaviours in rodents (2). Despite the greater prevalence of chronic pain in women (3), the vast majority of preclinical studies focus on males only. The aim of this study was to further characterise the behavioural effects of spared nerve injury (SNI), a neuropathic pain model, in male and female Sprague-Dawley rats.

Methods: Please find attached Figure 1.

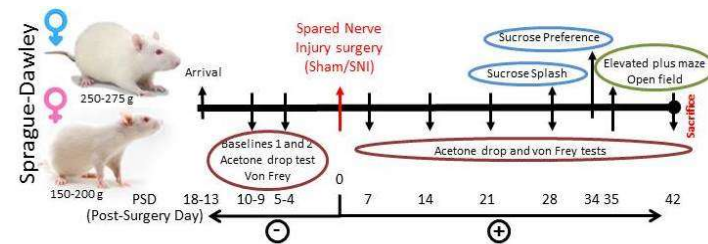


Figure 1. Experimental design. In brief, male and female Sprague-Dawley rats ($n=10$ per group) underwent Sham or Spared Nerve Injury surgery. They were exposed to the von Frey and Acetone Drop tests on post-surgery days (PSD) 7, 14, 21, 28 and 42 to determine mechanical and cold thermal allodynia respectively. To analyse the emergence of depression-like behaviours (i.e. anhedonia) Sucrose Splash and Sucrose Preference tests were run on PSD28 and 34 respectively. On PSD35 animals were exposed to the Open Field (OF) to analyse locomotor activity and the Elevated Plus Maze to measure anxiety-like behaviours.

Here, we are presenting the data obtained from the acetone drop, von Frey, sucrose preference and open field tests.

Approach for statistical analysis: Open field and sucrose preference test data were analysed using two-way ANOVA, followed by Tukey post-hoc test. Von Frey and acetone drop tests were analysed by non-parametric tests (Kruskal Wallis and Mann-Whitney). $P < 0.05$ was considered significant.

Results and conclusions: SNI resulted in sex-dimorphic mechanical and thermal allodynia. Females displayed a lower response threshold to von Frey filaments. Over the time course of the experiment, males tended to recover from SNI-related thermal allodynia but not females. SNI surgery did not induce any changes in sucrose preference. In the open field, SNI reduced vertical activity in male rats but not females. SNI-females tended to exhibit higher horizontal locomotor activity than SNI-males. Although further analyses are required, our current results demonstrate differential development of nociceptive behaviours between males and females suggesting important sex-dimorphic modifications in pain pathways which seems to persist at least 40 days after SNI surgery.

Acknowledgements: Funded by IRC Laureate Award (IRCLA/2017/78).

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Poster number: PM174 (SP)

Theme: Sensory and motor systems

Anisotropic chromatic processing in the larval zebrafish inner retina

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Introduction: Colour vision, the ability to differentiate wavelength independent from intensity, is an essential evolutionary trait that allows animals to efficiently forage for food, avoid predation or find sexual mates. Zebrafish are an interesting model to study colour vision as they are tetrachromats and hold the potential to process numerous chromatic computations. In this study we focused on bipolar cells, the first projection neurons in the retina, receiving input from the photoreceptors and sending their axon to the inner plexiform layer.

Methods: Using 2-photon imaging of light-driven calcium signals, we functionally surveyed the entire bipolar cell class *in vivo*. We adopted a tetrachromatic white noise approach to assess bipolar cell synaptic terminals' chromatic sensitivity and unveiled an unprecedented degree of visual specialisation.

Results: We have defined specialised regions of the retina, dedicated to light-guided behaviours, and have correlated those regional characteristics to functional bipolar cell types. Those functional types were strongly associated with the bipolar cells retinal position and their axonal stratification. This new categorisation led us to characterise a number of functional bipolar cell types which supplants the traditional phenotypical classification of those neurons.

Conclusions: Our findings bring a better understanding of colour vision processing in the inner retina and suggest that, this dominant feature is already encoding complex chromatic responses in the inner plexiform layer before driving retinal ganglion cells.

Poster number: PM175 (SP)

Theme: Sensory and motor systems

Identifying how neural activity encodes both the action performed and instruction used

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Introduction: In humans as well as in animal models, neural activity in motor cortex has been shown to encode specific hand and arm movements. How neural activity in motor cortex changes when making the same movement in response to different sensory information is not well understood. Behavioural tasks involving voluntary movements typically use a single instruction paradigm (such as lights turning on) to instruct movements. Understanding how instructions of different sensory modalities affect motor cortical activity is important to identify neural pathways involved in voluntary movements.

Methods: Fourteen healthy human participants (ages 18 to 32) performed an object-manipulation task in which different objects were indicated using either visual or auditory instructions containing information about the target object's identity or how it should be used. During the task, neural activity was recorded using electroencephalography (EEG). Event-related potentials (ERPs) were measured from each participant, averaged across participants, and aligned on the time of hand movement. Separate ERPs were computed for trials involving each of the different instruction types and each of the different target objects.

Approach for Statistical Analysis: Two-way analysis of variance (ANOVA) was applied to the ERP waveforms aligned on movement onset to detect significant variation related to instruction method or target object.

Results and Conclusions: Each participant used the different instructions to perform the associated movements. Neural activity differentiated both the instruction delivered and the movement performed. Across participants, electrodes located on the frontal, contralateral side demonstrated distinct ERP waveforms differentiating both the sensory modality of the instruction ($p < 0.001$) and the target object ($p < 0.001$). Thus, ERPs were able to distinguish both the action performed and the instruction used to perform that action in the same electrode location. Future work will identify effective connectivity between electrodes to determine how information communicated between cortical areas changes based on the instruction used or action performed. Identifying the neural pathways involved in voluntary movements is important in order to understand how sensory information is integrated into the performance of voluntary movements.

Poster number: PM176 (PP)

Theme: Sensory and motor systems

Expectations shape the dynamics of binocular rivalry

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Predictive coding (PC) models, in which perception is cast as an inferential process, are increasingly influential in neuroscience, but await comprehensive empirical validation. Here, we test the ability of these models to account for binocular rivalry. According to PC models the regular alternations between rivaling percepts are accounted for by the effect of descending sensory predictions cancelling out half of the incoming sensory information. From this perspective, the dominant image at any given moment is expected, while the stream of incoming sensory information from the suppressed image is unexpected and is encoded as 'prediction error'. The accumulating prediction error demands a revision of the expectation until an alternation occurs and the process restarts. This study seeks to test this account by quantifying the extent to which expectations alter the dynamics of binocular rivalry.

Methods: 20 participants will be presented with rivaling sinusoidal gratings, one with a leftward tilt (135°) and one with a rightward tilt (45°). The gratings will be presented through a mirror stereoscope so that only one grating is visible to each eye. After an initial baseline measurement of the gratings' relative dominance, participants' expectations will be biased towards one of the tilted gratings. A binocularly-consistent, 3 minute 'learning phase display' will be presented, where the grating's orientation updates at 4 Hz and, on each testing day, one orientation (either 45° or 135°) has a 25% probability of being shown, while all other orientations are equiprobable. Following this learning phase, subjects will be presented with rivalrous gratings and asked to continuously report their dominance over 2 minutes.

Approach for Statistical Analysis: The overall effect of expectation will be assessed by individually baselining the data and comparing the mean dominance of the expected oriented grating to that of the unexpected grating using a t-test. The data will then be binned and the temporal profile of the effect analysed with multiple regression. PC would

predict an initial bias in dominance toward the expected stimulus, which erodes over time as conflicting information accumulates. Traditional models of rivalry would not predict such a modulation of early sensory conflict based on stimulus history.

Poster number: PM177 (SP)

Theme: Sensory and motor systems

Getting ready for Mars: perceiving new simulated gravity environments

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Introduction: On Earth, we are continually exposed to gravity. Sensory signals are integrated to form an internal model of gravity which allows us to perceive and interact with the surrounding environment. Typically, people exhibit a “gravitational advantage” in their perceptual experiences: for instance, precision is higher when judging the speed of falling, gravity-congruent, versus rising, gravity-incongruent, objects. However, it is unclear whether the model of gravity is fixed to terrestrial gravity or whether it can be applied to new gravitational environments. Here we explored whether participants can adapt to a new, Virtual Reality (VR)-simulated gravity environment. First we explored whether participants show the gravitational advantage when observing objects accelerating according to Mars (3.71m/s^2) and Earth (9.81m/s^2) gravity. Second, we tested whether perceived gravity might influence perceptual judgements that implies a computation of gravity magnitude, such as weight.

Methods: Participants were immersed in VR environments in which objects accelerated according to Earth or Mars gravity. In Experiment 1, participants judged the speed of an upwards or downwards-accelerating object in each gravity condition. In Experiment 2 participants observed objects accelerating downwards according to each gravity condition while they judged the weight of different spheres applied to their hand.

Statistical Analysis: In Experiment 1 a general linear mixed model was applied to Just-Noticeable Differences in each experimental condition. In Experiment 2 perceived weight was expressed as a proportion of actual weight, with negative values indicating an underestimation, and entered in a 5 (Object weight: 20-40g in 5g increments) x 2 (Gravity: Earth vs Mars) repeated measures ANOVA.

Results and Conclusions: Participants showed a significant gravitational advantage when judging the speed of falling objects (Wald $\chi^2=5.19$, $p=.023$). No interaction with gravity was found ($p=.93$), suggesting that the gravitational advantage was similar in both gravity environments. Moreover, participants perceived object weights as significantly lighter in the Mars relative to Earth condition ($F(1,12)=5.79$, $p<.05$, $\eta_p^2=0.33$), suggesting that the perceived magnitude of gravity influences perception. Although the internal model of gravity has been built up under terrestrial gravity, it can quickly expand to novel non-terrestrial gravitational environments.

Poster number: PT001 (SP)

Theme: Attention, motivation, behaviour

The Neurobiology of Inhibitory Control in HIV+ Individuals with a History of Cocaine Dependence

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Introduction: Cocaine use is associated with high-risk sexual practices that accelerate the spread of human immunodeficiency virus (HIV) infection. In HIV+ individuals, current cocaine use is associated with reduced adherence to antiretroviral medication, decreased condom usage, increased rates of neurocognitive impairment, and faster disease progression compared to HIV+ non-users. Inhibitory control, or the ability to withhold a thought, feeling, or action, is a central construct involved in the minimization of impulsive behaviors. Although recent behavioral and neuroimaging evidence indicates normalization of inhibitory control processes in former cocaine users as function of drug abstinence, it is unknown whether this recovery trajectory persists in former users with comorbid HIV.

Methods: Here, we employ a Go/No-Go task to investigate the behavioral and electrophysiological correlates of inhibitory control in abstinent cocaine users with and without HIV and healthy controls using EEG.

Approaches for statistical analysis: For behavioral data, D' , a measure of signal detection sensitivity, will be calculated for each subject. D' values will be averaged across subjects in each group, and compared between groups using a one-way ANOVA and pairwise t-test. For EEG analysis, following standard preprocessing procedures, data will be aligned to stimulus onset and averaged across subjects to grand-average traces for each group. Topographic maps of scalp voltage at the time of maximum N2 amplitude will be constructed for each group for visualization purposes.

Results and conclusions: Consistent with prior literature, we found that both behavioral performance and electrophysiological markers of inhibitory control at task-relevant scalp sites did not differ substantially between HIV- abstinent cocaine users and healthy controls, suggesting a partial recovery of inhibitory control capabilities in former cocaine users. However, HIV+ individuals demonstrate formalization of the N2 component in conjunction with poor behavioral task performance compared to HIV- individuals. Preliminary data suggests that that neural and behavioral deficits in inhibitory control are more severe in HIV+ individuals with a history of cocaine dependence compared to HIV+ individuals without former cocaine dependence. Taken together, these data indicate that inhibitory control capabilities in HIV+ former cocaine users do not normalize to the level of HIV- individuals, suggesting that further or more targeted interventions may be needed to facilitate positive health outcomes in this vulnerable population.

Poster number: PT002 (SP)

Theme: Attention, motivation, behaviour

Differential effects of morphine on social responding in the VPA model of social impairment

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Introduction: The mu-opioid receptor (MOP) is widely known to modulate social responding. While MOP agonism increases social play behaviour in juveniles, the effects on social investigation depend on both context and internal state[1]. There is a paucity of data examining the effects of MOP modulation in models of altered social responding.

Prenatal exposure to the anti-epileptic valproic acid (VPA) results in a number of behavioural alterations including social impairments during adolescence and adulthood[2]. This study investigated if VPA-exposure was associated with altered expression of genes encoding MOP and endogenous opioid peptides in discrete brain regions and the effect of MOP agonism on social motivation and cognition.

Methods: Pregnant Sprague-Dawley rats received either saline or VPA (500mg/kg, s.c.) on GD12.5. Male adolescent offspring received morphine(1mg/kg) or vehicle(saline) i.p. 30mins prior to the 3-chamber sociability test. Discrete brain regions were dissected from a cohort of behaviourally naive animals. Expression of genes encoding MOP and endogenous opioid pre-propeptides was determined using qRT-PCR.

Statistical analysis: Data were analysed using an independent samples t-test, repeated-measures ANOVA followed by SNK *post-hoc* or Kruskal-Wallis H-test followed by Mann-Whitney U-test where appropriate. P<0.05 was deemed significant.

Results and conclusions: Gene expression analysis revealed no difference in MOP expression between saline and VPA-exposed rats. POMC expression was higher in the amygdala and prefrontal cortex (PFC), p-pENK was higher in the amygdala, and p-pDyn was lower in the cerebral cortex and PFC of VPA-exposed rats, compared with controls. Morphine reduced social motivation and social novelty preference (SNP) behaviour in saline- but not VPA-exposed rats. SNP behaviour was impaired in VPA-exposed animals, an effect not altered by morphine. These data demonstrate that VPA-exposed rats exhibit altered expression of components of the MOP system, possibly accounting for the lack of effect of morphine on sociability in the model. These data add to the existing literature implicating the MOP system in social responding and disorders of sociability.

This study was supported by funding from Alkermes Inc and Science Foundation Ireland(14/SPP/B3051).

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Poster number: PT003 (SP)

Theme: Attention, motivation, behaviour

Functional interactions of the left inferior frontal gyrus underlying morphological processing of pseudowords: FMRI study of Russian inflectional verb morphology

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Many studies of the brain basis of language processing focus on the organization of the mental lexicon. One of the key debates in this domain concerns the distinction between regular and irregular inflectional morphology. The proponents of the dual-route approach assume that regular forms are processed by rule application (e.g. adding the -ed suffix to the stem to produce past tense: work – work-ed) and irregular ones by predominant involvement of lexical memory-base processes (i.e. go – went), while those who adopt the single-route approach assume no such distinctions.

In the dual-route approach, it is largely accepted that regular processing is supported by the left-lateralized fronto-temporal brain network, and irregular processing is associated with activity within bilateral superior temporal gyri. However, all previous studies addressing this problem investigated real words, and whether a similar distinction can be found for pseudowords or to which extent morphological processing of complex words depends on their lexicality remains underinvestigated.

To answer this question, we analyzed pseudoword data from a previous fMRI study on Russian. It was performed on 3 Tesla Philips Achieva. 21 right-handed native speakers (13 women, age: 19–32 years) were instructed to generate overtly present tense forms from regular and irregular real verbs and from pseudoverbs modeled after them. To reveal changes in the psychophysiological interactions (PPIs) associated with processing of pseudoverbs, the PPI analysis was performed for the VOI in the left IFG. Paired t-tests with a subsequent correction for multiple comparisons (FWE $p < 0.05$ at the cluster level) were applied.

We found that regular pseudoverbs were characterized by decreased PPIs between the left IFG and the left posterior STG, hippocampus and cerebellum and by increased PPIs with bilateral IFG and left middle orbital gyrus, as compared to regular real verbs. Obtained data support the dual system approach, assuming the involvement of the left fronto-temporal network specifically for regular real verb processing, and bilateral network for all other forms including irregular verbs and pseudoverbs.

The study was funded by RFBR, research project #18-00-00646 (K).

Poster number: PT004 (PP)

Theme: Attention, motivation, behaviour

Anticipatory biasing of visuospatial attention in deaf children

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Introduction: Historically, deaf children have been reported to have greater distractibility-hyperactivity problems, lack of inhibitory control, and demonstrate impulsive behavior. Deaf children have also demonstrated poorer performance on visual continuous performance tests compared to age-matched hearing children, suggesting that deaf children may have poorer cognitive control and visual attention. Some argue audition plays a critical role in the shaping of cognitive processes and auditory deprivation can lead to cognitive deficits. However, these studies reporting deficits in visual attention were conducted on deaf children born to hearing parents and they were not native users of American Sign Language (ASL). The effect of early ASL acquisition was examined and no statistically significant difference was found between deaf native users of ASL and age-matched hearing children on a sustained attention task. Little is known about the cortical processes involved in the modulation of visual attention in deaf children. In hearing subjects, enhanced α -band oscillatory EEG activity has been observed over the retinotopic area likely to contain distracter stimuli in the cue-stimulus interval during a selective attention cueing paradigm, demonstrating that α -gating plays a role in the suppression of distracting visual stimuli in a retinotopic fashion. A greater understanding of the underlying physiology of attentional processes in deaf children would lead to more appropriate early interventional strategies. Attention and impulse control are critical for learning and academic performance and the proposed research may lead to novel strategies for improving educational outcomes in deaf children.

Methods: 15 deaf native users of ASL and 15 hearing controls between the ages of 6-13 will be administered an instructional endogenous visuospatial cueing task while wearing a 128-channel EEG cap. Continuous EEG will be acquired through the ActiveTwo Biosemi electrode system. A 1000-Hz EyeLink eye tracking system will be used to ensure strict eye fixation. Task design is described in detail in Vollebregt et al. (2015).

Approach for statistical analysis: Cue-locked ERPs will be derived for leftward cues versus rightward cues. Alpha-band oscillatory activity will be characterized in the cue-stimulus interval by the temporal spectral evolution technique (TSE). Topographic analysis will be conducted to observe the distribution of alpha-band oscillatory activity related to preparatory attention.

Poster number: PT005 (SP)

SP = Standard poster

PP = Preregistration poster

Theme: Attention, motivation, behaviour

Choice history biases in perception and metacognition: how confident are you now?

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The term “metacognition” refers to the ability to accurately judge our own decision-making, and over the years research has revealed how important it is to adaptive behaviour within humans. However, metacognitive accuracy is often suboptimal due to several factors such as internal biases. One such bias is choice history bias – an influence of previous choices on current choices. Serial dependence/choice history bias has been found to exist across perception, memory and attention. The aims of the current study were to investigate whether choice history bias could account for part of the suboptimality frequently observed in metacognitive performance, and also to reproduce findings from prior work that demonstrate the effects of serial dependence on a perceptual decision-making task. Neurologically healthy participants with normal vision ($n = 37$) performed an orientation judgement task, in which they were instructed to respond whether they perceived the stimulus (Gabor patch) to tilt either “leftward” or “rightward” relative to the vertical plane, followed by a confidence report (1 (low) to 4 (high)) in their perceptual decision. The results revealed a significant difference in orientation judgements between ‘post left response’ trials and ‘post right response’ trials, with participants’ choices tending to be biased toward the Gabor orientation of the previous trial. A significant positive correlation was also found between confidence reports on previous and current trials, suggesting that participants were more likely to respond with high confidence if they had reported high confidence on the trial before, and vice versa for low confidence. It is thus concluded that choice history bias occurs in both perceptual and metacognitive decision-making, leading to possible theories of a continuity field for metacognition as well as perception. While this bias is often considered an adaptive mechanism to maintain visual continuity and avoid constant generation of novel confidence assessments, it results in suboptimal performance when previous inputs are not predictive of upcoming inputs as is often observed in perceptual and metacognitive psychophysical judgement tasks.

Poster number: PT006 (PP)

Theme: Attention, motivation, behaviour

Investigating the relationship between perceptual decision-making, metacognitive confidence and dimensions of personality and cognition

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Introduction: Great strides in our understanding of the neural mechanisms for decision-making and metacognition have been achieved by study highly simplified perceptual tasks in which participants must translate elementary sensory information into an appropriate action. The work has resulted in a powerful theoretical framework which suggests that the same evidence accumulation process may underpin both decision making and the associated metacognitive confidence judgments. However, the degree to which the paradigms that have been studied successfully tap into cognitive operations that generalise beyond simple perceptual tasks has yet to be adequately explored. The current study aims to investigate this question by relating behavioral and computational measures of decision formation and confidence in a perceptual decision-making task with self-report measures of personality, economic decision-making, and everyday beliefs about metacognition.

Methods: In the present experiment data were collected from a sample of 450 adults, providing 80% power to detect an effect size of 0.1, using the online crowdsource platform Amazon Mechanical Turk (mTurk). Participants performed a standard random dot motion task, where they indicated the dominant motion direction of a circular patch of noisily moving dots. After each choice participants reported their confidence in the decision on a 7-point

Likert scale. Performance was titrated throughout the task to ensure that subjects were maintained at ~70% throughout task performance. Following the perceptual task participants were given 7 questionnaires that assessed various aspects of personality and decision-making in naturalistic settings.

Analysis approach: The distinct information processing components underpinning decision formation will be decomposed using the drift-diffusion model, which models two-choice decision-making as an integration of noisy sensory evidence up to an action-triggering boundary. Metacognitive abilities will be measured through an extension of signal-detection theory, by computing the average *meta-d'* and *metacognitive efficiency* scores, which reflect the probability to use higher or lower confidence ratings independent of the accuracy of the motion judgments. Finally, the average scores on each subscale and questionnaire will be computed for each subject. Linear regression analyses will be used to examine the relationship between the measures of personality, daily-life metacognitive beliefs, decision-making, and the task-related variables.

Poster number: PT007 (PP)

Theme: Attention, motivation, behaviour

The effect of task load on the temporal EEG dynamics of switching between a visuospatial task and a continuous visuomotor task

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Introduction: Task switching is a common ecological challenge. One such challenge is in semi-autonomous driving, where a passive driver is required to take over from the vehicle in complex driving situations. When the driver is involved in an unrelated task, their current activity may affect their response time to a take-over request, or their driving performance (Wandtner, Schömig, & Schmidt, 2018). Several studies have investigated the take-over time under the presence of a non-related driving task, but the continuous performance of the driving task is often ignored. If neurophysiological signals are able to predict a negative impact on task performance, a driver assist system could employ safety-orientated actions.

Methods: Participants will partake in a laboratory experiment requiring them to switch from a visuospatial task (visual search) to a continuous visuomotor driving related task (compensatory tracking). The participant will perform the visual search before receiving visual and auditory cues to reorient their attention towards the tracking task. A within-subject protocol will require participants to partake in two randomised experimental conditions differing by task difficulty of the visuospatial task: 1) Easy, 2) Hard. Neural oscillatory activity (EEG) will be recorded continuously throughout. Mean accuracy and response time measures will be recorded from the visual search and tracking task.

Approach for statistical analysis: Mean reaction time and accuracy data will be subjected to a paired samples t-test to investigate the differences between task difficulty (easy vs hard). The evoked and induced neural oscillatory activity will be explored using a time-frequency analysis using a Wavelets approach. Subject specific time-frequency electrode windows will be extracted from the condition-average results, focusing on theta and alpha oscillations over the frontal and parietal electrodes before and after the cue. A repeated-measures ANOVA will investigate the differences between task difficulty. Multiple comparisons will be controlled for via the Benjamini & Hochberg (1995) procedure. A regression analysis will investigate whether preparatory theta and alpha activity can predict continuous task performance on the visuomotor task.

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Poster number: PT008

Theme: Attention, motivation, behaviour

Chemogenetic analysis of GPCR signalling in subdivisions of the mPFC underlying attention and impulsivity

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Introduction: A lack of proper attention and impulse control have been found in many psychiatric disorders, such as ADHD, IED, ODD, substance abuse or bipolar disorder. The medial prefrontal cortex has been implicated in attentional control and various forms of impulsivity, e.g. waiting impulsivity, stopping impulsivity, delayed and probabilistic discounting. For example, lesion studies targeting the anterior cingulate (ACC) or infralimbic cortex (IL) have shown effects on impulsivity, whereas prelimbic cortex (PrL) lesions did not. Decreased GABA-binding has been found in the ACC of high-impulsive rats, whereas similar animals also showed decreased myo-inositol in the IL. Lesions of the ACC and PrL have also been shown to disrupt attention. Therefore, it is unclear to date, which subregion of the PFC is the key regulator of each of these cognitive functions. We therefore wish to examine the role of excitatory cells of prefrontal subregions in attention and waiting impulsivity.

Methods: We will use a chemogenetic approach to activate distinct G-protein-cascades in excitatory cells of single subdivisions of the murine mPFC using Designer-Receptors-Exclusively-Activated-by-Designer-Drugs (DREADDs). The mice will be trained and tested on the 5-choice-serial-reaction-time task (5CSRTT). Sustained attention and impulse control are assessed on this task by presenting distinct challenges, e.g. by decreasing the stimulus duration or by increasing the inter-trial interval, respectively. During those challenges, DREADDs are activated by application of different doses of CNO in a latin-square design, counterbalancing for targeted subregion and DREADD/control vector.

Approach for statistical analysis: Read-outs for attentional processes will be the accuracy and omissions the mice show on the task, while motor impulsivity is indicated by premature responses. Other read-outs serve as secondary measures of related cognitive functions, such as reward latency for motivation/locomotor drive or preservative responses for perseverance. All statistical analysis will be performed in SPSS. Repeated-measures two way ANOVA will be used to analyse between-group effects, effect of chemogenetic activation at different doses of CNO and interactions between both factors. Within DREADD-transfected groups repeated-measures ANOVAs will be used for within-subject analysis.

Poster number: PT009 (SP)

Theme: Attention, motivation, behaviour

Detection gains to multisensory stimuli: do integrative processes impact detection of liminal stimuli?

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Introduction: Decades of research on multisensory integration have demonstrated that the simultaneous presentation of cross-modal unisensory stimuli, forming a multisensory stimulus, results in a variety of perceptual advantages, including decreased reaction times and improved recognition. Additionally, neurophysiological data has shown non-linear increases in responses to relatively harder to detect multisensory stimuli, a phenomenon known as inverse effectiveness. Despite numerous studies investigating the extent of multisensory integration effects surprisingly little attention has been paid to whether integrative effects impact the detection of liminal (at the threshold of detection) stimuli.

Methods: In the present study we initially titrated, at the individual level, a psychometric function describing the detectability of auditory and visual stimuli embedded in continuous noise. Participants were instructed to press a button on detecting any auditory or visual stimulus in a yes/no detection paradigm using preset stimulus intensity values. After determining an individual's psychometric function for the detection of the unimodal stimuli, we then calculated stimulus intensity parameters that would create stimuli at desired probabilities of detection. The detectability of these unimodal stimuli were then re-tested, and combined in multisensory blocks, where equally detectable auditory and visual stimuli were paired and the detectability of the resulting multisensory stimulus was assessed.

Analysis approach: A model of statistical facilitation was used to predict the detectability of multisensory stimuli, where the expected detectability of a multisensory stimulus is given by the linear sum of the detectability of its unimodal components, minus their joint probability. In order to determine if multisensory detection is significantly different from that predicted by the model a t-test was performed across individuals for each level of unimodal combinations, comparing the recorded detectability of the multisensory stimulus to its predicted detectability.

Results and Conclusion: Surprisingly, we found that while multisensory stimuli saw improved detection over their constituent unimodal components, these gains did not exceed those predicted by statistical facilitation. This was true at both the individual, and group level. Furthermore, detection gains did not seem to follow the principle of inverse effectiveness, meaning detection gains were not more robust for stimuli of relatively lower intensity values.

Poster number: PT010 (PP)

Theme: Attention, motivation, behaviour

Role of the extended amygdala in ethanol modulated social behaviour

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Introduction: Alcohol is known to facilitate social interactions and to alleviate anxiety (Varlinskaya & Spear, 2002), but the neural mechanisms driving ethanol-modulated social behaviors, especially considering same- versus opposite sex interactions, are incompletely understood. Acute alcohol exerts effects on neurons in the bed nucleus of the stria terminalis (BNST; Sharko et al., 2016), a region known to mediate behaviors related to anxiety. Thus, it is plausible that neural mechanisms within BNST may be involved in ethanol-modulated social interactions. Identifying BNST as a locus for alcohol-related social behavioral effects may prove important for the treatment of social anxiety disorder.

Methods: We will use in vivo electrophysiology to record neural activity in the BNST during a mouse social interaction task both prior to and following acute ethanol administration. Preliminary data show that a subset of neurons in BNST are responsive to social interaction, and evidence indicates some of these neurons may also be modulated by ethanol. In addition to electrophysiology recording studies, we will use chemogenetic methods (designer receptors exclusively activated by designer drugs, or DREADDs) to manipulate activity in BNST, in order to investigate a causal role for BNST in ethanol-modulated social behavior.

Approach for statistical analysis: For electrophysiological recording studies, individual neurons' firing rates during epochs of social interaction with a novel conspecific will be compared to baseline (home cage) and control (novel object) firing rates to determine whether neural activity changes as a function of social interaction. We will also determine whether any modifications to social interaction following ethanol administration result in modulated neural encoding in BNST by analysing firing rate changes in the pre- versus post-ethanol social interaction epochs. Furthermore, we will examine whether social interaction-responsive neurons encode behavior differently for same-sex versus opposite-sex interactions by comparing firing rate changes for each interaction type. For chemogenetic experiments, baseline social interaction behavior for each animal will be compared with behavior following inactivation of BNST neurons to determine whether BNST is necessary for the effects of ethanol upon social interaction.

Poster number: PT011 (SP)

Theme: Attention, motivation, behaviour

The Neurobiology of Error Processing in HIV+ Individuals with a History of Cocaine Dependence

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Introduction: Individuals with human immunodeficiency virus (HIV) with a history of cocaine dependence are at risk of engaging in behaviors that interfere with treatment, such as medication non-adherence, unprotected sex, and needle sharing. The ability to suppress such behaviors relies critically on "action monitoring," or the ability to assess a cognitively demanding situation, entertain multiple response-alternatives, and execute an appropriate response. To better understand the action-monitoring deficits underlying risky behavior in the high-risk population of individuals with comorbid HIV and history of cocaine dependence, we examine the neural and behavioral mechanisms of action monitoring as patients perform a Go/NoGo task. High-density electroencephalography (EEG) data are collected during task performance. By building a deeper understanding of the neural substrates associated with maladaptive action monitoring, we hope to pave the way for targeted treatments aimed to reduce risky behavior and facilitate positive health outcomes.

Methods: We use EEG to measure post-error positivity (Pe) as an index of error awareness, post-error negativity (ERN) as an index of error processing, and behavioral response time following error as an index of error adjustment.

Approaches for statistical analysis: Post-error reaction-time slowing, a measurement of strategy adjustment after error, will be calculated for each subject in each stimulus condition. Values will be compared between conditions and groups using a two-way ANOVA with 'group' and 'condition' as factors. For EEG analysis, following standard preprocessing procedures, data will be aligned to button-press onset and averaged across subjects to obtain grand-average traces for each group. Topographic maps of scalp voltage at the time of maximum ERN and Pe amplitude at electrode FCz will be constructed for each group for visualization purposes.

Results and conclusions: We observe reduced behavioral performance in all patient groups relative to healthy controls, with the greatest performance reduction observed in HIV-positive individuals with a history of cocaine dependence (HIV/Coc). Error-related negativity was observed in all groups during incorrect NoGo trials, and error positivity within 200-300ms after, consistent with previous studies. Topographic maps show frontally-concentrated Pe and ERN components in HIV-positive (HIV+) and HIV/Coc, which suggests enhanced engagement of frontal areas in HIV+ relative to HIV-negative during error processing.

Poster number: PT012 (SP)

Theme: Attention, motivation, behaviour

Influence of tactile stimulation in adult rats on neurochemical and behavioral parameters in a depression model

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Introduction: Depression is a common chronic disease that pharmacological treatments relieve symptoms; however, they are still far from the ideal. Tactile stimulation (TS) has shown beneficial influences in neuropsychiatric disorders, and its action mechanism is poorly understood. In this study, we investigated the influence of the TS applied to adult female rats previously exposed to a reserpine-induced depression-like animal model.

Methods: Immediately after reserpine (1 mg/Kg/mL, 1x/day, for 3 days), the animals were submitted to TS (15 min, 3x/day, for 8 days, applied with experimenter's hand) or not (unhandled). Imipramine (10 mg/kg/mL) was used as positive control. After, the animals were submitted to forced swimming test (FST) and sucrose preference test. After behavioral assessments, the animals were euthanized to collect plasma and brain tissue to corticosterone measure and western blotting analysis, respectively. This experimental protocol was approved by the Comissão de Ética no Uso de Animais (CEUA-UFSM, number 2359150517, June, 2017), which is affiliated to the Council for Control of Animal Experiments (CONCEA).

Analysis Approach: To statistical analysis, two-way ANOVA followed by Newman Keuls post-hoc test was used for all analysis, when appropriate. One-way ANOVA, followed by Newman Keuls post-hoc test, was used to compare with the positive control. All data are expressed as means \pm SEM and $P < 0.05$ was considered statistically significant.

Results and Conclusion: Behavioral observations in FST and sucrose preference, confirmed the reserpine-induced depression-like behavior, which was reversed by TS. Our findings showed that reserpine increased plasma levels of corticosterone, and TS decrease these levels and reestablished GR in the prefrontal cortex (PFC). Also, reserpine decreased BDNF and TrkB, and increased proBDNF immunoreactivity on PFC, which were reversed by TS. Our outcomes are showing that TS applied in adulthood exerts a beneficial influence in depression-like behaviors, more effective than imipramine. Based on this, our proposal is that TS, in a long-term, could be studied in humans and considered a new therapeutic strategy for neuropsychiatric disorders improvement in adult life, and it may represent an interesting contribution to conventional pharmacological treatment.

Poster number: PT013 (PP)

Theme: Attention, motivation, behaviour

Drosophila models for studying the role of GABA and its receptors in alcohol-induced behaviours**Authors:** Mr Daniel C Ranson¹, Dr Samir S Ayoub¹, Prof Olivia Corcoran¹, Dr Stefano O Casalotti¹¹University of East London, London, United Kingdom

Introduction: Long term use of alcohol can have multiple adverse effects including development of addictive behaviours. The GABA-B receptor is believed to play a role in some of the physiological and behavioural changes that characterise the development of tolerance in response to alcohol(1). We previously demonstrated *Drosophila* as a pharmacological model to demonstrate that administering a GABA-B agonist and antagonist increase and reduce sensitivity to alcohol respectively. These interventions affect the rate of tolerance development, altering the time to sedate 50% of flies per vial following repeated ethanol exposures. To elucidate the role of GABA and its receptors in the development of tolerance, we are now exploiting the extensive genetic tools that this model provides.

Methods: We have developed fly lines in which the expression of Glutamic Acid Decarboxylase (GAD), the enzyme responsible for the synthesis of GABA, is downregulated in an inducible and cell specific manner. Flies expressing GAD siRNA (short interfering RNA) under the control of UAS promoter were crossed with flies expressing both GAL4 (which activates UAS) and the temperature sensitive Gal80ts which inhibits UAS activation at temperatures below 20°C (2).

Analysis approach: In these flies we will be able to downregulate GABA production at specific times during the process of tolerance and other alcohol related behaviours by moving the flies from 18°C when normal production of GAD will occur to 30°C where the GAD RNAi will be expressed. In this model we will be able to better understand the role that GABA plays in tolerance development and to better distinguish the relative contribution of GABA-A and GABA-B receptors in alcohol induced behaviours by using receptor subtype specific agonists and antagonists. The overall aim of these studies is to contribute to the refinement of pharmacological strategies for treating Alcohol Use Disorders.

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Poster number: PT014 (PP)**Theme:** Attention, motivation, behaviour**Comparing behavioural measures of intentional binding****Authors:** Mr Philipp Kaniuth^{1,2,3}, Prof Anil Seth^{1,2}, Dr Warrick Roseboom^{1,2}¹Department of Informatics, University of Sussex, Brighton, United Kingdom, ²Sackler Centre for Consciousness Science, Brighton, United Kingdom, ³Leverhulme Doctoral Scholarship Programme, Brighton, United Kingdom

Introduction: The *Sense of Agency* (SoA) denotes the subjective experience of planning and executing a voluntary action (Haggard & Eitam, 2015). A supposed implicit measure of SoA is *intentional binding* (IB), in which the temporal interval between a voluntary action and its sensory effect is apparently contracted (Haggard, Clark, & Kalogeras, 2002). Three different methods/tasks have been used to measure IB: the Libet clock method (Haggard et al., 2002), interval estimation (e.g., Engbert et al., 2008), and action-effect delay judgments (Kawabe et al., 2013). To date, no evidence exists to support that these tasks measure the same thing - putatively IB. This study seeks to clarify the methodology behind IB, by comparing the perceived intervals between action and effect as measured by the three

methods. If all three track a common process, such as IB, we expect that the magnitudes of the corresponding measures will be correlated within the same participant.

Methods: Each method will be tested in a separate session, and every participant will use all three methods (order counterbalanced). On each trial, participants will voluntarily press a key which will cause a tone after a certain delay (fixed 250 ms in Libet clock; 150, 250 or 350 ms in interval estimation; between 0-500 ms in delay judgement). Depending on the session, participants will (i) report the timing of either their action, or of its putative effect, in the Libet clock task, (ii) directly estimate the delay in interval estimation, or (iii) report whether the putative effect appeared delayed from its action in delay judgement.

Approach for statistical analysis: We will directly compare the magnitude of IB within participants, between tasks, using standard correlation measures (Pearson's correlation coefficient if assumptions met, otherwise Spearman's rho). Bayesian statistics, with the prior for the predicted correlation indicated by test-retest results from existing studies in the perception literature, will be used to infer whether participants exhibit related magnitudes of IB across tasks, and therefore, whether the tasks are likely measuring the same underlying effect of IB. Hypotheses, analyses, and exclusion criteria will be pre-defined and pre-registered using AsPredicted on the Open Science Framework.

Poster number: PT015 (SP)

Theme: Attention, motivation, behaviour

Can't shake this feeling: dorsal ACC GABA+ linked to individual differences in emotional recovery following social evaluative stress

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Introduction: The dorsal anterior cingulate cortex (dACC) plays a crucial role in guiding behavioural responses to environmental challenges. Altered dACC function and GABA+ levels have previously been found in individuals with mood and anxiety disorders. High levels of neuroticism, and its two aspects, withdrawal and volatility, constitute a known risk factor for mood disorder. Neuroticism can be conceptualised as altered threat appraisal and increased reactivity to, and/or poor recovery from, stress, with social stressors being particularly potent.

We hypothesised that dACC GABA+ is linked to trait neuroticism, which in turn is linked to increased stress reactivity and/or slower recovery.

Methods: Twenty-five female participants (mean age 24years) firstly completed the Perceived Stress Reactivity Scale (PSRS) and Big Five Aspects scale (BFAS). On a separate day, participants underwent a ¹Hmagnetic resonance spectroscopy (MRS) scan, using a 20x30x40mm³ voxel to sample dACC. On a third day, the Trier Social Stress Test (TSST) was conducted.

Statistical analysis: Water-referenced, tissue-corrected dACC GABA+ concentrations, corrected for tissue volume, were quantified using Gannet. Self-reported anxiety ratings before, during and after the TSST were analysed using area under the curve (AUC) measures for the 'stress' period (anticipation+task) and the 'recovery' period (Figure 1A). Relationships among PSRS and BFAS neuroticism scores, AUC measures and dACC GABA+ were assessed using Pearson's correlations.

We ran a mediation model, (using PROCESS in SPSS) to test the prediction that dACC GABA+ indirectly influences TSST reactivity via neuroticism.

Results and conclusions: dACC GABA+ correlated positively with neuroticism ($p=0.049$); this was driven by the emotional volatility component of neuroticism ($p=0.018$). dACC GABA+ also correlated with participants' self-reported anxiety during the TSST recovery period (Figure 1B), suggesting that dACC GABA+ levels are associated with how quickly individuals recover from a stressful experience. Supporting this, the only PSRS score that dACC GABA+ correlated significantly with was prolonged reactivity ($r=0.539$; $p=0.007$). The effect of dACC GABA+ on AUC-recovery was however not significantly mediated by neuroticism/volatility.

Our findings suggest that emotional volatility is a risk factor for prolonged reactivity to a stressful social experience. Increased dACC GABA+ correlated positively with both task (TSST) and questionnaire measures of prolonged reactivity.

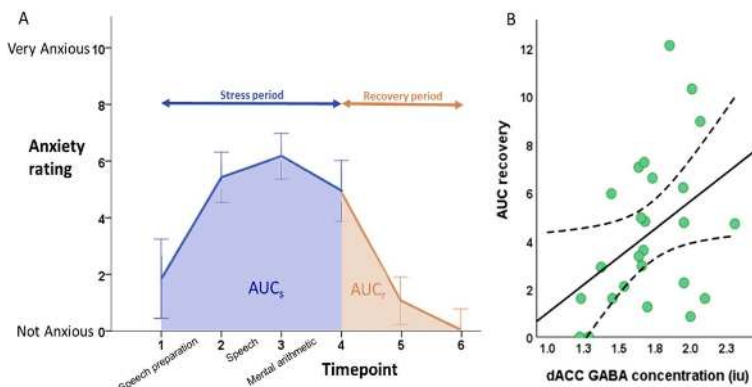


Figure 1: [A] Example participant's self-reported anxiety ratings during the TSST. [B] Scatterplot showing correlation between dACC GABA and AUC. Dotted lines show 95% confidence interval. AUC_S = area under the curve during the stress period; AUC_R = area under the curve during the recovery period.

Poster number: PT016 (PP)

Theme: Attention, motivation, behaviour

Individual differences in perception – linking variability in sensory sensitivity, adaptation and internal noise

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Introduction: For some people, simple sensory stimuli, e.g. certain noises, are reliably aversive. Atypical sensory sensitivity is found in the neurotypical population as well as specific groups, notably autism spectrum disorders, and could be underpinned by atypical adaptation (cf. Lawson et al, 2018) or internal noise (Simmons et al, 2009). In atypical adaptation, stimuli could fail to attenuate over time, becoming aversive, consistently salient and eliciting enhanced neural activity. Such enhanced activations could also be caused by high internal noise (random fluctuations in neural activity), as non-sparse responses have been suggested to cause discomfort (Juricevic et al, 2010). In fact, there might be a link between these two accounts (Mattar et al, 2018). The aim of this study is to examine the hypothesized correlations between adaptation, internal noise and sensory sensitivity, disentangling the latter from the broader autistic phenotype using a within-subject design.

Methods: Participants will be screened for autistic traits and sensory sensitivity through self-report questionnaires. Exp. 1: After adapting to a specific blur level, participants will indicate whether test images with different blur levels appear too blurred/sharp to determine their point of subjective neutrality (PSN) (see Fig. 1). Data will be fit to a function which describes PSN vs. blur, a stable individual trait (Vera-Diaz et al, 2010).

Exp. 2: After adapting to a certain colour distribution, participants will search for a target on a background of distractors with the same/different distribution. Reaction time and accuracy, specifically the facilitation effect of adaptation to a similar background before the visual search task, will serve as measures of adaptation (McDermott et al, 2010).

Exp. 3: Participants will choose the higher-contrast stimulus of two sequentially presented stimuli, which may be the same or not. Performing each comparison twice provides consistency and accuracy measures, used to estimate internal noise (Vilidaite et al, 2017).

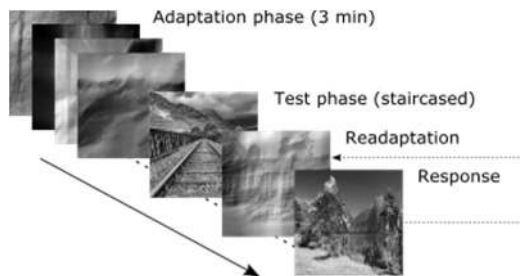


Figure 1: Example trial in exp. 1

Approach for statistical analysis: Linear regression will be conducted using the function parameters from exp. 1, the performance and facilitation effect from exp. 2 and the internal noise estimate from exp. 3 as dependent variables, and sensory sensitivity and autistic traits as independent variables.

Poster number: PT017 (PP)

Theme: Attention, motivation, behaviour

Investigating mental toughness and cognitive performance in pharmaco-resistant epilepsy: a functional near-infrared spectroscopy study

Authors: Mr Ryan McGrath¹

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Introduction: The concept of Mental Toughness (MT) is defined as a personality trait that can determine how people cope with pressure and challenges in life (Clough et al., 2002). MT encompasses Challenge, Control, Commitment and Confidence. However, to date, application in neurological setting awaits empirical investigation. Clough et al. (2002) support that MT should be applied broadly.

The proposed study will monitor functional near-infrared spectroscopy (fNIRS) in patients with epilepsy (PWE), enabling assessment in cognitive abilities and neurological responses across PWE and matched controls.

An impact on quality of life and cognitive impairments particularly in patients with refractory seizures, potentially due to seizure frequency, social stigma, and pharmacological interventions (Taylor et al., 2010).

Assessing performance in cognitive tasks during fNIRS in the proposed sample will offer insight for future application of behaviour change. PWE can later be offered 'Cognitive Profiles' in aid of improving MT and Quality of Life where appropriate.

The study hypothesises a difference between level of Mental Toughness and haemodynamic responses to cognitive testing in PWE when compared with matched controls. Further, a difference in performance is expected.

Methods: Consistent with previous related studies, an opportunity sample of 40 PWE and matched controls of 40 'neurotypical' individuals is proposed. PWE will experience refractory epilepsy, *i.e.*, received >2 unsuccessful anticonvulsants (Kwan et al., 2010).

Participants will complete a 48-item Mental Toughness Questionnaire (Clough, 2002). Sixteen-optode fNIRS will monitor haemodynamic responses in pre-frontal cortices (PFCs) during a range of cognitive tasks: *e.g.*, Colour Stroop, *n*-back, Flanker or Go/No-Go tasks.

Conducive with investigation by McGrath and Marrow (2017), participants will be required to refrain from alcohol for 24 hours beforehand: alcohol can negatively affect cognitive performance thus usage measures are required.

Additional self-report measures of seizure-types, frequencies and medications can assess related anticonvulsant unwanted effects.

Approach for statistical analysis: Three (Task), 2x2 ANOVA (MT group x Control) will be conducted to assess for differences between groups and the three cognitive tasks. A 16x2 (voxel x group) ANOVA will determine any difference between groups by optode, and 2x2 (hemisphere x group) ANOVA. Pairwise comparisons conducted when appropriate.

Poster number: PT018 (PP)

Theme: Developmental neuroscience

An investigation of the relationship and interchange between conduct-related problems and mental health across development in children

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Introduction: Mental health problems as well as conduct-related problems pose significant challenges to the psychosocial well-being of individuals across their lifespan. Early conduct problems in particular are a developmental precursor to adverse outcomes including poor mental health, such as depression and emotional anxiety (Fergusson et al., 2005). We are modelling the relationship between early conduct-related problems and mental health and the interchange between them over development to provide insight for etiological research and to inform policies that combat childhood mental disorders (Kim-Cohen et al., 2003). Understanding this relationship longitudinally will help clarify the variables that can influence it and establish sensitive periods for the interplay between these different symptom domains.

Methods: This study will assess the association between conduct-related problems and mental health in a large-scale population-representative sample of UK children from the Millennium Cohort Study (MCS; Centre for Longitudinal Studies). These measures will be assessed from MCS sweeps 4, 5, and 6 during which the sample was at ages 7, 11, and 14, respectively. Conduct-related problems will be derived from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), while mental health will be calculated as a latent variable from a factor reduction of items of self-report questionnaires regarding feelings and emotional states.

Approach for statistical analysis: From the Child's Health interview completed by the parents, the sample will be clustered into profiles of those who do not exhibit mental health issues and those who have mental health illnesses. This grouping will be compared to the groups provided by clustering on SDQ conduct problems scores for consistency. Linear regressions will be done to assess whether children who score high on conduct problems from the SDQ predict decreased mental health with age, sex, and SES as covariates. Longitudinal analyses using structural equation modelling will be completed to explore whether conduct-related problems relate to symptoms of mental health changing at a developmental range and if this model varies depending on health profiles, age, sex, and SES.

Poster number: PT019 (SP)

Theme: Developmental neuroscience

Methylmercury exposure causes developmental delay in drosophila larvae

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Introduction: We have recently reported that methylmercury (MeHg) in the diet inhibits the activity of alcohol dehydrogenase in *Drosophila melanogaster* (fruit fly), which results in increased recovery time after alcohol exposure, and it also causes sexual dysfunction. We have now studied the effects of MeHg (5-20 μ M) on the development of *Drosophila* larvae. Different stages of *Drosophila* development are: embryo 1st instar larva 2nd instar larva 3rd instar larva pupa fly.

Methods: Various concentrations of MeHg were mixed with the food. Flies were transferred to culture vials in the evening and removed next day in the morning. The development of larvae was investigated. Total number of flies coming out of food containing various concentrations of MeHg were counted. The length of flies was measured after 5th day of MeHg exposure. Larvae (1-5 ½ days old) were transferred to food vials containing 20 μ M MeHg, and their development was studied. The movement of larvae was investigated by video monitoring, and analyzing the data with worm track (wrMTrack) program using ImageJ.

Statistical analysis: The data was analyzed with Student t-test.

Results and Conclusions: We have observed that MeHg affects the development of larvae in a dose-dependent manner. At 20 μ M MeHg exposure, the development of larvae was completely inhibited. MeHg also decreases the length of larvae in a dose-dependent manner. To understand whether MeHg affects all stages of *Drosophila* development, we treated different stages of *Drosophila* with 20 μ M MeHg. Our data suggest that MeHg exposure to larvae until 3rd day affected the development. If the larvae are exposed to MeHg on 4th, 5th and 5 ½ days, the effect of MeHg decreased depending upon the age of larvae. If larvae were exposed to MeHg on 5 ½ day, there was no effect on metamorphosis from pupae to fly. We also studied the effects of MeHg (7.5 μ M) on the larvae behavior (movement) after 5 days of exposure. The results indicate that MeHg affects the behavior of larvae, suggesting that MeHg exposure may also affect neuronal functions.

Poster number: PT020 (SP)

Theme: Developmental neuroscience

Perceptual closure in children with autism spectrum disorder

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Introduction: Visual objects may be easily identified from a picture or a line drawing of the object. Up to a point, objects can also be identified from partial line drawings from which segments have been removed, but when objects are sufficiently fragmented they are no longer recognizable. When the process is reversed and unidentifiable fragmented images are first presented and in subsequent presentations segments of the image are added, there is a point at which the object is recognized or “closed” despite remaining incomplete. Using high-density electroencephalography (EEG) it is possible to detect the moment of closure in the larger negativity, localized over lateral occipital regions ~250-400 ms after stimulus presentation, when participants report the object recognized. Although previously shown in adults, here we used this approach to determine whether the closure negativity (Ncl) is also present in typically developing (TD) children ages 6-17 and also in children with autism spectrum disorders (ASD). We hypothesize that the ASD group may have difficulty closing fragmented line drawings and will show reduced or absent Ncl.

Methods: High density (128 electrode) EEG was recorded as images were presented. Each image was presented centrally for 750ms. The screen was blank for the subsequent 800ms after which the participant reported whether they could identify the object. If 'no', the next image in the sequence with additional segments was presented. If 'yes', the fragmented image of a new object was presented. A total of 250 images were presented across 25 blocks. Epochs around image presentations were, post hoc, sorted into 4 groups: identification, 1, 2, and 3 prior.

Approach: We compared the Ncl amplitude in TD children, TD adults, and children with ASD using one-way analysis of variance. Parieto-occipital and occipitotemporal sites consistent with dorsal and ventral Ncl generators were used for analysis.

Results: TD children have a clear Ncl, although it appears reduced compared to that observed in adults. Children with ASD show an even further reduced Ncl when compared to TD children.

Poster number: PT021 (SP)

Theme: Developmental neuroscience

Developmental changes in synaptic and dendritic structure and function in the mouse barrel cortex

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Introduction: Appropriate establishment of synaptic compartments during development is essential for functional synaptic transmission. Synaptic receptors are clustered by members of MAGUK scaffolding proteins. SAP102 is expressed early postnatally and is involved in receptor trafficking, while PSD95 is the main MAGUK in the mature brain and it promotes synaptic stability. To assess developmental patterns of MAGUK expression, we measured location-specific distribution of these proteins at early postnatal stages in the mouse barrel cortex. In mature circuits, dendritic spikes are local nonlinear dendritic potentials that increase the computational power of neurons and contribute to synaptic plasticity. We investigated the presence of dendritic spikes in immature brain slices in order to establish their relation to synaptic maturation.

Methods: Thalamocortical brain slices from P5-20 PSD95-eGFP, SAP102-mKo knock-in mice were imaged using 2-photon and confocal microscopy. Profiles of fluorescence across cortical layers in the barrel cortex were extracted using ImageJ.

Whole-cell patch clamp recordings of layer 4 spiny stellate neurons and focal synaptic stimulation were used to stimulate synapses on a single dendritic branch at increasing intensities to elicit dendritic spikes in acute barrel cortex slices. Input-output curves of the synaptic responses of the spiny stellate neurons were analysed to assess dendritic spikes emergence during postnatal maturation.

Approach for statistical analysis: MAGUKs: average profiles of fluorescence across different layers and the areas under the curve for each layer were calculated in each age group. Comparisons of group means were tested using two-way repeated-measures ANOVA with Bonferroni's post hoc test. Throughout, significance threshold was set at $p < 0.05$.

Dendritic spikes: the average maximal EPSPs in control and hyperpolarised conditions for each age group were tested using paired Student's two tailed t-test.

Results and conclusions: Fluorescent puncta of both proteins first localised in layer 1, barrels in layer 4, and layer 5A. Subsequently, the fluorescence increased in layer 2/3. Both proteins followed a similar distribution pattern, but SAP102 preceded PSD95.

Synaptic stimulations did not lead to a nonlinear response in the input/output curve, characteristic of dendritic spikes, at any of the ages investigated (P5-20), suggesting dendritic spikes were not elicited in these young neurons.

Poster number: PT022 (PP)

Theme: Developmental neuroscience

Morphological profiles and the link to cognitive performance in childhood

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Introduction: We are starting to observe how changes in cognition and behavior are linked to changes in the network organization of the brain. We can construct a structural connectome during aging and examine which mechanisms shape the developing organization of the connectome. The classical approach is to define groups using a behavioural phenotype and compare brain measurements across these groups. But many of behavioral measurements involved a degree of subjectivity, and we may be grouping individuals with diverse underlying etiologies. We have become interested in whether we use neural data itself to create profiles, and then test how these neural groups relate to behavioural and cognitive measures. This approach holds the potential to identify groups of children with more homogenous underlying brain organization. Morphological brain measures are quite variable between individual subjects, so a big sample size is necessary to get a robust and reproducible result. We expect to find gray matter patterns (networks) specific to different cognitive profiles. We will use data from a large-scale (N=**) study of cognitive difficulties in childhood, called CALM (Center for Attention, Learning and memory), which contains right cognitive, behavioural, learning and neural measures.

Methods: We will use surface-based morphometry measurements, including thickness, gyrification and sulci depth extracted from anatomically-defined regions. These measures will be introduced to a clustering pipeline, including multidimensional scaling and subsequent density based clustering. If we can establish that there are different groups of children, who are distinguishable at a level of cortical morphology, then we will examine how they differ on our other measures. Finally, we would like to apply structural equation modelling to understand relationships between the behaviour and brain morphology to make a link between them.

Approach for statistical analysis: We will use a density based clustering algorithm like HDBSCAN. We will perform a Silhouette analysis for internal validation and cross validation for generalizability dividing the data set in training and testing subsets. If robust groupings exist within the neural data then we will use these to explore the cognitive and behavioural consequences of these different group allocations within our sample.

Poster number: PT023 (SP)

Theme: Developmental neuroscience

Induced pluripotent stem cell modelling for the role of NRXN1 deletion in Autism Spectrum Disorder

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Introduction: Autism spectrum disorder (ASD), a multi-factorial disease, has co-morbidity with epilepsy, intellectual disability and developmental delay. The pre-synaptic protein Neurexin1 (*NRXN1*) signals bi-directionally through both excitation and inhibition, by forming synaptic complexes with various post-synaptic proteins. Deletions and/or mutations of the *NRXN1* gene have been implicated in a number of neurodevelopmental diseases including ASD. However, patient-derived disease models are lacking. Induced pluripotent stem cells (iPSCs) have the potential to revolutionize human disease modelling *in vitro* and to target unmet clinical needs. We hypothesize that *NRXN1* α gene deletion may dysregulate the balance of synaptic excitation and inhibition.

Methods: Using skin biopsies from ASD patients with *NRXN1* α deletion and healthy donors, we converted dermal fibroblasts into iPSCs by reprogramming. The iPSCs were differentiated into cortical neurons. Neuronal function were investigated using single cell patch clamping and calcium imaging. Furthermore, RNA sequencing was performed to investigate the underlying molecular mechanism.

Approach for statistical analysis: Statistical analysis was performed using ttest or Mann Whitney U test with a level of significance set for $p < 0.05$.

Results & Conclusions: 100-day neurons with *NRXN1* α deletion displayed higher potassium and sodium currents, with selectively impaired depolarization and repolarization characteristics. The action potential amplitude was significantly increased, whereas the action potential threshold was decreased in *NRXN1* α deletion neurons. The repolarization slope was significantly increased and consequently, the repolarization duration was decreased. live cell calcium imaging on the 100-day neurons with Fluo4-AM showed neuronal networks displayed inherent spontaneous firing activity with a significant increase in the frequency and duration of calcium transients in *NRXN1* α deletion neurons. The transcriptome analyses have demonstrated substantial up-regulation in ion channels and transporter activity, with voltage-gated calcium channels (VGCCs), voltage-gated potassium channels (VGKCs) and voltage-gated sodium channels (VGSCs) being mostly enriched among the differentially expressed genes. In addition, the KEGG pathway analyses have revealed further impairments in calcium signaling, vesicle exocytosis and synaptic transmission. Our results show for the first time that heterozygous deletions of *NRXN1* α gene impair the electrical firing of human neurons, in addition of their calcium transients, illustrating the value of this patient-derived iPSC model with *NRXN1* α deletion for studying ASD disease phenotypes.

Poster number: PT024 (SP)

Theme: Developmental neuroscience

Foetal origins of cortical differences: Normal birth weight variation, cortical morphology in adolescence and risk of psychopathology

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Introduction: Being born underweight (< 2.5 kg) is a risk factor for a range of adult psychiatric disorders. Most studies have focused on differences between low and normal birthweight individuals, however the effect of birthweight (birthweight) on the odds of developing a psychiatric illness appears to be a linear one that spans both categories: the odds of having any adult psychiatric diagnosis is significantly elevated even for the lower end of normal birthweight (2.5-3.5kgs) compared to the higher end of “normal” (3.5-4.5kg)¹. Reports have found surface area (rather than thickness) in late-developing areas of cortex (rather than subcortical or primary sensorimotor areas) is the structural neural measure that most closely covaries with normal variation birthweight². In this study we investigate: (i) normal variation in birthweight and cortical surface area in a general population sample of adolescents (age 12-17) and (ii) the relative effects of birthweight on a range of emotional, social and cognitive constructs.

Method: A general population sample of children (mean age 12) completed clinical psychiatric interviews, cognitive testing and psychological questionnaires. Cases of birthweight (recorded from retrospective parental reports) outside the 95% CI were removed and the resultant range (1.2-4.5kg) was split into tertiles. T1 weighted 3T sMRI scans were acquired for 95 children (44 female) and analysed in Freesurfer (v6.0.0). Variation in cortical surface area (whole hemisphere & regional) was compared across birthweight groups (low, middle, high) controlling for sex, age at the scan and intracranial volume.

Preliminary Results: Those with the lowest birthweight (1.2-3.35kg; n = 31) had significantly lower surface cortical area in the left hemisphere globally compared to the other tertiles, which was driven by differences in specific higher-order association cortex, and right fusiform gyrus. These group difference remained significant even after removing those with low birthweight (< 2.5kg). Functional correlates of these birthweight-related regions are tested and discussed.

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Poster number: PT025 (SP)

Theme: Developmental neuroscience

Parvalbumin interneurons disruption in a mouse model inflammatory perinatal brain injury

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Altered function of parvalbumin interneurons has been associated with a number of neurodevelopmental disorders, having been implicated in the neurobiology of working memory and attentional shift. Preterm birth, affecting approximately 50,000 babies in the UK each year, increases the risk of developing cerebral palsy, autism, attention deficit hyperactivity disorder and other neurodevelopmental disorder. A delayed appearance of interneurons has recently been describe in the preterm brain (Panda et al 2018), but comparisons with control brains is difficult in human studies. Here investigate interneuron maturation in a well-established and controlled mouse model of inflammatory-perinatal brain injury.

CD1 mice were treated with IL-1 β or saline (5 μ l per animal) in bi-daily i.p. injections from P1 to P4, with a final injection on P5 as previously described (Favrais et al 2011). Treated animals were terminally anaesthetised at P10 or P40, and brain tissue was perfusion fixed with 4% PFA. Tissue was dehydrated, embedded in paraffin and cut in 10 μ m coronal sections. Tissue sections were stained with antibodies against interneuron markers parvalbumin, neuropeptide Y, VIP. Cell counts were performed using ImageJ.

At P10 in this mouse model there are no gross changes in cortical structure. However, we found a significant decrease in the number of parvalbumin interneurons in layers IV, V and VI of the somatosensory (barrel) cortex at

P10. These neurons also showed reduced arborisation (hopefully this is true! any details to add here?). By P40, there was still as small, but significant difference in the number of these neurons in the somatosensory cortex. However, there were no changes in the number of NPY or VIP positive interneurons in the same brain region. The work shows a disruption in parvalbumin interneurons that occurs from early in brain development, and persists in a mild form to the mature brain. The functional consequences of these morphological changes need to be further assessed, but likely to contribute to the behavioural dysfunction previously reported in this model.

Poster number: PT026 (SP)

Theme: Developmental neuroscience

High-Density Electrophysiological measures of auditory sensory processing as potential biomarkers of CLN3 disease

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Background: CLN3 disease is among a group of lysosomal storage disorders that lead to neurodevelopmental regression. This decline renders behavioral assessment of sensory-perceptual and cognitive function difficult, at best. High-density electrophysiological recordings allow for objective examination of sensory-perceptual and cognitive processing. Here, we characterize auditory sensory memory in CLN3 with the mismatch negativity (MMN) of the auditory evoked potential (AEP) to duration changes.

Methods: AEPs to regularly occurring tones (1 kHz; 100ms duration) occasionally interrupted by longer duration deviants (1 kHz; 180ms) were recorded from 22 participants with CLN3 who were divided into three CLN3-disease-stage groups (mild n=9; moderate n=9 and severely impaired n=4) based on clinical phenotypes and 22 age-matched typically developing (TD). MMN was measured by comparing the standard and deviant responses for 3 experimental conditions, where stimulation rate was varied. Effects of disease severity on AEPs were assessed using the Rett Syndrome Severity Scale.

Analysis approach: The primary outcome measures are electrophysiological response amplitudes (P1, N1, MMN, P3a). Comparison of electrophysiological measures among groups will be performed using mixed-effects models. Advantages of this approach in modeling EEG data have been previously described (Payne et al., 2015; Tremblay & Newman, 2015). Allowing for the modeling of both discrete and continuous variables at multiple levels of variation, mixed-effects models are particularly useful when analyzing complex data. Importantly, compared to the traditional ANOVA approaches, mixed-effects models are a) more flexible in dealing with unbalanced and missing data; and b) more flexible regarding statistical dependencies arising from repeated measures.

Results and Conclusion: Preliminary data acquired from fronto-central scalp electrodes revealed striking within group (CLN3) differences across all experimental conditions. Specifically, the mildly impaired group produced robust duration-evoked MMN responses that were comparable to those produced by age-matched controls across all conditions. The MMN response was progressively reduced in amplitude as a function of disease severity. These disease-stage specific AEPs are promising biomarker candidates that may have utility in tracking the natural progression of CLN3 and efficacy of current and future therapies in the absence of overt behavioral responses, particularly in CLN3, where conventional cognitive evaluation becomes increasingly challenging with disease progression.

Poster number: PT027 (PP)

Theme: Developmental neuroscience

From Blastula to Infinity: Pax6 and Cortical Cell Specification

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Introduction: Two broad cell types can be found in the neocortex: principal cells (PCs) (mostly glutamatergic) and cortical interneurons (cINs) (mostly GABAergic). cINs progenitors are born in the ganglionic eminences (GEs) of the ventral telencephalon and then migrate to their final position at the cortex. PC progenitors (radial glia) are born in the cortex and eventually give rise to postmitotic PCs via direct lineage and differentiation or via intermediate progenitors. Pax6 is a transcription factor expressed at different points during mammalian neural development (Manuel et al., 2015). In a Pax6 conditional knockout mouse model we found that the removal of Pax6 in the cortex generates an ectopic population of cells under the cortex (ectopia). These are cortical born (cKO GFP reporter) but express GABAergic markers GAD67 and Dlx1. The aim of this project is to understand what the role of Pax6 is in the highly organized cytoarchitecture of the cortex and explore the possibility that the absence of Pax6 may lead to an increased probability of radial glia to generate interneuron-like neurons.

Methods: Patch-clamp electrophysiology was used to investigate the electric properties of ectopic cells and layer V PC of the somatosensory cortex of postnatal mutants and controls (P3-P10). Preliminary results indicate that cell at the ectopia have a very limited ability to fire action potentials. The intrinsic properties of mutant mice appear to be within the range expected for somatosensory cortex PCs. The morphology of these cells can be recovered using biocytin-streptavidin binding. The synaptic properties of will also be explored using electrophysiology. We are also interested in whether we can detect cortical born interneurons in the adult mouse using immunohistochemistry.

Analysis Approach: We aim to describe the cells at the ectopia in order to determine their level of development. At the somatosensory cortex we want to explore and compare the developmental trajectory of PCs electrophysiological properties from P3 to P10 (using Signal, R and Python software). Sholl analysis to be used for neuronal morphology exploration.

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Poster number: PT028 (SP)

Theme: Developmental neuroscience

Adaptive Working Memory Training Increases Functional Connectivity within the Dorsal Attention Network

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Introduction: Working memory training typically improves performance on untrained working memory tasks, but we know little about the cognitive and neural mechanisms that explain transfer.

Methods: In this study, 28 typically developing children aged 10-14 years completed a battery of eight working memory tasks and resting-state fMRI before and after either an adaptive or a non-adaptive working memory training programme.

Analysis Approach: Functional connectivity was examined between four regions within the Dorsal Attention Network.

Results and Conclusions: Overall working memory performance significantly improved in the adaptive training group compared to the non-adaptive training group ($p = 0.021$). Furthermore, adaptive training was associated with increased functional connectivity within the dorsal attention network, between the left and right intraparietal sulci ($p = 0.005$), compared to non-adaptive training. Working memory training may increase performance on working memory tasks through attentional mechanisms, whereby the repeated co-activation of fronto-parietal regions during training enhances connectivity and attentional control.

Poster number: PT029 (SP)

Theme: Learning and memory

Identification and characterisation of a gene cluster core to hippocampal memory formation

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Memory formation and recall are fundamental processes that involve information processing and consolidation that control cognitive function. During the learning event, a cascade of molecular signals are initiated recruiting genes that translate to proteins to mediate morphological alterations of synapses in the hippocampus, a central region for memory consolidation. Previous studies suggest that the early phase (0-6h) of memory consolidation involve several waves of transcriptional regulation and subsequent protein expression changes that drive synaptic remodelling and restructuring resulting in formation of new synaptic connections. This growth phase seems to be followed by selective retention and pruning of synapses to restore the circuit to the baseline level of connectivity. Much of the molecular underpinnings of these events remain poorly elucidated.

Recently, we have revisited a temporal microarray study we conducted looking at increasing time points following either water maze or passive avoidance learning. We found 609 and 700 genes to be transcriptionally regulated across 24h post-learning following spatial learning and passive avoidance conditioning, respectively. Comparing those gene lists, we were able to find an overlapping cohort of 135 genes regulated following both tasks. This cohort could identify a core memory consolidation-specific program that is recruited regardless of the nature of the task. We have begun to characterise the function and transcriptional regulation of these genes. Using primary hippocampal cultures, we were able to characterise morphological changes exerted by two members of the cluster, midkine and klotho, which seem to mediate distinct effects on the growth of neuronal processes. Furthermore, we have been able to show that the excitatory neurotransmitter glutamate controls the expression of both proteins. We then tested the potential precognitive effect of midkine through ICV cannulation and we found that midkine enhances the recall in water maze and olfactory reward association learning paradigms. Finally, we have used genomatrix promotor analysis software to identify several potential transcriptional regulators of the cognition-associated genes and have confirmed the classic, memory-associated transcription factor CREB to be a regulator of several genes in the cognition-associated cluster. These studies begin to dissect the function and transcriptional regulation of a core cognition-associated gene cluster regulated during memory consolidation.

Poster number: PT030 (SP)

Theme: Learning and memory

Neural mechanisms of age-related decline in episodic memory precision

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Episodic memory declines with older age, but the neurocognitive mechanisms of this decline remain debated. Recent work has highlighted reduced precision of retrieved memories as one factor contributing to age-related memory loss, however the neural underpinnings of this deficit are yet to be characterised. In the current functional magnetic resonance imaging (fMRI) study, healthy young and older participants encoded stimuli displays that consisted of one object overlaid on a scene background. The location and colour of the objects at encoding were randomly selected from circular feature spaces (0-360 degrees), and at retrieval, participants reconstructed either the location or the colour of each object using a continuous response dial. Computational modelling of retrieval errors allowed for detailed assessment of memory fidelity. Behaviourally, we observed age-related decreases in retrieval precision across the two feature conditions. At the neural level, univariate fMRI analyses indicated that retrieval-related activity in the angular gyrus tracked memory precision in both age groups. However, at encoding, we observed a diminished relationship between activity in visual regions and subsequent memory precision in the older group. Furthermore, encoding activity in the lateral prefrontal cortex was a significant predictor of memory precision in the young group only. Together, the results implicate functional differences at encoding as contributing to the age-related deficit in episodic memory precision.

Poster number: PT031 (SP)

Theme: Learning and memory

Fast mapping (fm) in adults: a proposed attempt to replicate evidence from implicit memory

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Introduction: It has been claimed that adults can learn new knowledge within the same day using a Fast Mapping (FM) procedure, and that this occurs directly in cortex without hippocampal involvement (Cooper et al., 2018). Using an implicit reaction time (RT) measure of lexical competition, Coutanche and Thompson-Schill (2014) reported that non-words were learned (consolidated) as the names of novel objects under FM, but not under standard explicit encoding (EE). We recently failed to replicate this same-day competition effect, and found instead evidence of semantic priming. Here, we preregister a further replication study.

Methods: Healthy adults (18-40), tested online, complete one study condition (either FM or EE), and then an implicit (and explicit) memory test after a 10-minute delay. Study involves learning non-words (e.g. "ganaxy") as the names of unknown objects (presented as pictures). One half of objects are natural; the other half man-made. In the FM condition, the name is inferred from a question pertaining to the unknown object and a second, known object; in the EE condition, participants are presented with just the name and unknown object and told to learn.

In the implicit test, RTs for a "natural/man-made" decision to probe words (e.g. "galaxy") are contrasted as a function of whether or not a competitor ("ganaxy") was presented at Study. This competition effect is then compared for competitors learned as names of natural vs man-made objects.

Approach for statistical analysis: To replicate our previous difference in competition effect for natural versus man-made words in the FM condition, N=30 participants provides 90% power. Coutanche and Thompson-Schill's fast mapping account predicts a slowing of RTs in FM but not EE condition, regardless of natural/man-made category. Our semantic priming account predicts that RTs depend on congruence between probe word category and object category (faster when congruent and slower when incongruent), in both FM and EE conditions.

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Poster number: PT032 (PP)

Theme: Learning and memory

Thermo-ingrams: innate neural representations of temperature regulation

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Could instincts and memories have isomorphic underlying neural mechanisms to sense and react to the environment? It is known that the brain instinctively responds to hot or cold environments through the activation of specific neuronal populations in the hypothalamus known as warm-sensitive neurons (WSN) and cold-sensitive neurons (CSN), which relay information to downstream areas of the brain and periphery to initiate physiological or behavioural mechanisms to keep the core temperature within the homeostatic range. Similarly, the memory recall process requires neurons encoded in a memory engram to be activated by artificial or natural cues to elicit recall. We hypothesize that identifying and activating WSNs and CSNs in the hypothalamus at room temperature will elicit a behavioural response similar to the natural response elicited by a hot or cold environment.

To better understand the distribution of WSNs and CSNs, we will focus on the preoptic area (POA) of the hypothalamus, which plays a critical role in both warm and cold-sensing. To identify CSNs and WSNs, we will expose adult (p56) C57BL/6J mice to a temperature challenge (cold=4°C and warm=37°C, n=4/group) for 4 hours, followed by immediate perfusion, extraction of brains, and immunohistochemistry. Expression of the immediate-early gene *c-fos* will identify WSNs and CSNs in the POA. *c-Fos*⁺ neurons will be counted and compared across cold, neutral, and warm conditions using an ordinary one-way ANOVA and Tukey's multiple comparison test.

After identifying CSNs and WSNs, engram labelling techniques will be used to tag hypothalamic neurons *in vivo* that are active during an experience of hot or cold exposure (n=10/group). Once the CSNs and WSNs are labelled, we will optogenetically re-activate these neuronal populations by administering blue light to the POA. To see whether activating these neural networks is sufficient to drive behavioural responses, we will measure hot/cold-seeking behaviours during the temperature challenge and compare these results (using ordinary one-way ANOVA and Tukey's multiple comparison tests) to the behavioural responses exhibited during optogenetic activation of CSNs/WSNs when the animal is at room temperature. The results of these experiments will elucidate the fundamental neurobiological representations underlying instinctual homeostatic responses to hot and cold exposure.

Poster number: PT033 (SP)

Theme: Learning and memory

Emergence of working memory in macaque cortical areas with high neurotransmitter receptor density

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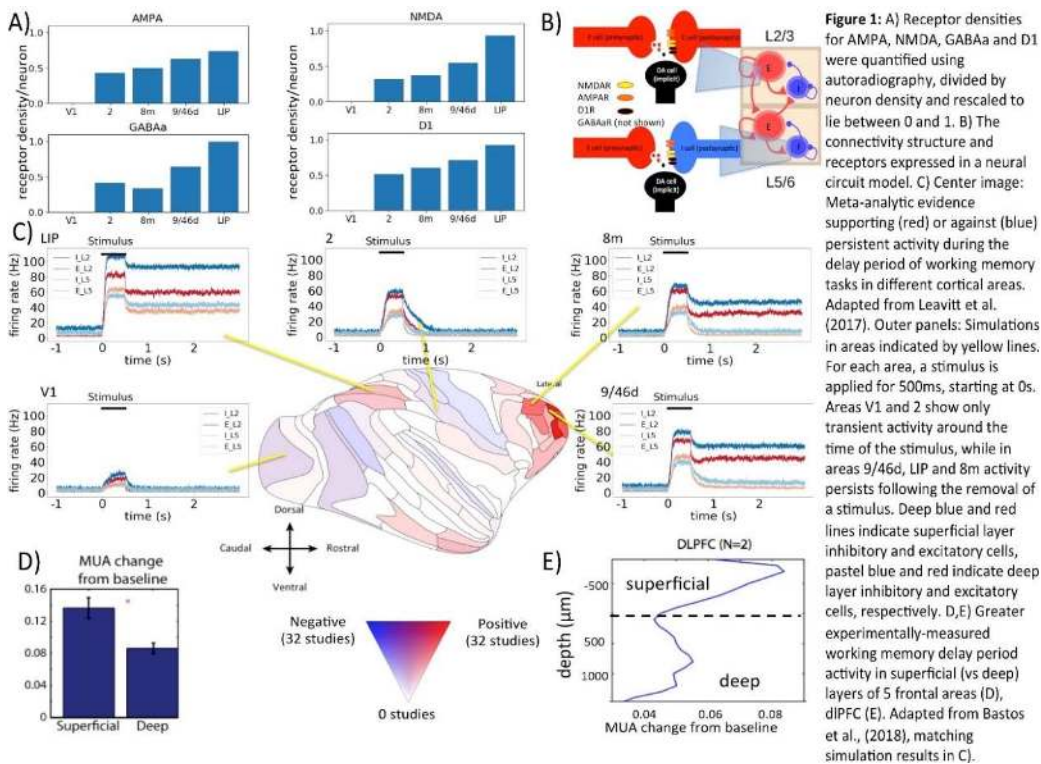
Introduction: The rapid advance in the ability to concurrently record activity from large parts of macaque cortex has led to a surge in interest in distributed cognitive functions such as working memory. This requires a theoretical framework capable of explaining how working memory activity emerges in some areas of cortex, but not others (1). We set out to investigate whether measured differences in densities of neurotransmitter receptors across macaque cortex could explain this phenomenon.

Methods: We quantified NMDA, AMPA, GABA_A and dopamine D1 receptor densities in macaque areas V1, LIP, 2, 8m, and 9/46d using in vitro receptor autoradiography (2) (Fig1A). Receptor densities were divided by neuron density (3). For each area, we simulated a neural circuit model of interacting excitatory and inhibitory neurons in superficial and deep layers, with realistic synaptic dynamics (Fig 1B). Critically, the circuit models for each area were identical except for the experimentally measured receptor densities. We simulated the effect of a brief stimulus input to each area.

Approach for statistical analysis: A null distribution was created by running simulations based on 1000 receptor patterns, randomly drawn from within the experimentally-observed range.

Results and conclusions: The examined areas differ considerably in their receptor expression patterns (Fig 1A). Early sensory areas (V1 and 2) showed a transient response to a stimulus, while multimodal frontal and parietal areas (LIP, 8m, 9/46d) showed persistent activity after the stimulus was turned off, matching experimental findings (Fig 1C) (1), and differing from chance (p=0.03). Furthermore, superficial layers showed greater delay period activity compared to deep layers (Fig 1D), replicating recent findings from laminar recordings during working memory tasks (4). Thus, differences in receptor densities across cortical areas may explain why persistent activity during the delay-period of working memory tasks is observed in some, but not all areas of cortex.

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Poster number: PT034 (SP)

Theme: Learning and memory

Distinct hippocampal-thalamic-prefrontal circuits for associative recognition memory encoding and retrieval

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Associative recognition memory, the ability to associate an object with its location or position in a sequence, is critically dependent upon a neural network which includes the medial prefrontal cortex (mPFC), hippocampus (HPC) and nucleus reuniens (NRe) of thalamus (Barker & Warburton 2011, 2018) which are anatomically interconnected. While the key nodes for associative recognition memory have been identified, how these brain regions interact during the different stages of memory formation is poorly understood. This study aimed to investigate how information moves between these brain regions during the encoding and retrieval of associative recognition memory by deactivating specific anatomical projections between these brain regions.

Projection specific deactivation was achieved using either optogenetic or chemogenetic approaches in male lister-hooded (LH) rats. To deactivate a projection with optogenetics an AAV vector expressing the inhibitory opsin ARCH3.0 was injected into the somatic site of the projection and optrodes were implanted into the axonal target, thus to deactivate NRe→mPFC projections, the AAV vector was injected into NRe and the optrode was implanted into mPFC. The projections deactivated with optogenetics were: iCA1→mPFC, NRe→mPFC and mPFC→NRe. NRe→HPC projections were investigated via chemogenetic manipulation through injection of an AAV vector expressing the inhibitory DREADD receptor (hM_{Di}) in NRe combined with guide cannula implantation into both the dorsal and intermediate HPC. Associative recognition memory was tested using a range of different spontaneous preferential exploration tasks with deactivation of the projections during either memory encoding or retrieval. Performance in associative recognition memory tasks was compared using a two-way or one-way ANOVA and post-hoc comparisons used a Bonferroni correction.

Deactivation of CA1→mPFC and NRe→mPFC projections selectively impaired associative recognition memory encoding, in contrast deactivation of mPFC→NRe projections selectively impaired memory retrieval but not encoding. Deactivation of NRe→HPC projections impaired both the encoding and retrieval of associative recognition memory but with distinct anatomical loci in dHPC and iHPC between encoding and retrieval. Thus this study has revealed distinct networks which are critical for associative recognition memory encoding and retrieval.

All animal procedures were performed in accordance with United Kingdom Animals Scientific Procedures Act (1986) and associated guidelines.

Poster number: PT035 (SP)

Theme: Learning and memory

Catecholaminergic neuromodulatory system in the nucleus reuniens and its role in recognition memory

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There is growing evidence concerning the role of the nucleus reuniens (NRe) of the thalamus in several cognitive domains. For example, recent work has demonstrated that the NRe is critically important for the acquisition and retrieval of long-term associative recognition memory (Barker & Warburton, 2018). However, little is known about the neurochemical features of the NRe and its functional implications. Therefore, this study aimed to provide an anatomical description of the catecholaminergic system in the NRe and to investigate the contribution of the catecholaminergic system within the NRe to recognition memory formation.

Retrograde tracers fast blue (3% solution in PBS), cholera toxin subunit B (1% solution in dH₂O) and fluorogold (4% solution in dH₂O) were injected into the NRe. Following a 7 day survival period, coronal brain sections were prepared and stained with an antibody against tyrosine hydroxylase (TH). To investigate the role of catecholaminergic neuromodulation in the NRe in recognition memory, male Lister-hooded rats received intra-NRe injections of the neurotoxin 6-OHDA to create selective catecholaminergic lesions. A sham control group also underwent surgery.

Distinct components of associative and non-associative recognition memory were assessed by using variations of a spontaneous preferential exploration task (Dix and Aggleton, 1999).

Independent samples t-test were performed to examine the effects of 6-OHDA lesions on recognition memory. All data was normally distributed and equal variances was assumed (tested using the Shapiro-Wilk test and Levene's test, respectively).

The retrograde tracing study revealed that the NRe receives a catecholaminergic input from the A13 cell group (located in the medial zona incerta) and A6 cell group (locus coeruleus). Further, we found that 6-OHDA lesioned animals were impaired in an associative recognition memory task, object-in-place when tested at a 3-hour delay but not following a 5-minute delay. Performance deficits were also observed in an object temporal order task while performance in a novel object preference task and object location task was unimpaired. Taken together our data suggests that long-term associative recognition memory is dependent on catecholaminergic neuromodulation in the NRe which may be modulated by catecholaminergic input from the A13 and/or A6 cell group.

Poster number: PT036 (SP)

Theme: Learning and memory

Time course of multisensory processing for audiovisual object recognition

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Introduction: The majority of objects that we interact with in the natural environment are multisensory, stimulating multiple sense organs and leading to representations in a distributed sensory cortical network. Multisensory objects that are frequently encountered lead to strong associations across this network, with the end result perception of a unitary object. However, we know relatively little about the cortical processes sub-serving multisensory object formation and recognition. This is surprising given their relevance to learning to read (e.g., associating graphemes with phonemes) and to ubiquitous other tasks. To advance our understanding in this important domain, the present study investigated the brain processes affected by the learning and identification of novel visual-auditory objects.

Methods: Thirty adults were remotely trained for a week to recognize, with 100% accuracy, a novel class of multisensory objects (3D shapes paired to complex sounds), while data were live streamed to the lab via an Android device. High density event related potentials (ERPs) were recorded to the unisensory (shapes or sounds only) and the multisensory (shapes and sounds) stimuli, before and after the intensive training.

Approach for statistical analysis: We differentiated multisensory effects by comparing individual ERPs to the multisensory versus the unisensory stimuli, and the summation of the unisensory responses. Moreover, we compared ERPs before and after training, to map the evolution of multisensory cortical responses between initial exposure to full consolidation (post-training) of these audiovisual pairings into a well-learned class of multisensory objects.

Results and conclusions: We report three major multisensory effects: 1) a before-training enhancement of the late responses (400-700 ms) over frontal scalp, possibly reflecting an initial object learning process; 2) an early after-training enhancement (100-150 ms) over left parietal regions, consistent with modulation of the visual N1 for object recognition and 3) another after-training enhancement (150-200 ms) with a topography over parieto-occipital scalp in response to the general multisensory object class. Results from this study provide support for multiple stages of processing of multisensory object learning and recognition that is subserved by an extended network of cortical

areas. This innovative work significantly contributes to our understanding of multisensory object representations, and could shed light on developmental learning disorders associated with multisensory integration.

Poster number: PT037 (SP)

Theme: Learning and memory

Rule-based modelling of AMPA receptor regulation at the synapse

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Introduction: Long-term potentiation involves an increase in AMPA receptor number and activity in the postsynaptic neuron. This process is finely regulated and the overall AMPAR conductance depends on a combination of features, including subunit composition, phosphorylation, ubiquitination, ligand binding, and anchoring in the post-synaptic density.

We present here a computational model of synaptic AMPAR regulation that takes all those functional states into account. Our aim is to use this model to explore how AMPARs are stabilised at the synapse, and which factors play major roles in this stability. We also aim to explore the unstable state definitions leading to LTP and LTD proposed by Benke & Traynelis (2018), and how well this model agrees with their proposals.

Methods and Analysis Approach: The multitude of functional states makes it difficult to model AMPA receptor regulation computationally: Methods that require the explicit specification of all possible states and reactions (such as those used by ODE-based simulators) become highly impractical as the combinatorial complexity increases (reviewed in Stefan et al., 2014). However, building models that explore all states and configurations is necessary to accelerate our understanding of AMPAR dynamics, especially to determine common state profiles in basal and plasticity conditions. To overcome this problem, we have built a rule-based model of AMPAR regulation using the open-source Kappa language (Danos & Laneve, 2004). This method vastly reduces the number of reactions and species needed to be defined explicitly, and allows us to combine fast timescale models of AMPAR conductance profiles (Dutta-Roy et al., 2015) with longer timescale models of phosphorylation, ubiquitination, and recycling (Gallimore et al., 2016; Hayer & Bhalla, 2005).

Results and Conclusions: We present here the current iteration of the model, highlighting the interplay between AMPAR functionality and kinase/phosphatase profiles. We also model the response of the system to calcium events.

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Poster number: PT038 (SP)

Theme: Learning and memory

Place cells in head-fixed mice navigating in a flat real-world environment

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Introduction: "Place cells" encoding spatial information have been observed in the hippocampi of rodents moving freely [1] and head-fixed while navigating in virtual reality environments [2]. Recently, a real-world environment system for head-fixed mice consisting of an air-lifted platform has been developed [3]. This system allows sensory feedback but lacks vestibular input. Until now, the presence of place cells in such an environment has not been shown.

Methods: We injected mice with hSyn1-GCaMP6s-mRuby in the hippocampal subfield CA1. After two weeks, a 3-mm diameter craniotomy was made, the cortex above the injection site was aspirated, an imaging cannula was fitted and a headplate was glued to the skull. A week later, animals were put under water restriction and were trained to move along a circular linear track lined with visual cues. The track floats on an air table (Neurotar Ltd) under a two-photon resonant scanning microscope (Scientifica Ltd) and is fitted with a magnet-based position tracking system. Animals were trained in 45 min sessions twice daily and were given a water reward of 4 μ L per loop traversed. After 12 sessions, two-photon calcium imaging was done. Calcium imaging videos were corrected for movement artefacts and segmented for cell regions. Histogram-based place field analysis was performed to monitor the changes in neural activity across the track across several imaging sessions.

Approach for statistical analysis: We computed the mutual information (MI) between neuronal activity and track position. Place field maps above the MI threshold were sorted in order of vector average place preference. To verify that increase in firing rate in place fields was statistically significant, we performed a bootstrap shuffle test.

Results and conclusions: Consistent place cell tuning was observed in a substantial fraction of cells. Moreover, place cells remapped when the animal was in a novel environment. To our knowledge, this is the first demonstration of place cells in head-fixed mice navigating on an air-lifted platform.

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Poster number: PT039 (SP)

Theme: Learning and memory

Nitric oxide is involved in the mechanism of ampa receptors incorporation into dendrites of pyramidal neurons in hippocampus

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Introduction: AMPA receptors are ionotropic glutamate receptors that may consist of 4 types of subunits: GluR1, GluR2, GluR3 and GluR4. In adult animals, almost all of the mRNA of GluR2 subunits in the brain undergoes editing, which leads to the replacement of the neutral aminoacid glutamine with a positively charged arginine. Such a replacement alters electrophysiological properties of the GluR2-containing AMPA receptors (GluR2⁺). GluR2⁺ and GluR2⁻ AMPA receptors play different roles in mechanisms of plasticity, development, pathologies and are contained different concentrations in synapses of mature neurons.

Methods: It was shown that nitric oxide is involved in the mechanisms of membrane embedding of both types of AMPA receptors. To investigate the effect of nitric oxide on the distribution of AMPA receptors in various dendrites of pyramidal neurons in the hippocampus, we performed electrophysiological experiments on brain slices of mice

aged 25-40 days. We used patch-clamp method in the whole cell mode. Synaptic responses were induced via stimulating electrodes located in st. radiatum and st. oriens.

Analysis approach: All data are presented as means \pm SE. Significance values were determined using Mann-Whitney U-test, $p < 0.05$ was considered as statistically significantly different.

Results and Conclusions: We found that the contribution of GluR2⁻ AMPA to the currents in the apical dendrites is significantly greater (4 ± 0.2 , $n=7$) than the contribution observed in the basal dendrites (3 ± 0.1 , $n=7$; $p \leq 0.01$). Under nitric oxide blockade this difference disappeared by changing the index of contribution of the apical dendrites (apical 2.8 ± 0.3 , $n=6$; basal 2.6 ± 0.2 , $n=6$). In addition, we specifically blocked GluR2⁻ AMPARs by NASPM ($100 \mu\text{M}$), and found that EPSCs of apical dendrites decreased significantly stronger than EPSCs of basal dendrites and that difference is leveled by the NOS blockade. We believe that this effect is due to the fact that additional GluR2⁺ channels are incorporated into the apical dendrites, because by recording the AMPA/NMDA ratio we found that under the nitric oxide blockade the contribution of AMPA channel currents tends to increase in comparison with the control. Supported by Russian Academy of Sciences, RFBR grant 17-04-01796 A.

Poster number: PT040 (SP)

Theme: Learning and memory

An investigation into the cognitive correlates of concealed information

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Introduction: Recent times have seen the development of combined behavioural and neuroimaging techniques to predict lie-telling (Meijer et al., 2016). Although 'lie detection' tests are considered admissible evidence in Japan, the western world has yet to acknowledge their reliability or validity in legal contexts, or otherwise. An open question within the literature is the involvement of executive function (EF) cognitive-neural processes underpinning the concealment of information. A recent meta-analysis suggests that the orienting response (OR) may underlie detection in a concealed information task (CIT); whereas response inhibition (RI) may differentially contribute to concealment in the Detection of Detection (DoD) task (Meijer et al., 2016). The present within participant study investigates the involvement of OR and RI in concealed information in two tasks: CIT and DoD.

Methods: 60 participants from the healthy adult population will be recruited to complete EF tasks such as the Go-No task, and the Attentional Network Task (ANT), as well as the CIT and DoD.

Analysis approach: Behavioural data (reaction time and accuracy) was inspected for significant correlations between tasks. Predictors of performance were identified using multiple linear regressions in order to determine if OR or RI predicts performance on concealed information tasks, or if there are any meaningful relationships between concealed information performance on the CIT and DoD. The bootstrap processing approach was also employed to disentangle accuracy and its relationship to EF processes during concealed information tasks.

Results and Conclusions: Analyses of RTs using multiple regression ($n=37$) reveal that OR is not a significant predictor of CIT or DoD performance. An analysis of CIT errors shows that commission errors occur more frequently when concealing compared to omission errors, implicating response inhibition ($p < .05$). Implications of these results will be considered in terms of the involvement of EF in predicting successful concealment of information.

Poster number: PT041 (PP)

Theme: Learning and memory

In vivo electrophysiology combined with behaviour as a tool to investigate central effects of peripherally administered GABAA receptor modulators in mice

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Neuronal oscillations measured *in vivo* are a sensitive readout of synaptic activity, and changes in response to drug administration can be observed in real time in awake, behaving animals. Hippocampal oscillations such as theta (5.5-8.5Hz) and gamma (30-80Hz) and their temporal relationships have been strongly linked with Learning and memory. $\alpha 5$ -GABA_AR receptors are densely expressed in the hippocampus and inhibitors of $\alpha 5$ -GABA_AR are currently being investigated as cognitive enhancers. We aimed to investigate the time course of changes in hippocampal activity after systemic administration of such inhibitors.

Our hypothesis is that if $\alpha 5$ IA is enhancing Learning and memory, this should be reflected in changes in the oscillations underlying these functions. These oscillations are, however, also strongly modulated by behavioural states such as movement speed, attentional state and environmental stimuli. In many experiments it is not clear how these non-specific effects of environment are controlled for and subtle changes in behaviour caused by administration of a drug may cause large differences in recorded signals in vehicle vs drug conditions.

We have designed a protocol in which mouse activity is carefully controlled by maintaining trained walking behaviour on a fixed speed rotarod at specific time points in a familiar environment. Using this protocol we are measuring the time course of changes in oscillations produced by systemic $\alpha 5$ IA administration using NeuroNexus multisite silicon probes implanted into hippocampal CA1 and overlying cortex.

Data are currently being collected from 4 wild type male C57Bl6J mice in drug and vehicle conditions (within subject design) and will be analysed using repeated measure analysis over 8 timepoints before and after drug administration. Drug, vehicle and no injection conditions will be compared. We will investigate theta and gamma frequency, temporal relationships between theta and gamma and the presence of other oscillations including high-frequency sharp wave ripple activity in the hippocampus and posterior parietal cortex.

Additional benefits of this paradigm for the less-computational lab such as ourselves include simplified analysis- no requirement for speed filtering or position tracking - and large amounts of robustly comparable data with minimal noise collected over short sessions, also reducing file size.

Poster number: PT042 (SP)

Theme: Learning and memory

A novel Autobiographical Think/No-Think paradigm to study the cognitive mechanisms of intrusive negative autobiographical memories

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Introduction: The flow of human thoughts is frequently plagued by unwanted cognitive activity, which has the unfortunate power to interfere with task performance, planning, social behaviour, and many other aspects of our lives (Clark and Rhyno, 2005). Importantly, unwanted thoughts and memories play a major role in psychopathology. Inhibitory deficits are thought to play a key role in maintaining intrusive memories and thoughts in PTSD, OCD, and depression. Drawing on Benoit's Imagine/No-Imagine study based on personally relevant future fears, we developed the Autobiographical Think/No-Think paradigm, a modified version of Anderson's Think/No-Think task (Anderson & Green, 2001) based on autobiographically grounded word pairs to study recurrent upsetting memories and

intrusions. This represents the first attempt to use intrusion ratings in an Autobiographical Think/No-Think study. This novel paradigm enables us to elicit the recall of autobiographical intrusive involuntary memories in a controlled way.

Methods: 40 participants were tested for this behavioural study at the MRC Cognition and Brain Sciences Unit, University of Cambridge. Unlike most studies, no standardised materials were used; rather, participants generated their own materials because of our focus on autobiographical memories. Participants were instructed to generate a list of twenty-two upsetting intruding events happened in the past three years and to select two key words (“cue word” and “code word”). Then they completed the pre-TNT phase, the TNT phase, and the post-TNT phase.

Analysis and Results: We predicted that memories would frequently intrude into awareness involuntarily initially, but that with repeated attempts to stop retrieval, intrusion frequency would decline. Our one-way ANOVA analysis confirmed that intrusions declined significantly from the first block to the fourth, declining significantly from the first suppression attempt to the sixteenth.

Conclusions: These preliminary results indicate that participants gained increasing control over the intrusions of unwanted memories. This improved regulation of intrusive memories may reflect a mixture of increasing success at controlling retrieval and inhibition of suppressed traces that make them less intrusive over trials. Skin conductance data, post experimental questionnaires, phenomenological perspectives on intrusions and neuroimaging data will shortly be added to this study, providing novel and insightful views on this topic.

Poster number: PT043 (PP)

Theme: Learning and memory

Synaptic and structural analysis of engram cell plasticity

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Engrams are defined as the material changes in the brain that occur during learning, and account for specific memories. Long-term memory engrams are thought to be encoded through connectivity changes between ensembles of neurons active in the brain during a salient experience. Activation of these cells is sufficient (Liu *et al.* 2012, Ramirez *et al.* 2013, Ryan *et al.* 2015) and necessary (Denny *et al.* 2014, Tanaka *et al.* 2014, Trouche *et al.* 2016) for the recall of that memory. Engram ensembles can be created in the presence of protein-synthesis inhibitors and reactivated later using optogenetic tools (Ryan *et al.* 2015). The plasticity process(es) that lead to the formation of a stable engram are still not fully understood.

To address this question, we will label the engram cells unilaterally in the dentate gyrus (DG) following *in vivo* contextual fear conditioning experiences in the mouse hippocampus and medial entorhinal cortex using c-fos-tTA, TRE-mCherry, and CamKIIa-ChR2-EYFP adenoviral vectors. We then will study the synaptic and dendritic plasticity of engram and non-engram DG cells in *ex vivo* slice preparations. To do so, we will use whole cell recordings to examine the composition of the excitatory postsynaptic responses in both populations of neurons, following stimulation of presynaptic input from the medial entorhinal cortex. For structural analysis, two strategies will be pursued. With the electrophysiological recordings, the whole cell configuration will allow us to label engram and non-engram cells with biocytin to examine their structure. In parallel immunohistochemistry for labelled cells will permit us to analyse the dendritic morphology. The results of these experiments will give insight into the kinds of plasticity changes that occur in engram cells following long-term memory formation. Sample sizes will be estimated from relevant published studies (Ryan *et al.* '15) and the variance of initial pilot data.

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Poster number: PT044 (SP)**Theme:** Learning and memory**Seeking the supramodal inhibitory control network in the brain: the role of the right DLPFC and the basal ganglia in memory and motor control**

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Introduction: Memory inhibition and motor inhibition can be seen as fundamentally similar processes involving the stopping of prepotent responses. Various studies have hinted at a supramodal inhibitory control network in the brain which is engaged in the suppression of both unwanted memories and actions. A recent meta-analysis study showed that there are indeed overlapping cortical and sub-cortical regions which get activated in both memory and motor control tasks (Guo et al, 2018). In this study, we chose to investigate the role of the potential key players in this control network namely the right dorsolateral prefrontal cortex (DLPFC)- a candidate for being the top-down executive control node of the network, and the basal ganglia.

Methods: 33 healthy young adults were recruited for the study. All the participants performed two sessions inside the 3T scanner- the first being an inhibitory motor task which was a modified version of the Stop Signal paradigm, and the second being a version of the Think/No Think memory inhibition task.

Analysis Approach: Pre-processing and univariate analysis was done using Statistical Parametric Modeling (SPM). Further analysis plans include performing Dynamic Causal Modeling (DCM) on the data set.

Results and Discussion: The univariate group level analysis revealed that the conjunction of regions of activation seen in both the right DLPFC and the basal ganglia for the two inhibitory tasks closely overlap with the regions previously identified in the meta analysis. A DCM would now help elucidate the role of the key players in the supramodal network namely the right dorsolateral PFC and the basal ganglia, and help shed some light on how the network operates and produces inhibition of different target structures (for instance the hippocampus or the primary motor cortex.) This would further help investigate if this network can then be artificially 'entrained' by non-invasive brain stimulation to see if memory and motor control can be enhanced especially in people having difficulties in controlling unwanted memories. The possibility of aiding better cognitive memory control training through motor control training, can also be investigated.

Poster number: PT045 (PP)**Theme:** Learning and memory

Investigating neuronal representations of instinctive and learned behaviours

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Over the past decade, new technological advances have allowed the labelling of the neurons representing specific memories, referred to as engram cells. By manipulating their activity, it has been demonstrated that these cells are both sufficient and necessary for memory retrieval. While learning and storing new information is essential for survival, animals also have to rely on innate behaviours. However, the neuronal representations of instincts have rarely been examined. By using methods akin to those used for investigating engrams, we can characterise “ingram cells” and study their role in instinctual behaviour.

Here we aim to specifically characterise various instincts, and their corresponding labelled ingram cells, relative to their behavioural functions. In one experimental paradigm, mice are placed in an arena with a naturally meaningful odour introduced in a specific part of the arena. Trimethylthiazoline (TMT), a component of fox faeces and urine, triggers avoidance and freezing characteristic of fear responses. Butane-2,3-dione, with its strong buttery smell, is an appetitive compound for mice. In another paradigm, threatening visual stimuli are displayed on a computer monitor sitting atop an arena in which mice are placed. An expanding black disk imitating the visual form of raptors swooping toward their prey can elicit freezing or flight.

In order to label the ingram cells corresponding to these behaviours in an activity-dependant and temporally controlled manner, the AAV-TRE-ChR2-EYFP and AAV-c-fos-tTA adenoviral vectors are injected in regions of interest of mice brain. The labelled neurons can then be optically activated with blue light, which should trigger a behaviour similar to the one elicited by natural stimuli.

Behaviour will be analysed in terms of freezing, approach, avoidance and flight. Labelled cells will be counted and overlap with cells active upon re-exposure to the stimuli will be quantified. Standard parametric statistical tests will be employed where appropriate. These experiments will shed light on the nature of instincts in the brain and their relationship with memories.

Poster number: PT046 (SP)

Theme: Learning and memory

Pharmacological evaluation of an unconditioned memory test in zebrafish

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Neuropsychiatric disorders characterised by mnemonic and cognitive deficits are on the rise, generating a great need to better understand the underlying mechanisms. The zebrafish (*Danio rerio*) has fast established itself as a relevant model organism for studying these neuropsychiatric disorders by easily lending itself to a range of cognitive tasks. Here we use a novel unbiased y-maze protocol to identify the mechanisms of memory involved in novelty seeking and spontaneous alternation. Previously we have shown that moderate prenatal ethanol exposure caused an alteration in the search strategy employed by zebrafish in the y-maze. However, which aspects of Learning and memory were involved in these changes had yet to be clarified. Therefore, in this study we have used two cognitive impairers- MK-801, a NMDA receptor antagonist, and scopolamine, a cholinergic blocker- to evaluate the mechanisms used in y-maze exploration. We found that both MK-801 and scopolamine resulted in reduced number of alternations compared with untreated controls, with the greater decrease seen in fish treated with MK-801. MK-801 caused an increase in the relative number of turns, whereas scopolamine showed a dose dependent decrease. In conclusion, our results show that an unbiased, unconditioned y-maze protocol can be used to measure impairments

in memory formation via glutamatergic and cholinergic systems. Thus, showing the y-maze to be a rapid and diverse test which can be used to measure Learning and memory deficits associated with complex neuropsychiatric disorders.

Poster number: PT047 (PP)

Theme: Learning and memory

Cognitive enhancing compounds can be evaluated in wild-type mice using an adapted morris water maze protocol to test memory and learning

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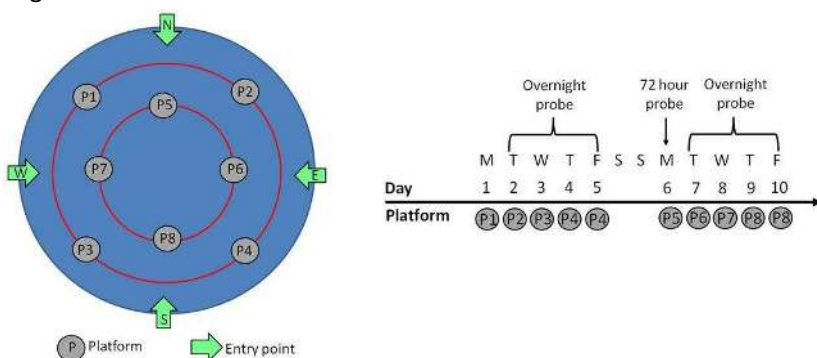
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Downregulation of $\alpha 5$ -GABA_A receptor activity is currently being explored as a potential target for novel cognitive-enhancing compounds to treat various dementia-related neurodegenerative diseases. These receptors are known to have a role in Learning and memory and are abundantly expressed in the hippocampus. We aimed to test $\alpha 5$ GABA_ARs negative allosteric modulators (NAMs) in mice on a Morris Water Maze protocol, a paradigm known to be hippocampal-dependent.

Our hypothesis is that if we apply a challenging Morris Water Maze protocol then we will have scope to improve the performance of the task through administration of $\alpha 5$ GABA_ARs NAMs. We have utilised a protocol in which 8 different platform locations are presented over 2 weeks, meaning that flexible learning has to occur in order to learn new spatial locations (Figure 1). In order to test long-term memory, an overnight probe trial will be carried out to measure if the mice remember the platform location from the previous day. Furthermore, at the end of the first week a 72 hour probe will be carried out to test the mice on an extended long-term memory challenge. By providing multiple flexible learning challenges alongside variable memory retention intervals we will create memory challenges for even wild type mice.

A range of known $\alpha 5$ GABA_ARs NAMs are being tested in 3 months old, male C57Bl6/J mice. Experimenter will be blind to treatment group. Data will be analysed using repeated measures statistics across the experimental timeline (Figure 1) and one-way ANOVA to probe long-term memory. Benefits of this paradigm are the avoidance of additional pharmaceutical interventions to induce Learning and memory deficits. Additionally, this paradigm could be extended to test cognitive enhancing abilities of compounds in disease models of Learning and memory loss.

Figure 1



SP = Standard poster

PP = Preregistration poster

Poster number: PT048 (SP)**Theme:** Learning and memory**Dissociable roles of rat medial and lateral orbitofrontal cortex in visual reversal learning****Authors:** Dr Mona El-Sayed Havig^{1,2}, Dr Leanne Fiddian¹, Ms Louise Piilgaard^{1,2}, Mr Tadej Bozic^{1,3}, Dr Johan Alsiö¹, Professor Trevor W. Robbins¹¹University of Cambridge, Cambridge, United Kingdom, ²Copenhagen University, Copenhagen, Denmark, ³University of Ljubljana, Ljubljana, Slovenia

Introduction: The fundamental ability to flexibly change behavior in response to situational changes is disrupted in several psychiatric disorders including obsessive compulsive disorder, schizophrenia and autism. Instrumental reversal-learning paradigms are commonly used to assess flexible responding to changing reinforcement contingences across species, and much work suggests that reversal learning is mediated by cortico-striatal loop circuitries with the orbitofrontal cortex (OFC) playing a prominent role. Within the OFC functional dissociations exist between the rodent lateral (IOFC) and medial (mOFC) OFC. Although IOFC inactivation impairs deterministic visual serial reversal learning in rats, the effects of mOFC inactivation have not previously been determined. Some studies have also suggested the medial PFC (mPFC) and basolateral amygdala (BLA) to be associated with aspects of reversal learning. Therefore, we investigated the effects of inactivating the IOFC, mOFC, prelimbic (PrL) and infralimbic (IL) mPFC as well as the BLA on reversal learning.

Methods: Male Lister Hooded rats were trained in a deterministic touchscreen serial visual reversal learning task. We tested the effects of microinfusions of baclofen/muscimol (1mM/side; inducing inactivation) in the mOFC, IOFC, PrL, IL and BLA on performance in this task.

Analysis approach: We used a Latin-squared cross-over experimental design and performed within-subject analyses of reversal learning performance measures including perseverative errors, omissions and latencies.

Results and conclusions: We observed dissociable roles of the OFC and mPFC in deterministic serial visual reversal learning, with OFC inactivation affecting only perseveration and mPFC inactivation affecting learning overall. Moreover, we found that the mOFC and IOFC exhibited dissociable roles; inactivating the IOFC impaired, while mOFC inactivation improved, serial reversal learning performance. This was reflected by an increase and decrease in number of errors, respectively, confined to the perseverative phase of reversal learning. The improved performance after mOFC inactivation was associated with an enhanced sensitivity to negative feedback as reflected by an increased lose-shift tendency and faster latencies to collect earned food rewards. In contrast, IOFC inactivation produced a generally diminished sensitivity to both positive and negative feedback and slower magazine latencies. These results show dissociable roles of the rodent mOFC and IOFC in deterministic visual reversal learning.

Poster number: PT049 (PP)**Theme:** Learning and memory

Rhythms of the night – using human intra-cranial eeg to investigate the brain rhythms underpinning memory consolidation in sleep

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Introduction: One of the primary functions of sleep is the consolidation of memories, this is thought to be achieved through a complex interplay of hippocampal, thalamic and cortical brain rhythms. Scalp EEG is limited in its power to detect the specific relationships between these rhythms because of the deep location of the hippocampus and the capacitive effect of the skull. Our study aims to illuminate these areas using machine learning techniques to decode simultaneous scalp and intra-cranial EEG (iEEG) recordings alongside a behavioural memory paradigm.

Slow oscillation (0.5-2Hz whole brain, high amplitude rhythm) power and their synchronicity with sleep spindles (11-16Hz bursts of more local activity) are important elements of the consolidation process [1]. Re-activation of task related memories can be triggered by playing of tones during sleep associated with an episode or action during learning [2]. [2] trained a classifier on scalp EEG activity recorded during learning and showed above chance recognition of different tones during sleep. Recent joint EEG and iEEG recordings suggest, however, that synchrony between spindles detected via scalp and intra-cranial electrodes is very low - iEEG, therefore, represents a significantly different dataset to scalp EEG. We will test the hypothesis that reactivation of memories can be detected in human iEEG.

Methods: Selected patients undergo prolonged pre-operative recording from hippocampal deep electrodes in the Adult Epilepsy Surgery Programme at Southmead Hospital. These intra-cranial electrodes in conjunction with simultaneous scalp EEG will be used to record sleep activity overnight. Before and after this night's sleep a behavioural paradigm will be used to assess effectiveness of memory consolidation. A similar paradigm to that used in [2] will be employed to trigger reactivation of memories using associated tones during sleep. The sample size depends on clinical through-put but is estimated to be 20-50.

Approach to Statistical Analysis: Analysis techniques will be developed based on existing iEEG methods, in-cooperating a similar classifier as [2] to detect reactivation of memories.

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Poster number: PT050 (SP)

Theme: Learning and memory

The Mirror Memory Task: Clinical Utility in Lateralizing Visual Memory Function in fMRI Pre-Operative Epilepsy Surgery Assessment

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Introduction: Currently the most effective treatment for refractory temporal lobe epilepsy is resection of the likely epileptogenic zone(s), which may involve partial or entire removal of the right hippocampus. The prediction of post-operative memory deficit in this procedure is required to inform cost-benefit decision making for surgery and provision of informed consent. In addition, it also supports post-operative neurorehabilitation planning. In order to estimate post-operative risk, procedures are required to quantify and lateralise visuospatial memory function; the

relevant behavioural correlate of the right hippocampus. The development of visuospatial lateralisation paradigms is more challenging than verbal protocols, with left hemisphere processing biases and verbalisation strategies confounding the selectivity of existing tasks. This study aimed to determine the suitability of a newly-designed paradigm in quantifying visuospatial memory function and in selectively activating visuospatial neural substrates under fMRI to lateralise function.

Methods: 66 healthy controls and 20 patients with epilepsy underwent a forced-choice visuospatial recognition task, testing memory for orientation of a novel stimulus. fMRI data was also collected for 20 healthy controls and 12 patients.

Analysis and Results: Behavioural data was analysed to determine encoding efficacy and used to support analysis of fMRI data. Lateralisation indices of visual memory function were generated from ROI analysis. Convergent validity of the task against existing neuropsychological tests are reported. Behavioural data analysis demonstrated modest levels of recognition accuracy for visual scenes, therefore adequate opportunity for analysis of hits versus misses in an event related analysis. ROI analysis demonstrated recruitment of right hippocampus during successful encoding of visuospatial scenes in healthy controls. Selected patient data is presented to illustrate the utility of this paradigm in predicting post-operative memory outcome.

Conclusions: The Mirror Memory Task shows promise as a suitable tool in estimating post-operative memory decline in epilepsy surgery.

Poster number: PT051 (SP)

Theme: Learning and memory

The fine art of forgetting: L-DOPA modulates forgetting, not consolidating, of human memory

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Introduction: Successful forgetting of irrelevant information is pivotal for optimal memory. Retrieval induced forgetting (RIF) occurs when accessing previously stored information increases forgetting of competing information, possibly as re-tested information is 'tagged' as higher importance. In animal models increased dopamine (DA) in the hippocampus (HC) has been implicated to enhance consolidation, and in humans DA may increase working memory capacity and language learning.

Methods: We targeted long term memory processes to test DA's effect on encoding, consolidating, forgetting and retrieving. In two single-dose placebo-controlled double-blind randomised within-subjects trials, 67 (study 1 n=32; study 2 n=35) healthy elderly (65+ years) were dosed with L-DOPA/placebo on different visits. To target encoding (Study 1), volunteers learnt 98 words 2h after dosing. Recognition was tested immediately, 1, 3 days and 5 days later (24 targets at each test). To target consolidation (study 2), volunteers learnt 80 words and were dosed immediately after. Recognition was tested 2h later (ON drug), 12h later (OFF) following a full nights' sleep and 3 and 5 days later (Figure). 20 unique targets were used at each test except 12h when the 2h items were also re-tested (40 targets in total). Structural MRIs and polysomnography were also recorded in study 1.

Approach for statistical analysis: The main outcome measure across the experiments was D' (d-prime), a proxy for accuracy that considers both hits and false alarms. Results were analysed using the general linear model together with Bayesian approaches. Polysomnography were staged manually, and HC subfields were derived using an automated procedure (ASHS).

Results and conclusions: When L-DOPA as opposed to placebo was given during encoding, memory was enhanced 3 but not 1 or 5 days after testing ($p < 0.05$, $df = 25$) but this effect did not persist following multiple comparison

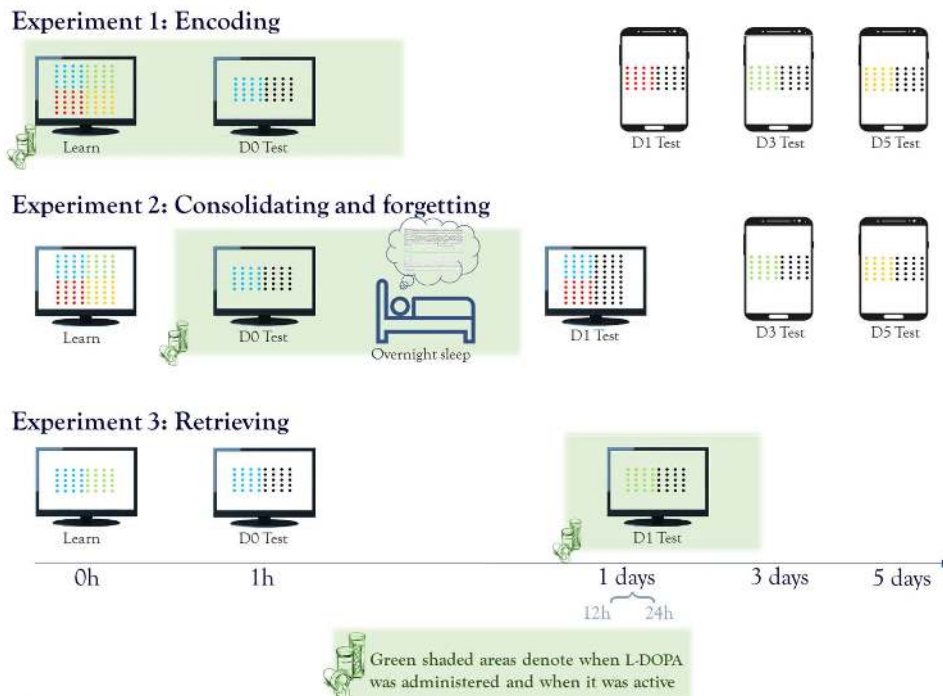



Figure: We targeted dopamine's effects on different memory processes by carefully timing the administration of L-DOPA (timing shown as ) across three experiments, volunteers learnt lists of words (targets) on a computer screen. Each dotted colour (•••••) represents an individual word. Their recognition memory was tested on the targets and unique distractors (•) using the Remember-Know paradigm either on-site using a computer screen or over the phone. Memory was probed on the day of learning (D0), and/or 1, 3 and 5 days (D1, D3, D5) later. Each volunteer completed both a L-DOPA and a placebo testing session.

correction. For consolidation, memory was impaired 12h after learning for items that were tested once, but improved for re-tested items. No differences were found 3 or 5 days later ($p < 0.05$, $df = 33$). L-DOPA had no effect during retrieval ($BF_{01} = 4.243$). DA may reduce forgetting of retrieved information at the expense of competing information, lending support to RIF.

Poster number: PT052 (SP)

Theme: Learning and memory

Modulation of distinct phases of reversal learning by dorsal and ventral striatal D1 and D2 receptors

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Introduction: Impaired cognitive flexibility in reversal-learning tasks has been associated with a wide range of neurological disorders. Reversal learning can be divided into different phases: early phase, where subjects need to abstain from a previously rewarded action, and later phases, which require a new learning approach, during which subjects become highly accurate with training. Although numerous studies have implicated dopamine D2 and D1-receptors (D2R; D1R), there exists no conclusive account of the contribution of these receptors within striatal sub-regions to the different phases of reversal learning.

Methods: This study investigated the involvement of D1R and D2R in the nucleus accumbens core and shell (NAcC; NAcS), the anterior and posterior dorsomedial striatum (aDMS; pDMS) and the anterior dorsolateral striatum (aDLS) on a visual serial reversal-learning task using touchscreen-operant chambers. Rats were trained to discriminate between two visual stimuli (CS+; CS-), which were later reversed. Prior to reversal sessions, animals received bilateral infusions of D2R antagonist, raclopride, or of D1R antagonist, SCH23390.

Approach for statistical analysis: Data from each reversal were collapsed over days. Trial outcomes were classified in three different phases: early, mid or late. Early phase was considered when animals had a significant bias to CS- (<11 correct responses/30 trials). Late phase was defined when performance was >19 correct responses out of 30, whilst the mid phase was defined by having ≥ 11 and ≤ 19 correct responses from a set of 30 trials.

Results and conclusions: Local administration of D2R antagonist, raclopride, improved performance of early stages in reversal learning when infused in the NAcC, but impaired early phases when infused in the aDLS or in late phases when infused in the pDMS. In contrast, D1R antagonist, SCH23390, improved reversal learning in early stages when administered in the NAcS and impaired performance when infused in the NAcC.

These findings indicate that striatal D1Rs and D2Rs have dissociable and sub-region-specific roles in modulating distinct phases of reversal learning. These findings indicate that deficits in behavioural flexibility linked to dysfunction of the DA system may be attributable to an imbalance of D1R and D2R function in distinct striatal sub-regions.

Poster number: PT053 (PP)

Theme: Learning and memory

Effect of negative emotions on early post-stimulus storage in working memory: a study of the C250 ERP

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Introduction: In this study we aim to investigate on one of the most important components of working memory (WM), namely early post-stimulus storage, as this has been sparsely studied (Chapman et al., 2015). We will look at the effect of negative emotion on the event related potential (ERP) C250 and further provide evidence of it being the temporal electrophysiological biomarker for early post-stimulus storage component of WM. We hypothesise that negative emotional affect will lead to higher amplitude of the C250 and enhanced WM function compared to neutral emotional affect.

Methods: An ERP study will be conducted on twenty healthy young adults. Participants will take part in an approximately two-hour electroencephalography (EEG) session during which they will be asked to perform a number-letter task (Chapman et al., 2015) testing WM while negative and neutral emotional affect would be induced using images from the International affective picture system. Simultaneous ratings of perceived affect will be acquired during the experiment.

Approach for statistical analysis: For ERP analysis, averages of artifact-free EEG trials will be generated for conditions of negative and neutral emotional affect. Grand-average ERP waveforms will be generated. This study will focus on the C250 ERP. To investigate the differences in effects of negative and neutral emotion on C250, we will apply a mixed repeated measure analysis of variance (ANOVA) to C250 amplitude and latency data with emotional affect (Negative, Neutral), task relevancy (Relevant, Irrelevant), stimulus types (Number, Letter), 4 Intratrial parts and Scalp regions (Frontal, Central, parietal and occipital) using SPSS. Effect size would be calculated as partial η^2 and statistical significance would be considered with $p \leq 0.05$. To see the correlation of C250 amplitude with rating of emotional affect, Pearson or Spearman correlation test will be performed depending on the normality of data.

Poster number: PT054 (SP)**Theme:** Learning and memory**The effect of Medial Septum Stimulation on Hippocampal Electrophysiology and Behaviour****Authors:** Mr Matheus Cafalchio¹¹*Trinity College Dublin, Dublin, Ireland*

Introduction: The medial septal area (MS) is the primary modulator of hippocampal oscillations, and it provides hippocampus with GABAergic, cholinergic and glutamatergic fibres which are intimately related to memory processing. The septum was the first brain region to be observed to elicit intracranial self-stimulation, animals were described to compulsively press a lever in order to receive an electrical stimulation in this area. Within the septal area, the medial septum displayed higher self-stimulation rates and lower self-stimulation thresholds. Pharmacological studies showed that the midline region of the septal complex promotes self-administration of GABA_A receptor agonist muscimol, suggesting that medial septal GABAergic neurons could be involved in septal electrical self-stimulation.

Methods: In this study rats were injected with a recombinant AAV to express channelrhodopsin-YFP under control of Hsyn promoter. Additionally, a transgenic rat model which allow for the specific expression of Chr2 in GABAergic glutamate decarboxylase 1 (GAD1) positive neurons was used to express channelrhodopsin-YFP in MS GABAergic neurons. These animals had optic fibre implanted into the MS and electrodes implanted into the hippocampal CA1 area. Single units were recorded during freely movement on an open field and also in a squared linear maze. We accessed the effect of the MS stimulation on the behaviour and hippocampal units.

Results: Our results showed that majority of the CA1 interneurons were disinhibited during MS stimulation. Consequently, CA1 pyramidal neurons were mostly inhibited. Interestingly, MS stimulation induced place field remapping in a sub population of place cells, suggesting that the septal inputs could modulate spatial processing. We also accessed the behavioral response of MS stimulation. Using a place preference paradigm, we showed that rats preferred the stimulation side of the arena. We showed that place preference could be induced by stimulation of MS GABAergic neurons. Suggesting that GABAergic neurons mediate the reward-related response of MS stimulation.

Poster number: PT055 (PP)**Theme:** Neurodegenerative disorders & ageing**Novel fluid biomarkers of inflammation in frontotemporal dementia****Authors:** Ms Elise Chan¹, Ms Carolin Heller², Ms Martha Foiani², Dr Ione Woollacott¹, Ms Katrina Moore¹, Ms Lucy Russell¹, Dr Amanda Heslegrave², Professor Jonathan Rohrer¹¹*Dementia Research Centre, Institute of Neurology, Queen Square, London, United Kingdom*, ²*UK Dementia Research Institute, Institute of Neurology, Queen Square, United Kingdom*

Introduction: Frontotemporal dementia is a common young onset form of dementia with both genetic and sporadic variants. Currently, there are no reliable biomarkers to differentiate the forms of FTD, however recent studies have shown a link between FTD and neuroinflammation. This project will aim to look at a new panel of markers to see if these differ between people with FTD and controls, and whether there is any association of these markers with clinical, cognitive and imaging measures.

Methods: We will investigate whether plasma levels of three cytokines differ between FTD and controls, across different clinical and genetic subtypes of FTD, or between individuals with FTD due to AD versus non-AD pathology (based on CSF neurodegenerative biomarkers). We will also assess relationships between cytokines and other clinical markers and age and disease duration. IL-6, IL-10 and TNF α levels will be measured using the Cytokine Panel A on the Simoa platform (Quanterix, Massachusetts) in a group of healthy controls and patients with FTD including those with both the behavioural and language variants clinically, and with different genetic mutations (progranulin, tau and C9orf72).

Approach for statistical analysis: Plasma levels will be compared between groups using a linear regression model on Stata v.14. Initially, we will compare whether the cytokine concentrations differentiate significantly FTD patients from controls. Subsequently, we will investigate differences in levels between clinical and genetic subgroups, focusing also on the impact of specific mutations. Finally, we will investigate whether age, gender, disease duration or other variants would account for the variability in concentration between and within groups. We expect to see an increased in cytokine concentration in FTD compared to controls, particularly in the progranulin mutation cases, which have been shown to be associated with chronic immune dysfunction and microglia activation.

Poster number: PT056 (SP)

Theme: Neurodegenerative disorders & ageing

Ultrastructural characteristics of endothelial cell dysfunction in cerebral small vessel disease

Authors: Dr Jonathan Moss¹, Prof Joanna M. Wardlaw^{2,3}, Prof Anna Williams¹

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Cerebral small vessel disease (SVD) is the leading cause of vascular dementia; it worsens the symptoms of Alzheimer's disease and is responsible for up to 45% of all dementias. Underlying these dementias are white matter abnormalities, which appear in magnetic resonance scans in SVD patients. We sought to find the mechanistic pathological link between blood vessels and white matter vulnerability.

Although hypertension has been suggested as the primary cause of sporadic SVD, a recent alternative hypothesis implicates dysfunction of the blood-brain barrier. Previous work in a well-characterised rat model of SVD (the stroke-prone spontaneously hypertensive rat), has shown that endothelial cell dysfunction is the first identifiable stage in SVD development (at 5 weeks), and that dysfunctional endothelial cells secrete heat shock protein 90 α (HSP90 α), which blocks precursor differentiation into myelinating oligodendrocytes, contributing to white matter vulnerability (Rajani *et al.*, 2018).

Upstream of endothelial cell dysfunction, Rajani *et al.* identified a mutation in the SVD-model rat (also in SVD patients with white matter abnormalities), in the gene encoding ATPase11B; a flippase enzyme essential for endothelial cell protein transport and plasma membrane integrity. Its loss results in the aberrant secretion of deleterious factors such as HSP90 α into the extracellular matrix (Rajani *et al.* 2018), and loss of flippases in general can lead to blebbing of the plasma membrane and secretion of extracellular vesicles (Bern, 2017).

To determine if these ultrastructural characteristics are present early in SVD progression, and might explain how white matter myelin damage occurs, we used correlative light and electron microscopy to examine the endothelial cells of the corpus callosum deep white matter, comparing 5-week-old SVD-model rats to wildtype controls.

To date, we have found endothelial cells with increasing signs of dysfunction in the SVD-model rats; from those with very little membrane blebbing akin to control animals, through to those with extensive blebbing and/or a blackened appearance indicative of programmed cell death. These analyses, and those ongoing, will narrow down precisely how dysfunction associated changes to endothelial cells lead to the increased white matter vulnerability seen in SVD pathology.

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Poster number: PT057 (SP)

Theme: Neurodegenerative disorders & ageing

Fornix degradation and between-network increases in functional connectivity in preclinical Alzheimer's disease

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Introduction: The earliest changes in the brain due to Alzheimer's disease are associated with the neural networks related to memory function. The objective is to investigate the changes in functional and structural connectivity among regions that support memory function in preclinical Alzheimer's disease, i.e., during the mild cognitive impairment (MCI) stage.

Methods: Thirty-three older healthy controls (HC) and 25 adults with MCI underwent multimodal MRI scanning (Philips Intera 3T; T1w: 0.9*0.9*0.9 mm; DWI: 2.3*2.3*2.3 mm, 60 directions, bval =2000, 17 m; T2*w: 3.5*3.5*3.5 mm with 0.35 mm gap, 210 volumes, 7 m). Limbic white matter tracts – the fornix, parahippocampal cingulum, retrosplenial cingulum, subgenual cingulum and uncinate fasciculus – were reconstructed in ExploreDTI using constrained spherical deconvolution-based tractography. Using a region-of-interest approach, resting-state functional connectivity time-series correlations among the default mode and limbic networks, hippocampus, amygdala, and the thalamus were calculated in CONN.

Analysis: Bonferroni-corrected linear regressions of diffusion measures conditional upon group were performed. Two-sided FDR corrected t-tests of the Fisher z-transformed correlation coefficients of functional connectivity were conducted. All tests controlled for age, education, and gender.

Results & Conclusion: Higher fractional anisotropy ($p = .036$) and lower dominance of fibre direction ($p = .032$) of the left fornix, lower mean diffusivity of the left and right fornices ($P_s < .0001$) and smaller volume of the right parahippocampal cingulum ($p = .016$) were present in the MCI compared to the HC group. This pattern indicates impoverished structural integrity of the fornix. Five instances of higher functional connectivity between sub-regions of the default mode (all within the medial prefrontal cortex) and limbic networks (orbitofrontal cortex, temporal pole), $P_s < .033$, were seen in the MCI compared to the HC group. One instance of functional connectivity within sub-regions of the limbic (temporal pole parcellations, $p = .039$) network and one between network instance (within temporal lobe, $p = .041$) were higher in the HC compared to MCI group. These functional connectivity differences are suggestive of compensation strategies to overcome the structural insults that accompany MCI. This work was funded by The Meath Foundation, Tallaght University Hospital, Dublin.

Poster number: PT058 (SP)

Theme: Neurodegenerative disorders & ageing

Elucidating the mechanism of action of the novel myelin repair agent nefiracetam

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Multiple sclerosis (MS) is a progressive autoimmune disorder which occurs when autoreactive T-lymphocytes infiltrate the central nervous system and damage the oligodendrocytes responsible for maintaining the axonal myelin sheath (Loma and Heyman, 2011). Initially, the damage is repaired through the activation of a repair process called remyelination. However, as the disease progresses, remyelination begins to fail leaving the denuded axons vulnerable to damage and subsequent degeneration (Harlow *et al*, 2015). The accumulating loss of chronically demyelinated axons causes a steady decline in neuronal activity, resulting in progressive disability. Current therapies target the immune component of the disease but do not address the myelin repair deficits which underlie the disease progression (Murphy *et al*, 2013). Thus, there is a clinical need for the development of myelin repair therapies to considerably improve treatment outcomes.

We have found that the nootropic nefiracetam accelerates remyelination in the cuprizone model of demyelination. Moreover, in the gold standard experimental autoimmune encephalomyelitis model, nefiracetam reduces white matter lesions in the spinal cord and, when used in combination with the immunosuppressant dexamethasone, restores normal motor function. Transcriptomics studies on the corpus callosum of cuprizone-fed animals revealed 246 genes that are regulating during the early phase of nefiracetam-mediated acceleration of myelin repair. In particular, the data implicate the regulation of glutamate receptors in the myelin repair action of nefiracetam. Preliminary data from pure oligodendrocyte precursor cell primary cultures support the potential role of glutamate signalling in nefiracetam's mechanism of action. Our results provide compelling evidence that nefiracetam may be a novel myelin repair agent for the treatment of MS and highlight a possible role for glutamate signalling in the remyelination process.

Poster number: PT059 (SP)

Theme: Neurodegenerative disorders & ageing

Novel targets for the treatment of Neuronal Ceroid Lipofuscinosis

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Introduction: The Neuronal Ceroid Lipofuscinoses (NCLs) are a group of rare lysosomal storage disorders that occur in children and young adults and cause severe neurodegeneration, leading to premature death. Only limited treatment options are available, and it is essential therefore, to target therapies (e.g. gene therapy) to all affected areas. Recently, it was shown that one form of the disease, Cln1, exhibits profound and progressive spinal cord pathology early on. Following this, our project focusses on characterising pathology outside the brain, including spinal cord and peripheral nervous system pathology in mouse models of Cln3 and Cln7 disease.

Methods: After histological processing of spinal cord and dorsal root ganglia (DRG) tissue of *Cln3*^{Δex7/8} and *Cln7*^{Δex2} mice at different times of disease progression, we carried out an unbiased stereological assessment of neuron and volume loss, as well as quantitative thresholding analysis to determine the extend of astrocytosis and microglia

activation. We used fluorescent immunostaining as another way to assess neuron numbers and to quantify CGRP sprouting in the spinal cord, as well as neuron loss and immune activation in the DRGs.

Approach for statistical analysis: We used the Student's t-test to assess significance ($p < 0.05$) between wildtype and affected mice at each stage of the disease and a two-way ANOVA test to detect any differences between groups.

Results and Conclusion: *Cln3^{Δex7/8}* mice showed no significant loss of interneuron populations in the spinal cord at late-stage disease, but significant astrocytosis was present from late-stage disease in the spinal cord and significant microglia activation was evident from early disease stage in the spinal cord. *Cln7^{Δex2}* mice showed loss of different interneuron populations from late stage disease and significant astrocytosis and microglia activation in the spinal cord at an age that is considered pre-symptomatic. The results highlight that, while spinal cord pathology is evident in both *Cln3* and *Cln7*, the progression and severity can vary between forms of NCL. This emphasizes the need to properly characterise pathology outside the brain, as well as within to be able to successfully treat the NCLs in the future.

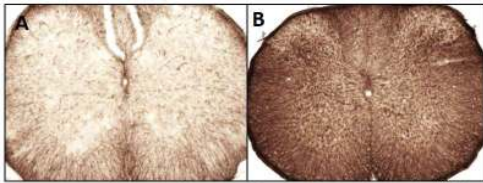


Fig.1 Spinal cord sections of disease end-stage wildtype (A) and *Cln7^{Δex2}* (B), immunostained for GFAP to assess astrocytosis.

The NCLs are a group of rare lysosomal storage disorders that occur in children and cause severe neurodegeneration and premature death, as only limited treatment options are available. The situation is especially difficult for transmembrane protein-deficient forms of NCL, as enzyme replacement therapy cannot be applied. It is essential therefore, to target therapies to all affected areas. Recently, it was shown that *Cln1* disease exhibits profound and progressive spinal cord pathology early on. Following this, my project aims to define pathology outside the brain, including spinal cord and peripheral nervous system pathology in mouse models of *Cln3* and *Cln7* disease.

Poster number: PT060 (SP)

Theme: Neurodegenerative disorders & ageing

The brain ↔ gut axis in Parkinson's disease: enteric nervous system pathology and gut microbiome alterations in the AAV-alpha-synuclein rat model

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Introduction: Gastrointestinal pathophysiology is a primary symptom of Parkinson's disease (PD), which precedes motor symptoms by many years. α -synuclein, the major pathogenic species in PD, is present in the enteric nervous system (ENS), and PD patients have an altered gut microbiome. It is proposed that α -synuclein may transit from the ENS to the brain to initiate PD, and α -synuclein is known to transit bidirectionally between gut and brain in animal models. This study aimed to determine whether a brain-initiated rat model of PD, the adeno-associated-virus(AAV)- α -synuclein model, altered the integrity of the ENS and gut microbiome, to provide better insight into brain ↔ gut communication in PD, essential for improving diagnostics and therapeutics.

Methods: AAV-driven overexpression of human- α -synuclein in the adult rat substantia nigra was employed as a model of PD. The integrity of enteric neuronal and glial systems was investigated in wholemount dissections of the ileum by immunofluorescence. Gut microbiota composition was analysed via 16S next generation sequencing and sequenced using Illumina MiSeq, bile acid composition was quantified using UPLC mass spectrometry. Groups of rats were allowed free access to running-wheels to investigate the impact of voluntary exercise on measures of gut health.

Approach to statistical analysis: Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test or unpaired Students T-test.

Results/Conclusions: Results show, for the first time, that bilateral intranigral overexpression of α -synuclein significantly alters the gut microbiome at the genus level. Similarly, faecal bile acid levels were significantly increased in the PD model, including a number of primary, secondary, tertiary and free bile acids. Significant correlations were evident between specific bile acids and certain microbiota at genus level. Overexpression of α -synuclein resulted in significant neuronal loss in the ileal submucosal plexus, and a significant increase in glial cell number in the myenteric plexus, indicative of inflammation. Voluntary running protected against both neuronal loss and increases in glial cells, and selectively affected the gut microbiome in the PD model. Together, these results reveal that developing brain pathology and motor function in this PD preclinical model exerts significant alterations in the gut microbiome and gut ENS, and indicates a brain to gut relationship in PD.

Poster number: PT061 (PP)

Theme: Neurodegenerative disorders & ageing

Classification of mild cognitive impairment, Alzheimer's disease, Parkinson's disease and healthy adults using eeg spectral power.

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Introduction: Alzheimer's disease (AD) affects 50 million people worldwide¹. Identifying biomarkers of AD and its prodromal stage Mild Cognitive Impairment (MCI) is crucial for early intervention. Electroencephalography (EEG) has become increasingly popular as a candidate biomarker of AD/MCI in recent years due to its low cost and portability. However, progress in EEG-based research has been hindered by small sample sizes and difficulty in group matching². Furthermore, previous EEG studies have reported poor specificity for AD/MCI relative to other disorders that cause dementia (e.g. Parkinson's disease; PD)².

Our aim was to evaluate the utility of EEG spectral power as a specific and reliable classification biomarker for MCI and AD.

Methods: Participants were patients with MCI ($n=64$), AD ($n=60$), PD ($n=50$) and controls (HC; $n=65$) matched for age, sex and education. Groups completed the Mini-Mental State Examination (MMSE) and EEG resting state recordings (3 minutes eyes open and 3 minutes eyes closed; 30 scalp electrodes). Absolute and relative power for each electrode was extracted for seven frequency bands: delta (1-4Hz), theta (4-8Hz), alpha1 (8-10Hz), alpha2 (10-13Hz), beta1 (13-18Hz), beta2 (18-30Hz) and gamma (30-45Hz). This resulted in 210 features (30 channels x 7 frequencies) per condition (eyes open/closed, absolute/relative power). Each feature represented activation in one scalp location in one frequency band.

Approach for statistical analysis: We will perform a machine learning classification analysis with penalised logistic regression³ using MMSE scores and EEG features. First, we will test the accuracy of MMSE scores in distinguishing between groups. As the most widely used measure of cognitive ability in AD, the MMSE will provide a comparison for EEG model performance. Models will be assessed for accuracy, sensitivity and specificity. Second, we will evaluate EEG classification accuracy. Each condition will be examined separately. Features with the best predictive power (i.e. above minimum thresholds for accuracy/stability) will be identified. Third, we will include MMSE and EEG features in a joint model to determine their combined predictive value.

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Poster number: PT062 (SP)

Theme: Neurodegenerative disorders & ageing

Activation of TRPML1 prevents phosphoinositide-induced dysfunction of the endosomal-autophagic-lysosomal system: relevance to Alzheimer's disease

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Introduction: Alterations in endosomal-autophagic-lysosomal(EAL) systems can precede accumulation of amyloid-beta and tau pathogenesis in Alzheimer's disease(AD). However, the key components of the EAL machinery that become defective in AD and could be targeted therapeutically are unclear. TRPML1(transient receptor potential cation channel, mucolipin subfamily1), a major endo-lysosomal Ca²⁺ release channel, represents one such component, being essential for fusion and degradation of endosomal and autophagic cargo by lysosomes. TRPML1 is a phosphoinositide(PI)-gated channel activated and inhibited by PI(3,5)P₂ and PI(4,5)P₂ respectively. We observed that many late-onset AD(LOAD) risk genes, including ApoE4, converge to regulate PI levels, essential for TRPML1 and EAL function. Here we aim to investigate the integrity of TRPML1 homeostasis in AD systems and determine whether targeting TRPML1 can remediate AD-like EAL defects.

Methods: HPLC/MS was employed to quantitate PI levels in post-mortem brain material from AD patients and controls. TRPML1 activity was measured in a human neuronal model of LOAD, derived from isogenic induced pluripotent stem cells carrying either ApoE3, ApoE4, ApoE2 or an ApoE knock-out. Lysosomal calcium was quantified using Fura-2 traces following the sequential depletion of ER calcium by ionomycin and rupture of lysosomal membranes with glycyl-L-phenylalanin-2-naphthylamide(GPN). Rat primary cortical neurons were depleted of TRPML1 agonist PI(3,5)P₂ using the PIKfyve inhibitor YM201636 and investigated for AD-like EAL pathology, and for rescue of these pathologies using the TRPML1 agonist ML-SA1.

Statistics: Significance was assessed using unpaired t-test or one-way ANOVA followed by Tukey post-hoc test.

Results/Conclusions: Levels of the endogenous TRPML1 antagonist PI(4,5)P₂ were significantly increased in AD brain samples compared to matched controls, and lysosomal calcium was significantly increased in ApoE4 and ApoE knock-out compared to ApoE3 or ApoE2 neurons, together indicating reduced TRPML1 activity in LOAD. Blocking TRPML1 activity via depletion of its agonist PI(3,5)P₂ induced a time- and concentration dependent swelling of early and late endosomes and impaired autophagy in rat cortical primary neurons, pathologies also described in AD patients. Re-

activation of TPRML1 using ML-SA1 mitigated endosomal swelling and prevented the accumulation of autophagic vesicles. Furthermore, ML-SA1 caused an intracellular shift towards non-amyloidogenic APP fragments. This renders TRPML1 as a potential therapeutic target for AD.

Poster number: PT063 (PP)

Theme: Neurodegenerative disorders & ageing

Users point of view on a point-of care mobile application to collect and visualize biomarker and lifestyle information of patients with mild cognitive impairment involved in longitudinal clinical studies

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Introduction: The World Alzheimer Report 2016 states that worldwide 47 million people live with dementia and the estimated total cost is US\$ 818 billion [1]. The European H2020-EU.1.3.1.-MSCA-ITN-ETN-2016 project "Blood Biomarker-based Diagnostic Tools for Early Stage Alzheimer's Disease (BBDiag)" aims at identifying and testing blood biomarkers in patients with mild cognitive impairment due to Alzheimer's disease and developing ICT solutions to manage blood, neuropsychological, and lifestyle markers. To collect and visualize patients' data a mobile application is developed with a user-centred design based on the needs of patients, caregivers and medical professional.

Methods: Interviews and questionnaires based on the technology acceptance model (TAM) [2] and the technology usage manual (TUI) [3] will be done with all stakeholders. The TUI divides the questions into two main categories pre and post exposure to the technology. This study uses the pre-part of the TUI to ascertain user curiosity and user anxiety towards new technologies. A post exposure survey is planned in the future.

Approach for statistical analysis: Statistical analysis of the variables is based on non-parametric correlation analysis with the Spearman-Rho rank correlation coefficient and a two-sided significance testing to find dependencies between the variables as well as the t-test [4]. The qualitative results are discussed in the light of the current ICT literature on dementia.

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Poster number: PT064 (SP)

Theme: Neurodegenerative disorders & ageing

Oligomeric tau injection alters action-potential dynamics and disrupts cortical synaptic transmission in vitro

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Introduction: Tau protein modulates microtubule stability. When hyper-phosphorylated it forms toxic oligomers and then tangles, which are known to correlate with Alzheimer's disease progression. Despite this, little is known about what effect oligomers have on the electrophysiological properties of single neurons.

Methods: In this study, whole-cell patch-clamp recording has been used in combination with computational modelling to determine how the intrinsic properties and synaptic transmission of cortical neurons alters over time, following the injection of oligomeric wild type full length tau (40-450 nM).

Approach for statistical analysis: Non-parametric Wilcoxon rank sum tests and ANOVAs were used to test for statistical differences amongst conditions.

Results and conclusions: Significant changes to the amplitude and duration of action potentials were observed following tau injection (after ~40 mins) with little change in the subthreshold properties of neurons. Studying synaptic transmission between pairs of layer V cells showed that tau presence in the presynaptic neuron resulted in a rapid run down of transmission. This experimental design allowed the first assessment of the acute effects of oligomeric tau injection into neurons to be characterised in real time.

Poster number: PT065 (PP)

Theme: Neurodegenerative disorders & ageing

Development of a human cerebroid model of Alzheimer's disease

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Introduction: In spite of decades of research, effective treatments for the devastating neurodegenerative condition Alzheimer's disease (AD) remain elusive. The reason(s) for this is unclear but it may, in part at least, be due to the fact that putative therapies have been almost exclusively developed using animal models of AD^{1,2} which may not fully replicate the complexities of human pathology³. For this reason, we plan to utilise cerebral organoids derived from *human* induced pluripotent stem cells (iPSCs) to investigate the aetiology underlying AD in the hope that we may be able to identify characteristics of the disease unique to human neurons. Specifically, in the first instance, we wish to investigate the hypothesis that neuronal calcium dyshomeostasis may be one of the early initiators and/or markers of AD^{1,2}. As such, one of the initial aims of the proposed study is to determine if previous work in our lab, demonstrating that intracellular calcium regulation is disrupted in hippocampal neurons of a transgenic mouse model of AD (3xTgAD mouse), relative to wildtype controls, is also found in human cerebral organoids derived from patients with familial forms of AD.

Methods: iPSC lines derived from familial AD patients will be used to generate cerebral organoids⁴. Modified organoid air-liquid interface slice culture preparations will be prepared in order to facilitate neuronal maturation. Test groups will include mutation-specific disease forms, healthy controls and homeostatic stressor exposed cohorts. Intracellular Ca²⁺ dynamics will be assessed using calcium imaging combined with confocal microscopy. Microelectrode array electrophysiological, immunofluorescence and western blot techniques will also be employed to assess potential developmental alterations between the different genotypes of organoids.

Approach for statistical analysis: Non-parametric statistical analyses will be employed as appropriate to assess if there are any differences in Ca²⁺ handling, electrophysiological and receptor characteristics between the various organoid genotypes and phenotypes.

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Poster number: PT066 (SP)

Theme: Neurodegenerative disorders & ageing

tRNA fragments generated by the ALS-associated ribonuclease angiogenin deliver novel and accessible biomarkers of disease progression in ALS

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Introduction: Angiogenin is a ribonuclease linked to the pathogenesis of amyotrophic lateral sclerosis (ALS) and released from motor neurons under stress conditions. ALS shows considerable clinical heterogeneity with some patients showing rapid decline and death within 2 years of onset whilst others show a much slower disease progression, therefore there is a great need to identify prognostic biomarkers for use in ALS.

Methods: Here we identify angiogenin substrates in a glial-derived cell line using small RNA sequencing.

Analysis Approach: We developed a custom pipeline for bioinformatics analysis of small RNA seq data.

Results & Conclusions: We identified a specific subset of tRNAs that were predominantly cleaved in the anticodon loop, from which only one half was retained. Stress-induced tRNA-derived fragments (tiRNAs) were validated by northern blotting and found to be generated and secreted from neuronally-derived cell lines. As tRNA cleavage constitutes an evolutionarily conserved stress response, we explored whether tRNA fragments indicated disease progression in preclinical ALS models and ALS patients. tiRNAs were elevated at disease onset in slowly-progressing but not rapidly-progressing mutant SOD1 ALS mice, suggesting that tiRNA formation indicates neuroprotective stress signalling mediated by angiogenin. tiRNA levels were elevated in spinal cord and serum collected at symptom onset from a second ALS mouse model (FUS (1-359)). Finally, we could show that serum tiRNA levels were significantly higher in slowly-progressing ALS patients compared to faster-progressing patients or healthy controls, mirroring the preclinical findings. Interestingly, we find serum 5'ValCAC tiRNA provides prognostic value to patients with spinal onset ALS. Our report identifies a novel and accessible biomarker of disease progression in ALS.

Poster number: PT067 (SP)

Theme: Neurodegenerative disorders & ageing

Control of the blood-brain barrier integrity during seizures via the ATP-gated P2X7 receptor

SP = Standard poster

PP = Preregistration poster

Authors: Dr Laura De Diego Garcia¹, Mr Jonathon Smith¹, Dr Tobias Engel¹

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Introduction: Epilepsy is a chronic neurological disorder affecting more than 60 million people worldwide. Despite more than 25 anti-epileptic drugs available, 30% of patients are still pharmacoresistant. The blood-brain barrier (BBB) is a specialized regulator that separates the bloodstream from the brain parenchyma. A functional BBB is crucial in maintaining brain homeostasis and preventing the entry of aberrant compounds and immune cells into the Central Nervous System (CNS). However, during epilepsy the permeability of the BBB may increase, resulting in blood-borne molecules and cells entering the CNS. Leakage of the BBB is one of the earliest characteristic disturbances following status epilepticus and may play an important role in the development of epilepsy. The purinergic P2X7 receptor has been associated with numerous damaging mechanisms related to epileptogenesis, such as inflammation and inducing leakage of the BBB. However, we do not know whether seizure induced changes of the BBB are dependent on P2X7 signalling and whether this process can be targeted.

Methods: P2X7's impact on the BBBs integrity during seizures was studied using the intra-amygdala kainic acid model in a newly developed P2X7 overexpressing mouse model. Brains were removed at different time-points, post-status epilepticus and were analysed by immunohistological techniques. Then changes in Podocalyxin (PODXL) due to play crucial roles in the proper functioning of the BBB as well as in disease progression were evaluated.

Approach for statistical analysis: Measures within the study are qualitative outcomes of immunohistology, measures of statistical significance are not applicable.

Results and conclusions: Here, we identified an overall increase in the expression of P2X7 receptor at 4 and 8hours post-status epilepticus. Moreover, in these overexpressed P2X7 cells there was an enrichment in PODXL expression. Our study demonstrates that during status epilepticus there is an increase in both P2X7 and PODXL expression that can disrupt tight junctions and relocalize tight junction proteins. This result indicates that P2X7 signalling may underlie pathological changes in BBB permeability and have an impact in the epileptogenesis process. Consequently, drugs targeting BBB function and P2X7 receptor may represent novel treatment strategies in epilepsy.

Poster number: PT068 (SP)

Theme: Neurodegenerative disorders & ageing

Mobile brain/body imaging in cognitive impairment

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Introduction: The prevalence of Alzheimer's disease (AD) increases with age and as mean population age also increases the number of AD cases is expected to grow substantially over the next few decades. Although current therapeutic discovery and development has focused on disease modification, early identification of cognitive decline could prove critical to developing effective intervention strategies. Effects from dual-tasks in which participants perform both a cognitive task and a motor task (such as walking) have been shown to predict progression of dementia among patients with Mild Cognitive Impairment (MCI). Using electroencephalography (EEG) based Mobile Brain/Body Imaging (MoBI), we are assessing healthy adults, patients with MCI, and patients with AD to identify and characterize neural, kinematic, and behavioral signals that indicate transitions from healthy aging to cognitive decline.

Methods: Adults between the ages of 18 and 32 years old have completed a 2-alternative forced choice task while either sitting (single-task) or walking on a treadmill (dual-task). High density EEG, motion capture, and cognitive task performance were recorded across 5 dual-task walking blocks and 5 single-task seated blocks. Analyses were performed in Matlab using the EEGLab open source software as well as custom analysis scripts. The next phase of our study will recruit older adults that are either healthy, have MCI, or have AD to perform the single- and dual-tasks.

Approach for Statistical Analysis: Coefficient of variation is calculated for stride-time and stride-length. Sensitivity index values are calculated from percentages of correctly performed trials. Analysis of variance (ANOVA) will be applied to ERP waveforms aligned to subjects' responses. Spectral power analysis of EEG will be performed aligned to subjects' gait cycles.

Results/Conclusion: Preliminary results have revealed no significant difference in gait variability between dual-task conditions in our current cohort of young, healthy adults. However, early indications suggest changes in gait variability that are time-locked to task errors. Additionally, no significant difference in performance of the task was observed between single- and dual-tasks. These results suggest healthy individuals were not affected by our dual-task design. We hypothesize that both task performance and gait kinematics will be affected in older healthy and patient populations.

Poster number: PT069 (PP)

Theme: Neurodegenerative disorders & ageing

Characterising neuroinflammation in frail mice

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Introduction: Growing evidence continues to define the crucial role inflammation plays in the progression of neurodegenerative diseases and ageing. It has emerged that inflammation outside the brain significantly contributes to inflammatory and degenerative changes inside the brain at least partly via alteration of the properties of microglial cells, the key brain immune cell population. Age-associated low-grade inflammation may contribute to brain aging but varies significantly among individuals, consistent with the idea that chronological ageing has limited predictive power for brain ageing. We hypothesised that frailty, a state of increased vulnerability due to the accumulation of multiple deficits in physiological systems, may contribute to the development of neuroinflammation.

Methods & Analysis: We utilise physiological and cognitive frailty indices to investigate whether microglial activation and consequent vulnerability to secondary insults increases with age contingent upon the frailty of the individual. Cognitive function in mixed gender C57BL6 mice at ages 6, 17 & 24 months, were assessed using a hippocampal dependent working memory T-maze alternation task and then stratified into cognitively frail and non-frail consequent on their failure in working memory following systemic inflammatory challenge with LPS (100µg/Kg). All data were analysed by two-way ANOVA and selected pairwise comparisons made by Bonferroni post hoc tests.

Results: Immunohistological analysis of microglial activation revealed age to be a stronger predictor of microgliosis than frailty. However, there was a significant increase in cell number and activation in aged frail mice compared to aged non-frail within white matter regions including fimbriae and corpus callosum. To examine molecular neuroinflammatory correlates of frailty we conducted quantitative PCR in mice assessed using a Cumulative Frailty Index to evaluate markers of microglial activation and acute inflammatory mediator production. A stronger correlation was found between microglial activation and age than with frailty. Further analysis of regional differences in the brain's underway. These data suggest that across the lifespan age more strongly predicts microgliosis, but that within tighter age brackets, frailty adds to the neuroinflammatory status. The extent to which

this increases an individual's vulnerability to secondary inflammatory insults has implications for our understanding of the interrelationship of frailty and dementia and remains the subject of further study.

Poster number: PT070 (PP)

Theme: Neurodegenerative disorders & ageing

Effect of transcranial direct current stimulation on cortical activity and muscle activity during gait in Parkinson's disease

Authors: Ms Aisha Islam¹, Dr Kianoush Nazarpour¹, Professor Lynn Rochester¹, Dr Annette Pantall¹

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Introduction: Parkinson's disease (PD) is characterised by gait impairment and is associated with increased falls risk and mortality due to basal ganglia pathology leading to a loss of automaticity during gait. Transcranial direct current stimulation (tDCS) may facilitate motor skill acquisition and retention through modulation of neuroplasticity. Underlying theories include increased cortico-spinal excitability and/or modulation of reciprocal 1a spinal inhibition. Application of tDCS to the primary motor cortex (M1) combined with physical therapy may improve gait in PD [1]. However, the effect of tDCS on cortical activity and muscle activity during gait is unknown. This prospective pilot study aims to investigate the effects of tDCS on cortical and muscle activity over a 3-week intervention using functional-near infrared spectroscopy (fNIRS) and surface electromyography (EMG) during overground and treadmill walking in individuals with PD.

Methods: Participants with PD (n=20) will be randomised into sham-stimulation group (n=10) or real-stimulation group (n=10) before undergoing testing at baseline, immediately after the intervention and at 3-week follow up the gait laboratory. The home intervention consists of anodal tDCS stimulation over the M1 for 10 mins at 2mA delivered x3 a week for 3 weeks through electrodes incorporated into neoprene caps (anode - M1 and cathode - contralateral supraorbital bone) combined with a gait training programme (Fig.1). Gait laboratory assessments walking under single and dual-task conditions overground (2 mins) and on a treadmill (10 mins) with muscle and cortical activity recorded.

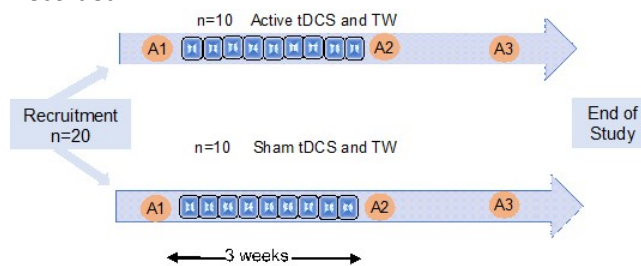


Fig.1

Statistical analysis: Statistical analyses will be conducted using SPSS (, USA). Linear mixed models with factors for group (physical training + real a-tDCS vs physical training + sham a-tDCS) time (0, 3, and 9 weeks), and group-by-time interaction will be used to determine the effect that different tDCS interventions have on and gait. Potential factors such as the participant's age and time since diagnosis will be used as covariates for analyses within our models. EMG signals will be compared using ANOVA.

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Poster number: PT071 (SP)

SP = Standard poster

PP = Preregistration poster

Theme: Neurodegenerative disorders & ageing

CSF and neuropsychological classification in typical and atypical prodromal Alzheimer’s disease according to biomarkers’ positivity likelihood

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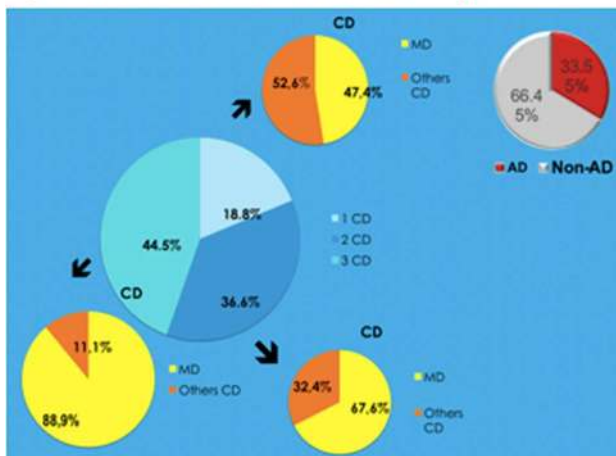
Introduction: A reliable early diagnosis of Alzheimer’s Disease (AD) at the prodromal stage is a key goal for both clinicians and researchers. However, diagnosis is often missed or delayed in daily practice partially due to ‘atypical’ presentations with impairment of other cognitive domains (CD) rather than memory. Cerebrospinal Fluid (CSF) biomarkers provide real added value for their ability to tackle the pathophysiological process underlying cognitive impairment. The aim of this study is to investigate the association between CSF “AD signature” and the occurrence of amnesic and non-amnesic presentations.

Methods: 301 cognitively impaired patients were recruited from the Memory Clinic of the University of Rome Tor Vergata. LP and neuropsychological assessments as follows were performed for all patients: Rey Auditory Verbal Learning Test –Delayed Recall, Rey-Osterrieth Complex Figure Copy, Semantic Fluency Test and the Frontal Assessment Battery. According to these scores the patients were categorized according to the presence of impairment in memory (MD), language (MD), executive functions (ED) and visuospatial (VD) domains.

Approach for statistical analysis: We subdivided the patients according to the likelihood of the CSF biomarkers in highly, intermediate or low likelihood. The highly likelihood group had a low value of Abeta42 together with an high T-tau or P-tau in the CSF (known as “AD signature”), the intermediate had either high T-Tau or P-Tau or low Abeta42, and the low likelihood had normal CSF. The association between impairment in CD and CSF typical “AD signature” was assessed by chi-2 analysis.

Results and conclusions: In the highly likelihood group, 26.7% patients showed a non-amnesic presentation with an impairment in 1, 2 or 3 CD. 52.6% of patients with impairment in 1 CD showed a non-amnesic presentation (VD or ED). 32% patients with decline in 2 CD had a non-amnesic presentation, and 11% with 3 CD affected (see fig 1). In conclusion, atypical neuropsychological presentations are common even in patients with a CSF “AD signature.”

Fig 1: Overview of the CD and CSF subtypes



Poster number: PT072 (SP)

Theme: Neurodegenerative disorders & ageing

SP = Standard poster

PP = Preregistration poster

Can we identify an optimal subset of tests for dementia severity based on current cognitive and functional assessments?

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Introduction: Cognitive and functional assessments (CFAs) within the dementia care pathway can take too long to evaluate within limited clinical consultation time. The goal of this study is to obtain an optimal battery of sub-assessments from current assessments to derive a more efficient CFA for dementia diagnosis.

Methods: The open source ADNI dataset was used. Clinical Dementia Rating Sum of Boxes (CDR-SB) was recoded into 4 classes of Alzheimer's disease (AD) disease severity and used as the objective outcome variable. The sub-scores (features) from the CFAs MoCA, MMSE, ADAS-Cog, and FAQ were amalgamated into one dataset.

Approach for statistical analysis: Various feature selection techniques were used including univariate selection techniques which rank features individually by measures such as random forest importance (RFI) and by information gain with the class variable (IG). The multivariate selection technique known as correlation-based filter selection (CFS) was also used. CFS compares all possible subsets of variables, optimising for maximum information relevant to the outcome, while minimising redundant variables. Multiple approaches to model building with the selected features were used, including an association rules learner based on repeated incremental pruning to produce error reduction, (RIPPER) which creates a scoring process which is transparent to clinicians.

Results and conclusions: The same features were selected using different feature selection methods. CFS selected an optimum subset of 18 features out of a total of 64. The 18 top-ranked features from RFI and IG were compared – 14 features were selected by all 3 algorithms, and another 2 features were selected by both CFS and IG. The transparent RIPPER based classifier had a classification accuracy of 70% over 4 classes, using the 18 features selected by CFS. Overall, our approach showed promising applications within the dementia care pathway through identification of key sub-assessments and enhancing the efficiency of the diagnostic process. Future work will include adding assessments from the Neuropsychological Battery, optimising feature discretisation to increase accuracy, validating the results on the NACC dataset, developing tests for different subpopulations, and optimising the test and scoring algorithm for simplicity.

Poster number: PT073 (SP)

Theme: Neurodegenerative disorders & ageing

Ghrelin receptor expressing neurones within the rostral dentate gyrus regulate hippocampal neurogenesis in adult mice

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Introduction: The dentate gyrus (DG) is a neurogenic niche in the adult mammalian brain where new neurones are formed from neural stem/progenitor cells (NSPCs) throughout life in a process called adult hippocampal neurogenesis (AHN). These new adult-born neurones play a key role in Learning and memory. Calorie restriction (CR)

has been shown to modulate the DG and improve cognitive function. Indeed, we show that CR increases AHN via ghrelin-receptor (Growth Hormone Secretagogue Receptor (GHSR)) signalling.

Methods: GHSR is highly expressed within mature neurones of the granule cell layer of the DG. To determine whether DG GHSR regulates neurogenesis we performed selective ablation of GHSR⁺ nerve cells within the rostral DG of adult mice. 8 week-old male GHSR-Cre mice received an injection of AAV-Cre dependent Caspase into the rostral DG of the hippocampus to ablate GHSR⁺ neurones. Subsequently, mice were intraperitoneally injected with Bromodeoxyuridine (BrdU, 50mg/kg) for 4 days to label dividing cells.

<https://en.wikipedia.org/wiki/Bromodeoxyuridine> After 4 months mice were killed under terminal anaesthesia and coronal sections of the brain were prepared for immunohistochemistry (IHC) against BrdU (new adult-born cell survival), Sox2 (type II stem cell), Ki67 (proliferation) and doublecortin (Dcx, immature neurone).

Statistical analysis: Student's unpaired *t*-test

Results and conclusions: Ablation of GHSR⁺ rostral DG neurones significantly reduced the number of BrdU⁺, Ki67⁺ and Dcx⁺ cells within the rostral DG. These reductions were not observed in the caudal DG. These data suggest that ghrelin-signalling via GHSR within the DG is important for adult neurogenesis. Further research is on-going to delineate the functional consequences of this ablation and whether acyl-ghrelin can rescue the AHN decline observed in ageing and neurodegenerative disease models.

Poster number: PT074 (SP)

Theme: Neurodegenerative disorders & ageing

The ZQ175 (190CHDIJ) mouse model of Huntington's disease exhibits locomotor dysfunction before psychiatric or memory deficits are observed

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder arising from the expansion of the CAG trinucleotide repeat section in exon 1 of the huntingtin *Htt* gene. Heterozygous knock-in models are the class of HD mouse model most genetically comparable to human patients. They typically exhibit age-appropriate symptom progression which means they are well suited for studying the prodromal psychiatric and cognitive symptoms of HD, before the onset of overt motor symptoms. The zQ175 (190Chdij) mouse (Jackson Laboratories strain # 027410) is a recently developed knock-in HD model with a human *Htt* exon 1 with 190 CAG repeats inserted into the endogenous mouse *Htt* gene. To determine its validity for HD research, this study aimed to phenotype the zQ175 mouse model (zQ175 n=10, wild-type n=10) at 7-8 months of age using various psychiatric and locomotor testing methods, as well as a prototype of a novel, continual trials cognition testing apparatus (Campden Instruments). Data analysis was performed with one-way ANOVA tests, with Tukey post-hoc tests used when comparing multiple

groups. Forced locomotion coordination on the rotarod showed a significant deficit in the zQ175 mice, with the zQ175 mice falling of the rotarod on average 3 minutes earlier than wild-type controls at 40rpm. No difference was seen between genotypes in spontaneous locomotor activity in open field. Neither anxiety testing in the elevated plus maze nor anhedonia measurements in a chocolate-consumption test showed a difference between genotypes. zQ175 mice showed a deficit in the burrowing of food pellets, but not of lighter bedding material, suggesting that this deficit is likely locomotor, and not of the burrowing behaviour itself. Neither novel-object-recognition or object-position-recognition tests in the automated apparatus nor T-maze memory testing showed a difference between genotypes. This data suggests that the zQ175 model does not exhibit an early cognitive or psychiatric phenotype mimicking the prodromal symptoms of HD, which makes it unsuitable as a model for our planned studies of cognition enhancement in the prodromal stages of HD.

Poster number: PT075 (PP)

Theme: Neurodegenerative disorders & ageing

Dry-electroencephalography and machine learning methods for differential profiling of mild cognitive impairment and dementia in Parkinson's disease – a feasibility study.

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Introduction: Cognitive impairment is prevalent in Parkinson's disease (PD), with 50% of patients developing dementia (PDD) within 10 years (Williams-Gray et al., 2013). The presence of mild cognitive impairment (MCI), particularly visuospatial dysfunction, has been associated with increased PDD risk. EEG has previously been shown to have predictive value for patient outcomes in MCI associated with Alzheimer's disease (AD-MCI), yet there is little information on the electrophysiological correlates of PD-MCI. Dry-EEG offers an inexpensive, non-invasive and faster method to assess cognition in aging clinical groups. However, as dry-EEG signal suffers from higher levels of noise, the feasibility of using this method to track cognition in these patient groups must first be established.

Methods: A 12-month follow-up study will be conducted. PD patients (n=60) and matched controls will complete a comprehensive neuropsychological assessment and a battery of EEG tasks. These tasks will assess resting state activity, attention, language, memory and visuospatial cognitive domains. The PD patient cohort will consist of PD-NC (normal cognition) and PD-MCI patients. A cross-sectional study of Alzheimer's disease (AD), Lewy-body dementia (LBD) and PDD patients (n=30) at one time-point using the same assessment tasks will also be conducted.

Analysis Approach: The primary outcomes for this study will be the ability of dry-EEG to differentially discriminate between these patient groups and to track changes in PD cognitive status over 12 months. Previous studies of cognitive dysfunction in PD have identified EEG slowing (for example decreased alpha/theta ratio) and delayed or absent ERP components (Seer et al., 2016). For each task, power spectral analysis will be computed and the relevant ERP components (such as the P300 and MMN from the auditory oddball task) will be analysed. Differences between groups will be assessed using randomisation tests with FDR-corrected pairwise comparisons. Correlation analysis with validated clinical measures such as the MoCA will also be performed. Machine learning algorithms such as the 'Elastic Net' (Zou & Hastie, 2005), random forests and k-nearest neighbour models will be used to identify EEG features which discriminate between patient groups and which are associated with cognitive outcomes (i.e. stability or worsening) at follow-up.

Poster number: PT076 (SP)

SP = Standard poster

PP = Preregistration poster

Theme: Neurodegenerative disorders & ageing

Impact of the ATP-gated P2X7 receptor on status epilepticus-induced neurogenesis

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Introduction: New neurons are generated continuously during the entire lifespan in the adult brain of mammals, including humans. These new neurons are generated in neurogenic niches: the subventricular zone in the walls of the lateral ventricles and the subgranular zone in the dentate gyrus of the hippocampus. This physiological process is upregulated following acute insult, such as traumatic brain injury, stroke or status epilepticus. Emerging data has demonstrated a prominent role of extracellular ATP in regulating neurogenesis. While P2X7 has been shown to alter the rate of neurogenesis, however, whether P2X7 also alters status epilepticus-induced neurogenesis has not been fully addressed.

Methods: Using an intra amygdala kainic acid mouse model of status epilepticus, with a range of transgenic mouse lines (P2X7 KO, P2X7 overexpression), we used immunohistochemistry to visualise changes in the distribution of markers of neuronal development (e.g. Nestin, Doublecortin, NeuN) and trackers such as Iodo/Chloro-deoxyuridine (IdU/CldU), injected respectively 3 days and 17 days after the kainic acid injection.

Approach for statistical analysis: Two-way ANOVA was used to measure statistical differences between groups, with Tukey's HSD test performed for post-hoc analysis.

Results and conclusions: The rate of neurogenesis in the dentate gyrus is increased in kainic acid-injected mice, with an evident presence of newly generated neurons, with a visibly aberrant morphology, located ectopically in the hilus. P2X7 increased not only the number of trackers positive cells in the subgranular zone and in the granular layer of the hippocampus, but also on status epilepticus-induced aberrant neurogenesis with several cells detected in the hilus. Furthermore, an increasing IdU+ cells, more than CldU ones, was observed also in other sectors of the hippocampus, like the CA3 and CA1, suggesting an activation of the gliogenesis process. No difference were detected between WT and KO mice.

Poster number: PT077 (SP)

Theme: Neurodegenerative disorders & ageing

Investigating the relationship between polyglutamine repeat length and the age of onset of different symptom sets in Huntington's disease

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Huntington's Disease is a genetic neurodegenerative disorder caused by a microsatellite mutation resulting in an expanded polyglutamine (CAG) repeat region in the gene encoding Huntingtin protein. When exceeding a threshold of 36 repeats^[1] this mutation leads to the cleavage and aggregation of polyglutamine fragments in cells, increasing cellular toxicity through a range of molecular pathways and macroscopic changes in the brain resulting in a range of motor^[1] & psychiatric symptoms^[2]. It is well known that locomotor symptoms correlate well with CAG repeat length but the psychiatric and dementia-like symptoms, as well as the potential role of the wild-type (WT) allele, are less well characterised. Our aims were to characterise the relationships between the age of onset of different symptom sets and CAG repeat length; quantify the risk of patients developing different symptoms dependent on disease

status; and investigate potential geographical differences in the age of onset of these symptoms relative to repeat length. This was accomplished through use of the Enroll-HD database. We demonstrate that the age of onset of 7 symptom sets exhibit a significant decrease in the age of onset as mutant CAG repeat length increases, but not with (WT) CAG repeat length in Huntington's disease patients using logistic regression. This strengthens the dominant hypothesis that Huntington's disease symptoms are caused by a gain of function of the mutated protein. The age of onset of cognitive symptoms is significantly higher in patients in Europe than globally, but significantly lower in 4/5 studied psychiatric conditions in Northern America. This could be explained by the need for definitive psychiatric diagnoses in order to access treatment in Northern America. A fuller understanding of the relationship between CAG repeats and different symptoms in Huntington's Disease may contribute to a more precise and informed prediction of symptom onset and risk for genetically diagnosed patients, and therefore allow for forward planning of treatment options.

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Poster number: PT078 (SP)

Theme: Neurodegenerative disorders & ageing

Therapeutic efficacy of GDF5 viral vectors in the α -synuclein rat model of Parkinson's disease

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Introduction: Neurotrophic factors hold significant promise as neuroprotective therapies for Parkinson's disease (PD). While viral vector-mediated delivery of neurotrophic factors to the PD brain is safe and clinically feasible, clinical trials of two well-known neurotrophic factors, GDNF and NTN, have failed to meet their primary end-points. Here we sought to determine whether viral delivery to the adult rat brain of a novel neurotrophic factor, growth differentiation factor (GDF)5, could protect dopaminergic neurons and their axons from α -synuclein-induced degeneration, which is the primary neuropathological hallmark of PD.

Methods: All procedures were carried out under license with full ethical approval. Adult Sprague-Dawley female rats received unilateral injection of AAV-Null or AAV- α -synuclein viral vector into the substantia nigra (SN), together with AAV-Null or AAV-GDF5. Behavioural tests of sensorimotor function were carried out at 4, 8, 12, 16 and 20 weeks, prior to post-mortem analysis of α -synuclein pathology and nigrostriatal integrity at 20 weeks.

Approach for statistical analysis: Behavioural changes were analysed using two-way repeated measures ANOVA (n=10 per group). Differences in midbrain dopaminergic neuron number and striatal dopaminergic innervation were analysed using one-way ANOVA. Post-hoc Bonferroni tests were performed in both cases.

Results and conclusions: Post-mortem immunohistochemistry revealed strong overexpression of α -synuclein that had spread throughout the midbrain and to the ipsilateral striatum. pSer129- α -synuclein immunostaining for the pathological form of α -synuclein revealed strong expression in dopaminergic neuronal soma and neurites in the SN, characteristic of Lewy bodies and Lewy neurites. Quantification of nigrostriatal integrity showed that α -synuclein led to reductions in striatal dopaminergic innervation and midbrain dopaminergic neuron number, that were prevented by AAV-GDF5. This neurodegeneration was not sufficient to lead to significant behavioural changes in this model. These findings are an important step in rationalising the further development of AAV-GDF5 vectors for neurotrophic therapy in PD.

Poster number: PT079 (PP)

SP = Standard poster

PP = Preregistration poster

Theme: Neurodegenerative disorders & ageing

Studying mitochondrial bioenergetics of ghrelin-mediated neuroprotection in neurodegenerative disorders

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Introduction: Alzheimer's disease (AD) and Parkinson's disease (PD) are age-related neurodegenerative disorders characterised by progressive memory loss (AD) and motor and cognitive decline (PD). Calorie restriction (CR) is known to prevent cognitive deficits in mouse models of AD and PD and in aged humans. We recently showed that CR-mediated neuroprotection, neurogenesis and memory are dependent on the hormone ghrelin, which is produced and activated (acylated) in the stomach in response to changes in metabolic status. Acyl-ghrelin (AG) activates Growth Hormone Secretagogue Receptor-1a (GHSR) in several areas of the brain and is known to modulate mitochondrial function. Here, we have characterised the expression of ghrelin-axis proteins in post-mortem human AD and PD brain. Moreover, we analysed the effect of AG on mitochondrial function in human neurones.

Methods: Human neural stem cell-derived neurones (ReNVM) were differentiated for 28 days. To model AD, cells were treated with amyloid-beta (1-42) oligomers (A β Os), a protein known to induce neuronal toxicity and mitochondrial dysfunction in AD neurones. To model PD, cells were treated with the electron transport chain inhibitor, rotenone, which is known to induce oxidative damage and death of dopaminergic neurones. In these models, the effect of AG on mitochondrial bioenergetics, MMP and mitochondrial fusion/fission were investigated using the "mitotracker" dye and antibodies targeting the phosphorylated forms of the DRP1 protein. Finally, we are currently assessing the expression levels of GHSR and other ghrelin-associated proteins (GOAT, APT1) in post-mortem brain tissue from AD and PD patients, using a combination of immunohistochemistry and BaseScope[®] assays.

Analysis approach: In-vitro immunofluorescence images were captured using confocal microscopy. Whilst human brain tissue, immunostained for GHSR mRNA (BaseScope[®]) and other ghrelin-associated proteins (IHC-DAB) were imaged using bright-field microscopy. Images are currently being analysed using the free-source software packages, CellProfiler and QuPath. Student's *t*-test will be used to analyse two groups. When more than two groups will be analysed a one-way ANOVA and appropriate post-hoc multiple comparison will be used.

Poster number: PT080 (SP)

Theme: Neurodegenerative disorders & ageing

Cognitive impairment in perimenopause: the role of oxidative stress and antioxidants

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Increase oxidative stress from reduced levels of oestrogen may be responsible for the increased neuropsychiatric symptoms seen in perimenopause. This study investigated the effect of antioxidants on cognitive function in perimenopausal rats. Immature female Sprague-Dawley rats postnatal day 28, divided into 3 groups; (1) Control injected with Corn-oil (2.5 μ l/g BW) for 15 days; (2) VCD, injected with 4-vinylcyclohexene diepoxide (160mg/kg BW) diluted in Corn-oil for 15 days; and (3) Aged group (left to age till 180 days). Fourteen weeks after VCD/corn-oil administrations, and 180 days in Aged group, rats were further divided into 3 sub-groups: L-Arginine (100mg/kg), D-ribose (200mg/kg), and a third sub-group received neither for additional 30 days (distilled water).

At 150 – 165 days in Control and VCD, 205 – 215 days in Aged on diestrus morning, animals were subjected to acute restraint stress for 30 minutes, followed by 30 minutes recovery period. Animals were humanely sacrificed, hippocampus carefully isolated from the rest of the brain and homogenized for the measurement of oxidative stress parameters.

The percentage correct alternation was higher in the Control group compared to VCD and Aged groups ($P < 0.05$). There was no significant difference in the percentage correct alternation between distilled water group compared to L-Arginine and D-ribose groups in the VCD and Aged groups. In the hippocampus, there was reduced catalase activity in the VCD and Aged groups compared to Control ($p < 0.05$). D-ribose group had a significantly higher ($p < 0.05$) level of catalase compared to the other groups. L-arginine also significantly reduced ($p < 0.05$) malondialdehyde levels. There was no significant change in the activities of superoxide dismutase and glutathione.

Perimenopause is associated with a reduced cognitive function which was not improved with antioxidants. This suggests that the major mechanism of cognitive impairment may not be related to oxidative stress.

Poster number: PT081 (SP)

Theme: Neurodegenerative disorders & ageing

Ghrelin regulation of adult hippocampal neurogenesis in models of Parkinson's disease

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Introduction: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder in humans. It is characterised by the progressive loss of dopamine neurones in the Substantia Nigra Pars Compacta (SNpc) resulting in resting tremor. PD is also associated with non-motor impairments, including a reduction in adult hippocampal neurogenesis (AHN) and cognitive decline. Here, we test whether the stomach-hormone, acyl-ghrelin, can promote neurogenesis in *in-vivo* and *in-vitro* models of PD.

Methods: In the *in-vivo* MPTP and 6-OHDA-toxin models of PD acyl-ghrelin prevents SNpc DA neurone loss in an acyl-ghrelin receptor-dependent manner (Andrews et al.2009 & unpublished data). Here, using immunohistochemistry against doublecortin (Dcx), we tested whether acyl-ghrelin treatment was able to protect new adult-born hippocampal neurones from toxin-mediated inhibition. Similarly, using a neural stem cell line (ReN cells) we determined whether acyl-ghrelin was able to promote neurogenesis and neuronal function in neurotoxin-treated cultures *in-vitro*.

Statistical analysis: Two-way ANOVA (*in-vivo*) and one-way ANOVA (*in-vitro*) were used, followed by post-hoc multiple comparison testing.

Results and conclusions: Acyl-ghrelin preserved wild-type levels of hippocampal neurogenesis (Dcx⁺) in neurotoxin-treated animals. We also show that immature ReN-derived neurones were susceptible to a neurotoxin-mediated reduction in neurogenesis. Further studies are ongoing to determine whether acyl-ghrelin mediates direct effects on neurones *in-vitro*.

Poster number: PT082 (SP)

Theme: Neurodegenerative disorders & ageing

Tau blocks amyloid-beta effects and silences neural circuits in Alzheimer models in vivo

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Introduction: Alzheimer's disease is manifest neuropathologically by widespread amyloid- β (A β) plaques and tau neurofibrillary tangles (NFTs) in the brain. Plaques and tangles are associated with neural system failure and cognitive deterioration, however the neuronal mechanisms are unclear.

Methods: Here we used in vivo calcium-imaging of large populations of layer 2/3 cortical neurons in mice expressing both human A β and tau.

Analysis approach: We assessed the effects of A β and tau alone as well as the combination of both proteins on spontaneous cortical activity.

Results and conclusions: We reveal a strong tau-dependent suppression of activity and silencing of a vast number of neurons, which appears to dominate A β -dependent neuronal hyperactivity. We show that NFTs are not required for the silencing phenotype, and that soluble tau is sufficient. We demonstrate that by repressing tau gene expression the silencing phenotype can be rapidly rescued in tau mice. Surprisingly the same treatment was ineffective in mice harboring both A β and tau. Together, these new data may help explain the numerous failed clinical trials directed at reducing A β in the brains of patients, since the combination of A β and tau in the brain leads to a phenotype that is different than A β alone, and which is dominated by tau neural system silencing.

Poster number: PT083 (SP)

Theme: Neurodegenerative disorders & ageing

Clinical index of metabolic risk factors for predicting disease progression in dementia

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Introduction: Certain cardio-metabolic implications are associated with an increased risk for dementia. However, several studies have shown a degree of variability which complicate our understanding of the role of such risk factors on dementia. This study aims to further understand such risk variability by evaluating the association of these risk factors with respect to the progressing of the disease across different time points.

Methods: The National Alzheimer's Coordinating Centre (NACC) database, one of the largest and most comprehensive longitudinal databases for dementia research, was used in this study. The risk factors considered in the data consisted of age, gender, smoking, body mass index (BMI), alcohol/substance abuse, stroke/heart attack/cardiac arrest, geriatric depression scale (GDS), prescription data, diabetes, hypertension and hypercholesterolemia. In addition, various possible combinations of the above-mentioned variables will be evaluated and ranked on the basis of increasing risk. These analyses are categorised by gender and different age groups. We then proposed a clinical index of the ranked output which will allow predictive risk association of disease progression (from healthy to dementia, and from mild cognitive impairment or MCI to dementia) for various dementia subtypes (including Alzheimer's disease, lewy body dementia, frontotemporal and vascular dementia).

The effects of different types of antihypertensives on disease progression were also analysed.

Approach for statistical analysis: Descriptive statistics were used to describe the basic features of the data, followed by multivariate logistic regression to analyse odds ratios (OR) associated with all the variables.

Results and conclusions: In terms of progressing from healthy to dementia, the highest risk (OR: 2.3138, p: 1e-04^{***}) was linked to GDS score (≥ 6) compared to all the other risk factors. For MCI to dementia progression, diabetes (OR: 0.8, p: <0.005^{***}) and BMI (≥ 30) significantly associated with lowered risk (OR: <0.7, p: <2e-04^{***}).

For healthy individuals, ACE inhibitors, antiadrenergic agents, beta blockers and calcium channel blockers can increase the risk of having dementia (OR: 1.11-1.24, p: <0.005^{***}), whereas antihypertensive combination therapy, diuretics and angiotensin II inhibitor lower the risk (OR: 0.73-0.81, p: <2e-04^{***}).

Further research will employ survival analyses to assess the time period for progressing to dementia using the patient's metabolic conditions.

Poster number: PT084 (SP)

Theme: Neurodegenerative disorders & ageing

Mid-Life Stroke Risk Has Unique Effects on Brain Integrity in Later Life

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Introduction: Multi-measure cardiovascular and stroke risk scores, such as the Framingham Risk scores [1] predict subsequent cognitive decline, grey matter volume reduction and white matter changes [2]. The aims of the present analysis was: 1) to establish whether there is an association between the Framingham Stroke Risk Profile (FSRP) in mid-life across five phases (P) and reduced structural brain integrity beyond the effects of age, and 2) to establish whether the predicted effects on brain structure reduction in older age are the same 5 (P9), 10 (P7), 15 (P5) and 22 (P3) years before as at the time of the scan (P11) [3].

Methods and statistics: T1 and dMRI scans from 566 Whitehall II participants [4] were analyzed (age 69.9 \pm 5.2yrs, M=450). Negative correlation between FSRP and gray matter density (GMD) and fractional anisotropy (FA) at each phase was assessed using FSL-VBM and TBSS [5]. Correlations with FSRP at P11 including P3–P9 as regressors were also run (multiple comparisons corrected, significance level TFCE $p < .05$).

Results: Each FSRP predicted widespread GMD and FA reduction. After controlling for confounders including a quadratic age term (biological age) reduced GMD was present in right medial temporal lobe (MTL) and medial temporal gyrus. FSRP at P11, controlling for P9 didn't predict GMD reduction. Controlling for P3–P7 it predicted GMD reduction in medial temporal lobes (MTL). FSRP at P5–P11 and at P11 controlling for P3–P9 predicted widespread FA reduction.

Conclusions: FSRP predicts reduced GMD 22yrs and FA 15yrs before the scan. FSRP predicts reduced GMD and FA beyond the effects of biological age. Additional GMD reduction is predicted in later life compared to 10-15-22yrs before the scan in MTL, due to the plasticity of these areas, but not in posterior/cortical areas. FA associations are significantly different in four phases compared to in later life. They become more widespread the earlier the FSRP is.

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Poster number: PT085 (SP)

Theme: Neurodegenerative disorders & ageing

Olfactory bulb and DOPAL: a novel ex vivo model of prodromal Parkinson's Disease

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Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting more than 10 million people worldwide. The olfactory bulb (OB) is one of the first places affected in PD and it is thought to be involved in the disease pathogenesis (Hawkes, 1999; Doty, 2012). Indeed, a reduced ability to detect odours (called hyposmia), is one of the prodromal symptoms, affecting patients up to decades before the diagnosis of the disease is made. In order to understand the mechanism underlying the prodromal stage of PD, OB organotypic slices have been used in combination with DOPAL, a toxic metabolite of dopamine, physiologically present in the OB and whose concentration is increased in PD patients (Goldstein *et al.*, 2011).

Methods: Organotypic OB slices were cultured for 7 days in vitro (DIV) followed by 3 DIV of DOPAL treatment and other 4 DIV of recovery. Slice viability has been assessed using the alamarBlue® assay and the media collected for analysis of nitrite and reactive oxygen species (ROS) at DIV 7, 10, 14. The effects of DOPAL on the bioenergetic performances of OB cells have been studied using the MitoStress Test assay and the Seahorse XFp analyser.

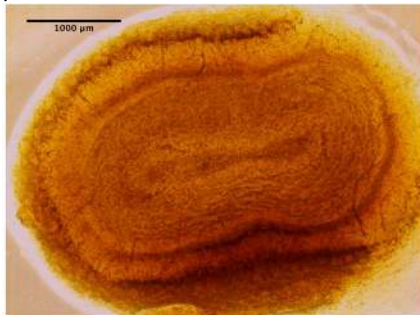


Fig1: OB slice at DIV1. All the main structures of the OB are well preserved. (scale bar = 1000μm).

Approach for statistical analysis: All statistical analysis were performed using GraphPad Prism 7 and data were compared using one-way ANOVA. Data were obtained from at least 3 experimental replicates and are presented as mean ± SEM.

Results and conclusions: DOPAL increases the content of ROS and nitrites, resulting in reduced viability of treated slices. A possible mechanism of action is through the damage of mitochondria and the impairment of the physiological energy homeostasis in the cells. Signs of mitochondrial damage, like an increased proton leak or a decreased coupling efficacy and spare respiratory capacity, appear minutes after DOPAL is added to the culture media. In conclusion exposure of cultured olfactory bulb slices to DOPAL caused toxicity that mimics aspects of PD pathology. They novel experimental platform show great promise as an innovative, easy and accessible technology for the development of new treatments for PD and raises the enticing possibility of early-stage intervention.

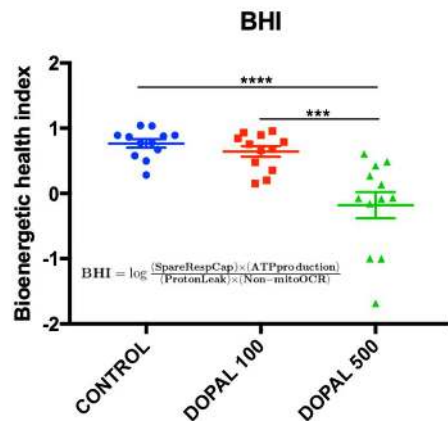


Fig2: Bioenergetic health index is decreased in DOPAL-treated cells, a clear sign of impaired mitochondria

Poster number: PT086 (SP)

Theme: Neurodegenerative disorders & ageing

Reminiscence therapy in an individual with transient epileptic amnesia: impact on autobiographical memory

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Introduction: Transient epileptic amnesia (TEA) is a rare memory condition associated with confusion and severe memory loss during epileptic attacks. Although these attacks can be treated with anticonvulsant medication, there is often a clear impairment in autobiographical memory, regardless of whether such attacks are still occurring. There is a lack of published work on psychosocial interventions in TEA. Reminiscence therapy is a form of semi-structured psychosocial intervention that has been used to maintain autobiographical memory in people with disorders that can affect memory (e.g. dementia, major depression).

Methods: The current report describes a reminiscence therapy intervention in an individual with TEA, a retired, white British male. The client completed five sessions of simple reminiscence therapy, with prompts being used to encourage memory from various phases of the lifespan. Before and after the reminiscence intervention, we assessed autobiographical memory across various life epochs (birth-15 years of age, 15-30 years, 31-45 years, 46-last 5 years, last 5 years), using the Episodic Autobiographical Memory Interview (Irish et al., 2008).

Approach for analysis: Descriptive statistics were calculated for the relevant measures.

Results and conclusions: At baseline, there was a clear temporal gradient in autobiographical memory retrieval, with poorer recall of memories for more recent periods in life. This decline in autobiographical memory over the lifespan

also appeared to be more severe for episodic memory than semantic memory. The client commented that retrieval of autobiographical memories appeared to be the problem, and that recognition memory was relatively intact. Following reminiscence therapy there was a modest overall improvement in autobiographical memory; although episodic memory was poorer for middle age, it was improved for more recent memory. It should be borne in mind that, due to the rarity of this condition, we only recruited one participant with TEA. These results tentatively suggest reminiscence therapy was of some benefit for this individual with TEA, but highlight the variability of impairment (and possibly treatment effects) across life epoch.

References

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Poster number: PT087 (PP)

Theme: Neurodegenerative disorders & ageing

Investigating the effects of oscillating sounds on memory function in older populations

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Introduction: Memory functions are associated with various oscillations of electrical activity in the brain, and disruptions of those rhythms can be observed in many neurological syndromes, including Alzheimer's Disease. Oscillations at the theta (3-7 Hz) frequency, in particular, are thought to play an important role in memory. The peak frequency and amplitude of the theta frequency are modulated by age and could be a useful target to combat the cognitive decline commonly associated with aging. Previous studies have induced theta oscillations using transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS). We hypothesized that oscillatory auditory stimulation could similarly entrain theta rhythms in a less invasive, more cost-efficient manner. Preliminary data collected from young adults indicated a positive relationship between theta entrainment and improved short-term visuospatial memory.

Methods: We recorded the neural activity, using electroencephalography (EEG), from participants aged over 50 while they completed a spatial memory task. Three groups of participants with varying memory ability were recruited—healthy controls (n = 25), individuals with subjective memory complaints (n = 25), individuals with Mild Cognitive Impairment (MCI; n=25). During the first part of the task, participants listened to amplitude modulated noise at 3, 4, 5, 6, and 7Hz to determine which frequency within the theta band induced the strongest increase in

theta power with respect to a pure noise control. Next, participants learned the locations of 30 objects via a spatial memory task administered on a computer. Each object was consistently paired with one of three types of pink noise—constant noise, individualized theta frequency-modulated noise (3, 4, 5, 6, or 7Hz), and 15-Hz-modulated noise (beta).

Analysis Approach: Induced theta and beta power will be calculated using EEGLab to quantify the impact of the sounds on neural activity. The scalp distribution of theta power will also be compared between the three groups to detect difference between the three experimental groups. A Two-way ANOVA will be used to identify if sound type or experimental group, or interaction between both factors impacted memory performance. We hypothesize the individualized theta frequency condition will be associated with improved spatial memory.

Poster number: PT088 (SP)

Theme: Neurodegenerative disorders & ageing

Longitudinal mapping of cognitive decline in female C57BL/6J as a model for healthy brain ageing

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Introduction: Longitudinal cognitive testing in humans has revealed differences in the ageing process between individuals. Animal studies are vital in order to understand the biology of the ageing process, but few studies have tracked cognitive decline in individual mice across their lifespan. The aim of our study was to examine the trajectory of individual mice and identify any early indicators of age-related cognitive decline in these mice. This data will be used to determine whether changes in neuronal connectivity associate with good and bad ageing trajectories in mice.

Methods: Female C57BL/6J mice (Charles River, UK) were kept under 12h light/12h dark cycle at 23±1 °C, 4 mice per cage with ad libitum access to food and water. Individual mice were tested at 4, 8, 12 & 18 months of post-natal age using a 3-dimensional maze to assess spatial Learning and memory while simultaneously establishing any age-related changes in anxiety and locomotor activity. These mice were also assessed for Non-spatial Learning and memory using novel object recognition and novel object location tests.

Approach for statistical analysis: For 3-dimensional maze, Mice were video-tracked for a maximum of 10 minutes, once every 16 days, and parameters such as mean decision-making time between arm visits, number of total arm visits and number of visits to the same arm were measured. Changes in the performance of 58 mice was quantified from 4 to 18 months of age. Object recognition and object location tests were performed using 1 min and 10 min delay for each test.

Results and conclusions: The rank order of the mice remained fairly consistent with age in terms of the processing time needed to make nine choices and the number of arm visit repeats. It was also apparent from these data that animals taking longer to decide to enter the arms were more likely to re-visit arms and, therefore, explore fewer arms in the time available.

Poster number: PT089 (SP)

Theme: Neuroendocrinology and autonomic systems

A central role of the adipokine chemerin in energy balance regulation and neuroinflammation

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Introduction: Chemerin is a newly discovered chemoattractant adipokine, involved in inflammation, adipogenesis, angiogenesis and energy metabolism. It has been proposed as a link between inflammation, obesity and the development of type II diabetes. In support, local chemerin gene expression and circulating levels are elevated in humans affected by obesity. In animal studies, chemerin has been shown to modulate hypothalamic neuropeptides that control feeding and energy homeostasis. Chemerin and its G protein-coupled receptor, chemokine-like receptor 1 (Cmklr1) is expressed in tanycytes lining the third ventricle and neurones of the arcuate nucleus indicating a possible neuroendocrine role of chemerin. Here, we used a combination of *in-vivo* and *in-vitro* studies to investigate signalling pathways activated by chemerin and the underlying molecular mechanism in hypothalamic glia cells and neurones.

Methods: Mouse hypothalamic E44 cells and primary tanycyte cultures were stimulated with chemerin (10nM) every minute for 20 minutes. Immunoblots were probed with anti-ERK1/2, pERK1/2, Akt and pAKT antibodies. Changes in neuropeptides involved in appetite regulation (AgRP, NPY) and inflammatory markers (Il-6, TNFalpha) were measured using qPCR. E44 cells and primary neuronal cultures were treated with 10nM chemerin for 6 hours. *In-vivo* studies were performed in male C57BL/6 mice. Chemerin (100nM) was administered to mice by nasal route and compared against appropriate controls (n=6/group). Mice were killed 15 min after intranasal administration, brains were dissected and RNA and protein was isolated using the PARIS kit.

Approach for statistical analysis: Data were analysed by two-tailed Student's t-test or one-way factorial ANOVA as appropriate.

Results and conclusions: Using single-cell RNA sequencing, we found cell-specific expression of chemerin and Cmklr1 in mouse hypothalamic tanycytes, neurones and macrophages. Chemerin activates ERK1/2 and Akt pathways *in-vitro* and *in-vivo* suggesting that it may be involved in key cell signalling events. Interestingly, chemerin treatment results in an increased expression of pro-inflammatory markers thus it may play a role in acute hypothalamic inflammation. Furthermore, chemerin treatment upregulates appetite regulatory genes suggesting that it contributes to the neuroendocrine control of appetite. Our data demonstrate that the adipokine chemerin is a promising candidate for urgently needed pharmacological treatment strategies for obesity.

Poster number: PT090 (SP)

Theme: Neuroendocrinology and autonomic systems

Heteromeric mineralocorticoid (MR) and glucocorticoid receptor (GR) interactions

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Effective responses to stressful events involve modification of cognitive processes in the brain improving coping mechanisms to future stressors. Glucocorticoids (GCs) are released from the adrenal glands into the circulation where they mediate their effects in the brain via the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), producing both physiological and adaptive responses to stress. MR and GR are highly abundant in the hippocampus, an area vital for Learning and memory (1). Ligand activated MR and GR undergo dynamic conformational changes and remodelling of stabilising chaperone complexes, allowing accessibility to the nuclear localisation signal (NLS). The receptor-ligand complex then translocates into the nucleus where it associates with glucocorticoid response elements (GREs) in the promoter regions of glucocorticoid target genes to modulate transcription (2). Classically, MR:MR and GR:GR dimers were believed to regulate transcription of GC targets,

however recent evidence has proposed heteromer models, although the manner of interaction requires further clarification. The oligomerisation of the two interacting receptors must be in the same subcellular compartment and in close enough proximity to allow for direct receptor-receptor interaction. This has been difficult to study in native tissues due to a lack of sensitive and selective tools capable of demonstrating the proteins are in sufficiently close proximity to interact. Using a proximity ligation assay (PLA) I demonstrate direct MR-GR interactions both in Neuro-2-a (N2a) cells close to the inner nuclear membrane and in rat hippocampus. Furthermore, synthetic steroids might alter gene expression via disruption of the MR:GR heteromer ratio (3). Upon treatment with the selective GR agonist dexamethasone, endogenous GC release is impaired and MR transactivation is reduced. As GR overexpression has been shown to produce anxiety-like behaviour, whereas MR overexpression can reduce it (7), altering MR:GR ratios and GC signalling via these receptors (4), could produce adverse effects such as psychiatric disease (5,6). The data in this poster helps towards understanding of the MR:GR heteromer, its co-localisation and contact with subcellular proteins, and provides further understanding of how they may modulate the transcriptional regulation of GC responsive genes. Such findings should highlight a possible role for the MR:GR ratio in the control of emotional reactivity.

Poster number: PT091 (SP)

Theme: Neuroendocrinology and autonomic systems

Surveying the heterogeneity of hypothalamic agrp/npv neurons by single-cell RNA sequencing

Authors: Dr Brian Lam¹, Dr Irene Cimino¹, Ms Debra Rimmington¹, Dr Marcella Ma¹, Dr Anthony Coll¹, Dr Clemence Blouet¹, Prof Sir Stephen O'Rahilly¹, Dr Giles Yeo¹

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Over the past two decades, insights from human and mouse genetics have illuminated multiple pathways within the brain that play a key role in the energy metabolism. We now know that the leptin-melanocortin signalling within the hypothalamus is central to the control of food intake, with genetic disruption of components of this pathway resulting in severe obesity. In the hypothalamic arcuate nucleus there are two distinct but rare populations of leptin responsive neurons, namely agouti-related peptide and neuropeptide Y (AgRP/NPY) neurons, and Pro-opiomelanocortin and Cocaine- And Amphetamine-Regulated Transcript (POMC/CART) neurons, where they play opposite roles in the regulation of food intake.

Here, we isolated NPY-expressing cells from NPY-eGFP reporter mice using fluorescence-assisted cell sorting (FACS), followed by encapsulation of cells into oil droplets. These oil droplets contain unique molecular barcodes (UMI) and reagents required for reverse transcription and cDNA amplification, and thus allow us to generate uniquely tagged transcriptomes for each of the captured cells.

Using this technique, we captured a total of 11,506 cells. Based on their transcriptomic profiles, we can divide these cells into 2 neuronal and 15 other cell clusters, each expressing a distinct set of characteristic markers.

Understanding the heterogeneity of AgRP/NPY neurons and differential roles of each subtype will help explain and provide further insights into the interplay between various nutritional stimuli and neural circuits in the brain. The identification of different subtypes (and their response) will also enable us to discover potentially novel and perhaps more specific drug targets to improve the treatment of nutritional disorders.

Poster number: PT092 (SP)**Theme:** Neuroendocrinology and autonomic systems**Deconstructing the role of AgRP neurons in reproduction using DREADDs technology in mice****Authors:** Dr Caroline Decourt¹, Dr Greg Anderson¹¹*University Of Otago, DUNEDIN, NEW ZEALAND*

Introduction: The orexigenic Agouti-related peptide (AgRP) is co-expressed with neuropeptide-Y and gamma-aminobutyric acid in arcuate neurons. The activity of these neurons is modulated by metabolic hormones such as leptin, ghrelin, and insulin and therefore act to convey metabolic cues to the Hypothalamic-Pituitary-Gonadal axis. AgRP was found to have variable inhibitory (~10%) and stimulatory (~25%) effects upon GnRH neurons activity (Roa and Herbisson., 2012), and minimal AgRP mRNA expression was observed at the beginning of the day, followed by a gradually increase to reach maximal level of expression 6 hours after light off. The effect of AgRP neuronal modulation on reproductive function has yet to be clearly elucidated.

Methods: All the mice were housed in a 12/12 light cycle. Using 'Designer Receptors Exclusively Activated by Designer Drugs' technology, we selectively activated or silenced AgRP neurons non-invasively by administering the synthetic ligand CNO (Clozapine N-oxide) subcutaneously (1 mg/kg) in adult male and ovariectomized females mice. Control mice received the same treatment. LH concentrations from tail were assessed using a sensitive sandwich ELISA.

Approach for statistical analysis: Integrated LH secretory response after CNO injection was estimated by calculation of the area under the curve (AUC). The values for the AUC were compared using a t-test.

Results and conclusions: There was no effect on LH secretion when these neurons were inhibited or stimulated in males compared to controls. There was no effect on LH secretion when these neurons were inhibited in ovariectomized females compared to controls. However, there was a significantly increase of LH secretion when these neurons were activated during the afternoon ($p < 0.05$) but not during the morning. These data suggest that AgRP neurons could have a role on LH surge generation. Whether this effect occurred in response to AgRP itself or one of the other secreted products of these neurons remains to be determined.

Poster number: PT093 (PP)**Theme:** Neuroendocrinology and autonomic systems**The role of CRH neuronal activity in regulating glucocorticoid oscillations****Authors:** Dr Pauline Campos¹, Dr Jamie J Walker¹¹*University Of Exeter, Exeter EX4 4PS, United Kingdom*

Introduction: The hypothalamic-pituitary-adrenal (HPA) axis is the primary neuroendocrine system providing a rapid response to stress. Hypophysiotropic CRH neurons of the paraventricular nucleus play a crucial role in the regulation of adrenal glucocorticoid production through release of CRH in the median eminence (ME) to stimulate pituitary adrenocorticotrophic hormone release. All HPA hormones exhibit ultradian oscillations, and the underlying mechanisms driving these oscillations are complex and multifaceted; for example, ultradian rhythms in CRH have been observed, but at the same time the pituitary-adrenal system has been shown to function as an ultradian oscillator independently of pulsatile hypothalamic input. The goal of this project is to establish the role neuronal activity plays in regulating oscillating activity within the pituitary-adrenal system.

Methods: We will employ an approach that integrates *in vivo* experiments with mathematical modelling. Using viral technologies, we will generate a model in which CRH neurons can be selectively targeted. Wild-type rats will be

stereotaxically injected with adeno-associated viruses (AAV) driving the expression of fluorescent proteins under the control of the CRH promoter. To specifically target hypophysiotropic CRH neurons, we will take advantage of the retrograde properties of certain AAV serotypes by injecting viruses in the ME. Once specific targeting of hypophysiotropic CRH neurons has been achieved, we plan to assess their activity by using genetically-encoded calcium indicators. With the help of miniature head-mounted microscopes and gradient-index lenses, we will perform deep-brain imaging of multiple CRH neurons at single-cell resolution in freely-moving rats. In order to characterise the relationship between neuronal activity and glucocorticoid hormone release, and how this may change over the 24-hour period, we will use automated blood sampling to simultaneously collect blood samples at high frequency whilst recording neuronal activity.

Approach for statistical analysis: The relationship between neuronal calcium activity and circulating hormone concentration will be determined in both the time and frequency domains (e.g. cross-correlation and coherence). A suitable statistical test (e.g. ANOVA or a non-parametric alternative) will then be used to test whether or not this relationship between neural activity and hormone concentration changes significantly over the 24-hour period. These data will be used to refine our mathematical models describing HPA axis dynamics.

Poster number: PT094 (SP)

Theme: Neuroendocrinology and autonomic systems

Modelling stress and synthetic steroid affects on glucocorticoid rhythms – do ultradian pulses matter?

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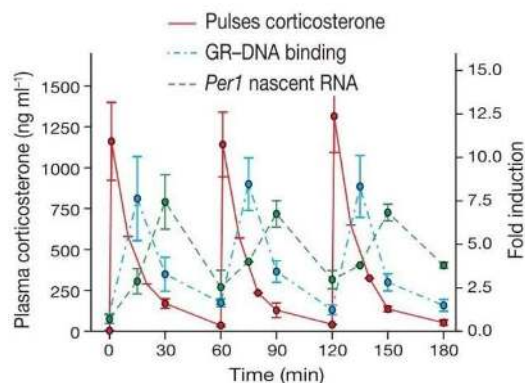
Inappropriate activation of the hypothalamic pituitary axis, via chronic stress or synthetic glucocorticoid treatment, dysregulates ultradian endogenous pulsatile release of glucocorticoid (GC) hormones and is associated with metabolic syndrome phenotypes (obesity, diabetes, etc.)¹. The glucocorticoid receptor (GR) is activated by corticosterone (CORT) and binds DNA at the CORT pulse peak before being lost within the nadir. As GR acts as a transcription factor (figure.1)², we hypothesize dysregulation of CORT patterns leads to aberrant RNA polymerase II (POL) action at glucocorticoid target genes associated with metabolic syndrome.

In adrenalectomised rats, CORT was replaced via pulsatile or constant infusions over 3 hours. Liver collected at the third pulse peak (140min) and nadir (180min), processed using chromatin immunoprecipitation assays with GR or POL antibodies. Time matched samples were taken for constant CORT and vehicle infusion groups.

Sequenced GR and POL ChIP enrichments and motifs were identified using HOMER analysis tools, statistically confident enrichments were filtered via an irreproducible discovery rate (<0.01) and differential enrichments were identified using DESeq2 (adj. p-value <0.05). Pathway analysis using the POL results were assessed using Ingenuity® Pathway Analysis software.

GR-DNA binding was detected at the CORT pulse peak (~1,600 sites) and completely lost within the nadir genome wide, whereas, constant CORT infusion sustained GR binding across time points (~900 sites). Increased and decreased POL binding (~470 sites) was detected at the pulse peak before returning to vehicle control levels within the nadir (~80 sites) whilst differential POL enrichments were detected across constant infusion time points (~250 sites at 140min and ~240 sites at 180min). Further, pathway analysis has indicated dysregulated glucose, carbohydrate and fatty acid metabolism in response to either pulsatile or constant infusion; the latter potentially leading to aberrant metabolic pathology.

In summary, we show genomic GR binding is tightly regulated by the pattern of CORT replacement. Sustained GR activation during constant CORT infusion, alters POL recruitment in a highly dysregulated manner at glucocorticoid target genes associated with metabolic syndrome phenotypes, providing a mechanistic basis for physiological effects of chronic stress and synthetic GCs.



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Poster number: PT095 (PP)

Theme: Neuroendocrinology and autonomic systems

Dysregulated feeding patterns emerge during ‘out of phase’ circadian corticosterone replacement in adrenalectomised rats

Authors: Dr Mitsuhiro Yoshimura^{1,2}, Mr Benjamin Flynn¹, Mrs Yvonne Kershaw¹, Mr Zidong Zhao¹, Dr Becky Conway-Campbell¹, Dr Stafford Lightman¹

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Introduction: Corticosterone (CORT) secreted from adrenal glands in rats has ultradian rhythmicity as well as circadian rhythmicity. Plasma CORT concentration elevates before the nocturnal period, and this is thought to prepare glucocorticoid target systems throughout the brain and body for the energy demands of the active phase. These rhythms can be dysregulated by stress, jetlag, or shift work with associated adverse metabolic effects. Here, we focused on dysregulated CORT pattern and resultant feeding behaviour.

Methods: Adult male SD rats were adrenalectomised, implanted with a jugular cannula and an intraperitoneal telemetry probe. Rats were kept under 12/12 light/dark cycle and provided with food and saline drinking water ad libitum. They were divided into 2 groups: FORWARD (n=8) and REVERSE (n=6). We used programmable pulsatile infusion system to deliver CORT-HBC, which is a water soluble form of CORT. In FORWARD, CORT-HBC infusion pattern was programmed according to the endogenous plasma CORT profile which was derived from an automated blood sampling system of intact animals. In REVERSE, total amount of CORT-HBC given per day was exactly same but infusion phase was reversed, that is, CORT pulsatility was the highest just before the onset of the light period (zeitgeber time (ZT) 0). Food and saline intake were measured every 12h and body weight were measured daily for 5 days. After the experiment, brains, livers, subcutaneous and epididymal fat, and blood samples were collected at ZT1 and ZT13.

Approach for statistical analysis: In FORWARD, the percentage of food intake in dark cycle (89.1%) was significantly greater compared to that in light cycle (10.9%), whilst, these were dramatically dysregulated in REVERSE (dark cycle (53.8%), light cycle (46.2%)). Saline intake was found to not be significantly different between FORWARD (dark cycle

(88.5%), light cycle (11.5%)) and REVERSE (dark cycle (79.0%), light cycle (21.0%)). We could not observe any change of body mass nor subcutaneous and epididymal fat mass between these groups. Locomotor activity profile was similar; however, core body temperature was altered in REVERSE compared to FORWARD. We now plan to analyse hypothalamic feeding-regulated neuropeptides, as a mechanism underpinning dysregulated feeding behaviour during circadian and glucocorticoid disruption.

Poster number: PT096 (SP)

Theme: Neuroendocrinology and autonomic systems

Characterisation of the acute effects of prolactin upon prolactin receptor-expressing neurones in the mouse hypothalamus

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Introduction: The anterior pituitary hormone, prolactin, a fundamental regulator of lactation, plays a role in many other physiological processes including maternal behaviour, reproduction, immune response and even energy balance. Indeed, prolactin receptors (Prlr) are widely distributed throughout the brain, further attesting to its pleiotropic nature. Previous research has identified key areas upon which prolactin exerts transcriptional effects, yet its acute modulation of electrical properties of Prlr-expressing neurones remains to be elucidated.

Methods: To identify and probe the function of these Prlr cells, we utilised a transgenic mouse line in which Cre recombinase is specifically expressed in the coding region of the prolactin long form receptor gene (*Prlr^{Cre}*). This mouse line was crossed with a Cre-dependent calcium indicator (GCaMP6s) transgenic mouse, allowing us to visually monitor the electrical activity of Prlr-expressing neurones in *ex vivo* 200 μ m brain slice preparations. Here we survey hypothalamic regions implicated in prolactin's diverse physiological functions such as: the arcuate nucleus of the hypothalamus (ARC), the medial preoptic area (MPOA), the ventromedial nucleus of the hypothalamus (VMH) and the paraventricular nucleus of the hypothalamus (PVN).

Approach for statistical analysis: The proportion of responsive cells is represented as a percentage of the total number of cells recorded in a particular brain region (n=3-4 animals, n>50 cells). To evaluate the magnitude of the responses observed in each brain region and in males, virgin females and lactating females, a one-way ANOVA was used to compare the mean fluorescence changes between baseline, prolactin application and wash.

Results and conclusions: We observe that in both males and virgin and lactating females, bath application of prolactin is able to induce electrical changes in a subset of Prlr-expressing cells that reside in the above-listed brain regions. The effects detected range from rapid or sustained increases in intracellular calcium to inhibitory effects, hinting at a heterogeneous nature of these Prlr-expressing populations. These results enhance our understanding of the neural circuits influenced by prolactin and provide a potential mechanism of prolactin's actions in the mouse brain.

Poster number: PT097 (SP)

Theme: Neuroendocrinology and autonomic systems

Effect of L-arginine and D-ribose L-cysteine supplementation on plasma/ovarian catecholamine and serotonin levels in animal models of perimenopause following acute restraint stress

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Perimenopause is a dynamic transitory period to reproductive senescence associated with fluctuating levels of hormones and neurotransmitters. Immature female Sprague-Dawley rats postnatal day 28, divided into 3 groups; (1) Control injected with Corn-oil (2.5µl/g BW) for 15 days; (2) VCD, injected with 4-vinylcyclohexene diepoxide (160mg/kg BW) diluted in Corn-oil for 15 days; and (3) Aged group (left to age till 180 days). Fourteen weeks after VCD/corn-oil administrations, and 180 days in Aged group, rats were further divided into 3 sub-groups: L-Arginine (100mg/kg), D-ribose (200mg/kg), and a third sub-group received neither for additional 30 days.

At 150 – 165 days in Control and VCD, 205 – 215 days in Aged on diestrus morning, animals were subjected to acute restraint stress for 30 minutes, followed by 30 minutes recovery period. Blood samples were drawn at rest, during stress and recovery period from tail vein, diluted in PBST solution, frozen at -70°C. Animals were humanely sacrificed, ovaries isolated, weighed, homogenized. Catecholamines and Serotonin were measured in blood and homogenate using 3-CAT Research and Serotonin Research ELISA kits (Rocky Mountain Diagnostics Inc., USA).

At rest and during recovery, plasma adrenaline and noradrenaline were significantly higher ($p < 0.05$) in VCD and Aged compared to Control and antioxidants did not reverse this increase. At rest, plasma dopamine was significantly higher ($p < 0.05$) in VCD compared to Control and Aged. During recovery, plasma dopamine was significantly lower ($p < 0.05$) in VCD and Aged compared to Control. During stress, L-ARG and D-Ribose significantly reduced ($p < 0.05$) dopamine in VCD and Aged compared to Control.

Ovarian adrenaline was significantly higher ($p < 0.05$) in VCD compared to Control and Aged while noradrenaline was not significantly different amongst groups. Dopamine was significantly higher ($p < 0.05$) in VCD and Aged compared to Control. L-ARG and D-Ribose significantly reduced ($p < 0.05$) dopamine in Control compared to other groups. Ovarian serotonin was significantly higher ($p < 0.05$) in VCD compared to other groups. Ovarian weight was significantly lower ($p < 0.05$) in VCD and Aged compared to Control and antioxidants did not reverse this increase. L-ARG and D-Ribose were protective against neurotransmitter fluctuations in perimenopausal rats.

Poster number: PT098 (SP)

Theme: Neuroendocrinology and autonomic systems

Distinct preoptic neurons connect sleep onset and body cooling in response to a warm stimulus

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Introduction: Animals use thermoregulatory behaviours to prepare for sleep. Mammals build nests, use bedding and curl up into sleeping postures to create warm microclimates that are permissive for sleep. Disruption of this behaviour is associated with insomnia. This behaviour is strongly conserved and may contribute to the homeostatic function of sleep, but it may also be just a matter of comfort without such function.

Methods: We have used activity-tagging, in the preoptic hypothalamus, to test our hypothesis that neuronal circuits detect environmental temperature and directly influence the onset of sleep. Activity-tagging allows us to understand the functions of neurons responding to specific stimuli, based on their expression of c-Fos. We also use retrograde viruses to understand how neurons receive sensory information.

Analysis and Results: We have activity-tagged preoptic neurons that increase their c-Fos expression in response to a warm stimulus. We found that, on reactivation, distinct populations of warm-tagged nitroergic-glutamatergic neurons could induce both sleep and body cooling, whereas a separate population of warm-tagged GABAergic neurons could

induce sleep without body cooling. We are working to understand the brain the regions that provide sensory inputs to these neurons and the regions they communicate with.

Conclusion: We suggest the existence of a neuronal hub that uses sensory temperature cues to coordinate simultaneous sleep and body cooling. The projections of these neurons are still unknown. The efficient linking of these physiologies suggests that one function of sleep is to regulate energy expenditure. Body cooling may also be important for the homeostatic functions of sleep.

Poster number: PT099 (SP)

Theme: Neuroendocrinology and autonomic systems

Regulation of Uroguanylin in Healthy Weight and Overweight/Obese Humans

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Introduction: Uroguanylin is a neuroendocrine hormone released from the gut that is thought to act at the hypothalamus as a post meal signal of satiety. Uroguanylin circulates as its pro-hormone, prouroguanylin. There has been limited investigation into the regulation of prouroguanylin by food; therefore we investigated prouroguanylin regulation following meals.

Methods: Healthy males (n=7) ingested a 1451kcal (Study 1) and 725kcal (Study 2) high fat breakfast. Blood samples were taken for prouroguanylin measurement at fasting, and 15, 30 60 90 and 120 minutes post meal. Study 3- Healthy weight (n=9) and overweight/obese (n=9) males and females ingested a 722.5kcal high carbohydrate breakfast. Samples were taken at fasting, and 30, 60 and 120 minutes post meal.

Approach for statistical analysis: Data was analysed using repeated measures ANOVA (study 1 and 2) or Repeated Measures Two way ANOVA (study 3).

Results and Conclusion: The 1451kcal meal increased prouroguanylin levels, versus fasting at 60 (P<0.05), 90 (P<0.01) and 120 (P<0.001) minutes. Following the 725kcal meal hormone levels were significantly increased versus fasting levels only at 120 minutes (P<0.01). The high carbohydrate breakfast 722.5kcal (Study 3), led to an initial suppression of hormone levels at 30 mins post meal (P<0.05) followed by an increase in levels until they were significant versus fasting at 120 mins (P<0.01). Overweight/obese participants had lower fasting prouroguanylin levels (P<0.05), but post meal levels did not differ between the groups. We concluded there is a delayed increase in prouroguanylin levels following, large and regular sized mixed macronutrient meals rich in fat or carbohydrate. This suggests uroguanylin is unlikely to be involved in feelings of satiety immediately after a meal, but may be a delayed satiety signal. In addition, our data suggests regulation of prouroguanylin may differ between people who are healthy weight and overweight/obese.

Poster number: PT100 (PP)

Theme: Neuroendocrinology and autonomic systems

Investigating the effects of stress hormones and neurotransmitter systems on locus coeruleus activity and reward

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Apathy is a very pervasive psychiatric symptom, present in most neurodegenerative and psychiatric conditions [1]. It is defined as a profound lack of motivation, which results in functional impairment. Therefore, it is unsurprising that apathy substantially reduces quality of life [2], sometimes even more so than physical symptoms of disease. Despite this, there are no approved treatments for apathy, and this is likely due to a lack of understanding regarding its underlying mechanisms. Addison's disease represents a small patient group, who commonly present with apathy [3], and have a well-defined pathology, which is characterised by the insufficient production and secretion of cortisol. This suggests that abnormal cortisol dynamics are involved in the mechanisms of apathy. There is also evidence to suggest that the locus coeruleus (LC), which has recently been implicated in motivation and reward, becomes dysfunctional in Addison's disease [4]. Together, this indicates that abnormal cortisol signalling in the LC could disrupt networks of motivation and reward, resulting in the development of apathy. We plan to investigate this notion by administering mifepristone (400mg), spironolactone (400mg), propranolol (80mg) and a placebo to healthy human volunteers in separate treatment arms. Within each arm, measures of pupil size and reward sensitivity will be administered as markers of LC activity and apathy, respectively. This will allow us to explore the relationship between disrupted cortisol signalling, disrupted reward networks and LC activity.

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Poster number: PT101 (SP)

Theme: Neuroendocrinology and autonomic systems

Ethnic differences in diurnal cortisol profiles and cortisol awakening responses in healthy adults: a systematic review and meta-analysis

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Context: Cortisol is a well-known biomarker of the physiological stress system; atypical cortisol patterns have been linked to many psychological and physiological illnesses. Previous studies have found vast health disparities amongst ethnic groups; however, studies examining the relationship between cortisol and ethnicity have found mixed results. This meta-analysis investigated whether there are differences in diurnal cortisol outcomes amongst ethnic groups, while considering the moderating roles of various individual factors and methodological approaches.

Methodology: Search phrases were entered into MEDLINE, PsycINFO, Embase, Cochrane Library, CINAHL, Scopus, and Web of Science. Effect sizes were extracted for ten diurnal cortisol outcomes, including waking, thirty minutes after waking, cortisol awakening response, slope, area under the curve, urinary twenty-four-hour secretion, total cortisol output, and midday, evening and bedtime concentrations, for eight ethnic group comparisons, including Asians, Blacks, Hispanics, Indigenous people, Whites, Minority and Majority groups, and Multiethnic groups. Moderator analyses, including variables such as gender, age, and number of cortisol collection time points, were conducted.

Results: The search initially yielded 1882 articles, and 16 studies were included in the meta-analysis. The meta-analysis demonstrated that there were significant ethnic differences in diurnal cortisol profiles, including cortisol awakening responses, with more robust differences in ethnic comparisons that included White participants. Overall, minority groups, apart from Asian individuals, displayed blunted diurnal cortisol profiles, including blunted cortisol awakening response (CAR), when compared to Whites. When comparing minority groups, ethnic differences were most prevalent in CAR and at bedtime, with Blacks displaying the most blunted profiles. Differences in diurnal cortisol profiles were also moderated by gender, mean age, and sample size.

Implications: This meta-analysis supports the notion that ethnic groups exhibit distinct diurnal cortisol profiles, which, according to the biopsychosocial model of health, may be a result of unique sociocultural experiences, such as racial discrimination. When examining individual differences in diurnal cortisol profiles, future research should consider the unique contributions of ethnicity, gender, age, and sociocultural experiences. Future studies should also refrain from collapsing ethnic minorities into a single group, since each ethnic group's unique sociocultural experiences are reflected in their diurnal cortisol patterns.

Poster number: PT102 (SP)

Theme: Neuroendocrinology and autonomic systems

Addressing the role of tachykinin receptor 2 signalling in the neuroendocrine control of reproduction: studies in the TACR2 null mice

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Introduction: Tachykinin (TAC) signalling has been recognized as essential pathway in the central regulation of GnRH/LH secretion in mammals, putatively acting in a kisspeptin-dependent and/or –independent manner. The TAC family is mainly composed of substance P (SP), neurokinin A and neurokinin B (NKB), which bind preferentially to NK1R, NK2R and NK3R, respectively. However, some cross-reactivity between TAC and their receptors has been documented, which appears to be critical for their full actions. To date, most of the studies have focused on the NKB/NK3R system and to a lesser extent the SP/NK1R system; yet, the relevance of TAC signalling via NK2R remain poorly understood. To characterize the roles of NK2R signalling in the regulation of the reproductive axis, we report herein initial studies on the reproductive phenotyping of a novel NK2R knockout mouse, named hereafter *Tacr2*^{-/-}.

Methods: RT-qPCR, phenotypic analyses of reproduction, ELISA for LH determinations, pharmacological LH-response tests and behaviour tests. Approach for statistical analysis: The groups were compared using a two-tailed, unpaired Student *t* test (GraphPad Prism 6).

Results and conclusions: As predicted by genotyping, *Tacr2*^{-/-} mice showed absent expression of the mRNA encoding NK2R, while *Tacr2*^{-/-} female mice displayed blunted LH responses to the NK2R agonist, GR 64349. In spite of this, phenotypic analyses of puberty onset revealed normal timing in *Tacr2*^{-/-} mice, as revealed fully conserved ages of

preputial separation in males, and vaginal opening and the first oestrus in females. In addition, basal LH levels and oestrous cyclicity were grossly conserved in *Tacr2*^{-/-} mice. However, our initial fertility tests showed a slight increase in the breeding intervals in *Tacr2*^{-/-} females crossed by wild-type males, as well as in wild-type females mated with *Tacr2*^{-/-} males. Additional ongoing analyses include assessment: (i) of pulsatile secretion of LH; (ii) of LH responses to central injection of TAC agonists and kisspeptin-10; (iii) profiling of hypothalamic expression of *Kiss1*, *Tac1*, *Tac2* and *GnRH*; and (iv) behavioural studies of social interaction and urine sniffing tests in the *Tacr2*^{-/-} model. As a whole, these analyses will help to enlighten the physiological roles of NK2R signalling in the neuroendocrine control of reproduction.

Poster number: PT103 (SP)

Theme: Neuronal, glial and cellular mechanisms

Molecular mechanisms underlying depression in chronic inflammatory diseases

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Background: Depression is a common condition affecting up to 15% of the population with a substantial gender bias: women are more prone to depression with twice the lifetime risk of developing Major Depression. (MD) As well, women's symptoms are determined by multiple depression scales to be more severe than men's. Current understanding of the underlying causes of depression are poor and treatments are often ineffective for many patients. There is, however, a growing body of evidence linking the immune system and chronic inflammatory diseases like psoriasis or rheumatoid arthritis (RA) to the development of depression. The finding that many patients suffering from inflammatory conditions also suffer from depression suggests that there is a common cause for both diseases.

Methods: This project uses a recently established novel animal model (the collagen-induced arthritis (CIA) mouse model) as a model for depression induced by chronic inflammation. The focus of this project is to investigate the association between inflammation and depression, elucidate the underlying disease mechanisms, test novel treatments for inflammation induced depression and investigate sex specific differences in inflammation induced depression.

Analysis approach: Behaviour is analysed using paradigms such as the sucrose preference test and the open field test. Using isolated synaptosomes and radiolabelled serotonin, function of the serotonergic system is investigated in CIA mice. Tissue and serum harvested are analysed for relevant protein alterations related to the immune and serotonergic systems.

Results: CIA mice exhibit depression-like symptoms that correlate temporally with altered SERT function in the hippocampus. Treatments that target TNF α signalling normalises both behaviour and SERT function without eliminating joint inflammation in male mice. As well CIA induction on its own cannot induce depressive behaviour or alter hippocampal SERT function in female mice but can cause increased function in cortical SERT when administered together with the anti-estrogen drug fulvestrant.

Conclusion: So far this project has verified the CIA model as a viable model of chronic inflammation induced depression, identified TNF α as a potential target for novel treatment of depressive symptoms and highlights the role sex hormones play in the susceptibility to depression.

Poster number: PT104 (SP)

Theme: Neuronal, glial and cellular mechanisms

Change in ATF6 and CHOP expression in the brain, following ischemic stroke and reperfusion

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Introduction: Stroke is a leading cause of death and acquired disability worldwide. A hallmark of stroke is impaired function of the endoplasmic reticulum (ER) stress response. In order to restore ER function in stressed cells, the unfolded protein response (UPR) is activated, which then induces three arms of ER stress sensor proteins including activating transcription factor 6 (ATF6). Although a failed ER stress response has been linked to apoptosis, the ATF6 UPR branch has also been found to be crucial to ischemic stroke outcome, via a pro-survival pathway, but the mechanisms are yet to be fully elucidated. We aimed to evaluate ATF6 and CHOP expression in infarcted and normal appearing cerebral tissue, following occlusive stroke and reperfusion.

Methods: Focal ischemic stroke was created by transient (4h) occlusion of the middle cerebral artery in Sprague Dawley rats (n=4/5 per group), followed by 2h full reperfusion or no reperfusion and sham operated controls. ATF6 and CHOP expression was assessed in 30 μ m perfusion-fixed tissue sections by immunohistochemistry.

Approach for statistical analysis: Results were analysed by two-way ANOVA with Bonferroni post-hoc and expressed as mean \pm SEM.

Results and conclusions: An assessment of ATF6-expression found significantly higher levels in the 4h-occluded ipsilateral hemisphere with (F(1,149)=63.65), p<0.0001) or without reperfusion (F(1,149)=102.8), p<0.0001), but more so in the normal appearing frontal cortex than the lesioned temporal cortex (F(1,149)=37.83), p<0.0001). An assessment of CHOP expression also found significantly higher levels in the 4h-occluded ipsilateral hemisphere, with (F(1,190)=29.5), p<0.0001) or without, reperfusion (F(1,190)=81.19), p<0.0001), when compared to the contralateral hemisphere, particularly in the frontal cortex (F(1,190)=75.27), p<0.0001) in comparison to the lesioned temporal cortex.

High expression of ATF6 and CHOP particularly in the ipsilateral frontal cortex suggests that conflicting pro- and anti-apoptotic signals are present. Promotion of the pro-survival ATF6 arm could be critical if expansion of the lesion is to be prevented.

Poster number: PT105 (SP)

Theme: Neuronal, glial and cellular mechanisms

Investigating inhibitory restraint in a chemoconvulsant model of epilepsy in awake animals

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Introduction: A failure of the inhibitory system underlies cortical seizure generation and propagation, and two alternate mechanisms have been proposed to play a crucial role in this breakdown. The first is that accumulation of extracellular K⁺ (either because of intense activity or because of Cl⁻ and K⁺ efflux from neurons mediated by KCC2) creates a hyperexcitable environment conducive to seizures. The second is that GABAergic inhibition fails, either because GABA release cannot be sustained (for instance because interneurons enter a state of depolarization block), or because the Cl⁻ reversal potential in principal cells becomes depolarized following persistent activation of GABA_A receptors.

Here, we investigated whether inhibition promotes (K⁺ accumulation hypothesis) or prevents (inhibitory restraint hypothesis) hyperexcitable activity using a combination of two-photon imaging and optogenetic manipulation in an *in vivo seizure* model.

Methods: We used closed-loop optogenetic manipulation (Channelrhodospin-2 (ChR2), or Archaeorhodopsin (Arch3.0)) in combination with a wireless EEG recording system to activate or inhibit interneurons on demand during chemically-induced seizures in awake adult mice (P60-100; Pilocarpine: 3.5 M, 200 – 400 nL). In addition, we took advantage of two-photon imaging combined with a genetically-encoded calcium indicator (GCaMP6) to directly observe calcium transients.

Approach for statistical analysis: All statistical data analyses were performed using IBM SPSS. Repeated one-ANOVA, two-tailed unpaired and paired t-tests were used as appropriate.

Results and conclusions: Calcium imaging of parvalbumin-positive (PV+) as well as neurogliaform interneurons indicates that at least these two interneuron populations are active during interictal activity and seizures. In addition, optogenetic depolarization of PV+ and somatostatin-positive (SOM+) interneurons suppresses interictal activity while PV+ cell hyperpolarization promotes it. Together, these findings are in favour of the inhibitory restraint hypothesis showing that somatic and dendritic inhibition are still functional during pathological discharges and could prevent hyperexcitable activity. We are now investigating the mechanisms that contribute to the breakdown of this inhibitory restraint and the transition to seizures.

Poster number: PT106 (SP)

Theme: Neuronal, glial and cellular mechanisms

Investigating molecular and epigenetic mechanisms of ghrelin-mediated adult hippocampal neurogenesis

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Introduction: Adult hippocampal neurogenesis (AHN) is the process of generating new mature and functional neurones from pools of neural stem cells, located in the dentate gyrus of the hippocampus. This process is important in Learning and memory. Dysfunction of AHN has been implicated in many neurodegenerative diseases. Acyl-ghrelin (AG) promotes AHN and enhances pattern separation memory in rats (Kent et al. 2015). However, the mechanisms underpinning AG-mediated AHN are still not fully understood. This study examines AG-induced molecular and epigenetic mechanisms linked with AHN.

Methods: Two key neurogenic genes include BDNF and FGF1 (Ma et al., 2009). We used a neuronal cell-culture system (SN4741 cell-line) to examine the effect of AG on these genes using RT-qPCR. To examine epigenetic mechanisms, we performed methylation (MeDIP) and hydroxy-methylation (hMeDIP) analysis. Chromatin Immunoprecipitation (ChIP) was used to assess MeCP2 binding to BDNF IV. AG-treated primary rat hippocampal neurones were used with the EdU-ClickIT assay to assess proliferation and survival.

Statistical analysis: RT-qPCR, MeDIP, hMeDIP and ChIP studies: student's t-test

RHN studies: Ordinary one-way ANOVA

Results and conclusions: RT-qPCR analysis showed AG treatment caused a significant upregulation of FGF1b and BDNF IV gene expression ($P < 0.05$). MeDIP showed significant de-methylation of the gene promoters for FGF1b and BDNF IV ($P < 0.01$ & $P < 0.05$). hMeDIP analysis showed a significant reduction in hydroxy-methylation in FGF1b following AG-treatment ($P < 0.01$), but an increase in BDNF IV ($P < 0.05$). ChIP analysis showed a significant reduction in MeCP2 binding to the BDNF IV promoter ($P < 0.05$).

In primary hippocampal neurones, AG caused a significant increase in proliferation after 24h ($P < 0.01$) and enhanced survival after 4 days in culture ($P < 0.001$).

This collective *in vitro* data suggests that AG promotes the de-methylation of FGF1 and BDNF gene promoters resulting in increased gene expression. In the case of BDNF, de-methylation results in dissociation of repressive MeCP2. AG enhanced proliferation and survival in RHN cell culture. Further studies are underway to test this putative molecular mechanism *in vivo* and to determine whether AG regulation of adult brain plasticity is mediated by dynamic epigenetic change.

Poster number: PT107 (SP)

Theme: Neuronal, glial and cellular mechanisms

Investigating rodent behaviour and prefrontal cortex network oscillations in an NMDA receptor antagonist model of schizophrenia

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Introduction: Schizophrenia is a psychiatric disorder affecting 1% of the world's population. A hallmark of the condition are cognitive deficits, such as working memory and attention impairments. Underlying a number of cognitive functions, are synchronized beta (15-30 Hz) and gamma (30 – 80 Hz) frequency oscillations, evident in various sub-regions of the prefrontal cortex (PFC), including the anterior cingulate cortex (ACC). Such oscillatory activity is known to be orchestrated by inhibitory GABA-ergic parvalbumin-positive interneurons. Emerging evidence demonstrates that, in patients with schizophrenia, GABA-ergic transmission and synchronous oscillatory activity are disrupted.

Methods: Our aim was to evaluate changes in the network properties of the rat ACC using *in vitro* electrophysiology in an established sub-chronic phencyclidine (scPCP) model of schizophrenia. Female Lister Hooded rats (15 in each group) were treated with either 2 mg/kg scPCP or saline twice daily for 7 days. Following a 6-week washout period, animals were behaviourally assessed in a novel object recognition test.

Analysis approach: Results were grouped and compared using Mann-Whitney test, data are presented as median and inter-quartile range (IQR).

Results and Conclusions: Behavioural testing confirmed a cognitive deficit in the scPCP-treated animals ($p < 0.05$). To determine the ability of the ACC network to generate rhythmic activity *in vitro*, we evoked beta-low gamma (20 – 35 Hz) oscillations by bath-application of 800 nM kainic acid. Preliminary results show that, despite the behavioural deficit observed in the scPCP group, the ACC was able to generate oscillations similar to those in the saline group (peak frequency 24 IQR 22.1 – 26 Hz [$n = 31$ slices] in saline vs. 25.1 IQR 22.7 – 26.9 Hz [$n = 38$ slices] in scPCP group, area power of oscillations was 83.6 IQR 27.5 – 166 μV^2 in saline group vs. 49 IQR 17.8 – 144 μV^2 in scPCP group, both $p > 0.05$). Current work is investigating the impact of acute PCP application on the ongoing rhythmic activity in ACC slices from scPCP-treated rats. Differences may be revealed when the network is challenged with PCP, as studies

have demonstrated that NMDA receptor antagonists (e.g. PCP, ketamine) exacerbate symptoms in patients and animal models.

Poster number: PT108 (PP)

Theme: Neuronal, glial and cellular mechanisms

The P2X7 receptor's contribution to neonatal seizures and the development of later life epilepsy and neuro-cognitive deficits

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Introduction: Neonatal seizures are a neurological emergency. Hypoxic-ischemic encephalopathy accounts for 60% of neonatal seizures and is associated with development of epilepsy and neuro-cognitive deficits in later life. Current treatments for neonatal seizures remain largely ineffective. The P2X7 receptor (P2X7R) is an ionotropic ATP-gated ion channel that is activated under pathological conditions, with a key role as a driver of inflammation. Antagonism of the P2X7R has been shown to reduce the seizure burden in neonatal mice exposed to global hypoxic conditions. The aim of this project is to further understand the mechanism of this action and the possible therapeutic use of P2X7R antagonism for neonatal seizures.

Methods: Seizures will be induced in 7 day old mouse pups by intraperitoneal injection of the convulsant kainic acid (1.5mg/kg) or by exposing pups to global hypoxia (5% oxygen) for 15mins. This study will use multiple transgenic mouse models that either globally overexpress or knockout the P2X7R. Acute electroencephalography and behavioural seizures will be recorded to investigate the P2X7R's immediate role in neonatal seizures. At various times following seizure induction, markers of inflammation will be analysed by immunohistochemistry and ELISA methodology. Seizure related neuronal damage will be investigated with use of the Silver Nissl or TUNEL stain. A reporter mouse in which green fluorescent protein is induced in response to the transcription of P2rx7 will be used to locate where and what cell types P2X7R upregulated following neonatal seizures. In a cohort of mice, a battery of behavioural assays and a seizure threshold test with kainic acid will be conducted 6 weeks post seizures after pharmacological antagonism of the P2X7R and in the transgenic models to investigate the P2X7R's role in the development of neurocognitive deficits and later life epilepsy respectively.

Approach for statistical analysis: GraphPad prism software will be used for statistical analysis. Between group comparisons will be made using unpaired Student's t-tests and Multi-group comparisons will be made using ANOVA followed by an appropriate post hoc test Bonferroni test (parametric) or Dunn's test (nonparametric).

Poster number: PT109 (SP)

Theme: Neuronal, glial and cellular mechanisms

The Study of FLRT3 Interaction with Latrophilin 1

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Introduction: Latrophilin-1 (LPHN1), a presynaptic adhesion G-protein coupled receptor (aGPCR), is mainly present in the brain¹. It binds several ligands: an exogenous agonist, α -latrotoxin (α -LTX) from the black widow spider, and two endogenous ligands which are cell-surface receptors, "fibronectin and leucine-rich transmembrane protein 3" (FLRT3) and Lasso/teneurin-2¹. Stimulation of LPHN1 by α -LTX or Lasso/teneurin-2 contributes to mobilisation of Ca²⁺

from intracellular stores and activation of store operated calcium entry (SOCE). However, it is not known whether FLRT3 can induce LPHN1-mediated signalling. Interestingly, LPHN1 and FLRT3 are both present in the blood of acute myeloid leukaemia (AML) patients², which makes AML cells an ideal biological system to study LPHN1-FLRT3 signalling pathways. Here, we study the binding of FLRT3 to LPHN1 and its signalling to intracellular Ca²⁺ using two different model cell systems.

Methods: Neuroblastoma cells (NB2a) expressing full-size LPHN1 or non-signalling mutant Δ LPHN1, and human AML cells (THP-1) were used. Cytosolic calcium concentration was measured by Fluoroskan Ascent using calcium sensor dye Fluo-4. Synchrotron radiation circular dichroism spectroscopy was used to study the interaction between purified LPHN1 and FLRT3.

Approach for statistical analysis: Experiments were performed at least three times and statistical analysis was conducted using ANOVA.

Results and conclusions: Our results show that FLRT3 binds to LPHN1 with K_d of 40 nM. Stimulation of cells expressing LPHN1, but not Δ LPHN1, with α -LTX in calcium-free conditions causes a gradual Ca²⁺ release from intracellular calcium stores. Addition of 2 mM extracellular Ca²⁺ induces SOCE. Stimulation of LPHN1 with FLRT3 in Ca²⁺-free buffer showed a small intracellular Ca²⁺ release compared to Δ LPHN1. Consequently, FLRT3 induced little or no SOCE after the addition of extracellular Ca²⁺. Stimulation of LPHN1 with FLRT3 in THP-1 cells showed a similar small effect. In conclusion, FLRT3 binds LPHN1 with a lower affinity than α -LTX and causes a small calcium signal compared to α -LTX. This suggests that FLRT3 signalling via LPHN1 is not linked to intracellular Ca²⁺ release.

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Poster number: PT110 (SP)

Theme: Neuronal, glial and cellular mechanisms

P2X7 receptor as a therapeutic target in drug refractory epilepsy

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Introduction: 60 million people worldwide suffer from epilepsy and there are currently approximately 25 marketed anti-epileptic drugs (AED). With almost 30% of epilepsy patients becoming refractory to these drugs, it is paramount to focus on targeting specific therapeutic areas of the brain to fully impact on disease progression. P2X7 has been shown to play a pivotal role in inflammation but the question still remains as to its specific behavior and how it can affect sensitivity to anti-convulsant treatment. It has been shown previously that P2X7 antagonism reduces seizure duration, seizure-induced neuronal death and was also neuroprotective. Here, we are attempting to understand its influence on anti-convulsant drugs and whether P2X7 antagonism is a potential therapeutic strategy to treat drug-refractory epilepsy.

Methods: We are using a novel, transgenic P2X7R overexpressing mouse to determine the effects of the receptor on the efficacy of anti-convulsants and its cell-specific expression. Green fluorescent protein (GFP) is bound on the promoter region of the P2X7 protein so that it is observable using fluorescent microscopy where the receptor is expressed. Investigation of the effects of P2X7 overexpression is carried out using a combination of EEG analysis, immunohistochemistry, western blotting as well as qPCR to determine the differences/patterns of seizure activity, protein and mRNA expression, cell death and response in epileptic mice.

Statistical Analysis: GraphPad Prism is used to carry out statistical analysis, where group comparisons will be analysed using unpaired t-tests and ANOVA analysis as appropriate.

Results and Conclusion: Firstly, we showed P2X7 activation occurs during inflammation. By injecting mice with lipopolysaccharide (LPS), we observed increased P2X7 at 72hrs. We then carried out intra-amygdala kainic acid (KA) injections to induce epilepsy. Following KA administration, we found no effect of P2X7 overexpression on the severity of electrographic seizures. Despite no difference in seizure severity, however, overexpression of P2X7 led to a marked resistance to lorazepam, with ongoing increased power in the EEG, compared to controls. We concluded that P2X7 may contribute to drug resistance during SE and epilepsy, thus, P2X7 antagonists may be a good as an adjunctive treatment for epilepsy.

Poster number: PT111 (SP)

Theme: Neuronal, glial and cellular mechanisms

Molecular mechanisms underlying the effects of naturally-derived polyphenols in protecting against corticosterone-induced cytotoxicity in primary cortical cells: implications for stress-related disorders

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Introduction: Dysfunction of the HPA axis and elevated concentrations of glucocorticoids have been associated with many neuropsychiatric disorders, including anxiety and depression. A growing body of evidence suggests that polyphenols may have therapeutic potential in treating chronic stress-related disorders. However, the underlying mechanisms are still unclear. We have previously demonstrated that prolonged exposure to a high concentration of corticosterone (CORT) exerts neurotoxic effects in primary cortical cells. Therefore, we decided to investigate the potential neuroprotective effects of the naturally-derived polyphenols xanthohumol and quercetin against CORT-induced neurotoxicity from rat primary cortical cell cultures.

Methods: Cell viability of rat primary cortical cells was assessed using the MTT assay and neuronal/astrocytic ratio was determined through immunocytochemistry. mRNA expression levels of BDNF, FKBP5 and Nrf2-activated genes were detected using RT-qPCR.

Approach for statistical analysis: All the data were analysed using one- or two-way ANOVA as appropriate and the results were presented as mean \pm SEM. A *p*-value of 0.05 was considered statistically significant.

Results and conclusions: We observed that both polyphenols prevented the reduction of cell viability usually caused by CORT exposure. Moreover, the polyphenols were able to attenuate CORT-induced alterations in neuronal and astrocytic concentrations. Basal levels of BDNF (neurotrophin involved in neuronal survival and plasticity) were also decreased after CORT insult, where expression was normalised by the polyphenol treatments. To determine the molecular mechanism involved in polyphenol-mediated neuroprotection, we examined the Nrf2 signalling pathway utilising the Nrf2 inhibitor trigonelline. Nrf2 is an important transcription factor involved in cytoprotective and antioxidant responses. Interestingly, trigonelline blocked xanthohumol, but not quercetin-mediated neuroprotection. Upon further examination, we found increased expression of FKBP5 (key protein involved in regulation and sensitivity of glucocorticoid receptor activity) mediated by quercetin, but not xanthohumol. This suggests that the glucocorticoid receptor negative feedback system is being activated. These results suggest that naturally-derived polyphenols protect cortical cells against CORT-induced cytotoxicity, and enhance cell survival, via modulation of the Nrf2 pathway and expression of FKBP5. Currently studies are investigating the potential in vivo effects of these polyphenols in reversing the behavioural effects of stress.

Poster number: PT112 (SP)**Theme:** Neuronal, glial and cellular mechanisms**The late-onset Alzheimer's disease risk genes *nedd9* and *cass4* direct human astrocyte morphology *in vitro*****Authors:** Ms Norah Elisa Ulzheimer¹, Dr Lisa Shaw¹, Dr Chris George Severin Smith¹, Dr Vicky Claire Jones¹¹*University of Central Lancashire, Preston, United Kingdom*

Introduction: The neurone-centric view of Alzheimer's disease (AD) has been challenged by increasing data indicating the near-ubiquitous role of glia in neurodegeneration. Recent studies have unearthed striking cell-autonomous atrophy of astrocytes in the early stages of AD, characterised by decreased cell size and processes loss. This aberrant astrocyte phenotype appears independently of senile plaques and manifests in both sporadic and familial AD models by an as-yet undescribed mechanism.

Multiple GWAS have implicated the cytoskeleton-regulating Cas-family proteins NEDD9 and CASS4 as genetic risk-factors for late-onset AD. Here we investigate whether CASS4 and NEDD9 act as regulators of astrocyte morphology.

Methods: Primary human cortical astrocytes were transiently transfected *in vitro* with vectors mediating the overexpression or siRNA-induced knockdown of either NEDD9 or CASS4. Concurrent expression of GFP permitted the visualisation of complete cellular morphologies, including fine processes, using confocal microscopy. Analyses consisted of visually binning cells into morphological subtypes and 3D reconstruction followed by morphometric quantifications (e.g. surface area, volume). We also measured resulting expression levels of key astrocyte markers, including the glial fibrillary acid protein, GFAP, and the calcium-binding protein, S100B; both of which have been suggested to play important roles in AD pathogenesis.

Approach for statistical analysis: At least 20 cells from three separate experiments were analysed per transfection condition. Bias was minimised by random slide numbering prior to analysis. Overexpression or knockdown groups were compared to GFP-only or scramble-GFP controls using a Kruskal-Wallis test, followed by Dunn-Bonferroni pairwise comparisons.

Results and conclusions: Overexpression or knockdown of either NEDD9 or CASS4 induced significant changes in astrocyte morphology including altered cell shape, volume and surface area compared to controls. Moreover, manipulation of Cas-family protein levels resulted in altered expression of GFAP and perturbed sub-cellular distribution of S100B; mimicking the pathological phenotype reported in human iPSC astrocyte models of AD.

Hence, we show that both NEDD9 and CASS4 are capable of influencing human astrocyte morphology and expression of AD-linked astroglial markers. This may indicate a novel, astrocyte-based mechanism by which these risk-genes contribute to AD pathogenesis.

Poster number: PT113 (SP)**Theme:** Neuronal, glial and cellular mechanisms**P-glycoprotein determines GR sensitivity of Hippocampal cells****Authors:** Dr Felicity Stubbs¹, Miss Elizabeth Lieverse¹, Miss Emma Earl¹, Professor Stafford Lightman¹, Dr Becky Conway-Campbell¹¹*University of Bristol, Bristol, United Kingdom*

Introduction: *In-vivo* glucocorticoids (GCs) are regulated by the HPA axis and secreted in a circadian and an underlying pulsatile ultradian pattern (1-3). Glucocorticoids diffuse into cells and bind low affinity glucocorticoid

receptors (GRs). Synthetic glucocorticoids (sGCs), which bind GR with a higher affinity (4, 5), are clinically widely used but are associated with several side-effects and GC resistance. When GC levels are high, during endogenous ultradian peak pulses or use of sGCs, they travel through the blood-brain barrier that determines tissue-specific exposure, to access brain regions such as the GR enriched hippocampus. Hippocampal GC action regulates Learning and memory, which is often impaired with long-term GC exposure (6). Upon binding GCs, GRs translocate to the nucleus and act in a highly dynamic manner to bind specific chromatin regions to regulate gene transcription (7, 8). Previously, we have shown prolonged duration of GR activation with sGCs compared to corticosterone in rat hippocampal tissue. This is due to higher potencies, longer binding durations, and longer half-lives in the circulation. However, a shorter duration of sGC induced GR activation in the brain compared to the periphery may occur due to the multi-drug resistance protein, p-glycoprotein, actively shunting GCs from the brain (9, 10).

Methods: GR activity was assessed in a hippocampal, HT22, cell-line known to contain p-glycoprotein, cells were cultured and serum-starved prior to sGC treatment. Interestingly, high doses of sGCs were required for detectable GR, associated with the chromatin template, compared to Corticosterone. Verapamil, a p-glycoprotein inhibitor, was added to assess a role in regulating GR levels at chromatin template.

Approach and Statistical analysis: ImageJ was used to quantify the protein from western blots.

Results and Conclusions: The addition of Verapamil significantly increased GR levels compared to controls, following sGC treatment. This suggests P-glycoprotein inhibitors may be useful to provide alongside lower doses of sGCs, especially to patients considered GC resistant, to prevent use of higher doses associated with greater side-effects. Verapamil is already prescribed to treat cardiac arrhythmias (11) so could safely treat other conditions. Further studies are required to investigate the effects of p-glycoprotein on GR dynamics in the hippocampus and explore how they could be a therapeutic target.

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Poster number: PT114 (PP)**Theme:** Neuronal, glial and cellular mechanisms**Single cell genomics of experience-dependent plasticity in adult-born neurons****Authors:** Dr Marcela Lipovsek¹, Dr Matthew Grubb¹¹*King's College London, London, United Kingdom*

Introduction: Experience shapes neuronal circuits through many interacting forms of activity-dependent plasticity that occur at multiple levels, comprising changes in functional properties, neuronal morphology, synaptic connections, gene expression and epigenetic state. In some areas of the adult mammalian brain, the ultimate form of plasticity is the incorporation of newly-generated neurons into mature circuits. These adult-generated neurons undergo an initial period of heightened functional and morphological plasticity. However, little is known about the cellular processes that govern either their incorporation into circuits or their differential plastic capabilities. Here, we propose to address these questions by studying a specific sub-class of adult-generated neurons: dopaminergic interneurons of the olfactory bulb (OB).

Methods: We will aim to analyse the transcriptome, methylome and chromatin accessibility of resident and adult-born dopaminergic neurons, both at baseline and after 24 hours of sensory deprivation. OB dopaminergic neurons are readily identified in DAT-IRES-Cre x ROSA26-Flox-tdT mice. We will label adult-born neurons via EdU injections (4 x 5mg/kg injections at 2 hours intervals in 2 month old mice). At time-points reflecting maturing and fully-mature cells – 5 and 9 weeks after EdU injection, respectively – we will perform either unilateral nose occlusion or sham surgery. After 24h we will dissect the ipsilateral olfactory bulb and fix it in RNAlater. We will prepare single nuclei suspensions and use FACS to collect individual nuclei, from both adult-born (tdT+/EdU+) and resident (tdT+/EdU-) dopaminergic neurons. Samples will be processed following the scNMTseq protocol, where the mRNA and gDNA fractions are first physically separated. The mRNA fraction will then be subjected to scRNAseq. The gDNA fraction will undergo GpC methyltransferase treatment to label open chromatin, followed by bisulfite sequencing to identify methylated and non-methylated cysteines.

Analysis approach: By analysing concomitant changes in gene expression, chromatin accessibility and DNA methylation during plasticity events in adult-born and resident neurons we will be able to unravel the cellular mechanisms that underpin this crucial event in neuronal circuit function.

Poster number: PT115 (PP)**Theme:** Neuronal, glial and cellular mechanisms**Patch-seq analysis of experience-dependent plasticity****Authors:** Dr Lorcan Browne¹, Dr Marcela Lipovsek¹, Dr Matthew Grubb¹¹*King's College London, London, United Kingdom*

Introduction: Experience is known to shape the brain through multiple interacting forms of neuronal plasticity. These include changes at the level of neuronal activity, their electrical properties and synaptic connectivity, as well as epigenetic modifications and changes in gene expression levels. Whilst such changes are well-characterised in some systems and in isolation, the complex interactions between functional and genomic forms of plasticity are less well understood. This is made more challenging by the extensive heterogeneity across and within neuronal populations. To begin to understand this relationship we propose to perform a simultaneous evaluation of functional and gene expression plasticity, induced by controlled alterations in sensory experience, on a cell-by-cell basis.

Methods: We will investigate this process in a population of cells renowned for their experience-dependent plasticity. Dopaminergic neurons of the mammalian olfactory bulb (OB) are inhibitory interneurons that regulate and refine the transmission of information at the earliest stages of olfactory processing. Their activity can be reliably perturbed by simple, physiologically relevant manipulations of the sensory environment. Therefore, we will carry out 24h unilateral naris occlusion or sham-control surgery in DAT-IRES-Cre x ROSA26-Flox-tdT mice, in which cells expressing the dopamine transporter are fluorescently labelled. These manipulations have been demonstrated to change activity-dependent gene expression in OB DAT-tdT-positive neurons. Whole cell patch clamp experiments will be performed on acute slices obtained from either occluded or sham-control mice, characterising a range of intrinsic passive and active membrane properties. The cell contents will then be aspirated, flash frozen and processed for sequencing.

Approach for statistical analysis: We will carry out sequencing to a depth of approximately 1.5 million reads per cell, quantifying approximately 4000 genes per cell, as observed from preliminary data. We will compare the transcriptomes from cells obtained from occluded vs shammed mice. Finally, we will combine our functional and transcriptomic approaches at the single-cell level by evaluating the interrelated plastic changes in electrophysiological properties and gene expression patterns triggered by sensory manipulation.

Poster number: PT116 (SP)

Theme: Neuronal, glial and cellular mechanisms

Understanding the role of zinc and zinc transporters in autism

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Introduction: Autism Spectrum Disorders (ASD) (present in 0.7-1.1% of the population) are a group of neurodevelopmental disorders characterized by impairments in communication, social behaviour and interactions, and by the occurrence of repetitive behaviours.

Methods: Recently, abnormal zinc homeostasis has been linked the aetiology of ASD. Here, we investigate the expression and localisation of zinc transporters in neural tissue (neurons and glial cells) with a particular focus on zinc transporter 5 (ZnT5). A mutation in the zinc transporter ZnT5 (missense mutation p.S561R) was linked to autism in human patients.

Perspectives: We hypothesise that a loss of function in the transporter ZnT5 in the offspring, despite normal zinc status of the mother, may lead to insufficient zinc supply during a critical time window in development.

Results and conclusions: Our first results confirmed the expression and the localization of ZnT5 in the placenta, in the brain and in hippocampal neurons on mRNA and protein level. On subcellular level, we could show that in neurons ZnT5 is found at synapses, and the Golgi apparatus. Further, ZnT5 expression levels do not respond to alterations in general zinc concentrations.

Thus, ZnT5 may have a more specialized role in neurons, and particular in synaptic zinc signalling that have not been described so far.

Poster number: PT117 (SP)

Theme: Neuronal, glial and cellular mechanisms

Reproducing peri-electrode gliosis using mechanically induced neuroinflammation

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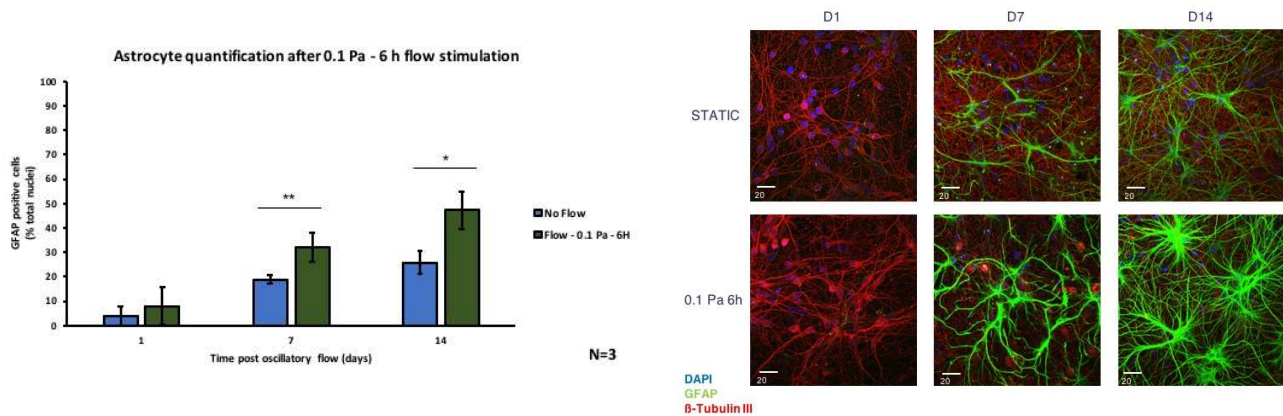
Introduction: Neuroprosthetic electrode implants have been under investigation for decades and have been proven to be safe and efficacious as therapeutic devices for multiple diseases of the central nervous system (CNS) including Parkinson's and Alzheimer's disease. However, studies indicate that, in situ, neuronal recording and charge deliverance decrease with time in implanted electrode systems. This loss of function can be attributed in part to an acute inflammatory reaction resulting from the initial mechanical shear stress experienced during the insertion of the neural electrode. This mechanical trauma results in an adverse tissue response characterized by glial scar formation and electrode encapsulation, causing the signal strength to decrease and adjacent neurons to move away from the electrode as a result of the surrounding region of gliosis.

Methods: Using a parallel-plate flow chamber system, ventral mesencephalic mixed primary cells were exposed to different level of pressure-driven fluid flow allowing to apply a defined shear stress (from 0.1 to 4 Pa) for either a 5-minute pulse to reproduce the insertion only, or up to several hours to mimic micro-motions between the implant and the tissue. The cells were then kept in culture for 14 days before being assessed for neuroinflammation. The morphology and protein expression of neurons and glial cells were quantified by image analysis. qPCR and Western-blot were used to detect the expression level of neuroinflammatory proteins.

Approach for statistical analysis: All results were obtained from 3 biological individuals in independent experiments, analysed with 2-way ANOVA followed by student t-test and expressed as standard deviation \pm mean.

Results and conclusions: Data have shown that applied shear flow leads to astrocyte reactivity and inflammatory environment. Shear stresses from 0.1 to 4 Pa have all significantly increased the GFAP protein expression and size of astrocyte cell body along with the up-regulation of several neuronal pro-inflammatory markers and reactive oxygen species release.

In conclusion, we developed a novel in-vitro model of neuroinflammation using parallel flow shear stress that mimics damages at the interface of the neuro-electrode. This model will certainly be a precious tool for future researchers developing anti-inflammatory and anti-gliosis molecules.



Poster number: PT118 (PP)

Theme: Neuronal, glial and cellular mechanisms

Lipophorin receptors participate in the development of drosophila melanogaster mushroom body

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Introduction: The very low density lipoprotein receptor (VLDL) and apolipoprotein E receptor 2 (ApoER2) are two proteins that in addition to their involvement in lipid uptake, have been recognized as receptors for Reelin. This is an extracellular glycoprotein that is responsible for neuronal migration, cerebral cortex patterning and neural plasticity. The Reelin effect depends on its receptors VLDL and ApoER2, and is mediated by Dab1. In *Drosophila melanogaster*, Lipophorin receptors (LpRs) mediate lipid uptake. Two LpRs have been described in *Drosophila*, LpR1 and LpR2, which are homologues of VLDL and ApoER2. Here we evaluated the role of LpRs in the development of *Drosophila* mushroom body (MB), a brain structure serving as the “fly hippocampus”.

Methods: We assessed whether mammalian Reelin (mReelin) affects the number and length of neurites in *Drosophila* MB neurons in culture prepared from wild-type flies and animals mutant for LpR1 and LpR2, and Dab, the fly homologue of vertebrate Dab1. Additionally, fly brain general anatomy was evaluated in these mutants.

Approach for statistical analysis:

To evaluate the development of neurites we used the conventional Sholl Analysis.

Results and conclusions:

Our results support the idea that LpR1 and LpR2 participate in MB development and that this effect is mediated by Dab.

Funded by Fondecyt 1141233 and Puente-PUC (JMC) and Fondecyt 1150444 (MPM). FR is supported by Conicyt Doctoral Fellowship.

Poster number: PT119 (SP)

SP = Standard poster

PP = Preregistration poster

Theme: Neuronal, glial and cellular mechanisms

Whole brain imaging to investigate neuronal population changes in rodent models of autism spectrum disorders

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Rodent models have generated insights into cellular and molecular changes that take place in autism spectrum disorders (ASDs). However, analyses of neural circuit components in rodent models are typically constrained to a single brain region of interest. This reflects limitations arising from sectioning and separately imaging tissue sections and prohibitive increases in time required to evaluate multiple regions. As a result, whole brain anatomical changes are largely unclear and the possibility that behavioral deficits of interest result from alterations to as yet unexplored brain regions is difficult to rule out.

The recently developed iDISCO clearing method¹ has enabled visualization of whole mouse brains providing a potentially powerful approach for unbiased identification of neuronal circuit changes mediating behavioural deficits found in ASD models. By keeping proteins in place while removing the light-scattering lipids, iDISCO clearing allows deep penetration of light that is advantageous for light-sheet microscopy. Here we evaluate the potential application of iDISCO clearing and immuno-labelling combined with whole-brain light-sheet imaging to investigation of rodent models of ASDs.

We cleared and labelled adult mouse and rat brains using a standard implementation of the iDISCO protocol¹. All cleared brains were imaged using a LaVisionBiotec Ultramicroscope II under identical illumination parameters. The image stacks were analysed using ClearMap software¹, which automatically detects labelled objects and registers the images to a reference atlas.

To validate the method, we tested multiple antibodies for c-FOS, parvalbumin, FOXP2, reelin, GFP, mCherry, Arc, calbindin and Egr1 in mice and rat, and developed protocols optimized to obtain brain-wide labelling. We used double- and triple-immunolabelling combinations to visualize neuronal types in parallel. With antibodies against c-FOS, Arc and FOXP2 we obtain clear labelling of neurons in mouse and rat brains. We are now using these approaches to compare behavioural activation of c-Fos in Fmr1y/- and control Long-Evans rats.

1. Renier, N. *et al.* Mapping of Brain Activity by Automated Volume Analysis of Immediate Early Genes. *Cell* 165, 1789–1802 (2016).

Poster number: PT120 (SP)

Theme: Neuronal, glial and cellular mechanisms

Activation of cortical layer 1 interneurons by higher-order thalamic afferents leads to UP-state termination via post-synaptic GABAB receptor activation

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Introduction: The neocortex is composed of excitatory and inhibitory neurons that are densely interconnected, allowing for the generation of sustained patterns of activity. During slow-wave sleep, anaesthesia, and quiet wakefulness, neuronal network is synchronised and fluctuates between periods of high synaptic activity (UP-states) and periods of relative quiescence (DOWN-states). UP-states are often seen as travelling waves, initiated in the

frontal areas and propagating towards the latero-caudal areas. If a majority of UP-states are indeed generated in the frontal areas, however, the termination of UP-states does not propagate across cortical areas. GABAB receptors activation has been shown to contribute to the increase of activity-dependent potassium conductance and thus promote the termination of UP-states. We hypothesise that the synchronised activation of certain population of Layer 1 (L1) interneurons across cortical areas is responsible for the synchronised termination of UP-state in the brain. Furthermore, we suggest that higher-order thalamic nuclei might coordinate the broad activation of L1 interneurons.

Methods: We use optogenetics activation of L1 or thalamic neurons and slice electrophysiology to characterise inhibitory currents in cortical circuits. We combine pharmacology, optogenetics and recordings of spontaneous UP-states in slice and in anaesthetised animals to investigate the role of L1 and thalamic neurons in UP-states termination. Finally, we recorded UP-states using multi-site LFP in the naturally-sleeping animal.

Approach for statistical analysis: For pharmacology and optogenetics experiments, we compare control and control + drugs/light conditions and performed paired non parametric rank tests. We compare spike timing distribution across the UP-DOWN state cycle against uniform distribution using Kolmogorov-Smirnov tests. Finally, proportions were compared against chance using two-proportions z-tests. All statistical tests were done in R (R-project.org).

Results: Our results show that higher-order thalamic neurons preferentially target L1 NGFCs and indirectly activate GABAB-mediated conductances in L2/3 pyramidal neurons. We suggest that higher-order thalamic nuclei activation could mediate the synchronous termination of UP-states throughout cortical areas during slow-wave sleep.

Poster number: PT121 (SP)

Theme: Neuronal, glial and cellular mechanisms

Guanosine attenuates neurotoxicity and behaviour impairments after traumatic brain injury by modulation of adenosinergic receptors

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Introduction: Traumatic brain injury (TBI) is one of the main causes of death worldwide. Its pathophysiology involves several neurotoxic events, such as glutamatergic excitotoxicity, mitochondrial dysfunction and inflammation, which are followed by neurodegeneration and behaviour impairments. The endogenous nucleoside guanosine (GUO) has been shown to present neuroprotective effects in various models of diverse brain pathologies through the modulation of A1 and A2A adenosine receptors. Here we aim to investigate the effects of GUO on TBI by analyzing short-term neurotoxic events and motor deficit as well as long-term behavioral, molecular and morphological disturbances. Moreover, we explored whether GUO effects would be involved with the main adenosine receptors in the brain.

Methods: Male adult Wistar rats were subjected to a moderate TBI (fluid percussion) and 40 min later treated with a single GUO injection (7.5 mg/kg i.p) or vehicle (saline 0.9%). Subsequent neurochemical analyses (ipsilateral cortex) followed 8 hrs after TBI. To determine the GUO long-term effects and its possible mechanism, a second cohort underwent TBI and 1 h later received GUO treatment, which was continued daily for 21 days. Prior to GUO treatment (30 min), these rats were injected with A1 (DPCPX 1 mg/kg; i.p) or A2A (SCH 58261 0.05 mg/kg; i.p) receptors antagonists.

Approach for statistical analysis: The normality of the data was analyzed by D'Agostino and Pearson's omnibus normality test. Data were analyzed by two-way ANOVA followed by *post hoc* comparisons using Newman-Keuls multiple test, unpaired t test or Scheirer-Ray-Hare test followed by Dunn's or Mann-Whitney *post hoc* test. Results were represented as mean \pm SEM or as median \pm interquartile range, accordingly to analysis. $P < 0.05$ was considered statistically significant.

Results and conclusions: GUO prevented short-term motor deficit and neurotoxicity after TBI through modulation of glutamatergic system function, attenuating mitochondrial dysfunction, pro-inflammatory cytokine levels and brain edema. A major conclusion of the present study is the requirement of adenosine A1 receptors for the neuroprotection played by GUO on long-term molecular and morphological alterations. However, the involvement of adenosine A2A receptors still cannot be discarded. Thus, these findings posit GUO as an attractive candidate for post-traumatic brain injury therapy.

Poster number: PT122 (SP)

Theme: Neuronal, glial and cellular mechanisms

Biocompatible two-photon polymerisable scaffolds for development of human induced pluripotent stem cell-derived cortical neuronal networks

Authors: Mr James Crowe¹, Dr. David Nagel¹, Dr. Eric Hill¹, Dr. Sergei Sokolovsky², Mr. Ayman El-Tamer³, Dr. Anastasia Koroleva³, Prof. Dr. Boris Chichkov³, Prof. Edik Rafailov², Dr. Rhein Parri¹

¹School of Life and Health Sciences, Aston University, Birmingham, United Kingdom, ²Aston Institute of Photonic Technologies, Aston University, Birmingham, United Kingdom, ³Lazer Zentrum Hannover, Hannover, Germany

Understanding the cellular and network mechanisms of human cortex is a key step in deciphering normal human brain function. The main barrier is a lack of tissue for study. Recent advances in the field of human induced pluripotent stem cells (hiPSCs) derived neurons have the potential to make this a reality. However, the 3D structure and connectivity of neuronal networks is poorly replicated by monolayer *in vitro* cultures. A solution could be generating microscale 3D scaffolds using two-photon polymerisation (2PP). A first step in achieving this is the identification of biocompatible and functional imaging amenable materials that enable the monitoring of network activity.

Candidate biomaterials were validated against three criteria: ability to achieve micrometre resolution during 2PP, appropriateness for optical interrogation use, compatibility for long-term neuronal culture. HiPSC-derived neural progenitors (Axol Bioscience Ltd., UK) were cultured upon planar biomaterials: Organically-modified silica (Ormosil), Polyethylene glycol diacrylate (PEGDA), Polylactic acid (PLA), and LT Dental Clear (DClear; FormLabs, UK) and control materials of tissue culture plastic (TCP) and glass. Development of neural progenitors was measured via phase-contrast microscopy, nuclei-counting, live/dead viability staining and fluorescence immunocytochemistry. Ormosil and PLA were excluded due to their autofluorescence levels at visible wavelengths. Upon counting cell nuclei no significant difference was seen 24 hours post-plating between TCP and any other material indicating suitable adherence (Unpaired t(8) = TCP-DClear, 0.6173, $p=0.5542^{ns}$; TCP-PEGDA, 0.5991, $p=0.5657^{ns}$, TCP-Glass, 1.1538, $p=0.2819^{ns}$). However, after 30 days *in vitro* there was a significant decrease in viability of cells cultured on PEGDA^{***} and DClear^{**}, but not glass, compared to TCP (Unpaired t(6) = TCP-DClear, 3.8501, $p=0.0085^{**}$; TCP-Glass, 0.4456, $p=0.6715^{ns}$; TCP-PEGDA, 6.0078, $p=0.0010^{***}$). Neural stem cell populations (PAX6⁺ / SOX2⁺ / NESTIN⁺) cultured on PEGDA and DClear differentiated into mature neurons (MAP2⁺ / TBR1⁺ / CTIP2⁺) by day 30 *in vitro* as assessed by fluorescence immunocytochemistry. PEGDA and DClear sustained cultures were imaged using Fluo-4AM calcium dye. Spontaneous activity was blocked by TTX (n=5). Glutamate application resulted in robust

global calcium elevations. The data indicate that data PEG-DA and DClear are suitable polymers for 2PP-fabrication of 3D biocompatible scaffolds for growing hiPSC-derived neuronal networks.

Poster number: PT123 (SP)

Theme: Neuronal, glial and cellular mechanisms

Characteristics of 5-HT₇ receptor-expressing neurons in the mouse basolateral amygdala

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Introduction: Depressive disorders involve dysfunctions in brain structures involved in emotional processing, including the hippocampus, frontal cortex and amygdala. Within the amygdala, groups of neurons express 5-HT₇ receptors, which suggests their contribution to emotional processing. To date, there have been almost no studies documenting 5-HT₇ receptor function in the amygdala, which is an oversight given the multitude of publications showing the role of this receptor in regulating the activity of other brain regions indicated in the pathophysiology of affective disorders.

Methods: In the current study we aimed to characterize the role of 5-HT₇-expressing neurons within the mouse basolateral amygdala (BLA). Utilizing a transgenic mouse model expressing EGFP under the Htr7 promoter, we selectively targeted 5-HT₇-expressing neurons in acute brain slices and performed whole-cell patch clamp recordings. We have also analyzed the effects of 5-HT₇ receptor activation on spontaneous postsynaptic currents (sPSCs) recorded from principal cells. Biocytin was included in the recording pipette to recover cell morphology. Immunohistochemical experiments allowed us to characterize the neurochemical phenotype of EGFP-expressing BLA neurons.

Approach for statistical analysis: Changes in neuronal excitability were analyzed by fitting a linear regression line to the frequency-current relationship for each cell. Gain values (slope) before and after 5-HT₇ receptor activation, as well as membrane resistance, were compared using a paired t-test. Distributions of sPSC frequencies and amplitudes before and after 5-HT₇ receptor activation were compared using the Kolmogorov-Smirnov test. Morphology of recorded neurons was qualitatively analysed using confocal z-stack imaging. Colocalization analysis of neurochemical markers was performed manually.

Results and conclusions: We found that 5-HT₇ receptor activation markedly increased spontaneous inhibitory postsynaptic current (sIPSC) frequency and amplitude recorded from principal cells. Immunohistochemical findings confirmed that the majority of EGFP-immunoreactive cells were GABAergic, most of them immunoreactive for parvalbumin. Application of a 5-HT₇ receptors enhanced the spiking behaviour of these neurons, promoting spontaneous activity. These findings suggest that 5-HT₇ receptors take part in regulating BLA activity by modulating inhibitory GABAergic transmission. This may prove significant for future research towards the physiology and pathophysiology mood regulation.

Funding for this study was provided by Polish National Science Centre Grant 2016/21/B/NZ4/03618

Poster number: PT124 (SP)

Theme: Neuronal, glial and cellular mechanisms

The roles of astrocytes in long-term synaptic plasticity in the somatosensory cortex

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Astrocytes are increasingly recognised as key partners in neuronal signalling and network function through active participation in neurotransmission and signal processing. Emerging evidence supports the key roles of astrocytes in afferent-signal integration and experience-dependent plasticity; however, the signalling pathways by which astrocytes govern the induction of synaptic plasticity, the molecular mechanism of Learning and memory, have been elusive. We aim to investigate the roles of astrocytes in long-term synaptic plasticity through characterising the impairments that parallel astrocytic calcium dysregulation, via inositol 1,4,5-triphosphate receptor subtype-2 (IP3R2) deletion, at L4-L2/3 synapses of the somatosensory cortex *in vitro*. Acute slices were obtained from 4-7 weeks old IP3R2-knockout (KO) and wild-type (WT) mice of C57B/L genetic background. Theta-burst (TBS) and low-frequency stimulation (LFS) protocols were used to induce long-term potentiation (LTP) and depression (LTD), respectively. Field excitatory post-synaptic potentials (fEPSPs) were evoked and recorded using Alpha MED Scientific (MED64[®]) microelectrode array system. The results show that LTD is impaired while LTP is still inducible in KO mice. The magnitude of LTP in KO (203.6±10.1% fEPSP slope 1h following TBS vs 115.9±13.1% baseline control, n=3, p<0.05) was comparable to WT control (224.3±12.7% vs 117.6±10.5%, n=3, p<0.05). On the other hand, LFS not only failed to induce LTD in KO mice but resulted in significant potentiation (181.4±9.2% 1h following LFS vs 119.0±15.9% baseline control, n=3, p<0.05), while in WT slices LFS induced sustained LTD (62.1±7.0% vs 122.3±10.1%, n=3, p<0.05). The application of the N-methyl D-aspartate (NMDA) receptor antagonist AP-5 (100µM) completely blocked the effects of both TBS (117.6±8.8% vs 224.3±12.7%, n=3, p<0.05) and LFS (98.9±6.1% vs 62.1±7.0%, n=3, p<0.05) in WT mice. Lastly, bath application of D-serine (100µM) failed to rescue LFS-induced LTD and caused stronger potentiation in KO mice (239.3±11.2 vs 181.4±9.2%, n=3, p<0.05). The current results illustrate that both LTP and LTD are NMDAR-dependent and that LTD, but not LTP, is dependent on astrocytic IP3R2-mediated calcium signalling.

Poster number: PT125 (SP)

Theme: Neuronal, glial and cellular mechanisms

Development of a human ipsc-derived model for seizure-liability testing

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Drug-induced seizure is a major reason for compound attrition during drug development, hence testing the potential of novel agents to induce such neurotoxic events is a vital process. Currently, the rat *ex vivo* hippocampal slice assay is most commonly used for seizure-liability studies; yet controversy over the relevance, efficacy and cost of animal-based approaches has led to interest in the development of human based models. Existing platforms utilise rodents, and so lack human receptors and other drug targets, which may produce misleading data, with difficulties in interspecies extrapolation. Human induced pluripotent stem cells (iPSCs) are a promising avenue for neurotoxicity testing, increasingly utilised in drug screening and disease modelling. Human neural precursor cells derived from iPSC were spontaneously differentiated in two different commercially available media ('A' and 'B') over 120 days. Additionally, iPSC-derived neurons were co-cultured with iPSC-derived astrocytes over 45 days. Immunocytochemistry (ICC) was performed at various stages of development to determine endpoints such as cell type and maturity. Concurrent fluorescent calcium imaging was used to investigate responses of cells in culture to different stimuli.

ICC illustrates the presence of extensive β -III-tubulin-positive neurons (n=6) and S100 β -positive astrocytes (n=6) in both media at 45 days *in vitro*, following spontaneous differentiation. Calcium imaging studies demonstrate that media A is an unsuitable perfusate for functional imaging experiments, whereas media B facilitates spontaneous activity of iPSC-derived cultures (A activity: 0.0±0.0 n=3, B activity: 22.3±2.7 n=3, P<0.05). Spontaneous calcium-mediated activity was blocked by 1 µM tetrodotoxin (n=5), indicating action potential dependent activity and calcium elevations were observed from 100 µM L-glutamate exposure (n=5), indicating the presence of functional glutamate receptors. Spontaneously differentiated cells grown in either media did not respond to the convulsant 4-

aminopyridine at any point in time (n=9), however in co-cultures of neurons and astrocytes, synchronised oscillatory activity was seen in magnesium-free perfusate at 45 days. The results suggest that methods co-culturing iPSC-derived neurons and astrocytes have potential use as a functional, predictive platform.

Poster number: PT126 (SP)

Theme: Neuronal, glial and cellular mechanisms

Temporal dynamics of post-injury degeneration and regeneration in the presynaptic terminals of olfactory sensory neurons

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Olfactory sensory neurons (OSNs) transduce odorant stimuli into electrical activity, then transmit that activity to the brain via their direct projection to the glomerular layer of the olfactory bulb (OB). Because of the dangers associated with their constant exposure to the external environment they are capable of regeneration throughout life, and even widespread injury to the olfactory epithelium (OE) can be followed by complete recovery of the OSN-to-OB projection. However, the functional properties of OSN presynaptic terminals in OB glomeruli during these processes of degeneration and regeneration remain unstudied. As a first step towards identifying the presynaptic changes associated with OSN regeneration, we have characterised the temporal dynamics of OSN terminals in OB glomeruli following wholesale degeneration and subsequent regeneration of the OE. To induce OE degeneration, we administered a single intraperitoneal injection of the olfactotoxin methimazole in adult mice, then sacrificed the animals after different time points between 3 and 90 days. We studied the distribution and density of OSN axons and presynaptic terminals in OB glomeruli using immunohistochemical labelling with antibodies for, respectively, olfactory marker protein (OMP) and the vesicular glutamate transporter 2 (vGlut2). Using quantitative measures of glomerular fluorescence intensity, we observed a decrease in both OMP and vGlut2 glomerular label in a degenerative period between 3-20 days after methimazole administration. This was followed by a period of regeneration between 20-45 days, after which methimazole-injected and sham controls were indistinguishable. This characterisation of OSN dynamics will underpin future studies of presynaptic function and plasticity during injury-induced regeneration.

Poster number: PT127 (SP)

Theme: Neuronal, glial and cellular mechanisms

Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability

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Autoantibodies against LGI1 have been detected in the serum of adult patients with limbic encephalitis, seizures and status epilepticus. It is not clear if the seizures are generated by inflammation due to the antibodies or through a direct effect of the antibodies on LGI1. LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein which interacts presynaptically with Kv1.1 potassium channels and ADAM23, a membrane-anchored protein with no catalytic effect. Postsynaptically, LGI1 influences AMPA and NMDA receptors through a direct link with the ADAM22 adhesion protein. Mutations in the gene encoding LGI1 lead to temporal lobe epilepsy in humans and animal models.

We, therefore, asked if an acute reduction in LGI1 was sufficient to increase network excitability and promote seizure activity.

For this purpose, we chose and validated a silencing RNA (shRNA) against LGI1. In neuronal cultures and in *ex vivo* granule cells, shRNA against LGI1 increased neuronal firing. Local field potential (LFP) of *ex vivo* slices after injection of shRNA-LGI1 in the hippocampus, revealed an increase in the facilitation of mossy fibers to CA3 pyramidal cell neurotransmission. Application of Kv1 family blocker, alpha-dendrotoxin, occluded the increased facilitation in shRNA-LGI1 injected mice.

These results indicate that an acute reduction in LGI1 is sufficient to increase neuronal network excitability. Specifically, acutely decreasing LGI1 protein affects synaptic excitability and short-term plasticity in DG-CA3 hippocampal circuitry.

Poster number: PT128 (SP)

Theme: Neuronal, glial and cellular mechanisms

Activity-dependent plasticity in adult-born dopaminergic neurons in the olfactory bulb

Authors: Ms Candida Tufo¹, Dr Menghon Cheah¹, Dr Marcela Lipovsek¹, Dr Matthew Grubb¹

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Introduction: In the olfactory bulb, local dopaminergic interneurons play an important role in shaping early sensory processing. These cells are known to be highly plastic and are generated throughout life through adult neurogenesis. However, the maturation of these adult-born dopaminergic neurons, as well as their precise plastic features following alterations in their activity, have yet to be qualitatively and quantitatively determined.

Methods: This study used DAT-Cre mice crossed with a tdTomato reporter line to label 'resident' dopaminergic neurons in the olfactory bulb. Labelling of adult-born dopaminergic neurons was achieved by targeting the rostral migratory stream (RMS) of these DAT-tdT mice with a floxed GFP-expressing adeno-associated-virus. Neuronal plasticity was induced *in vivo* by manipulating sensory experience through 24-hour naris occlusion at 5 weeks after the virus injection. The effects of this manipulation on neuronal function were then investigated with whole-cell patch-clamp recordings in acute slices. In particular, intrinsic passive properties including resting membrane potential (RMP), input resistance and membrane capacitance were compared between adult-born neurons at 5 weeks post-injection and the 'resident population' of dopaminergic neurons in the olfactory bulb, under control and occluded conditions.

Results: RMS injections with the floxed GFP-expressing adeno-associated virus resulted in sparse and selective label of adult-born dopaminergic neurons confirmed by co-label of GFP and tyrosine hydroxylase (n = 5 from 2 mice). Initial data from whole-cell recordings in immature adult-born versus resident dopaminergic neurons revealed no significant differences in any of their passive properties (RMP, n = 11 cells from 9 mice; input resistance and membrane capacitance, n = 13 cells from 11 mice).

Significance: This study shows the first electrophysiological characterization of adult-born dopaminergic cells as they

arrive in the olfactory bulb. Further analyses of passive and active membrane properties will continue to test the hypothesis that heightened intrinsic plasticity is expected in the dopaminergic neurons of the olfactory bulb at key maturational stages.

Poster number: PT129 (SP)

Theme: Neuronal, glial and cellular mechanisms

Adam proteins in the assembly of voltage-gated potassium channel complexes at the cerebellar pinceau

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The pinceau formation is a specialised cerebellar structure composed of 5-7 descending GABAergic basket cell terminals (BCTs) surrounding the initial segment of the Purkinje cell (PC) axon. As the sole cerebellar output, PCs integrate cortical and sensory inputs to regulate the initiation and coordination of movement, balance and posture. The pinceau has been suggested to tightly regulate PC outputs. Previous research suggested the GABAergic BCTs exert a strong inhibitory control through axo-somatic synapses but not axo-axonic synapses on the PC axon initial segment (AIS) as the latter are extremely rare. Moreover, astrocytic processes cover most of the PC AIS thus preventing direct interaction between the BCT and PC-AIS membrane. It has been suggested that the pinceau modulates PC output through ephaptic inhibition via the enriched presence of the voltage-gated potassium channel subunits Kv1.1 and Kv1.2. Mutations in *Kcna1* and *Kcna2*, the genes encoding Kv1.1 and Kv1.2 have been associated with ataxia and human cerebellar disease, highlighting their functional importance in the cerebellum. The molecular mechanisms underlying the assembly of the pinceau structure and the localisation of Kv1 channels remains poorly understood. Kole et al., (2015) showed that loss of the catalytically inactive disintegrin and metalloprotease (ADAM) protein 11 resulted in the loss of Kv1.1 and Kv1.2 subunit accumulation at the pinceau and thus a loss of electrical (ephaptic) transmission. More recently, ADAM23 has been shown to be necessary for the clustering of Kv1 channel complexes at the juxtaparanode of peripheral axons, however, whether ADAM23 may play a role in Kv1 channel clustering at the pinceau remains unexplored. Here we show that ADAM23 is localised to the pinceau. Furthermore, loss of ADAM11 prevents its accumulation, highlighting ADAM11 as a key mediator in the formation of the pinceau region. Selective loss of ADAM23 from BCTs and PCs does not affect ADAM23 localisation at the pinceau, which could suggest that ADAM23 is expressed in the astrocytic processes that ensheath the PCs AIS. We will present our ongoing studies into the role of ADAM23 into pinceau assembly and function.

Poster number: PT130 (SP)

Theme: Neuronal, glial and cellular mechanisms

Anti-TLR2 antibody triggers oxidative phosphorylation in microglia and increases phagocytosis of beta-amyloid

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Introduction: Microglia are multifunctional cells that are primarily neuroprotective and a deficit in their functional integrity is likely to be a contributory factor in the deteriorating neuronal function that occurs with age and neurodegeneration. One aspect of microglial dysfunction is reduced phagocytosis and this is believed to contribute to the accumulation of amyloid- β (A β) in Alzheimer's disease (AD). Therefore enhancing phagocytosis should be beneficial in limiting the amyloidosis that characterizes AD. Analysis approach and methods. Here we investigated whether an antibody that targets toll-like receptor (TLR)2 might impact on phagocytosis and attenuate the inflammatory and metabolic changes induced by lipopolysaccharide (LPS) and A β . We evaluated the metabolic

changes using the SeaHorse Extracellular Flux Analyser, studied the expression of key enzymes driving glycolysis by western blotting and assessed phagocytosis by immunohistochemistry.

Results and conclusions: We have reported that, when exposed to an inflammatory stimulus, microglia switch their metabolism towards metabolically-inefficient glycolysis; this potentially impacts on metabolically-demanding functions like phagocytosis. Anti-TLR2 antibody increased phagocytosis of A β in LPS+A β -stimulated microglia and that this was linked with the ability of the antibody to attenuate the LPS+A β -triggered inflammasome activation. LPS+A β increased glycolysis in microglia and increased the expression of PFKFB3, an enzyme that plays a key role in driving glycolysis; these effects were inhibited when cells were incubated with the anti-TLR2 antibody. The data also show that antibody treatment increased oxidative metabolism. Thus microglia with an inflammatory phenotype, specifically cells in which the inflammasome is activated, are glycolytic; this may compromise the metabolic efficiency of microglia and thereby provide an explanation for the reduced phagocytic function of the cells. We propose that, by restoring oxidative metabolism and reducing inflammasome activation in microglia, phagocytic function is also restored.

Poster number: PT131 (SP)

Theme: Novel treatments & translational neuroscience

Xenon prevents injury development following blast-induced neurotrauma in vitro

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Introduction: Blast-induced neurotrauma (BINT) has a unique pathophysiology and is a 'signature injury' of recent military operations. Despite much recent research, there are currently no clinically effective treatments to limit the development of ongoing brain injury following blast. Xenon is a noble gas shown to be neuroprotective in models of blunt traumatic brain injury [1-3]. We developed a novel in vitro model of BINT to evaluate the efficacy of xenon as a potential neuroprotectant in BINT.

Methods: Organotypic hippocampal slice cultures (OHSCs) were prepared from day 5-7 mouse pups on tissue culture inserts and sealed in sterile polyethylene sample bags [2, 4]. Friedlander-type blast waves modelling real-life free-field explosions were generated using a shock-tube. The sample bag was clamped in a vertical position in front of the shock-tube and exposed to a single shockwave [4]. Following blast TBI the inserts were carefully transferred to six-well culture plates, and placed in a small custom-made treatment chamber. One hour after blast, xenon (50% atm) or control gas (helium) was applied as described previously [2].

Analysis Approach: Injury was quantified by measuring propidium iodide fluorescence OHSCs at 24 hours, 48 hours and 72 hours after BINT. Significance was assessed using a 2-way repeated measures ANOVA with Holm-Sidak post hoc test. Factor 1 was treatment (sham, xenon, control) and factor 2 (repeated) was time before or after the injury (-1 hour, 24 hours, 48 hours and 72 hours).

Results and Conclusions: Xenon had a significant ($p < 0.05$) protective effect against BINT at all time-points measured, reducing injury by 31%-47%. Treatment with xenon, starting 1 hour after trauma, limits injury progression following blast-induced traumatic brain injury in vitro. Injury in the xenon-treated blast-injured slices at 24 hours and 72 hours was not significantly different to uninjured sham slices. These findings support the idea that xenon could be used as a novel treatment for blast-induced TBI.

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4. Campos-Pires, R., et al. JoVE, 2018.e58400 doi:10.3791/58400 in press.

Poster number: PT132 (SP)**Theme:** Novel treatments & translational neuroscience**Improving and personalizing treatment options for paediatric brain tumour patients****Authors:** Ms Marie-claire Fitzgerald¹, Ms Haleema Azam¹, Dr Manuela Salvucci², Dr Darach Crimmins^{3,4}, Dr Philip O'Halloran^{1,4}, Dr Niamh Connolly², Dr Brona Murphy¹¹Department of Physiology, Royal College of Surgeons in Ireland, Dublin 2, Ireland, ²Centre for Systems Medicine, Royal College of Surgeons in Ireland, Dublin 2, Ireland, ³Children's University Hospital, Temple Street, Dublin 1, Ireland, ⁴Beaumont Hospital, Dublin 9, Ireland

Introduction: Medulloblastoma (MB) is the most commonly occurring brain tumour in children, and while the survival rate is approximately 70-80%, aggressive multimodal treatment - surgery, chemotherapy and craniospinal radiation therapy (RT) - is associated with severe side effects and significant radiation-induced brain injury. This highlights an urgent need for personalised approaches to select the most appropriate drug for each patient to (1) reduce/eliminate the need for RT and (2) reduce side effects associated with inefficient therapy. Mathematical modelling holds considerable potential for personalisation and optimisation of treatment strategies. Previously, we demonstrated that innovative, systems-based strategies (APOPTO-CELL, DR_MOMP) can predict responsiveness to standard chemotherapies in different cancer types by integrating quantitative apoptotic protein signalling that occurs both upstream and downstream of mitochondrial outer membrane permeabilisation. Our group also developed a principal component-based statistical model (SYS-ACT) to predict responsiveness of adult brain tumour cell lines to various drug combinations. We aim to explore the applicability of these tools in the paediatric setting.

Methods/Approach for Statistical Analysis: A panel of 10 MB cell lines was established, and treated with varying concentrations of standard, clinically relevant chemotherapeutic agents to identify sensitivity/resistance. Additionally, the expression of key pro- and anti-apoptotic proteins was quantified across the panel via western blot and densitometry analysis. These results were then utilised as input to our computational models.

Results: We identify considerable heterogeneity both in the response of the MB panel to standard, clinically relevant chemotherapies, and in apoptotic protein expression profiles. Subsequently, these results were utilised as input to our computational models, correlating the unique apoptotic signature of each cell line with its therapeutic response in vitro.

This work has potential to create a clinical decision-making tool to facilitate de-escalation of therapy and elimination/reduction of RT in specific patient cohorts, thus reducing long-term sequelae. Critically, it could also be used to identify patients with aggressive/chemoresistant disease who could benefit from newer, targeted agents to sensitise their disease to standard chemotherapy, further reducing the requirement for RT.

Poster number: PT133 (PP)

Theme: Novel treatments & translational neuroscience

Microglial trajectory in human traumatic brain injury: dynamics and its modulation

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Recent studies indicate that inflammation has a temporally biphasic behavior and acts as a double-edged sword, not only exacerbating secondary brain injury, but also contributing to brain recovery after injuries. We started digging to explore the trajectories (dynamics and modulation) of Central Nervous System-immunological cells, microglia in traumatic brain injury. A crucial problem in traumatic brain injury (TBI) is damage due to neurotoxic behaviour of microglia, whose inflammatory response has both beneficial and/or detrimental effects on neurons. Using intracranial dialysis on patients, we are studying the temporal dynamics of microglial phenotypes via single cell ex-vivo transcriptomics. By collecting samples from multiple patients at multiple time points, we are trying to identify the switch time event, after TBI, when the initial microglial M2 population (neuroprotective) shifts to M1 (neurotoxic). We are applying the fluorescent activated cell sorting (FACS) strategy for isolating pure single cell suspension of microglia. Then 10,000 microglial cells will be used for single cell RNA sequencing. t-distributed stochastic neighbour embedding (t-SNE) method will be applied to sort the different clusters of microglia. We are further trying to investigate the microglial function in relation to the canonical phenotypes designated M1 and M2. Next we will relate the cytokines and chemokines milieu after severe traumatic brain injury with microglial transcriptomic data. Finally, we will relate the empirical evidence from human TBI and screen the putative agents further through pharmacoinformatics to select the candidate(s) that have maximal therapeutic potential.

Poster number: PT134 (SP)

Theme: Novel treatments & translational neuroscience

A feasibility randomised controlled trial of neurostimulation for functional neurological (conversion) symptoms ('tonics' trial)

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Introduction: Functional neurological disorder (FND) presents with neurological symptoms that are distressing and/or debilitating, without underlying neuropathology. There is currently a limited evidence base for treatment of FND and a clear need for accessible and cost-effective interventions. Transcranial magnetic stimulation (TMS) is a potentially beneficial treatment (Pollak et al., 2014); however, there have been few randomised controlled trials (RCTs) testing its efficacy in FND. We sought to examine the feasibility of an RCT of TMS for functional motor symptoms, with a novel protocol.

Methods: The study was a double-blind feasibility RCT. Patients with DSM-5 diagnosis of FND (limb weakness) received two sessions of either active (single pulse TMS to M1 above motor-threshold) or inactive TMS (single pulse TMS to M1 below motor-threshold). The primary outcome measure was patient-rated symptom change (Clinical Global Impression – Improvement scale, CGI-I). Secondary outcomes included clinician-rated symptom change,

manual muscle testing, psychosocial functioning, and disability. All measures were completed at baseline, TMS visits and 3-month follow-up.

Approach for statistical analysis: The aim was to estimate feasibility parameters (recruitment, retention, patient satisfaction, adverse events), so descriptive statistics were used primarily. Inferential statistics generated confidence intervals and effect sizes, where appropriate. All analyses adopted the intention-to-treat principle, carried out by the blinded trial statistician (JH).

Results & conclusions: Twenty-two patients were recruited in 6 months. Twenty-one patients (96%) were randomised (active=10; inactive=11). There were no withdrawals and 19 (91%) patients were included at follow-up (2 patients unable to attend). Patients were highly satisfied with their overall experiences of the trial, although satisfaction ratings were slightly higher for patients receiving the inactive treatment. The active treatment was not associated with an increased rate of adverse events, but a proportion of patients in both groups reported headaches. Treatment effect sizes for patient-rated CGI-I scores were moderate/small (Cliff's delta 0.3 at TMS visit 2 and 0.1 at follow-up), reflecting a more positive outcome for active TMS. Effect sizes for secondary outcomes were variable. The findings indicate that our protocol is feasible and that supra-motor threshold TMS of M1 may be an acceptable, safe and beneficial treatment for functional motor symptoms.

Poster number: PT135 (SP)

Theme: Novel treatments & translational neuroscience

Antagomir suppression of microRNA-134 reduces kainic acid-induced seizures in a model of paediatric onset status epilepticus

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Summary: Paediatric epilepsies affect 0.5%-1% of children and a significant proportion of those are drug refractory. Failure to control seizures in early infancy and childhood may impact on normal neurodevelopment and lead to life-long problems with brain function. Thus, there is an urgent and unmet clinical need to identify novel targets for the control of early-life seizures. MicroRNAs (miRNA) are small non-coding RNAs that regulate protein levels and shape the physiological properties of the brain. Previous research has shown that expression of miR-134, a brain-enriched miRNA, is increased in the hippocampus and cortex of adults with temporal lobe epilepsy (TLE) and in multiple rodent models of adult-onset status epilepticus (SE). Silencing miR-134, using antisense oligonucleotides called antagomirs, has been shown to have potent and long-lasting seizure-suppressive effects.

Objective: We sought to characterise the expression of miR-134 during brain development and to determine whether early-life seizures alter miR-134 levels. Next, we explored whether targeting miR-134 can reduce or delay seizures in the immature brain.

Methods: Expression of miR-134 was investigated in P7-P42 C57BL/6 male mice. Seizures were induced in 21 day old mice by a single systemic injection of kainic acid. miR-134 expression was determined using Taqman-based assays and miR-134 was inhibited by central injections of an antagomir.

Results: Status epilepticus was consistently triggered in P21 mice by an IP injection of 5 mg/kg of KA. This was associated with an overall neuronal injury in the hippocampus. Expression of miR-134 showed limited developmental regulation and was not differentially expressed after seizures in the model. Nevertheless, injection of antagomirs targeting miR-134 prior to seizure induction delayed seizure onset and reduced severity, and attenuated the expected neuronal death.

Conclusions: Silencing miR-134 in the developing brain can reduce seizures. These results indicate a broader application of this novel therapeutic approach to include the treatment of paediatric epilepsies in the future.

Poster number: PT136 (SP)

Theme: Novel treatments & translational neuroscience

Histological characterization of ‘white’ clots retrieved by mechanical thrombectomy from acute ischemic stroke patients

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Introduction: Advances in mechanical thrombectomy have created the unique opportunity to study the acute ischemic stroke clot material. However, there is a lack of uniformity in the histopathologic characterization of thrombi. Many clots are mainly red in colour and predominantly composed of Red Blood Cells and Fibrin. In this context, ‘white’ clots represent a less common entity and their histological composition is largely unknown. We investigated the histopathological features of 21 ‘white’ clots retrieved by thrombectomy. To our knowledge, this is the first series reported to date.

Methods: Twenty one mechanically extracted ‘white’ thrombi were collected from two partner hospitals: Beaumont Hospital and Sahlgrenska University Hospital. Clots were immediately formalin-fixed and subsequently embedded in paraffin. For each case, serial sections of 3- μ m thickness were cut and stained with Hematoxylin & Eosin and Martius Scarlett Blue (MSB) for the identification of main clot components. The MSB-stained slide underwent whole slide scanning (Olympus VS120) and histologic quantification was performed using Orbit Image Analysis Software (Orbit Image Analysis, Idorsia Ltd.). Von Kossa staining was performed to confirm calcification when suspected. The presence of specific components was assessed by immunostaining for platelets (CD42b), von Willebrand Factor (vWF) and fatty-acid binding protein (FABP4) for adipocytes.

Results: The quantification identified the Platelets as the major component in ‘white’ clots’ accounting for up to 90% of their composition. The main components showed mean values of 75.67% for Platelets, 13.36% for Fibrin, 5.07% for Red Blood cells and 3.75% for White Blood Cells. Immunostaining confirmed the presence of CD42b and vWF in all cases. Collagen and calcification were present in one case. Interestingly, adipocytes represented the main component in two cases.

Conclusions: Platelets are the key component of ‘white clots’. Calcification and adipocytes are also found occasionally. Increased levels of platelets and calcium confer resistance to thrombolysis and may render clots stiffer and less accessible for stent retrievers leading to low recanalization rates. The presence of adipocytes may represent a histological marker of fat embolism when suspected or a vulnerable atherosclerotic plaque, especially if associated with collagen.

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Poster number: PT137 (SP)

Theme: Novel treatments & translational neuroscience

Finding treatments for drug resistant epilepsy: identification of novel anti-convulsant compounds using diverse model organisms

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Introduction: Epilepsy is the most prevalent neurological disorder, affecting 1% of the population. One third of these patients do not respond to available therapeutics. This presents an unmet clinical need for new anti-epileptic compounds, however, the prevalently used rodent models are low-throughput and expensive. By modelling this disorder in simpler animals (*C. elegans* and *Danio rerio*), before reaching higher-tier rodent models, compound screening could become more efficient. We aim to establish a new paradigm in drug discovery, where the simple organisms *Caenorhabditis elegans* (nematode worm) and *Danio rerio* (Zebrafish) are used as front-line screening tools.

Methods: The convulsant pentylenetetrazol (PTZ) was applied to the bathing solutions of both *C. elegans* and *Danio rerio*. Convulsion behaviour was recorded followed by qPCR sample extraction. *C. elegans* genetic screen was conducted against a compound 11 induced paralysis phenotype, positive mutants were rescued via fosmid microinjection. Whole cell voltage clamp recordings were taken from thalamocortical relay neurons.

Approach for statistical analysis: Statistical analysis was performed using GraphPad Prism (Graphpad Software Inc) data analysis software. Statistical significance ($p < 0.05$) was calculated using one-way ANOVA and Dunnetts post-test.

Results and conclusions: An initial zebrafish screen showed that compound 11 could reduce PTZ induced gene upregulation. Compound 11 also showed anticonvulsant activity, reducing seizure-like behaviour in *C. elegans* and *Danio rerio* following PTZ treatment. Through a genetic screen of *C. elegans* mutants, compound 11's molecular target was established: GABA_A receptor alpha/gamma subunits. Compound 11 was also found to influence GABAergic activity in a mouse brain-slice preparation. Analysis of compound 11 shows an encouraging consistency between the *C. elegans*, *Danio rerio* and mouse model. This highlights the potential of these models to provide a cheaper, more efficient method of epilepsy drug discovery.

Poster number: PT138 (SP)

Theme: Novel treatments & translational neuroscience

An FMRI study of emotional processing during pulsatile glucocorticoid replacement in Addison's Disease

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Previous studies in animals indicate that dynamic oscillations of glucocorticoids are important for normal physiological transcriptional and behavioural responses, and that in healthy volunteers ultradian rhythmicity of circulating cortisol is critical for the response of the brain to emotional stimuli. We have now conducted a double-blind, placebo-controlled, two-way crossover study in patients with Addison's Disease (AD), a condition arising from loss of adrenal function. These patients require hydrocortisone replacement therapy (HCRT) generally in the form of oral hydrocortisone three times a day. In this study, each study arm lasted for 8 weeks; 1 week run in on usual HCRT, 6 weeks study treatment and 1-week washout on usual HCRT. There was a minimum of 6 weeks between each study arm (range 6 weeks-1yr). During the study, participants were treated with HCRT in one of two delivery methods: oral tablets taken three times per day, or pulsatile subcutaneous infusion delivered via an infusion pump (approximated to follow both the ultradian and circadian variations of cortisol). Dosage varied from 20-40mg according to each patient's current prescription. At the end of each 6-week treatment period, the patients took part in a functional magnetic resonance imaging (fMRI) study during which they underwent a facial expression recognition task (FERT) in which they were shown blocks of fearful, happy and sad faces with rest blocks in between. Whole brain level fMRI analysis with 13 right-handed female patients showed differential activation in the fearful condition between our two treatment groups (investigators remain blinded) in the Middle Frontal Gyrus, Precentral Gyrus, Superior Frontal Gyrus, Supplementary Motor Cortex, Anterior Cingulate Gyrus and Paracingulate Gyrus. Therefore, activity in executive control regions is altered in response to fearful face stimuli, dependent upon pattern of HCRT in patients with AD. Further region of interest (ROI) analysis with pre-specified regions selected based on their known cortisol sensitivity and involvement in emotional processing, showed that two ROIs, the insula and amygdala, were also differentially activated between our treatment groups in the fear condition. These analyses indicate that cortisol dynamics may be important for the processing of negative emotional stimuli in the brain.

Poster number: PT139 (SP)

Theme: Novel treatments & translational neuroscience

Assessing toll-like receptor signalling as a cannabinoid target in immune cells: relevance to multiple sclerosis

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Introduction: Toll-like receptors (TLRs) are the sensors of pathogen associated molecules that trigger tailored innate immune signalling responses. TLRs have been implicated in many diseases, including neurodegenerative diseases such as multiple sclerosis (MS). Phytocannabinoids are biologically active compounds extracted from the Cannabis plant. The phytocannabinoids, THC and CBD, have shown efficacy in experimental autoimmune encephalomyelitis (EAE), the murine model of MS. However, the cellular mechanism(s) of action of THC:CBD (1:1) are still not fully understood, particularly in immune cells from people with MS (pwMS). A growing body of literature indicates that cannabinoids may interact with TLR signalling events and evidence exists which suggests that cannabinoids interact with viral TLR3 signalling and bacterial TLR4 signalling^{1,2}.

Methods: Human THP-1-derived macrophages/PBMCs were incubated with the TLR4 agonist LPS (100ng/ml) or the TLR3 agonist poly(I:C) (10µg/ml) in the absence/presence of THC, CBD (or a 1:1 combination of both phytocannabinoids at 10µM [GW Research Ltd]). ELISA, immunocytochemistry and real-time PCR analysis were used to assess inflammatory read-outs.

Approach for statistical analysis: Data were analysed using Student's *t*-test or ANOVA as appropriate. When ANOVA indicated significance ($P < 0.05$), the post hoc Student Newman-Keuls test was used. Data are means±SEM.

Results/conclusions: Data obtained illustrate that TLR3/TLR4 signalling can be modulated by THC, CBD, THC:CBD (1:1) in THP-1-derived macrophages, in terms of IFN-β and CXCL10 expression. Data also suggests that THC and CBD do not require CB₁ or CB₂ to elicit their effects. Finally, the effects of THC and CBD were examined in PBMCs isolated from pwMS, in terms of inflammatory read-outs. These findings identify THC and CBD as novel regulators of TLR signalling and highlight TLR3/4 signalling as a mechanism to be investigated in the development of new cannabinoid therapeutics for the treatment of disorders such as MS.

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Poster number: PT140 (SP)

Theme: Novel treatments & translational neuroscience

'Geneloop': gene therapy activated by seizures to treat epilepsy

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Introduction: Epilepsy is characterized by repetitive seizure episodes, it affects nearly 1 million people worldwide. Approximately 25-30% of them suffer from drug-resistant epilepsy which cannot be managed by medication. Recent developments in gene therapy hold promise to provide reversible and non-invasive alternatives. Current gene therapy strategies modify broad range of neurons with little discriminations between pathological and healthy cells. Over-suppression of healthy neurons may affect normal functions such as memory and learning. Our project aims to improve the precision of gene therapy for epilepsy by selectively targeting over-excitabile neurons in an epileptic network and suppressing epileptic events on-demand. The system is only activated upon seizure initiation and it will prevent subsequent seizures.

Methods: Neurons respond to intense signals by activating different signalling pathways. Those mechanisms can be useful to activate desirable genes. We start with known targets with promising outcomes from current strategies, for example *kcna1* gene which encodes Kv1.1 channel. Overexpressing specific ion channels can modulate the level of neuronal excitabilities and suppress firing. We design and create the constructs, followed by *in vitro* validation in cell cultures. We then apply it to animal epilepsy models and evaluate how effective and robust the system is *in vivo*. Appropriate behaviour experiments are also designed and conducted.

Approach for statistical analysis: For all the experiments described above, we perform parametric/non-parametric statistical analysis as appropriate (e.g. Student's *t*-test, paired *t*-test, ANOVA).

Results and conclusions: So far we have analyzed neuronal network activity with patch clamp and multi-electro array (MEA) recordings and showed significant decrease of overall neuronal excitability. Preliminary *in vivo* data are encouraging to suggest a potential new treatment for epilepsy.

Poster number: PT141 (PP)

Theme: Novel treatments & translational neuroscience

Characterisation of a photocrosslinkable hyaluronic acid hydrogel used for 3D printing nerve guidance conduits to promote axon regeneration after trauma.

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Introduction: Regeneration of the spinal cord after injury remains a great challenge due to the complexity of this organ. Inflammation and gliosis at the injury site hinder the outgrowth of axons and hence prevent synaptic reconnection and reinnervation paralysed tissue. Implantable biomimetic biomaterials have proven to be an exciting tissue engineering approach to promote axon outgrowth across the injury site. Hydrogels provide a substrate for cell adhesion and migration while also reducing inflammation after injury. Hyaluronic acid (HA) is the main component of the spinal cord extracellular matrix and plays a vital role in cell proliferation and axonal guidance. In this study, we have characterised a photocrosslinkable HA-tyramine hydrogel from a chemical, mechanical, electrical, and biological perspective.

Methods: Initially the mechanical properties of HA-tyr in response to incremental increases in UV exposure was measured and compared to that of isolated rodent spinal cord tissue. HA-tyr mechanical properties can be tuned to that of spinal cord tissue.

Potentiometry was used to measure the electrical conductivity of HA-tyr and compared to that of spinal cord tissue. Finally, the Nanoscribe two-photon polymerisation (2-PP) 3D printer, HA-tyr was photocrosslinked according to computer aided Design (CAD) created geometries.

The cytocompatibility of photocrosslinking HA-tyr was assessed using dorsal root ganglion explants and live/dead staining.

Approach for statistical analysis: Three experimental replicates will be conducted, and a student T-test will be carried out to determine significance.

Results: From our experimentation, we have examined the degree of tyramine functionalisation of HA via nuclear magnetic resonance spectroscopy. This parameter is important in determining the crosslinking efficiency of any photocrosslinkable bioink. We have found that the mechanical properties of HA-tyr can be tuned to mimic that of native spinal cord via optimization of the photo-initiator concentration and UV exposure. Using potentiometry, the electrical conductivity of photocrosslinked HA-tyr was assessed and compared to that of native spinal cord tissue at physiologically relevant voltages. Spinal cord tissue has greater conductivity which could be correlated with the isotropic structure and myelin presence. Using dorsal root ganglion explants, the tissue compatibility of photocrosslinked HA-tyr was assessed using live/dead cell staining. The laser power and scan speed of the 3D printer was optimised to facilitate hydrogel patterning with an optimal power at 35mW and 600mm/s scan speed.

Conclusions:

In this study, we have developed a biocompatible, biomimetic hydrogel that can be used to 3D print tissue engineered constructs for neural tissue engineering applications.

Poster number: PT142 (SP)**Theme:** Novel treatments & translational neuroscience**Characterization of photoactivatable probes for optogenetic control in cellular cytoskeletal signaling****Authors:** Ms Stephanie Sanchez¹, Mr. Angel Santiago-Lopez^{1,2}, Mr. Harris Rothaermel³, Dr. Ken Berglund², Dr. Claire-Anne Gutekunst², Dr. Robert Gross²¹*Petit Undergraduate Research Program, Georgia Institute of Technology, Atlanta, United States*, ²*Department of Neurosurgery, Emory School of Medicine, Atlanta, United States*, ³*Institute on Neuroscience Summer Program, Emory School of Medicine, Atlanta, United States*

The degradation of axons and its terminals is a hazard of the normal aging process. Axonal degeneration, a characteristic event in trauma and in neurodegenerative diseases, has been evidenced to underlie deficits of motor and cognitive function. To address this problem, we developed a project to characterize photoactivatable probes that would allow for optogenetic control of cellular signaling and behavior using external illumination (photostimulation). Two protein domains, Cryptochrome (CRY2) and Light-oxygen-voltage-sensing (Lov) were identified for sensitivity to blue light photostimulation. Both were later subcloned and fused to Deleted in Colorectal Carcinoma (DCC) or Rac1, effector proteins that recruit specific cellular components involved in guided axon attraction. Initial exploration of signaling cascades in cytoskeletal mechanisms linked to axonal pathfinding was induced using a photostimulation chamber, to observe if spatiotemporal regulation was similar to the neurodevelopmental process. Subsequent, live-cell imaging of cells transfected with mcherry-LOV-Rac1 revealed light-dependent cytoskeletal changes within 15 min of blue light (488-nm) stimulation using standard temporal plot. Future work will investigate long-term photostimulation response of probes and activation reversibility. This work is expected to provide new insights into current methods of optogenetic control utilizing cytoskeletal activity to promote axonal regeneration.

Poster number: PT143 (SP)**Theme:** Novel treatments & translational neuroscience**Controlling Abnormal Network Dynamics with Optogenetics targeting excitatory cells****Authors:** Dr Boubker Zaaimi¹, Dr Anupam Hazra¹, Dr Yujiang Wang¹, Prof Stuart Baker¹, Dr Marcus Kaiser¹, Prof Andrew Trevelyan¹, Prof Mark Cunningham¹, Dr Fiona LeBeau¹, Prof Andrew Jackson¹¹*Institute of Neuroscience, Newcastle University, United Kingdom*

Introduction: We are investigating feedback control of oscillatory network dynamics by using local field potential (LFP) recordings to drive closed-loop optogenetic stimulation (CLOS). The aim is to develop reliable methods to modulate normal and abnormal activity patterns via active cancellation or enhancement of oscillations, for scientific and therapeutic purposes.

Methods: Here we report results from *in silico* computational modelling, *in vitro* brain slice experiments with EMX-ChR2 mice as well as *in vivo* demonstrations under terminal anesthesia in EMX-ChR2 mice as well as non-human primates that had previously been injected with AAV8-CAG-Chronos-GFP.

Analysis approach: In these experiments, the LFP was first band-passed and phase-shifted using a finite impulse response filter. The output of the filter was half-wave rectified and modulated continuously the intensity of excitatory optogenetic stimulation. We examined the LFP power spectrum under CLOS with different filter frequencies (5Hz, 10Hz, 20Hz and 40Hz) and phase-shifts (0, 45, ..., 315 deg). In addition, we investigated the effect of CLOS on the duration of seizure-like events elicited by 4-Aminopyridine.

Results and Conclusions: CLOS produced a phase-shift-dependent modulation of LFP power for filter frequencies between 5 to 20 Hz but not at 40 Hz, with some phase-shifts eliciting a sustained oscillation at the filter frequency. At other phase-shifts, power was reduced relative to control conditions with no stimulation. Following bath application of 4-AP *in vitro*, or intracortical injection *in vivo*, bursts of oscillatory seizure-like events were elicited. As before, CLOS was capable of modulating the LFP power associated with these events. Moreover, phase-shifts that increased/decreased oscillatory power could also increase/decrease the duration of seizure-like events relative to control conditions with no stimulation.

These results could be explained by our *in silico* simulations using a Wilson-Cowen model in which seizures resulted from a bistable limit cycle in phase space. Excitatory stimulation delivered to the excitatory population at the appropriate phase-shift could destabilise this limit cycle and increase the probability of the network returning to the stable region of phase space. We conclude that CLOS is an effective means of modulating oscillatory activity at a range of frequencies.

Poster number: PT144 (SP)

Theme: Novel treatments & translational neuroscience

Deep brain stimulation of the nucleus accumbens in severe restrictive anorexia nervosa: a case series

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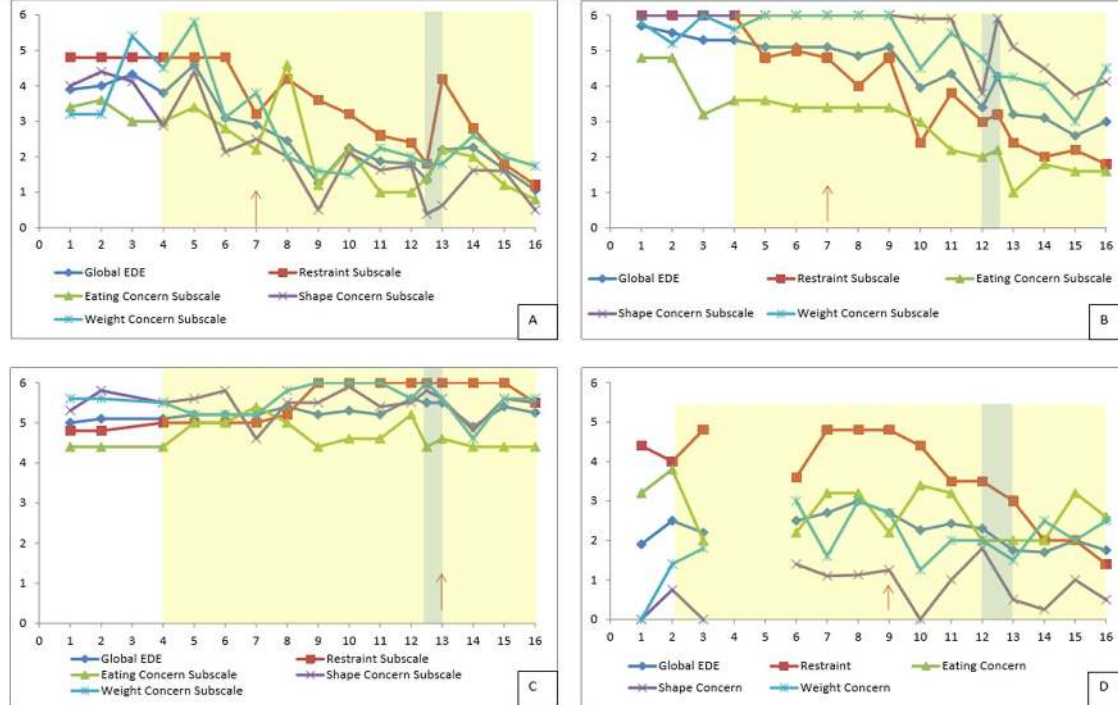
Introduction: Anorexia nervosa is one of the most debilitating psychiatric disorders, becoming severe and enduring (SE-AN) in a third of cases (Franko et al., 2013 *Am J Psychiatry* 170(8), 917-925). Few beneficial pharmacological Balestrieri et al., 2013 *Eur Eat Disord Rev* 21(5), 361-373) or psychological treatments exist (Watson and Bulik, 2012 *Psychol Med* 10, 1-24). DBS is a reversible, adjustable neurosurgical procedure, in which electrodes are inserted into specific neural targets, originally developed for movement disorders. Recently this has been trialled as a treatment for psychiatric disorders: OCD, depression and addiction. One trial applied DBS to the subcallosal cingulate in AN (50% responded) Lipsman et al., (2017). In this pilot study we targeted the nucleus accumbens (NAcc), a centre for hedonic reward processing which is dysregulated in AN (Park et al., 2014 *BRAT* 62, 47-59).

Methods: A case series of four patients with repeated measures pre- and post- DBS electrode implantation to the NAcc with a 12 month follow-up period and double-blind on-off phase (protocol: Park et al., 2018 *Front Psychiatry* 9, 24). We used quantitative and qualitative measures of eating disorder psychopathology (EDE, YBC-EDS, CIA) and comorbid psychiatric disorders (YBOCS, HAMD, HAMA) following DBS. Our primary objective was to explore whether DBS has beneficial symptomatic effects in a group of SE-AN patients. The secondary objective was to map neural mechanisms and symptomatic change resulting from DBS. We also aimed to explore ethical issues, capacity, consent and patients views pre- and post-DBS.

Approach for statistical analysis: As an exploratory pilot study, the small data set is not suitable for statistical analysis.

Results and conclusions: Patient 1 and 2 showed marked improvement in eating disorder psychopathology, mood and life quality. These scores worsened during the 2 week double-blind off period compared to on, suggesting that the DBS effect is genuine. Patients 3 and 4 did not show marked improvement, however they did not worsen, and both were making positive changes in their recovery. All four elected to continue with the DBS stimulator. Greater numbers are needed to further optimise DBS as a treatment for SE-AN.

Figure 2: Eating disorder examination, global EDE and subscales: panel A) Patient 1, B) Patient 2, C) Patient 3, D) Patient 4. Red arrow ↑ indicates dose optimised stimulator setting.



Poster number: PT145 (SP)

Theme: Novel treatments & translational neuroscience

Insulin related signaling – a novel mechanism underlying behavioural flexibility

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Introduction: Here we introduce the concept of insulin signalling as a key mechanism underlying the multimorbidity of mental and somatic illnesses. It is well known that aberrant insulin signalling causes an important health and socioeconomic burden through its role in diabetes, obesity, and metabolic syndrome. We posit that the impact of ‘insulinopathies’ is still largely underestimated, since insulin multimorbidity also extends to the brain, where altered insulin signalling is implicated in Alzheimer disease and – through our own pilot work - in mental illness characterized by compulsivity, especially obsessive compulsive disorder and autism. We therefore further posit that insulin multimorbidity evolves over the lifespan, necessitating a longitudinal approach. We conceptualize insulin-based mechanisms linking somatic illness and mental illnesses characterized by behavioural inflexibility.

Methods: Through an interdisciplinary battery of innovative approaches ranging from large genome wide association studies datasets in obsessive compulsive disorder to behavioural testing of behavioural inflexibility (spontaneous alternation, reversal learning and perseverative behaviour) in mice models of type I and type II diabetes (with associated gene expression data) and a novel transgenic constitutive knockout animal model targeting the top single

nucleotide polymorphism (*Kcnq1*) identified in the GWAS analyses, we have sought to clarify the mechanisms linking insulin-related illness, integrating across animal models and humans from molecule to cell, brain and behaviour. As a proof-of-concept, we also tested the type II diabetes (DM2) medication metformin for its ability to alter behavioural flexibility in a non-insulin related model, namely quinpirole-induced compulsive checking in the rat.

Approach for statistical analysis: Pathway analysis of GWAS data sets coupled to non-parametric statistics of behavioural datasets.

Results and conclusions: Our analysis suggests that a genetic network involving multiple insulin-related proteins underlies obsessive compulsive disorder. Conversely, Type II but not Type I diabetes animal models are associated with behavioural inflexibility and learning impairments. In addition, a novel mechanism (*Kcnq1*) controlling insulin release demonstrates marked decreases in behavioural flexibility further supporting a key role for insulin signalling. The type II diabetes drug metformin shows an ability to reduce compulsive checking with implications for the repurposing of insulin related drugs for use in psychiatry.

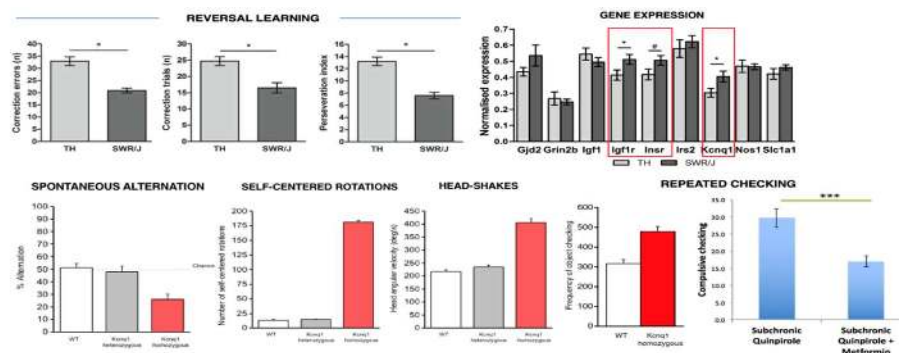


Figure 1. Top panels (grey). The DM2 model, the TALLYHO/*JngJ* (TH) mouse, demonstrates reversal learning impairments and an increased number of correction errors / trials and decreased perseveration index compared to SWR/J controls. In addition, TH mice show reduced spontaneous alternation. In those mice with reversal learning impairments, decreases in *Kcnq1* and *Igf1r* mRNA expression were noted in the cerebellum. Bottom panels (red). Abolition of *Kcnq1* expression in homozygous *Kcnq1* knockout mice (a model for RWS) produces a clear compulsivity-like phenotype. Reductions in spontaneous alternation, increased stereotypy / object checking behaviour are observed in *Kcnq1* knockout mice compared to wild-type controls. Bottom left panel (blue). In a non-DM2 rodent model, repeated checking induced by sub-chronic quinpirole was reduced by pre-treatment with the DM2 medication metformin.

Poster number: PT146 (PP)

Theme: Novel treatments & translational neuroscience

The modification of hyaluronic acid (HLA) with n-acetyl cysteine (NAC) to enable 3D printing of a robust nerve guidance conduit for peripheral nerve repair

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Introduction: Significant research is ongoing as scientists attempt to develop alternative strategies to enhance nerve regeneration following damage or disease. Many therapeutic options currently available are highly invasive and use materials commonly rejected by the body. Effective regeneration is not permitted without the use of a guidance conduit to bridge the defect in the event of a large gap in the peripheral nerve. Without a conduit, there is a high risk of fibrous scar tissue formation which inhibits migration of the regenerating axon. Hyaluronic acid (HLA) is a human endogenous polymer which has been shown to enhance nerve regeneration *in vivo* (1). Through the modification of HLA with N-acetyl cysteine (NAC), we hope to combine the nerve regenerating potential of HLA with the anti-oxidant and anti-inflammatory effects of NAC (2) and to produce a superior novel nerve guidance conduit.

Methods: HLA will be modified using the well-characterised Steglich esterification reaction to produce HLA-NAC. Once the nature of the product has been confirmed via ATR-FTIR and NMR, HLA-NAC will be photo-polymerised, to produce a biocompatible polymer of sufficient mechanical strength. Any bioactivity and/or cytotoxicity associated

SP = Standard poster

PP = Preregistration poster

with the above materials will be tested in neuronal and glial cell lines. Following successful testing, the material will be 3D printed as a conduit and undergo further testing in 3D neuronal co-cultures.

Approach for statistical analysis: All assay data will be analysed using one-way Anova with an appropriate post-hoc test to establish significant results. Additionally, all imaging will be performed double-blinded to prevent experimental bias.

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Poster number: PT147 (PP)

Theme: Novel treatments & translational neuroscience

Investigating the long-term efficacy of an “out of body illusion” in the management of chronic pain

Authors: Ms Tatiana Coli¹, Dr Jane Aspell¹

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Introduction: Recently Pamment and Aspell (2017) reported that it is possible to significantly reduce experienced pain intensity in patients with chronic pain by altering bodily self-consciousness via the “Full Body Illusion” (FBI). The main aim of the current study is to investigate how long-lasting the effects of such an illusion may be, as this could only be a useful paradigm to manage chronic pain if the effects outlast the immediate period around the experiment.

Methods: 20 participants with a range of chronic pain conditions will be randomly divided into two groups (experimental and control) who will be presented with different Virtual Reality (VR) paradigms. The experimental group will be exposed to the FBI: participants will view their own ‘virtual’ bodies in real time via a video camera placed behind them and a VR headset, and simultaneously feel gentle taps on their back from a long stick moved by the experimenter. Visual and tactile stimuli spatially and temporally match in the synchronous condition but do not match during the asynchronous condition. The control group will also wear a VR headset but will view a relaxing landscape scene for the same amount of time as the FBI. All participants will complete validated self-report questionnaire to measure the level of pain experienced before (baseline) and after the illusion. In order to analyse the long-term effects three follow-up measures of experienced pain will be submitted (online) by participants at 3, 24 and 48 hours after the experiment.

Approach for statistical analysis: A 2 x 4 mixed design analyses of variance (ANOVA) will be performed with a between-subjects variable of group (test, control) and a within-subject variable of experienced pain at four time-points (baseline, 3 hour, 24 hour, 48 hour post-experiment). We expect to see a greater reduction in pain (compared to baseline) at all time-points in the experimental group. Analysing the trend over time, we expect the level of pain to progressively increase due the short exposition of the illusion but we do not know over what time period the reduction in pain will be see following the FBI.

Poster number: PT148 (SP)

Theme: Other (e.g. teaching, history, outreach etc)

Exploration of the mouse anatomic gene expression atlas of Allen Institute: what can it tell us about glucocorticoid physiology, cytoskeletal and glutamate-GABA homeostasis?

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Introduction: The anatomic gene expression atlas (AGEA) of the adult mouse brain by the Allen Institute for Brain Science is an online, publicly accessible transcriptome-based atlas of the adult C57Bl/6J mouse brain, i.e. depicts the spatial registration of the expression intensity of 4376 mouse genes into 51533 cubic voxels of the mouse brain, based on the extensive *in situ* hybridization dataset of the Allen Brain Atlas (ABA) [1]. This work aims at (i) identifying new domains of potential neuroscientific interest for future translational research, and (ii) propose a simplified methodology for performing a targeted, prior knowledge-driven interrogation of the massive AGEA.

Methods: We've combined three techniques, the ABA-driven visualizations toolkit [2] and two different volumetric approaches of the ABA, to retrieve, normalize and visualize genomic data related to glucocorticoid physiology, cytoskeletal homeostasis and the balance between glutamate and γ -aminobutyric acid in the male adult mouse brain.

Analysis Approach: Volumetric analysis and data visualisation were performed using FSL software (www.fmrib.ox.ac.uk, University of Oxford) [3] and Microsoft Excel 2017. Statistical analyses were performed using IBM® SPSS Version 23.

Results and conclusions: Based on the expression profiles of various relevant genes, we were able to identify which parts of the mouse brain exhibit higher sensitivity to glucocorticoid effects, possess local steroidogenic capacity, show the strongest structural integrity, and highlight glutamatergic and GABAergic networks. Future work could expand this methodology by exploiting Allen Institute's databases from other species (non-human primates, human), introducing complex tools of data analysis, combined analysis of genomic data, connectivity data and transspecies analyses (i.e. merging different outputs from the Allen Institute's work) or the coregistration of brain maps containing different sources of data (genomic, structural, functional).

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Poster number: PT150 (SP)

Theme: Other (e.g. teaching, history, outreach etc)

Raising public awareness of epilepsy and the therapeutic effects of cannabidiol

Authors: Ms Caitlin Ray MacInnes¹, Ms Erin Hardee¹, Dr Colin Henderson², Dr Ros Langston²

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Introduction: Epilepsy is a neurological condition that has been documented for thousands of years, yet public understanding remains poor and discrimination is common. On November 1st, 2018, after months of high-profile campaigning, UK law changed to allow cannabidiol (CBD) to be prescribed to patients with severe treatment resistant epilepsy (TRE). With extensive media coverage awareness of this topic is high, however in a survey of the general public we found that there were clear gaps in their knowledge and understanding of the rationale for and legal status of CBD use in epilepsy.

Methods: A survey was generated and distributed amongst the general public to evaluate their knowledge and opinions on the topics of epilepsy and CBD. Analysis of the responses showed that those with qualifications in

science at university or upper high school level had a higher knowledge of epilepsy and CBD but a weaker opinion. Those with no qualifications in science had a lower knowledge but interestingly, stronger opinions. It was also shown that in a sample of 18-70-year olds that 26-30-year olds knew the most and had the strongest opinions on the topic. In order to address the gaps in public knowledge about seizure activity in the brain and how anti-epileptic drugs target this an interactive presentation was designed and targeted school aged children to introduce the concepts of neurotransmission, seizure activity and the actions of anti-epileptic drugs. The presentation included animation and a large-scale activity in which children acted out neurological signalling processes including memory and seizure activity. Fact cards with the key messages of the presentation were distributed to reinforce knowledge and encourage the guardians of the children to engage in discussion at home.

Analysis: Feedback from participants was very positive. 100% reported high levels of enjoyment and 85% indicated that they had learned from the activity. The activity has been used successfully in several engagement events and could help to change the way in which we educate people about neuroscience in general and epilepsy in particular.

Poster number: PT151 (PP)

Theme: Psychiatry and mental health

Profiling Peripheral Toll-Like Receptor Responses in Schizophrenia

Authors: Dr Laurena Holleran¹, Akhil Anthony¹, Catherine O'Donoghue¹, Dr Maria Dauvermann¹, Dr David Mothersill¹, Ruan Kane¹, Marcus Kenyon², Caroline Cullen³, Prof. Michael Gill³, Prof Aidan Corvin³, Dr Derek Morris¹, Prof John Kelly⁴, Dr Declan McKernan⁴, Prof Gary Donohoe¹

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Introduction: Schizophrenia is a chronic and severe mental health disorder with a lifetime prevalence of in Ireland of 1%. Recent studies suggest that the pathophysiology of schizophrenia is not exclusive to brain dysfunction, but includes central and peripheral inflammatory changes that impact illness onset. Furthermore, current evidence supports a genetic association between the onset of schizophrenia and the Major Histocompatibility Complex (MHC) region, a specific gene group that regulates proteins involved in the immune system. Here, we aim to establish the cytokine profile, key immune response regulators and inflammatory biomarkers, of patients with schizophrenia and healthy participants.

Methods: 80 patients with schizophrenia and 160 healthy participants were recruited through the iRELATE study. Blood samples taken from each participant were treated with toll like receptor (TLR) agonists, which play a key role in pathogen recognition and activation of innate immunity. Agonists consisted of heat killed listeria monocytogenes (HKLM)-TLR2 agonist, Polyinosinic-polycytidylic acid (Poly I:C)-TLR3 agonist, and lipopolysaccharide (LPS)-TLR4 agonist. Following stimulation, samples were incubated for 24 hours and centrifuged for 15 minutes for plasma isolation. Basal and TLR treated plasma levels of 3 inflammatory cytokines – interleukin 6 (IL-6), interleukin 8 (IL-8) and Tumour Necrosis Factor - alpha (TNF- α) were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) (supplied by Bio-Techne) for each participant.

Approach for statistical analysis: Plasma levels of IL-6, IL-8 and TNF- α will be compared between patients and control participants using either a one-way ANOVA or Kruskal–Wallis test. The exact statistical test applied will be determined based on the distribution profile of participant demographics and plasma cytokine levels. A correlation analysis will be used to examine the relationship between each cytokine, and tested to determine is this relationship is diagnostic dependent.

We hypothesise that patients with schizophrenia will have elevated cytokine plasma levels compared to healthy participants. This inflammatory profile indicates that an altered immune response is directly involved in the neurobiological processes associated with illness onset, and is a potential therapeutic target for the treatment of schizophrenia.

Poster number: PT152 (SP)

Theme: Psychiatry and mental health

Characterising the temporal map of hippocampal and cortical transcriptional dysregulation caused by isolation rearing in the wistar rat

Authors: Ms Amie O'Neill¹, Dr. Bartłomiej Lukasz¹, Dr. Judith ter Horst¹, Professor Keith J. Murphy¹

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Currently, development of novel therapeutics for schizophrenia and other neuropsychiatric disorders is hindered by the fact that the sequence of molecular, neurotransmission and synaptic-disruptions that underpin the emergence of such disorders remains to be established. As such, critical progress is only possible using animal models that replicate key features of the disease. We have used microarray approaches to provide a detailed characterisation of the temporal transcriptional dysregulation that accompanies the isolation-rearing rat model, an environmental model which recapitulates core aspects of brain dysregulation, behavioural upset and endophenotypes seen in human schizophrenics with high fidelity.

We have related the emergence of behavioural, neurochemical and synapse ultrastructure deficits to transcriptional dysregulation in both the medial prefrontal cortex and dentate gyrus of the hippocampus of Wistar rats reared in isolation. We have revealed a cascade of dysregulation of gene expression, which extends from the pre-symptomatic phase right through to the emergence of behavioural and cognitive deficits. We have found 1,162 genes to be dysregulated in the prefrontal cortex, and 494 genes dysregulated in the dentate gyrus following isolation-rearing. A temporal map of sequential dysregulation across ages in both brain regions has been established, gaining a unique insight into the potential pathology of the disease. The altered genes noted were from a wide range of functional domains including transcription regulation and splicing, epigenetic modulation and synaptic structure and function. Importantly, analysis of gene expression prior to the emergence of the sensorimotor deficits revealed a significant disruption in transcriptional control, notably of immediate-early and interferon-associated genes in both brain regions. The gene cluster of immediate-early-genes were profoundly suppressed from the first age measured and remained under-expressed throughout the isolation-period in both brain regions indicating possible early drivers of molecular dysregulation.

This study provides a molecular framework to understand the developmental emergence of transcriptional and behavioural characteristics that may in part define psychiatric illness. Further dissection of the transcriptional-drivers of gene expression alterations identified to be common to both brain regions may reveal key insight into the earliest cellular signalling pathways that drive neuronal circuitry dysregulation and subsequent emergence of neurocognitive and psychotic symptoms of schizophrenia.

Poster number: PT153 (SP)

Theme: Psychiatry and mental health

Using machine learning analysis to uncover the signature of psychotic experiences in young adolescents: a multi-modal analysis using structural/diffusion MRI, cognition and clinical data

Authors: Dr Joanne Kenney¹, Dr Laura Milena Rueda Delgado², Dr Erik O Hanlon¹, Lee Jollans², Mr Colm Healy¹, Ms Niamh Dooley¹, Mr Conor McCandless¹, Prof. Robert Whelan², Prof. Mary Cannon¹

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Background: Psychotic experiences (PEs) are commonly reported in early adolescence and are shown to be a risk factor for psychiatric conditions later in life. Machine learning approaches can be used to discriminate adolescents with PEs from controls using multi-modal data. Understanding the underlying signature of PEs can help uncover biomarkers of the experience and assist in developing early targeted therapies.

The aim of this research is to investigate if adolescents with PEs can be distinguished from controls based on their neuroanatomy, cognitive and clinical profiles.

Methods: A machine learning (penalised regression) approach was used to classify PEs versus controls at baseline (11-13years) with 1) a brain model consisting of structural and diffusion MRI data (n=77) and 2) a brain, cognitive and clinical model (BCC) (n=56). These baseline models were also used to classify PEs longitudinally at follow-up (19-20 years), (brain model (n=40), BCC model (n=27)).

Results: At baseline, the BCC model classified PEs with an AUC of 0.60, while the brain model alone had an AUC of 0.51. Clinical variables and white matter were the top discriminant features in the BCC model. In contrast, the brain model alone had a higher AUC (0.62) compared to the multi-modal model (0.30) when characterising PEs longitudinally. However, the BCC model had very low sample size (n=27).

Conclusions: Clinical features such as functioning, bullying, psychopathology and OCD items as well as white matter features appear to be the top discriminant features in the classification of adolescents with PEs compared to controls at age 11-13years. While we used the ICBM-DTI-81 atlas, an adult atlas, to isolate white matter tracts, future research will explore paediatric white matter atlases or impose a threshold on white matter measures from ICBM-DTI-81, to factor in the younger age of participants.

Poster number: PT154 (PP)

Theme: Psychiatry and mental health

The role of Omega-3 fatty acids on functional outcome in Psychosis

Authors: Mr Subash raj Susai¹, Dr David Mongan¹, Dr Melanie Focking¹, Dr David Cotter¹

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Introduction: Schizophrenia (SZ) is a neuropsychiatric disorder characterized by abnormal behavioural symptoms with cortical disruption. According to World health organization 21 million people worldwide have been affected with SZ in the year 2016. Even though the etio-pathology of the disease is not completely understood, observations at various timeline of the disease have led us to predict the clinical course. Functional disability has long been considered associated with various stages of schizophrenia. Various functional scales have given a wide range of information of the patient. In addition alteration in social, occupational and cognitive functional status has been observed in psychosis. Presence of various scales and subscales for functioning creates confusion for clinicians to decide the treatment options. Hence, this systematic review aims to provide an update regarding functioning status of ultra-high risk, first episode psychosis and schizophrenia patients in terms of social, occupational and cognitive status.

Methods: We will search PubMed, MEDLINE, Embase and PsycINFO from inception to current date using the basic search strategy. Searches and their results will be documented by date. Reference management software (EndNote X8) will be used to collate the reference lists from the databases and to remove duplicates. Remaining duplicates will be identified and removed manually. Remaining records will be examined to find studies meeting the eligibility criteria by two authors working independently. Differences will be resolved by discussion and involvement of a third author if necessary.

Approach for statistical analysis: Risk of bias in individual studies will be assessed using the RoB 2 (Revised Cochrane risk-of-bias tool for randomized trials). We will assess heterogeneity using the Q statistic. If studies are not excessively heterogeneous and number of studies allow, then we will perform meta-analyses. We will calculate effect size estimates using Hedges' g for individual functioning scores analysed in more than one study.

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Poster number: PT155 (SP)

Theme: Psychiatry and mental health

Stress in adolescence: brain connectivity changes related to negative life events

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Introduction: Stressful life experiences are thought to affect normal brain development. This study aimed to investigate the effect of stress on brain connectivity in an adolescent population using a graph theory approach. **Methods:** An adolescent subset (N=976, age= 14.45 ± 0.45) of the IMAGEN consortium (Schumann, Loth et al. 2010) was identified based on imaging quality control and completion of neuropsychological assessments, including the NEO Five-Factor Inventory, the Pubertal Developmental Scale (PDS) and the Life-Experience Questionnaire (LEQ). Twenty-one negative life events from the LEQ were used to separate the sample into two groups (Low stress/High stress). A subgroup (N=487) with extreme levels of stress in both groups was also considered. T1-w MRI scans were used to extract grey matter connectivity matrices using a published method (Tijms, Series et al. 2012). From these, four hundred ROIs were identified using a template (Schaefer, Kong et al. 2017) and graph theory measures were calculated.

Approach for statistical analysis: A MANCOVA was conducted on mean cluster coefficient, path length and small-worldness at three sparsity levels (5-10-15%) between the two groups, with age, gender, centre and PDS as control covariates. FDR-corrected two-sided t-tests on betweenness centrality and cluster coefficient were run per ROI at the local level. For the betweenness centrality, only ROIs at 2.5 SD > mean, identified as network hubs, were inspected. This was done for the entire population and the subgroup.

Results: The MANCOVA revealed no statistically significant differences between groups at any sparsity level. T-tests revealed decreased betweenness centrality in the left somato-motor network only at sparsity 5% (entire population: p=0.028; sub-group=0.000), and a decrease in cluster coefficient in the right somatomotor network of the subgroup at sparsity 10% and 15% (P_s=0.000).

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Poster number: PT156 (SP)**Theme:** Psychiatry and mental health**Association of zinc deficiency with gastro-intestinal abnormalities in an autism spectrum disorder mouse model**

Authors: Ms Ann Katrin Sauer¹, Ms Sigita Malijauskaite², Dr. Kieran McGourty^{2,3,4}, Dr. Andreas M. Grabrucker^{1,3,4}
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Genetic factors might be responsible or facilitate the occurrence of Autism spectrum disorders (ASD), a group of neurodevelopmental disorders affecting behaviour and communication but in addition to a combination of ASD-related genes, specific environmental factors may act as risk factors triggering the development of ASD.

A growing amount of research indicates that abnormalities in the gastrointestinal (GI) system during development might be a factor in ASD. Many patients with ASD have symptoms associated with GI disorders. We hypothesize that metal ion imbalances during pregnancy are linked to disturbances in the gastrointestinal (GI) tract and may be an important factor for the development of the ASD associated pathology. To investigate this, we performed in vivo studies using mouse models for zinc deficiency and in vitro studies using GI organoids. Using immunohistochemistry and protein biochemistry, we analysed overall gut morphology in zinc deficient animals, specific epithelial barrier proteins and metal transporters in the murine small intestine. Measuring gene expression of inflammatory marker genes, we analysed systemic as well as organ specific inflammatory status in zinc deficient animals compared to controls. Furthermore, we assessed gut microbial composition of zinc deficient animals using 16S microbiome profiling.

We demonstrated that maternal zinc deficiency leads to GI abnormalities in the offspring but also mediates inflammatory responses. We showed that maternal zinc deficiency causes alterations in the Microbiome of the offspring and alters specific inflammatory markers. The alterations were similar to reported differences in humans with ASD. Thus, we provided a link between several environmental factors in autism.

Poster number: PT157 (SP)**Theme:** Psychiatry and mental health**Changes in music-evoked emotion and ventral-striatum functional connectivity following psilocybin therapy for depression**

Authors: Ms Melissa Shukuroglou¹, Mr Leor Roseman^{1,2}, Dr Matthew Wall^{3,4}, Professor David Nutt¹, Dr Robin Carhart-Harris¹, Dr Mendel Kaelen¹

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Introduction: There has recently been renewed interest in the therapeutic potential of psychedelic drugs such as psilocybin¹. Music reliably evokes emotion², and the ability of psychedelics to enhance music-evoked emotion has been illustrated in the past, where the combination of psychedelics and music enhanced certain subjective experiences thought to be useful in the therapeutic context³. The present investigation sought to examine whether psilocybin therapy for treatment-resistant depression could elicit sustained changes in music-evoked emotion, and in ventral-striatum (VS) functional-connectivity (FC).

Methods: 19 patients with treatment-resistant depression received a low oral dose (10 mg) of psilocybin on the first session, and a high dose (25 mg) on another session, separated by one week. They underwent functional magnetic resonance imaging (fMRI) on two occasions, one week prior to the first session and one day following the second session. During each session, two scans were conducted; one without music, and one with music. Subjective ratings were completed after each scan, comprising of a visual analogue scale (VAS), and the 21-item Geneva Emotional Music Scale (GEMS). Given its role in musical reward, the ventral striatum (VS), specifically the nucleus accumbens (NAc), was chosen as region of interest (ROI)⁴, and changes in its functional-connectivity profile were assessed.

Statistical approach: A two-way repeated measures ANOVA was performed to test for differences between music- and no-music scans (a music-effect), before and after treatment (a treatment-effect) and an interaction-effect for in-scanner pleasure ratings. Paired two-tailed *t* tests were then performed to test for significant differences between conditions for the in-scanner ratings, as well as for the GEMS factors.

Results and conclusions: Results revealed a significant increase in music-evoked emotions following treatment with psilocybin. Moreover, decreased NAc FC with the default-mode network (DMN) was observed following psilocybin treatment during music listening. These results are consistent with current thinking on the role of psychedelics in enhancing the effects of music-evoked pleasure, and provide new insights into the functional brain changes underlying this. We suggest that NAc-DMN connectivity could reflect an inhibitory mechanism for the hedonic experience of music in depression, and that this mechanism is diminished following therapy with psilocybin.

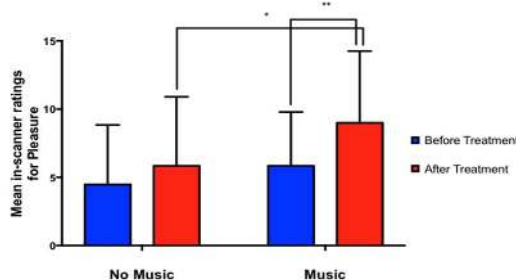


Figure 1. Bar plots of mean plus standard deviation for in-scanner ratings for pleasure during no-music scans (left) and music-scans (right), before treatment (blue) and after treatment (red). A two-way repeated-measures ANOVA analysis revealed a significant treatment effect ($F=5.74$, $df=18$, $p=0.028$), but no effect of music ($F=3.86$, $df=18$, $p=0.065$), and no interaction effect ($F=1.85$, $df=18$, $p=0.19$). Follow-up paired *t*-tests demonstrated a significant increase in ratings of pleasure between music-scans before treatment and music-scans after treatment (** $p=0.008$, $t=-2.963$, $df=18$), as well as increased ratings of pleasure between no-music- and music-scans post-treatment (* $p=0.019$, $t=-2.565$, $df=18$).

NAc functional connectivity changes (Music>Rest, After>Before)

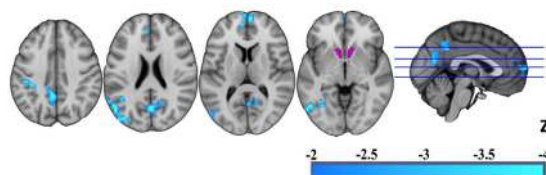


Figure 2. Seed-based functional connectivity (FC) analysis with the bilateral NAc seed (purple, for illustration purposes), showing significant decreased FC post-treatment (blue). Decreased NAc FC with the default mode network (DMN) is evident. Cluster-correction was applied to all images with a threshold of $p<0.05$, $Z>2.3$.

Poster number: PT158 (SP)

Theme: Psychiatry and mental health

Network based classification accurately discriminates connectivity disorder subtypes using single trial EEG

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Introduction: Disorders of cortical network connectivity are increasingly recognised as important contributing factors in the pathology underlying many psychiatric and neurological diseases. However, many of these conditions are still best described in terms of phenotypic and genetic subtypes, with the relationship of these categories to the actual underlying cortical network physiology remaining unclear. Rett Syndrome (RTT) is a neurodevelopmental disorder associated with an identified single-gene mutation producing abnormal synaptogenesis, which acts as a prototype of disorders of connectivity, facilitating exploration of the relationship between genetic abnormality, network level architecture and clinical phenotype.

Methods: We characterised the clinical and genetic subtypes of a large cohort (n = 42) of Rett Syndrome patients. We analysed the electrophysiological profiles of these patients using measures of spectral power derived from continuous resting-state EEG recordings. Statistical models of cortical network architecture were developed based on inter-electrode coherence measures in order to characterise electrical activity at the network level.

Approach for statistical analysis: Electrophysiological measures were compared between genetic and phenotypic groups. A group of subjects was followed up for twelve months in order to establish whether the electrophysiological patterns seen were stable over time.

Results and conclusions: We demonstrate the potential role for neural network architecture as an intermediate between genetic subtypes and clinical phenotypes in RTT and its variants. Analysis of these electrophysiological features reveals a role of occipito-temporal networks in RTT, further elucidating the underlying disease mechanisms. Furthermore, hemispheric distribution of power and network dysfunction are shown to correlate with epilepsy status and treatment responsiveness in these patients.

We further demonstrate that the network abnormalities are stable over time, suggesting a potential role for electrophysiological features as useful biomarkers in disorders of connectivity.

Functional network architecture appears to be a stable intermediary between genetic abnormalities of synaptic function and the resulting clinical phenotype. Electrophysiological analysis of network-level features therefore represents a potentially valuable method for the further investigation of RTT and other disorders of connectivity, and offers a non-invasive method for the objective assessment and classification of these conditions for determination of diagnosis and prognosis in a clinical setting.

Poster number: PT159 (SP)

Theme: Psychiatry and mental health

The therapeutic effect of a psychedelic experience: a prospective naturalistic study

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Introduction: Recent research has shown promise for the application of psychedelic compounds for treating clinical depression and anxiety. However, there is a great need for a better understanding of what factors might play a role for these therapeutic effects. The present study uses a naturalistic online approach to investigate whether 1) a self-initiated psychedelic experience leads to changes in clinical symptoms of depression and/or anxiety, and 2) any of the following factors have predictive value for their clinical effect; previous psychiatric history, drug pre-experience, therapeutic motive, drug dose, and intensity/nature of the acute psychedelic experience.

Method: 604 subjects who planned to undergo a psychedelic experience were enrolled in an online survey (www.psychedelicsurvey.com). Change in depressive and anxiety symptoms (assessed with QIDS and STAI-T, respectively) served as primary outcomes, measures of the acute experience (MEQ and CEQ) as mediators and dose, psychiatric history, therapeutic motive and drug pre-experience as predictors. Age, gender and education were included as confounders. All measures were self-reported and gathered online at four different time points.

Approaches for statistical analysis: Linear Mixed Models were applied using a step-up strategy for model building with *time* and either QIDS or STAI-T included as repeated effects and all covariates included as fixed effects. Each model also included an interaction term with time and the relevant predictor variable.

Results: Relative to baseline, marked mean reductions in QIDS scores were observed after 2 weeks (mean=-2.12±0.22, p<0.001) with sustained effects 4 weeks post-experience (mean=-0.07±0.19, p=0.71). Interaction analysis revealed that the following factors were associated with more pronounced decreases in depression (QIDS) scores; higher doses, presence of a history of self-reported diagnose of depression/anxiety, and report of a therapeutic motive. A post-hoc analysis of participants with moderate to severe depressive symptoms at baseline showed that MEQ was borderline significantly associated with reductions in QIDS ($\beta=0.059$, p=0.06) at 4-week follow-up. Marked and sustained improvements in anxiety (STAI-T) were also detected and changes were significantly associated with higher scores on CEQ and MEQ. This large-scale naturalistic study confirms previous antidepressant/anxiolytic findings from smaller lab-based trials, and identifies predictive factors for the clinical effects of a psychedelic experience.

Poster number: PT160 (SP)

Theme: Psychiatry and mental health

An exploration of the relationship between short-term habituation and locomotor activity in rodent models of psychosis and aberrant salience

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Introduction: Psychosis is a prominent feature of a number of neurological and psychiatric disorders such as Alzheimer's Disease, Bipolar disorder, and Schizophrenia. Aberrant salience to sensory stimuli appears to contribute significantly to the generation of psychotic symptoms such as delusions. The current study aims to evaluate a number of genetic and pharmacological rodent models of aberrant salience and deficits in short-term habituation to sensory stimuli.

Methods: Short-term habituation was assessed across a variety of behavioural tasks, including open-field, spatial novelty Y-maze, and novel context recognition. These assays were used to profile mouse models with short-term memory deficits relevant to habituation. Firstly, a hippocampal lesion mouse model was used to investigate the hippocampal contribution to habituation. Pharmacological models of psychosis were then assessed using acute

injection of either 0.2mg/kg MK-801 or 2.5mg/kg amphetamine. Finally, the role of a well-established risk gene in schizophrenia, *Gria1*, was examined using a genetic model. The *GluA1*^{-/-} mouse was profiled to investigate the contribution of AMPA receptor signalling to short-term habituation and attention.

Analysis Approach: All statistical analyses were performed in IBM SPSS Statistics 25. Statistical significance was defined as $\alpha = 0.05$. Where necessary, multiple post-hoc comparisons were corrected with the Sidak procedure, and the corrected *p*-value is reported.

Results and Conclusions: All models tested here displayed a pronounced hyperactive phenotype, consistent with that reported in the literature. *GluA1*^{-/-} have been shown previously to be impaired in tasks of short-term memory and habituation, and exhibit increased attention to recently-presented stimuli. The current study extends this finding and highlights the stimulus-specific nature of the hyperactive phenotype in these mice. Similar findings were observed in hippocampal lesion mice, with increased arousal only in a familiar context. Mk-801 administration induced a hyperactive phenotype that was not context-specific and also showed deficits in short-term memory, whereas amphetamine generated a hyperactive phenotype but did not impair performance on tasks of short-term memory or habituation. These contrasting forms of hyperactivity may be the result of different mechanisms and could reflect the heterogeneity in symptoms and aetiologies of psychosis.

Poster number: PT161 (SP)

Theme: Psychiatry and mental health

Dopamine D2 receptor TAQ1A genotype as a predictor of bold response to reward anticipation in substance dependence

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Introduction: The neuropathology of substance dependence is thought to involve dysregulation of multiple brain mechanisms including reward processing. This complexity poses a challenge when understanding risks of drug addiction. Current evidence suggests genetic risk factors may play a role in addiction vulnerability, but findings are mixed. In a multi-centre neuroimaging study (ICCAM; Paterson et al., 2015, J. Psychopharmacol), we sought to determine whether the presence of a dopamine receptor D2 (DRD2/Taq1A) polymorphism (rs1800497) contributes to differences in monetary reward processing in substance dependence. We hypothesised that the A1 allele of the Taq1A polymorphism would be associated with reduced BOLD response to reward and would be present in substance dependent relative to control cohorts.

Methods: Healthy controls (n=64) and abstinent substance dependent individuals (alcohol, cocaine and/or opiate, n=78) were recruited. Following informed consent (REC number 11/H0707/9), DNA was extracted from plasma and genotyped for Taq1A. The A1 variants were defined as 'risk' genotypes by *a priori* associations with neurobiological dysfunction and lower dopaminergic function. In a fMRI paradigm, the win>neutral anticipation contrast was used to capture the neutral correlates of reward processing within the Monetary Incentive Delay task, using a functional region-of-interest (striatal fROI) and whole brain approach.

Analysis Approach: A 2x2 factorial ANOVA compared effect of group (control vs dependent), genotype (A1A1 and A1A2 vs A2A2) and group*genotype interaction using FSL FEAT ($Z > 2.3$, FWE corrected, $P < 0.05$).

Results and conclusions: In whole brain analyses, a significant group*genotype interaction was observed such that BOLD response to reward anticipation was reduced in superior frontal gyrus (SFG) of substance dependent

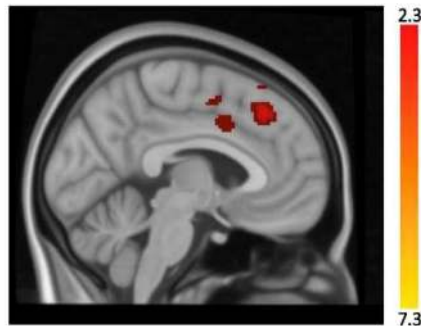


Figure 1. Threshold activation image revealing the significant clusterwise group*genotype interaction within the SFG (co-ordinates -4,32,44; $Z > 2.3$; $P < 0.05$ corrected) during the win>neutral anticipation contrast of the MID task

individuals with the A1 variant relative to controls (Figure 1). No effect was observed in the striatal fROI, and the proportion of A1 variants did not differ between groups. Previous studies have shown SFG to have a role in modulating impulsive behaviour, which could be associated with deficits in reward anticipation in addicts that possess the A1 variants. Future explorations are needed to validate mechanisms behind impulsivity and reward processing. Our results complement previous research suggesting lower dopaminergic activity in addicts, via possession of the A1 DRD2 variants, which could contribute to neurobiology driving addiction.

Poster number: PT162 (SP)

Theme: Psychiatry and mental health

Induced Anxiety Makes Time Pass Quicker

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Introduction: People often say that during unpleasant events, e.g. traumatic incidents such as car accidents, time slows down (i.e. time is overestimated). However aversive events can elicit at least two dissociable subtypes of reactions: fear (transient and relating to an imminent event) and anxiety (diffuse and relating to an unpredictable event). We hypothesised that anxiety might have an opposite effect on time perception compared to fear.

Methods: To test this we combined a robust anxiety manipulation (threat-of-shock) with a widely used timing task in which participants judged whether the duration of a stimulus was long or short.

Approach for statistical analysis: We used frequentist statistics to analyse our data considering the proportion of occasions participants responded with “long” under our anxiety manipulation and baseline.

Results and conclusions: In line with our hypothesis, across three experiments (with varying stimulus timings and shock levels), participants significantly underestimated time under induced anxiety, as indicated by a rightward shift of the psychophysical function (meta-analytic effect size: $d = 0.68$, 95% confidence interval: 0.42-0.94).

Our results suggest that experimentally inducing anxiety leads to underestimating the duration of temporal intervals, which might help explain different subjective experiences of disorders related to fear (e.g. specific phobias) and anxiety (e.g. generalised anxiety disorder).

Poster number: PT163 (SP)

Theme: Psychiatry and mental health

Emotional lability in focal hippocampal damage

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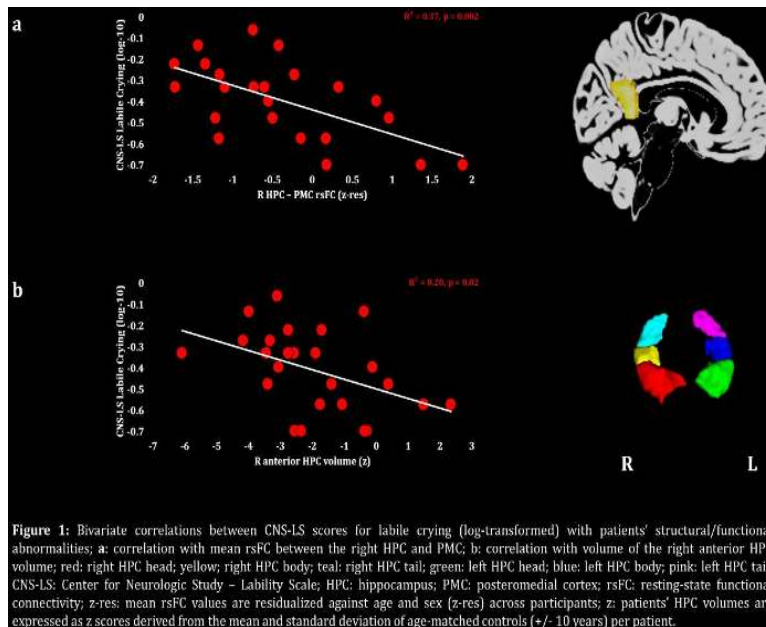
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Introduction: Basic research on animal models has established that the primate anterior hippocampus (ventral hippocampus in rodents) is embedded within networks regulating emotion and affect. Nevertheless, very little is known about emotional dysregulation in patients with hippocampal damage. We thus aimed to assess the negative emotional sequelae in focal hippocampal atrophy following autoimmune limbic encephalitis, a neurological disease typically associated with hippocampal damage and residual cognitive and emotional impairment. We focused on emotional lability and hypothesized that it would be associated with abnormalities in emotional networks involving the anterior HPC, the broader HPC-diencephalic-cingulate networks, the AMG, and cortico-ponto-cerebellar circuits.

Methods: We analysed acute neuroradiological reports, clinical notes, post-acute neuropsychological scores, along with structural MRI and resting-state fMRI datasets in relation to emotional lability in a large cohort of patients (n = 38) that had been treated for limbic encephalitis.

Approach for statistical analysis: The Holm-Bonferroni sequential method of correction for multiple testing was employed for comparisons between controls and patients in neuropsychological test scores, as well as for correlations between patients' scores and the mean values of clusters reflecting structural/functional abnormalities. For voxel-based whole-brain analyses (structural MRI and resting-state fMRI), FWE-correction ($p < 0.05$) was applied for cluster size or at voxel peak-level ($p < 0.001$ unc.).

Results and Conclusions: Emotional lability was present in 50% of the patients, yet selectively in the form of tearfulness. It was not associated with depression, impulsiveness, memory impairment, or executive dysfunction, and was unrelated to acute or post-acute amygdalar abnormalities. It correlated, however, with changes in specific emotional brain networks: volume reduction in the right anterior hippocampus and the cerebellum, abnormal hippocampal resting-state functional connectivity with the posteromedial cortex, and abnormal hemodynamic activity in the left posterior inferior temporal cortex and the ventral pons (fig 1). Pathological tearfulness is common in autoimmune limbic encephalitis, is not a manifestation of other neuropsychiatric features, and is underpinned by abnormalities in emotional networks beyond the acute hippocampal focus. Autoimmune limbic encephalitis provides novel insights into the nature and neural basis of emotional control and its dysfunction in disease.



Poster number: PT164 (SP)

Theme: Psychiatry and mental health

Electrical stimulation rescues the vulnerability to depression-induced midbrain dopaminergic neurodegeneration in rats

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Introduction: Deep brain stimulation is a promising therapy for patients with treatment-resistant depression. Although disruption of dopaminergic neurotransmission has been found in depression, it is unclear whether electrical stimulation reduces depression-like symptoms through a dopaminergic mechanism. In this study, we tested the hypothesis that high-frequency stimulation (HFS) induced neuroprotection on midbrain dopaminergic system using the stress resilience and vulnerability to depression rat model.

Methods: The characterization of animals on resilience and vulnerability to depression were based on the sucrose consumption levels following a 3-week chronic unpredictable stress (CUS) procedure. CUS-treated rats received HFS in the lateral habenula (LHb), ventromedial prefrontal cortex (vmPFC), nucleus accumbens, and they were subsequently tested for behavioural changes in levels of anxiety, anhedonia, and forced-swim immobility. The

morphological changes of midbrain dopaminergic neurons were evaluated by immunohistochemical staining methods and the level of stress hormone was measured using radioimmunoassay approach.

Analysis Approach: The results for behavioural and immunocytochemical studies were analyzed by either one-way or two-way ANOVA (with repeated-measures) or independent sample t-test, and Bonferroni post-hoc tests were used for multiple comparisons, as appropriate. All p -values < 0.05 was considered as significant.

Results and Conclusion: Our results demonstrated that 51% of CUS-exposed animals exhibiting significant reduction on sucrose consumption, thus, separating the resilience and vulnerability to CUS-induced depression groups. Interestingly, vmPFC HFS, but not LHb and nucleus accumbens HFS, significantly reduced the anxiety response, increased hedonia and food intake as compared to sham in the vulnerable group. We also found that HFS of the vmPFC and LHb reduced the forced-swim immobility in both the resilience and vulnerability to CUS-induced depression model. Importantly, our results demonstrated that vmPFC HFS rescued the stress-induced dopaminergic neurodegeneration in the ventral tegmental area and dorsal raphe nucleus. Overall, these findings suggest that the antidepressant mechanisms of vmPFC HFS were possibly mediated by neuroprotection of the midbrain dopaminergic system in vulnerability to CUS-induced depression model.

Poster number: PT165 (PP)

Theme: Sensory and motor systems

Saccade adaptation and autism spectrum disorder

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Introduction: Saccade adaptation is an oculomotor learning paradigm that introduces a visual error at the end of a saccadic eye movement. If the error is consistent, changes to the motor command are made to reduce it. The midline cerebellum has been demonstrated to be necessary for this adaptive process. However, in a subgroup of individuals with Autism, the structure and/or function of the midline cerebellum may be disordered. In such cases we hypothesize deficits in saccade adaptation which could be useful in identifying a sub-phenotype of ASD.

Methods: Individuals between the ages of 7 and 45 served as participants in this experiment. A portion had been diagnosed with Autism Spectrum Disorder (ASD) and others were typically developing (TD). Participants performed a saccadic adaptation task; Control trials started with the presentation of a fixation cross (T0) at the center of the screen that participants were required to fixate within $\pm 1.25^\circ$ for between 600 and 1200 ms. Then, T0 turned off and a new target (T1) was presented 20° to either the left or right of T0. Participants were instructed to look at T1. Initiation of the saccade was detected and T1 was turned off before the saccade was over. After 68 control trials, adaptation trials started. They were similar to control trials, but after the initial saccade ended a new target T2 was illuminated 5° closer to T0.

Approach for statistical analysis: Ratios of adapters to non-adapters for both groups were then calculated and a χ^2 -test was used to determine whether these ratios differed. In addition, the mean amplitude of the first 10 adaptation trials was compared to the mean amplitude of the last 10 using a t-test (single tailed, $p = 0.05$). All analyses and statistical tests were accomplished using Matlab (MathWorks, Natick, MA).

Results and conclusions: Our hypothesis is that proper cerebellar function is required to perform a saccadic adaptation task. However, a subgroup of individuals with Autism may have a disordered cerebellum. The data presented clearly show a difference in the ability of individuals with Autism to adapt to a persistent visual error.

Poster number: PT166 (SP)

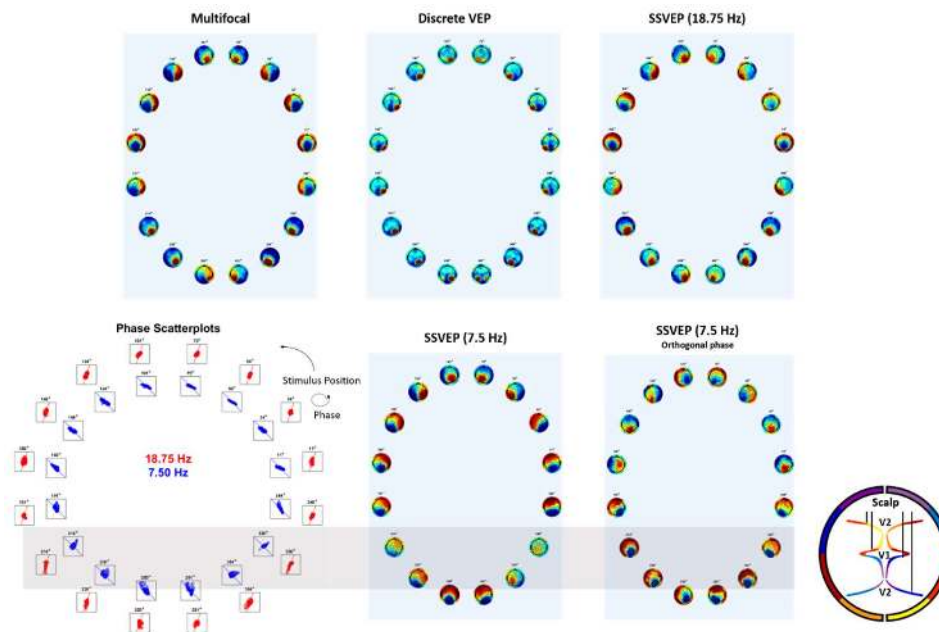
Theme: Sensory and motor systems

The contribution of V1 and V2 to early visual EEG responses: insights from cortical geometry and SSVEP phase shifts

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Crucial to the understanding of human cognition using EEG is to understand the sources of observed scalp signals. While it is well established that V1 contributes strongly to the C1 component (approximately 50-90 ms post-stimulus) of the visual evoked EEG potential (VEP), the contribution of V2 is a matter of ongoing debate. Here, we show early visual EEG responses to 3 stimulation protocols in a task-free context. Fifty subjects underwent a multifocal pattern-pulse stimulation protocol, which yielded topography shifts as a function of visual field (VF) location that can be explained entirely by a V1 source throughout the time course of the response. Using this protocol as a template for V1 activity, we compared evoked responses in a further 10 subjects who underwent this same protocol along with a standard discrete VEP protocol and a slow (7.5 Hz) and fast (18.75 Hz) steady-state visual evoked potential (SSVEP) protocol. Comparison of topographies across stimulation protocol suggested V1 sources across the board except for the lower VF in the 7.5 Hz SSVEP. Furthermore, while SSVEP phase was generally consistent across the VF, an orthogonal phase shift in the lower VF near the horizontal meridian was observed for the 7.5 Hz SSVEP. Simulations of the combination of two sinusoids, with V2 lagging V1, demonstrate that such a phase shift occurs when oscillations have equal magnitude and opposite polarities (mirroring the anatomical opposition of V1 and V2 near the horizontal meridian). This suggests that relative V2 contribution in the 7.5 Hz flicker may be stronger for the lower field than the upper field, consistent with its anatomical adjacency to the scalp at this VF location. Further simulations demonstrate that phase shift as a function of the relative magnitude of the oscillations undergoes a step change near magnitude equality for 7.5 Hz oscillations while the change is more gradual for 18.75 Hz. This may partly explain why the orthogonal phase shift was observed for the 7.5 Hz SSVEP but not the 18.75 Hz SSVEP. A second and not incompatible possibility is that there is greater V1-V2 dominance in faster than in slower flicker conditions.



Poster number: PT167 (SP)

Theme: Sensory and motor systems

Proposing a neurocognitive architecture by concurrently modelling behavioural and EEG data in audiovisual signal detection tasks

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Proposing a neurocognitive architecture by concurrently modelling behavioural and EEG data in audiovisual signal detection tasks

Introduction: The perceptual decision making framework describes how we translate noisy perceptual information to appropriate actions. However, it remains unclear how improved behavioural performance due to the presence of information in multiple sensory modalities can be explained within this framework. Here we used behavioural modelling based on the principle of drift diffusion, combined with electroencephalographic (EEG) decision signal analysis, to establish the neurocognitive architecture underlying audiovisual signal detection.

Methods: We recorded EEG while participants viewed a stream of noisy auditory and visual events, which could occur separately (A and V), or as co-occurring multisensory events (AV). Participants performed two detection tasks on these stimuli, in separate blocks. In task 1 participants reported any event, and in task 2 participants reported only bimodal AV events.

Approach for statistical analysis: We used t-tests to first test our prediction that responses to AV events would be faster than responses to either A or V events when participants performed task 1, but slower when participants performed task 2. In order to adjudicate between alternative proposed neurocognitive architectures, we analysed EEG components that reflect the accumulation of sensory evidence and motor preparation, respectively. We used standard parametric tests (e.g. T-tests) to evaluate differences and Bayesian tests in cases where an absence of differences was expected. The G^2 statistic was used to quantify the goodness of fit of our models, and alternative models were compared using the Bayes Information Criterion (BIC).

Results and conclusions: A neurocognitive architecture consisting of parallel auditory and visual information accumulation (with normalisation), which formed convergent inputs to a motor planning stage at which the ultimate action threshold was set, provided a good account of performance and neural effects of task 1.

EEG and behavioural data from task 2 could be explained by an architecture consisting of parallel auditory and visual information accumulation, but involving serial decisions that included thresholding at the accumulation stage.

Our findings shed new light on the sensorimotor architecture serving multisensory decisions, and demonstrate the explanatory power in combining neural and behavioural data in converging on a model accurately describing that architecture.

Poster number: PT168 (SP)

Theme: Sensory and motor systems

Investigation of the effects of pre-operative administration of FAAH inhibitors in a rat model of post-operative pain following inguinal hernia repair surgery

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Introduction: Hernia repair is a common surgical procedure that is associated with acute post-operative pain (POP) in approximately 40% of patients^[1]. Endocannabinoids have analgesic effects at peripheral, spinal and supraspinal levels^[2].

The aim of this study was to investigate the effects of pre-surgical administration of URB937, a peripherally restricted inhibitor of fatty acid amide hydrolase (FAAH), the enzyme that catabolises the endocannabinoid anandamide and related *N*-acylethanoamines, and URB597, a centrally active FAAH inhibitor, on POP-related behaviour in a rat model of inguinal mesh-based hernia repair surgery (hernioplasty).

Methods: Forty-two adult male Lister-Hooded rats were used (n=7 per group) and home-cage locomotor activity, open-field activity and hindpaw and inguinal area mechanical hypersensitivity (von Frey testing) were assessed 24hrs pre-surgery and 4hrs post-surgery. Rats received a subcutaneous injection of either vehicle, URB937 (1mg/kg) or URB597 (1mg/kg) immediately pre-surgery and underwent either a sham procedure or a hernioplasty under isoflurane anaesthesia. Tissue samples were analysed using HPLC-Tandem-Mass-Spectrometry.

Analysis Approach: Data were analysed by repeated measures or two-way ANOVA followed by Tukey post-hoc tests ($p < 0.05$ was considered significant). Non-parametric data were analysed by Kruskal-Wallis followed by Mann-Whitney tests.

Results and Conclusions: Surgery reduced home-cage locomotor activity and induced mechanical allodynia in the ipsilateral inguinal area and ipsilateral hindpaw. Both drugs partially attenuated mechanical allodynia in the ipsilateral inguinal area. URB597 attenuated allodynia in the ipsilateral hindpaw. Neither drug affected locomotor activity. URB597 elevated FAAH substrates in the PAG, neither drug had an effect in inguinal tissue. These results suggest that pre-surgical administration of peripherally restricted or centrally active FAAH inhibitors can attenuate POP-related behaviour in this model and indicate development of mechanical allodynia at a secondary site suggestive of a 'pain spreading' phenomenon. This phenomenon may be regulated by central FAAH substrates while allodynia at the surgery site may be regulated by both central and peripheral FAAH substrates.

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Poster number: PT169 (PP)

Theme: Sensory and motor systems

Neuronal mechanisms for colour vision in a bird retina

Authors: Mr Marvin Seifert¹, Mr Daniel Osorio¹, Mr Tom Baden^{1,2}

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Introduction: Vertebrate colour vision evolved >500 million years ago (Lamb et al., 2007) and since then different vertebrate groups have strongly shaped its underlying mechanisms to suit diverse ecological needs (Baden and Osorio, 2018; Osorio and Vorobyev, 2008). However, most knowledge on the retinal basis of colour vision stems from work in mammals, which underwent a nocturnalisation period during the age of the dinosaurs that greatly reduced their spectral photoreceptor complement. In contrast, we know very little about the retinal basis of colour vision in most other vertebrates. Here, we study the retinal mechanisms for colour vision in chicks.

Behavioural and morphological studies suggest that most birds have a highly sophisticated colour vision system built around the signals of 5 spectrally distinct cone-photoreceptor types (Ham and Osorio, 2007; Hart, 2001; Osorio et al., 1999; Wilby and Roberts, 2017). Using large-scale population recordings of chick retinal ganglion cells during visual stimulation we will test if the retina indeed supports tetrachromatic colour vision (Osorio and Vorobyev, 2008), and if the fundamental neuronal mechanisms underlying their tetrachromacy resemble those found in other tetrachromatic vertebrates such as teleost fish and reptiles (Baden and Osorio, 2018).

Methods: We will use a multielectrode array (BioCamX platform, 3D Brain, Switzerland, (Hilgen et al., 2017a, 2017b)) with high temporal and spatial resolution to record electrical signals from retinal ganglion cells in chicks. A set of LEDs at different wavelengths coupled to digital mirror device (DMD) projectors will be used to create temporal and spatial chromatic stimuli. Following a functional physiological characterisation of the chick RGC complement, we will thereafter probe specific circuits in more detail using 2-photon imaging and/or patch clamp recordings.

Approach for statistical analysis: Multielectrode array recordings produce large data volumes. We will use state of the art and freely available spike sorting algorithms to identify activity in individual neurons on a large scale (Hilgen et al., 2017b; Jouty et al., 2018). To identify specific types of retinal ganglion cells in an objective and quantitative way we will use an unsupervised clustering procedure (Baden et al., 2016).

Poster number: PT170 (PP)

Theme: Sensory and motor systems

Studying the relationship between motor learning and mri/tms measures in stroke survivors

SP = Standard poster

PP = Preregistration poster

Authors: Ms Emily L Hinson¹, Dr Melanie K Fleming¹, Professor Charlotte J Stagg¹

¹Wellcome Centre for Integrative Neuroimaging, University Of Oxford, Oxford, United Kingdom

Introduction: Motor rehabilitation for stroke survivors is frequently informed by research of motor learning in healthy controls, however it is not fully established if stroke survivors learn motor skills in the same way, therefore potentially questioning the validity of basing rehabilitation techniques on these models. This project aims to assess motor learning in chronic stroke survivors and age-matched controls on the same task. We will also collect MRI measures of brain structure and function, TMS measures of cortical excitability and neurotransmitter systems and measures of functional impairment. These measures will allow assessment of possible predictive relationships for behavioural performance in both cohorts.

Methods: 20 chronic stroke survivors (minimum 6-months post-stroke) and 20 age-matched controls will be recruited (Figure A).

Behavioural Motor Control Task:

Based on a Force Tracker Task design^{1,2}, surface EMG of the affected forearm will be used to control movement of a cursor to track a target on a computer screen. Participants control the cursor by modulating EMG signal (e.g. by contraction of the recorded muscle). (Figure B)

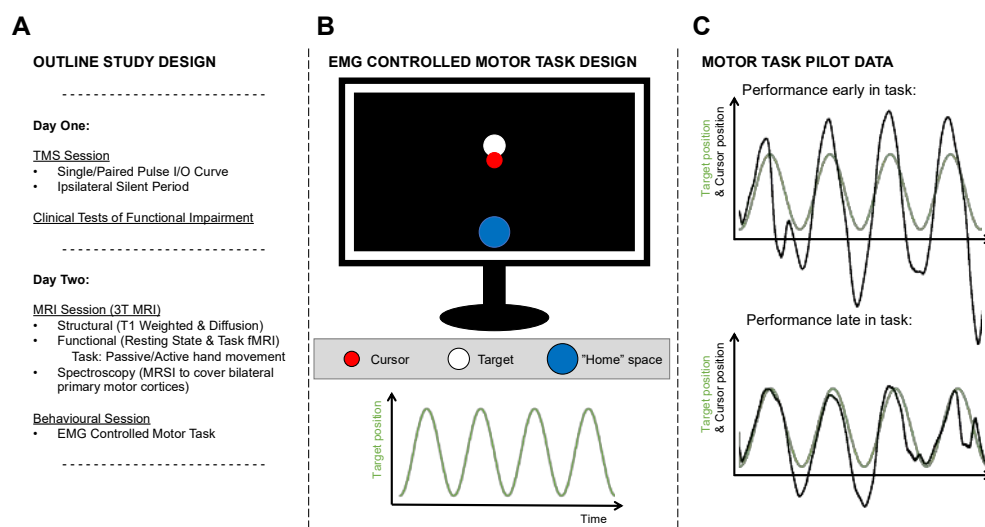


Figure:

A: Outline study design

B: EMG Controlled Motor Task: Top: Design of task on computer screen, Bottom: example target trace.

C: Motor task Pilot Data: Demonstration of improvement in performance over time as participants improve motor control with training.

Additional Measures:

In a TMS Session, bilateral single and paired pulse TMS, and ipsilateral cortical silent periods will be recorded. Structural, functional and spectroscopic MRI scanning will be performed. (Figure A).

Analysis: The primary outcome for this study will be improvement on the motor control task, measured by decrease in error (Figure C). We will additionally explore relationships between individual behavioural performance with measures from MRI and TMS sessions. We predict that we will be able to replicate previously observed relationships between behavioural performance and neurotransmitter systems in healthy controls^{3,4} and we will look to investigate if these relationships hold for stroke survivors.

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Poster number: PT171 (SP)

Theme: Sensory and motor systems

Transient receptor potential ankyrin 1 (Trpa1) is involved in nociception and spontaneous pain-like behavior in a mouse model of metastatic cancer pain

Authors: Dr Caren Antoniazzi¹, Dr Romina Nassini², Dr Francesco De Logu², Dr Gabriela Trevisan¹

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Introduction: Pain is one of the most feared consequence among cancer patients, and unrelieved cancer pain remains an important topic to be considered^{1,2}. It is relevant to research new targets involved in the cancer pain mechanism to indicate better therapies. The transient receptor potential ankyrin 1 (TRPA1) is an ion channel activated by oxidizing substances produced after tissue injury and was described to be involved in neuropathic pain^{3,4,5}. We evaluated the TRPA1 role in nociception observed in a mouse model of metastatic cancer pain, using pharmacological and genetic tools.

Methods: C57BL/6, wild-type (*Trpa1^{+/+}*) or TRPA1 homozygous deletion (*Trpa1^{-/-}*) adult male mice were used. Melanoma cells (2 x 10⁵ cells, 20 µL) or vehicle (PBS alone) were injected (s.c.) into the mice's right hind paw plantar region. Nociception measures (mechanical and cold allodynia), spontaneous pain-related behavior, and paw edema were assessed 14 days after tumor cells inoculation. Spinal cord and right hind paw skin samples were taken to determine hydrogen peroxide levels and NADPH oxidase activity. The study was approved by the Ethics Committee on the Use and Care of Laboratory Animals of the Federal University of Santa Maria (#7658240417) and University of Florence (#579/2017-PR).

Approach for Statistical analysis: Values were expressed as mean±S.E.M and analyzed by Student's t-test, One- or Two-way ANOVA followed by Bonferroni's post hoc test. The P<0.05 values denote significant difference among groups.

Results and conclusions: Mechanical and cold allodynia, and spontaneous pain were observed in this model. TRPA1 antagonists (HC-030031 and A-967079) and the antioxidant (α-lipoic acid) administration caused an antinociceptive effect in these parameters. *Trpa1^{-/-}* mice showed decreased mechanical and cold hyperalgesia, reduced spontaneous pain-related behavior when compared to *Trpa1^{+/+}* mice, and the antisense oligonucleotide injection produced similar anti-allodynic results confirming the TRPA1 involvement in the cancer-related pain. The presence of paw edema was noted, and increased levels of hydrogen peroxide and NADPH oxidase activity were detected in the sciatic nerve and hind paw skin. Considering our findings, it seems that TRPA1 activation is relevant to nociception in this mouse model of metastatic cancer pain and TRPA1 antagonists might be beneficial in cancer pain management.

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Poster number: PT172 (SP)

Theme: Sensory and motor systems

The influence of a full-body-illusion on body distance perception

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Introduction: The brain integrates multisensory input in coherent representations of the body. The so-called “somatoperception” includes an online postural schema, updated with movements, a body model of size and shape, and a superficial schema, based on somatosensory processes (Longo et al., 2010).

Visual illusions and virtual reality have been employed to alter body perception (Van der Hoort et al., 2011). We induced a Full Body Illusion through a set of Head-Mounted Displays to modify body metric perception.

Methods: We induced the Full Body illusion in 24 participants by three 360° videos, showing a pair of artificial legs of three possible length (Short/Standard/Long), in two possible orientations (Anatomical/Non-anatomical), stimulated by a visible stick (Figure1); at the same time participants received an equivalent tactile stimulation. We evaluated any subjective embodiment with a questionnaire. After each video, participants underwent a Body Distance Task (BDT): a 3x3 grid of points was stuck on their leg; on each trial, we stimulated two locations in sequence, and participants estimated the distance between the stimuli in two subsequent blocks. Subjects underwent two sessions, in which they viewed legs of standard size vs. either short or long ones, in both orientations.

Approach for statistical analysis: We considered the ipsatized average score to embodiment statements and applied Multidimensional Scaling to compute a dissimilarity index (Procrustes Distance) between the objective and the perceived distance grids obtained in the BDT.

We analysed data with repeated measure ANOVAs.

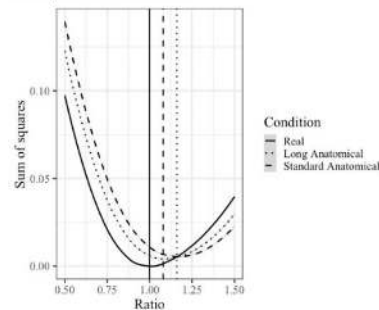
Results and conclusions: We found overall greater embodiment values in the anatomical condition, compared to the non-anatomical one [$F(1,23)= 10.35$, $p \leq .05$, $\eta^2= .31$], and with the standard and long size compared to the short one [$F(3,69)= 15.26$, $p \leq .001$, $\eta^2= .40$].

The Procrustes Distances analysis revealed a three-way interaction between Size, Orientation, and Block [$F(3,69)=2.81$, $p \leq .05$, $\eta^2 = .11$]. In the first block we found a similar distortion in all the conditions except for the long one, that discriminated between anatomical and non-anatomical orientation. The long legs presented in an anatomical orientation showed greater stretch in the proximo-distal axis than the standard one (Graph1). We suggest that the embodiment of the long legs induced participants to perceive their limbs as longer.

Figure 1: 360° videos used to induce the Full Body Illusion (Panel A: Short legs; Panel B: Standard legs; Panel C: Long legs).



Graph 1: mean Procrustes Distance in simulated grids stretched by different amounts. A ratio of 1 indicates a square grid; values greater than 1 indicate stretches in the proximo-distal axis, while values less than 1 indicate stretches in the medio-lateral axis. The vertical lines represent the stretch that minimizes the Procrustes Distance for subjective maps (dotted: the standard legs; dashed: long legs) and actual maps (solid). The long legs presented in an anatomical orientation showed values bigger than 1, indicating a greater stretch in the proximo-distal axis.



Poster number: PT173 (SP)

Theme: Sensory and motor systems

Impaired motor sequence learning after administration of a clinically relevant single dose of baclofen

Authors: Dr Ioana Grigoras¹, Ms. Ainslie Johnstone¹, Prof. Charlotte Stagg¹

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Introduction: Gaining a new motor skill is essential for many activities from walking and writing to mastering a musical instrument. Studies have shown that learning a motor skill is associated with a decrease in the levels of γ -aminobutyric acid (GABA) in the primary motor cortex (M1, Stagg et al., 2011), making modulation of GABAergic signalling a potential approach to influence motor learning. We therefore hypothesised that increasing GABA-mediated inhibition through administration of baclofen, a GABAB receptor agonist, would cause impairments in learning new motor skills.

Methods: We conducted a within-subject, double-blind, placebo-controlled study to evaluate the effect of a single, clinically-relevant, oral dose of 10mg of baclofen on motor learning in young healthy volunteers. Participants ($n=14$) participated in two testing days at least a week apart, when they received either baclofen or placebo. One hour after drug administration, they performed a non-learning motor task: the Action Selection (AS) task (O'Shea et al., 2008), and serial reaction time task (SRTT) to quantify learning. Alertness was controlled for by asking participants to complete mood questionnaires before and 1h after drug administration.

Analysis approach: We compared simple and choice response times during the AS task between baclofen and placebo using two t-tests. The slope of the mean response time on the SRTT was used to quantify motor learning between treatment conditions using a t-test. To quantify any effect of baclofen on alertness, we calculated alertness scores from the mood questionnaire data and performed RM-ANOVA with factors of time and drug.

Results and Conclusions: A single dose of 10mg baclofen significantly impaired sequence motor learning ($p=0.035$), while having no effect on motor execution time ($p=0.390$) or decision-making time ($p=0.818$). No significant effects of baclofen on the participants' alertness were noted (no main effect of time [$F(2,26)=1.802$; $p=0.185$], or drug [$F(1,13)=0.286$; $p=0.603$] or drug-time interaction [$F(2,26)=2.253$; $p=0.125$]).

SP = Standard poster

PP = Preregistration poster

These findings have important clinical implications, as baclofen is commonly prescribed to stroke survivors to treat spasticity. Our results suggest that, at a clinically-relevant dose, baclofen significantly reduces motor learning in healthy individuals, which might translate into hindered neurorehabilitation when patients receive baclofen after stroke.

Poster number: PT174 (PP)

Theme: Sensory and motor systems

Changes in motion sickness susceptibility following development of vestibular migraine

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Introduction: Motion sickness is a common and potentially disabling problem, attributed to “mismatch” between the visual and vestibular systems¹. Commonly triggered by motion in the environment or implied self-motion in a moving visual field, patients usually report symptoms such as headache, dizziness, nausea and vomiting. These are analogous to those of prevalent neuro-otological disorders, including vestibular migraine (VM)¹. Susceptibility to motion sickness is influenced by various factors². It is believed that childhood susceptibility is positively correlated with adult susceptibility, although motion sickness appears to be more common in the former, presumably due to habituation. Self-reported motion sickness is also higher among patients with migraine².

The aims of this study are to determine:

Whether presence of vestibular symptoms in the setting of migraine influences motion sickness susceptibility

The association between changes in childhood versus adult susceptibility to motion sickness after VM development

Methods: We will investigate differences in susceptibilities with a single protocol using the validated objective experimental (off-vertical axis rotation, OVAR³) and validated patient-centred measures of motion sickness susceptibility (MSSQ)⁴. Three groups of patients (n=60) will be studied:

VM

Migraine without vestibular symptoms

Benign paroxysmal positional vertigo (BPPV)

Patients' first childhood onset of motion sickness, time taken to develop nausea on the rotational chair and self-perceived susceptibilities before and after the onset of vestibular disease using the MSSQ will be recorded.

Approach for Statistical Analysis: All statistical analysis will be performed using SPSS Statistics (Version 24, IBM[®]). Participants will be matched for childhood susceptibility, degree of dizziness using the Dizziness Handicap Inventory, and psychological symptoms including anxiety and depression. A three-way ANOVA will be performed to determine if changes in motion sickness susceptibilities differed significantly between groups.

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Poster number: PT175 (SP)

Theme: Sensory and motor systems

The EEG Precursors to Voluntary Actions in Picking, Choosing, and Guessing

Authors: Dr Eoin Travers¹, Professor Patrick Haggard¹

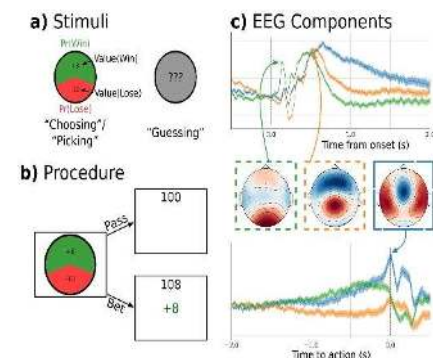
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Introduction: Voluntary actions are preceded by the Readiness Potential (RP), a slow-ramping EEG component generated in supplementary motor area. The RP is usually thought to reflect motor preparation occurring after a decision to act has been made. Recent work suggests instead that it may reflect the evidence integration process underlying the decision itself. For self-initiated actions, there is little input to this integration process, and so the integrator accumulates noise until it crosses a threshold for action.

Methods: We tested this account using a risky decision-making task. As EEG was recorded, participants decided to execute or withhold actions in order to accept or reject gambles. Gambles varied in expected value, providing strong or weak evidence that participants should bet or pass. We also presented guess trials, where participants did not know the parameters of the gamble but were told that 50% would have good outcomes. Thus, participants executed or withheld actions in the face of strong evidence (choosing), equivocal evidence (picking), or instructions to decide at random (guessing).

Approach for statistical analysis: We used surface Laplacian spatial filtering and PCA to isolate the motor RP from stimulus-evoked components. We used linear mixed models to compare each class of action while controlling for response latency and other covariates.

Results and conclusions: We present results comparing the neural activity and parameters of accumulation models between choosing, picking and guessing conditions. As the picking and guessing conditions are equivalent in terms of under-determination of action choice by evidence, yet differ in terms of how a decision to act is reached, we specifically focus on differences in neural activity between these conditions.



a) Gambles were presented as Roulette wheels. b) Participants had 5 seconds to either accept or reject the gamble shown. The default was chosen if no action was performed in this time. c) Visual, P3, and RP EEG components isolated using PCA and surface Laplacian filtering, locked to the time of stimulus onset (top) or action (bottom).

Poster number: PT176 (SP)

Theme: Sensory and motor systems

The relationship between movement accuracy and motor adaptation

SP = Standard poster

PP = Preregistration poster

Authors: Ms Alexandra Willcox¹, Professor Richard Apps¹, Professor Iain Gilchrist¹

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Motor Adaptation has been shown to decline with age, alongside movement accuracy (McNay and Willingham, 1998; Fernandez-Ruiz et al., 2000; Anguera et al., 2011, Sebastjan et al., 2017). However, to date, no study has investigated the link between these two age-related changes. We believe that increased movement variability may impair adaptation by generating uncertainty over the cause of movement error. For example, an individual with high movement variability, may display movement errors due to poor execution of the movement or because their movement was disrupted by a sensory perturbation. This uncertainty about the origins of the error would then slow the process of motor adaptation, by delaying the onset of adaptive motor changes.

Within an individual there is often variability in motor skill between the dominant and non-dominant hands. Here, we have used handedness in young adults to investigate the relative contribution of motor skill and movement variability to motor adaptation. Participants performed a visuomotor adaptation task, requiring them to aim an on-screen cursor to targets using a hand-held joystick. Following a brief training phase, a 35-degree clockwise rotation was applied to the movement of the cursor. Individuals completed the task twice, once with their dominant and again with their non-dominant hand. Block order was counterbalanced amongst participants. Measures included the difference in rate of adaptation and variability between the two hands. A regression analysis was used to predict the difference between rate of adaptation and baseline movement variability. Block order and handedness (Edinburgh Handedness Inventory) were included as co-variates.

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SP = Standard poster

PP = Preregistration poster

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Bayliss, J	PT081	Brennan, Gary	PM118, PS030, PM126
Bazer, Oren	PT020	Brennan, Gary	PS033
Bazzari, Amjad	PT124	Brennan, Gary P	PM152
Beamer, Edward	PM146, PT110, PT076	Brenton, Jake	PM098
Beart, Philip	PS091	Brickley, Stephen	PM063, PT088
Bechet, Sibylle	PS073	Brima, Tufikemni	PT026
Becic, Dzenana	PS094	Brindley, Elizabeth	PS030, PM126, PM152
Beglopoulos, Vassilios	PS094	Brittain, John-Stuart	PS170
Bekinschtein, Tristan	PM170	Britton, James	PT141
Bell, Jimmy	PS144		
Belle, Mino	PM007		

SP = Standard poster

PP = Preregistration poster

Belnap, Malia	PT010	Brookes-Howell, Lucy	PM150
Beltramo, Massimiliano	PS105	Brooks, Jonathan	PT138
Bemelmans, Alexis	PM069	Brooks, Jonathan C.	PM104
Benattayallah, Abdemalek	PT028	Brosnan, Laura	PM032
Bendotti, Caterina	PT066	Brouillet, Emmanuel	PM069
Benlaouer, Ouafa	PT109	Brown, Colin	PS097, PS099, PM101, PM102
Bennett, David	PM053	Brown, Eric	PT103
Bennett, Siobhan	PM113	Brown, Jonathan	PS062
Bennison, Emma	PM081	Brown, Jonathan T.	PM085
Benwell, Christopher	PT005	Browne, Lorcan	PT115
Berens, Philipp	PM174	Browning, Michael	PS009
Berens, Sam	PS042, PS050	Bruce, Kevin	PS143
Berglund , Ken	PT142	Brunner, HG	PM138
Bermingham, Niamh	PM124	Brunton, Paula	PS096, PS017
Bernardini, Sergio	PT071	Brzosko, Zuzanna	PM047
Bethlehem, Richard	PM161	Bubb, Emma	PM012
AI			
Bewick, Guy S.	PS066	Bucholc, Magda	PT083
Beyer, Rachael	PT005	Buckley, Ciara	PT146
Bhattacharyya, Sagnik	PM159	Buckley, David	PS137
Bianchi, Massimiliano	PM072	Buckley, Niki	PS100
Bielajew, Catherine	PT101	Buckley, Noel	PS094
Biggs, Manus	PT117, PT085	Buitelaar, Jan	PT145
Biggs, Manus	PS112	Bullmore, Ed	PS156
Bignardi, Giacomo	PS023, PM021	Buntwal, Luke	PT106
Bignardi , Giacomo	PM025	Burger, Marilise	PT012
Bigoni, Stefania	PT158	Burke, Teresa	PM072
Bijabhai, Aarifah	PS101	Burnet, Philip WJ	PM158
Bijsterbosch, Janine	PS165	Burns, Craig	PM035
Bilecki, W	PT123	Burrell, Astrid	PM150
Billinton, Andrew	PM067	Busche, Marc Aurel	PT082
Bin-jaliah, Ismaeel	PM080	Busse, Monica	PM150
Birnie, Matthew	PT094	Butler, Christopher R.	PM064, PT163
Bjorni, Max	PT010	Butler , Christopher R	PM046
Bjourson, Anthony J.	PM164	Byrne, Dwayne	PS087
Bjourson, Anthony, J	PM151		

C

Cabre, Silvia	PM069, PM076, PM082	Cleveland, Robin O.	PM064
Cabré, Silvia	PS089	Coad, Beth	PS063
Cafalchio, Matheus	PT054	Cobb, Stuart	PS111
Cahill, Emma	PS052	Codagnone, Martin	PM149
Cahill, Hannah	PM125	G	
Cairney, Scott	PS042	Cohane, Kenya	PM133
Cairns, Andrew	PM069, PM082	Cole, Laura	PT100
Calcagno, Patricia	PM172, PT002	Coleman, Michael	PT125
Caldwell, Maeve	PM096	Coli, Tatiana	PT147
Calero, Miguel	PM147	Coll, Anthony	PT091
Callaghan, Charlotte	PS008, PS014,	Colledge, William	PS102, PM109
K	PM006	Collingridge ,	PM088
Caltagirone, Carlo	PT071	Graham	
CamCAN,	PS070	Collins, Kathryn	PM054
Campbell, Aoife	PT135	Collins, Louise	PT078
Campbell, Rebecca	PM100	Collins , Andrew	PM153
Campbell, Veronica	PM132	Commins, Caitlin	PT082
Campion, Deirdre	PS122	Commins, Seán	PT086
Campos, Pauline	PT093	Comninos,	PS103, PM107
Campos-Pires, Rita	PS150, PM137, PT131	Alexander	
Campusano, Jorge	PT118	Comninos,	PM140
Canales-Johnson,	PM170	Alexander N	
Andres		Conboy, Karen	PM152
Cancedda, Laura	PS038	Concannon, Ruth	PT078
Cannon, DaraM	PM048	Conlan, Karen	PS159
Cannon, Mary	PS161, PS162, PT153, PT024	Connole, Laura	PT029
Cao, Zhewei	PT001, PT011	Connolly, Niamh	PS030
Cao, Zhewei	PS020	Connolly, Niamh	PT132
Carey, Daniel	PM070	Connolly, Niamh M.	PS126, PM077, PM128
Carhart-Harris,	PT157, PT159	C.	
Robin		Conte, Giorgia	PS034
Carisi, Carla	PT081	Conway, Michael	PS145
Carisi, M. Carla	PT079	Conway-Campbell,	PM103, PT113, PT094, PT095
Carlson, George	PT082	Becky	
		Cook, Christopher	PS098
		Coombes, Stephen	PS056
		Cooper, Daniel	PM042
		Cooper, Daniel D.	PM036

SP = Standard poster

PP = Preregistration poster

Carpenter, Jenna	PM134, PT140	Cooper, Elisa	PS051, PT031
Carpenter KLH,	PS141	Cooper, Scott	PM106
Carr, Will	PT051	Corbett, Elaine	PM005
Carr, William	PT049	Corbett, Grant	PM067
Cartier, Anna	PM133	Corcoran, Louise	PM011
Casalotti, Stefano O	PT013	Corcoran, Olivia	PT013
Cassaday, Helen J.	PS040, PM004	Cordero-Grande, Lucilio	PS024
Cassels, Laura	PM017	Cork, Simon C.	PM110
Cassol, Gustavo	PT121	Cornford, Jonathan	PM130, PT105
Cattaneo, Antonino	PM094	Corvin, Aidan	PT151
Cernik, Rebecca	PM105	Corvin, Aiden	PS031
Chabrol, Elodie	PT127	Cosemans, Nele	PT023
Chaddertom, Paul	PT088	Cosgrave, Aoife	PS131
Chamberlain, Sophie	PM044	Cosgrave, Eve	PM081
Chan, Dennis	PS070	Cosgrove, Donna	PS031
Chan, Elise	PT055	Costello, Derek	PS131, PM092
Chan, Jason	PT087	Cotter, David	PS161, PT154
Chan, Ying-Shing	PS163	Coulthard, Elizabeth	PM037, PM078, PT051
Chapman, Gareth	PM056	Coulthard, Liz	PT049
Chapman, Victoria	PS055	Counsell, John	PS100
Chaprov, Kirill	PM066	Counsell, Serena	PM026, PS024
Charlat, Maxwell	PS142	Courtney, Aidan	PS143
Chaudry, Emaan	PS142	Courtney, Amy	PM057
Chauhan, Abha	PM074, PT019	Cowen, Philip	PM141, PM163
Chauhan, Ved	PM074, PT019	Cox, Donal	PM087
Chazot, Paul	PT088	Craig, Emma	PS063
Cheah, Menghon	PT128	Craig, Michael	PM026
Cheetham, Sharon	PS100	Craigie, Kirsty	PT119
Chen, Allen	PT009	Crawford, Bonni	PT015
Chen, Chun	PM081	Creery, Jessica	PT087
Chen, Philip	PS133	Cremer , K	PM138
Chen, Tong	PS091	Cremisi, Federico	PM094
Cheng, Ying	PS077	Crespo, Andres	PT126
Chennu, Srivas	PM170	Crimmins, Darach	PT132
Chernigovskaya, Tatiana	PT003	Crivello, Martin	PT066
Chia, Germaine	PM107	Crockford, SK	PM161
Chiacchierini, Giulia	PM014	Cromarty, Ruth	PS081
Chichkov, Boris	PT122	Crompton, Lucy	PM096
Chisholm, David	PS146	Crowe, James	PT122
Cho, Jong-Wook	PS118	Crowley, Erin	PT060
Christnesen, Zachary	PM022	Crowley, Erin K.	PM041

P

SP = Standard poster

PP = Preregistration poster

Cimino, Irene	PT091	Cryan, John	PM114, PM149, PT111, PM033
Clark, Martin	PM115	Cryan, John F	PM052
Clark, Rosie	PT100	Cryan, John F.	PM119
Clarke, David	PT060	Cullen, Caroline	PT151
Clarke, Mary	PT024	Cunliffe, Vincent	PT137
Clarke, Morgane	PT002	Cunningham, Colm	PS113, PS080, PM122, PM087, PT069, PM097
Clarke, Sophie	PM107	Cunningham, Jacobi	PM149
Clarke, Sophie A	PM140	Cunningham, Mark	PT107
Clay, James	PM003	Cunningham, Mark	PT143
Claydon, Matthew	PM103	Curham, Lucy	PT139
Cleal, Madeleine	PS149, PT046	Cursano, Silvia	PM156
Clements, Leigh	PS049	Curtis, David	PS039
Cleren, Carine	PS138		

d

da Silva, Barbara	PS143	de Leo, Gioacchino	PT076
de Burgh, Ross	PS102	de Montigny, Jean	PS018
de Cates, Angharad	PM141, PM163	de Munnik, SA	PM138
de Diego-Garcia, Laura	PS034	del Rio, Magdalena	PT016

D

Daher, Ismaël	PS138	DiFeliceantonio, Alexandra G.	PS012
Dal Pizzol, Felipe	PS071, PS072	Dillon, Serena	PM078
Dale, Nicholas	PM146	DiMarco, Pietro	PT158
Dale, Tim	PM050	Dinan, Timothy	PM052, PT111
Dalley, Jeffrey W.	PT052	Ding, Xuemei	PT072
Dalmajjer, Edwin	PS023, PM025	Dingliana, John	PM171
Dand, Pawlina	PS143	Dinneen, David	PM009
Danjuma, NM	PS079	Dissing-Olesen, Lasse	PM133
Dansereau, Marc- Andre	PM097	Diviney, Mairéad	PM126, PM152
Dauvermann, Maria	PT151	Dmitriev, Ruslan I.	PT065
Davey, Catherine	PT038	Dobrachinski, Fernando	PT121
David, A	PM138	Dockery, Peter	PT023
David, Anthony	PT134	Dockree, Paul	PS011
Davies, Emma	PS085	Doherty, Colin	PT086

Davies, J	PT081	Doherty, Gayle	PS077
Davies, Jeffrey	PM121, PT106	Dolan, Ray	PS156
Davies, JS	PT073, PT079	Dolphin, Annette	PS172
Davies, Julia	PT106	Dombroski, TC	PM138
Davison, Luke	PS078	Dominguini, Diogo	PS072
Daw, Michael	PT027	Donamayor, Nuria	PS157
Dawes, Helen	PM093	Donohoe, Gary	PS088, PS031, PT151
Day, Harriet	PS041	Donoso, Francisco	PT111
De Benedictis, Chiara Alessia	PT116	Dooley, Niamh	PT153, PT024
De Burgh, Ross	PS106	Doran, Michelle	PS080
De Diego Garcia, Laura	PT067	Doty, Kevin	PS135
De Leon Edo, Alba	PT129	Douglas, Aaron K.	PT032
De Logu, Francesco	PT171	Douglas, Andrew	PM131, PT104
Deakin, JB	PM161	Douglas, Andy	PT136
Deakin, JFW	PT161	Dourmap, Nathalie	PS138
Dean, Philip	PS147	Dowd, Eilis	PS089, PM069, PM139, PM076, PM082
DeAndrea-Lazarus, Ian	PT004	Downer, Eric	PT139
Deary, Ian	PS036	Dowsett, Ross	PS164
Debus, Isabell	PS022	Doyle, Karen	PM131, PT104, PT136
Decourt, Caroline	PT092	Doyle, Seán	PS080
Del Gallo, Federico	PM145	Drake, Richard	PM157
Del Gallo, Frederico	PS030	Drew, Cheney	PM150
Delanty, Norman	PS030, PM146	Drysdale, Sophie	PM061
Delgadillo, Yuberki	PM086	Duguid, Ian	PT119
Delgado, Laura Milena Rueda	PT153	Dujardin, Simon	PT082
Delogu, Alessio	PM063	Dully, Jessica	PS168
Demetriou, Lysia	PS103	Dumanoir, Marion	PS139
Demnitz, Naiara	PM093	Dunn, Ian	PS109
Deperrois, Nicolas	PT120	Dunne, Aisling	PM087
DeSanctis, Natalie A.	PM019	Dunville, Keagan	PM094
Dev, Kumlesh	PS073, PS078, PS111, PS158	Dupré, Nicolas	PS138
Devarakonda, Kavya	PS012	Dupret, David	PM045
Devereux, Barry	PT075	Durazo-Barba, Miriam	PS058
Devine, Caitlin	PM164	Düssmann, Heiko	PS126, PM077
Dhillon, Waljit	PS100, PS103, PM140, PM107	Duyser, Fleur	PS160
Dhyllon, Inderpreet	PM167		

SP = Standard poster

PP = Preregistration poster

Di Primio, Cristina PM094
 Di Santo, Simona PT071
 Gabriella
 Dickinson, Robert PS150, PT131,
 PM137

E

Earl, Emma PT113
 Ebling, Fran PM106

Ebmeier, Klaus PM084, PM093
 Ebmeier, Klaus Peter PT084
 Ebrahim Amini, Aeen PM088
 Edgar, Julia PS136
 Edge, Christopher PS150, PT131,
 PM137

Edwards, A David PS024
 Edwards, David PM026
 Egan, John PT167
 Egerton, Alice PS028
 Eising, Else PS070
 El Nagger, Hany PS030
 Elaidiq, Malaz PS021
 Elfving, Betina PT103
 Elliott, Rebecca PM157, PT161
 Elnagar, Salmar PS051
 ElNaggar, Hany PM146
 El-Sayed, Mona PT052
 El-Tamer, Ayman PT122
 Emek-Savaş, Derya PT061
 Emek-Savaş, Derya PM070
 Durusu
 Emir, Uzay PS173

F

Fabene, Paolo PS030
 Fabene, Paolo F PM145
 Fagan, Steven PS073, PS078
 Fahey, Laura PS088
 Falappa, Matteo PS038

Dwyer, Dominic PS001
 Dyer, Adam PS090, PT158

Eng, Pei Chia PM140, PM107
 Engel, Tobias PS030, PM143,
 PM145, PM146,
 PM147, PT067,
 PT110, PS034, PT076

Engel, Tobias PT108
 Engels , H PM138
 Engen , Haakon G. PT042

England, Jennifer PM018
 Ennaceur, Abdel PT088

Ennis, Sean PT023
 Enright, Noelle PS033
 Enz, Nadja PS010
 Erickson, Jeff PM102
 Ernst, Monique PT162
 Erritzøe, David PT159
 Ersche, Karen D PT161
 Escayg, Andrew PS026
 Eskander, Amy PT134
 Esser, Patrick PM093
 Etem, Gigi PT010
 Evans, Kathryn PS036
 Evans , John PT015
 Evers, Judith PM083
 Eyerman, David J PS008, PM006

Ezquerro-Nassar, Alejandro PM170

Fletcher, Paul PS156
 Floresco, Stan B. PM028
 Flynn, Annabel PS025
 Flynn, Benjamin PT095
 Flynn, Benjamin P. PT094

Fandrey, Joachim	PS124, PS125	Flynn, Patricia	PM124
Farad, Nazar	PS112	Focking, Melanie	PT154
Farah, Adham	PS046	Foiani, Martha	PT055
Farina, Francesca	PM032, PT061	Foley , Jennifer	PS095
Farooq, Gala	PS100	Fonagy, Peter	PS156
Farrell, Dervla	PT057	Fontana, Barbara	PS149
Faulkner, Howard	PT049	Fontana, Barbara	PT046
Fawcett, Jonathan	PT042	Forman, Eva	PT023
M.			
Fearnhead, Howard	PM059	Fortuna , Wojciech	PM153
Feerick, Niamh	PT023	Foshage, Audra M	PS006
Feighan, Sarah-	PM013	Foulds , N	PM138
Marie			
Ferdousi, Mehnaz	PM172	Fowler, Philippa	PS075
Ferguson, Stuart	PM104	Foxe, John	PS020, PM155, PM175, PT001, PT004, PT020, PT009
Fernandes, Joana	PS017	Foxe, John J	PM022
Fernandes Gabriel,	PS071	Foxe, John J.	PT165, PT068, PT026
Filipe			
Fernandes-Freitas,	PS100	Foxe, John J.	PT036, PT011
Isabel			
Fernández-Blázquez,	PM147	Franchini, Daniela	PT021
Miguel			
Ferragud, Antonio	PM035	Franchini, Flaminia	PT071
Ferrè, Elisa Raffaella	PS164, PM177	Francisco, Ana	PM155
Fiddian, Leanne	PT048	Franke, Barbara	PT145
Fide, Ezgi	PM070	Franks, Nicholas	PS150, PT131, PM137, PT098
Filippini, Nicola	PT084	Franssen, Delphine	PT102
Filippini, Nicola	PT084	Franssen, Delphine	PT102
Filippini, Nicola	PM084	Frantz, Michael	PS167
Finn, Dave	PS137	Fraser, Graham	PM067
Finn, David	PS171, PM009, PM011, PM172, PM059, PT083	Freedman, Ed	PT020
Finn, David P	PM010		
		Freedman, Edward	PS020, PM175, PT001, PT004, PT009
Finn, David P.	PS166, PM023, PM173, PT002, PT072, PT168	Freedman, Edward G.	PT026
Finucane, Orla	PT130, PS114	Freedman, Edward G.	PT165, PT068

Fisher, Simon	PS070	Freedman, Edward G.	PT036
Fitzgerald, Jacqueline	PT023	Freedman, Edward G.	PT011
Fitzgerald, Joan	PS088	Frenguelli, Bruno	PM042
Fitzgerald, Marie-claire	PT132	Frenguelli, Bruno G.	PM036
Fitzgerald, Seán	PT136	Frontino, Anna	PM094
Fitzgerald, Una	PT104	Frost, Bethany	PM031
FitzGerald, Una	PT085	Froudish-Walsh, Sean	PT033
FitzGerald, Una	PS110	Fuchsberger, Tanja	PT120, PM047
Fitzpatrick, Johnmark	PT139	Fulling, Christine	PM052
Fitzpatrick, Richard	PT037	Fung, Man Lung	PT164
Flechais, Remy	PT161	Furlong, Rachel M.	PM091
Fleming, Melanie K	PT170	Fyfe, Cath	PS143
G			
Gadalla, Kamal K.E.	PS111	Goldschmidt, Jürgen	PS127
Gaetz, William	PM055	Gomez-Perales, Eamonn	PM105
Gallagher, Denis	PS142	Gonçalves, Sara	PS055, PM028
Gallagher, Louise	PS159, PS032, PT023, PM166	Goncerz, Ewa	PM166
Gallagher, Louise	PM013	Gonzalez, Bruno José	PS138, PS139
Gallagher, Maria	PS164, PM177	González-Rueda, Ana	PT120
Garcia Pardo, Maria Elena	PS076	Goodyer, Ian	PS156
Garden, Derek	PM029	Görß, Doreen	PT063
Gardiner, James	PS100	Goulart, Amanda	PS071, PS072
Gardner, John	PS143	Gould van Praag, Cassandra	PM163
Gaskell, Gareth	PS042	Goulding, Susan	PT078
Gaspar, Jessica	PM009	Grabrucker, Andreas M.	PT116, PT156
Gate, David	PS135	Grabrucker, Stefanie	PM041
Gauthier-Fisher, Andrée	PS142	Grabski, Meryem	PM104
Gavinley, Phillip	PT139	Grady, John	PM081
Gemo, Ilaria	PT158	Graham, Anthony	PM112
Gentleman, Steve	PM098	Graham, Kim	PS053

SP = Standard poster

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Georgescu, Teodora	PT096	Grainger, Ally	PT125
Georgiou, John	PM088	Grant, Seth G.	PT021
Gerbatin, Rogerio	PT121	Grattan, David	PS108
Giampietro, Vincent	PM159	Grattan, David R	PT096
Giannakeas, Nikolaos	PT148	Gray, Liam	PM150
Gianoli, Francesco	PS174	Greenspon, Charles	PS045
Gibney, James	PS090	Greve, Andrea	PS051, PT031
Gibson, David	PM148	Griep, Angelika	PM090
Gigg, John	PM162	Griffin, Eadaoin W.	PM097
Gil, Beatriz	PS083	Griffin, Juliet	PS156
Gilchrist, Iain	PT100, PT176	Griffiths, Phil	PS101
Gilissen, C	PM138	Grigoras, Ioana	PT173
Gill, Michael	PT151	Grillon, Christian	PT162
Gillespie, Amy	PS028, PM141	Grogan, John P	PT051
Gillespie, Amy	PM163	Gross, Robert	PT142
Gillespie, Dave	PM150	Grubb, Matthew	PT114, PT115, PT126
Gilligan, Therese M	PT057	Grubb, Matthew	PT128
Gilmour, Gary	PS145, PT160	Gruber, Jan	PS074
Giorgi-Coll, Susan	PS141	Guillot-Sestier, Marie-Victoire	PS069
Glennon, Jeffrey	PT145	Guo, Yuhua	PT044
Go, Mary Ann	PT038	Gupta, Utkarsh	PT053
Godlewska, Beata	PM141, PM163	Gutekunst, Claire-Anne	PT142
Goer, Franziska	PM157	Gwilt, Miriam	PS045, PS123, PM028, PM004
Goikolea Vives, Ane	PT025		
H			
H. Field, Robert	PM087	Heneine, Jana	PM134
Haarsma, Joost	PS156	Heneka, Michael	PM090
Haase, Jana	PT103	Heng, Boon Chin	PT164
Hackett, Róisín	PS131	Hengerer, Bastian	PS003, PS052
Hafezparast, Majid	PM062	Henley, Jeremy	PM113
Hager, Gordon L.	PT094	Hennessy, Edel	PM097
Haggard, Patrick	PT175	Hennessy, Edel	PM087
Haijen, Eline	PT159	Henshall, David	PS148, PM118, PS030, PM126, PM142, PT108, PM146, PS033, PS034
Hajnal, Jo	PS024	Henshall, David C	PM145, PM152
Hale, Ed	PS040, PS041	Henson, Richard	PS070, PS051, PT031

SP = Standard poster

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Hales, Claire	PS003	Henson, Richard N.	PS043
Hall, Alison	PS093	Hepplewhite, Philippa	PM081
Hall, Jeremy	PS153, PS154	Heras , Violeta	PT102
Halladay, Lindsay	PT010	HERBISON, A.E	PM111
Halvai, Delaram	PT099	Herd, Murray	PT137
Hamann, Martine	PM136	Herman, Pawel	PM095
Hammarsten, Carl	PM060	Heron, Rosalind	PS117
Hammarsten, Carl	PM060	Heron, Rosalind	PS117
Han, G	PT079	Herron, Caroline	PS083
Han, Gang	PT081	Hervig, Mona El- Sayed	PT048
Hand, Collette	PM124	Herzog, Herbert	PM110
Hanley, Jonathan	PM120	Heslegrave, Amanda	PT055
Hannah, Ricci	PS157	Hess, Grzegorz	PS175
Hannon, Eilis	PS028	Heuston, Cara M.	PM119
Hardee, Erin	PT150	Hidalgo-Lopez, Esmeralda	PS005
Harding, Edward	PT098	Hildesheim, Franziska	PS022
Harel, Antoine	PT045	Hill, Emily	PT064
Harhen, Brendan	PM059	Hill, Eric	PT122, PT124, PT125
Harkin, Andrew	PS084	Hill, Thomas	PS148, PS030, PM126, PM152
Harkin, Jim	PS130	Hillary, Robert	PS036
Harmer, Catherine	PS009, PM141, PT138	Hinchcliffe, Justyna K	PS004
Harmer, Catherine	PM163	Hind , William	PT139
Harmer, Catherine J.	PM104	Hindhaugh, Lauren	PS143, PM050
Harney, Sarah	PM097	Hinson, Emily L	PT170
Harold, Denise	PS031	Hirnet, Tobias	PM137
Haroon, Hamied	PS048	Hoban, Alan E.	PM033
Harrington, Jennifer	PM149	Hock, Rebecca	PS045, PM028
Harris, Katie	PT131	Hock, Rebecca	PS127, PM004
Harris , Sarah	PS036	Hockley, Mathew	PM056
Hartell, Nicholas	PM136	Hodgetts, Carl	PS053
Harvey, Jenni	PS046	Hodsoll, John	PT134
Harvey, Jenni	PS049	Hogan, Andrew	PS159
Hassett, Amy	PM057	Hogg, Marion	PT066
Hatcher, Abi	PT074	Holiday, Alison	PS077
Hatcher Davies, Abigail	PM058	Holland, Jessica	PS031
Hatcher-Davies, Abi	PM061	Holleran, Laurena	PT151

Hathway, Gareth	PS055	Holm Nilsen , Heidi Anett	PT099
Haugh, Orla	PM132	Hood, Kerry	PM150
Haugh, Orla	PM087	Horner, Aidan	PS042, PS050
Haunsberger, Stefan	PM128	Horsthuis, Douwe	PM155
Hawkins, Erin	PM020	Howard, Wendy	PM141
Hawkins, Phill	PT062	Howard, Wendy	PM163
Hawkins, Phillip T.	PM091	Howat, Alex	PT051
Hay, Audrey	PT120	Howden, Jack	PT107
Hayden, Lorna	PS110, PS136	Howe, W. Matthew	PS012
Hayes, Aoife	PM169	Howell, O	PT079
Haynes, Lee	PS092	Hu, Nengwei	PM068
Hazra, Anupam	PT143	Hu, Neng-Wei	PM067
Healy, Colm	PT153	Hu, Nen-Wei	PM071
Healy, Daire	PM125	Huepe, David	PM170
Healy, Dáire	PS080	Hueston, Cara M.	PM033
Healy, Dáire	PT069	Hughes, Edel	PT002
Hebert, Jennifer	PM158	Hughes, Edel M.	PM023
Heffer, Naomi	PM160	Hughes, Emer	PS024
Hegarty, Shane	PM089		
Heiland, Mona	PS148	Hulme, Sarah R.	PT021
Heimer-McGinn, Victoria	PM114	Humby, Trevor	PM008
Heisler, Lora	PS120		
Hejmadi, Momna	PS140	Hume, Catherine	PS104
Helfer, Gisela	PT089	Humphrey, Rachel M	PM010
		Humphrey, Rachel M.	PM023
Hellawell, Holly	PM035	Hunjan, Tia	PM140
Heller, Carolin	PT055	Hussain, Rohanah	PT109
Heller, Janosch	PS116, PM142	Hutchinson PJA,	PS141
Helmy, Adel	PT133, PS151	Hyland, Niall	PT060
Hemati Gourabi, Matin	PM062	Hyman, Bradley	PT082
Henderson, Hannah	PT010		
Henderson , Colin	PT150	Hynes, Stephanie	PM112
I			
Iaria, Giuseppe	PM167	Isa, AS	PS079
Ibanez, Agustin	PM170	Ishikawa, Masago	PS012
Ikrar, Taruna	PS167	Islam, Aisha	PT070
Im, Kwok	PS135	Islam, Md Nurul	PS008, PM006
IMAGEN Consortium,	PM015	Islam, Sadia	PM122
Imoesi, Peter	PS120		
		Isles, Anthony	PM008

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Inglis, George Andrew	PS026	Isles , Anthony	PS025
Inglis, Megan	PM099	Isotalus, Hanna	PM078
Ingram, Rachael	PS132	Isotalus, Hanna K	PT051
Irigoras Izagirre, Nerea	PT051	Ivanova, Deyana	PS107
Irvine, Alexander	PS023, PM025	Ivanova, Violetta	PT039
Irving, Andrew	PM127, PM132	Izzi-Engbeaya, Chioma	PS100, PM107
Irving, Andrew J	PS046		

J

Jackson, Andrew	PT143	Jeyapalan, Nishani	PM081
Jackson, Megan	PS007	Jicol, Crescent	PM160
Jackson, Robin	PS169	Jimenez-Mateos, Eva	PS030, PM145
Jager, Polona	PM063	Jimenez-Mateos, Eva	PT108, PM147
Jahns, Hanne	PM083	Jin, Lei	PM087
Jaisimha, Anirudh	PM089	Joensen, Bardur	PS042, PS050
James, Nicole Ellen	PT174	Johansen-Berg, Heidi	PM093
Jamieson, Bradley	PM100	Johnson, Amy	PT106
Jankovic-Rapan, Lucija	PT033	Johnstone, Ainslie	PT173
Jansen, Andreas	PS022	Jollans, Lee	PM070
Jansen, Michael	PM124	Jollans, Lee	PT153
Jansen , EJ	PM138	Jones, Adam	PS128
Janson, Jessica	PT063	Jones, Alistair	PT137
Jarrin, Sarah	PS171	Jones, Alistair	PS029
Jayasena, Channa	PM107	Jones, Jonathan	PT028
Jégou, Sylvie	PS139	Jones, Marggie	PM139
Jendelova, Pavla	PM065	Jones, Peter	PS156
Jendryka, Martin	PT008	Jones, Vicky Claire	PT112
Jenkinson, Ned	PS093, PS170, PS173	Joshi, Karishma	PM135
Jepson, James	PM134	Jost-Mousseau, Coline	PT155
Jespersen, Anders	PS035	Jowett, Adam	PS044
Jethwa, Preeti	PS016	Joyce, Susan	PT060

K

Kachynska, Tetiana	PM095	Kerr, Daniel M.	PT002
Kaelen, Mendel	PT157	Kershaw, Yvonne	PT095
Kaelen , Mendel	PT159	Kershaw, Yvonne M.	PT094
Kaiser, Marcus	PS081, PS082	Khachidze, Irma	PM095

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Kaiser, Marcus	PT143	Khairuddin,	PT164
Kalafatakis, Ilias	PT148	Sharafuddin	
Kalafatakis,	PM104, PT148	Khairuddin ,	PS163
Konstantinos		Sharafuddin	
Kalafatakis,	PT138	Khan, Naveed	PS163, PT164
Konstantinos		Ahmed	
Kamath, Tarun	PT082	Khan, Shakil	PS066
Kane, Ruan	PT151	Khatib, Thabat	PS146
Kaniuth, Philipp	PT014	Khiroug, Leonard	PT038
Kantamneni,	PT089	Kiddle, Bea	PS156
Sriharsha		Kievit, Rogier	PS070
Karaban, Irina	PM095	Kilcoyne, Michelle	PS112
Karl, Anke	PM160	Kilcoyne, Michelle	PM116
Kasstrup Muller,	PT103	Killen, Alison	PS081
Heidi		Killen MJ,	PS141
Kätzel, Dennis	PT008	Kilonzo, Kasyoka	PT008
Kauppinen, Risto	PM037	Kim, Hyoung-lhl	PS118
Kauppinen, Risto A.	PM078	Kim, Sohyoung	PT094
Kaur, Daman	PT083	King, Mary	PS033
Kaur, Prameet	PS074	King Lun Liu, Alan	PM098
Kavanagh, Lauren	PS094	Kinsey, Kris	PT007
Kealy, John	PS080	Kireev, Maksim	PT003
Kearney, Seamus	PT075	Kivimaki, Mika	PT084
Keefe, Francesca	PS019	Kivimäki, Mika	PM084
Kehoe, Elizabeth G.	PT057	Kjems, Jorgen	PM128, PM145
Keighron, Cameron	PM139	Lee, Kyung-Wha	PS118
Kellaghan, Beth	PM166	Kleefstra, T	PM138
Kelly, Adriona	PS112	Klickstein, Naomi	PT082
Kelly, Aine	PS068	Klyubin, Igor	PM071
Kelly, Clare	PM166	Knight, Michael	PM037
Kelly, David	PT168	Knight, Michael J	PT051
Kelly, John	PM172	Knight, Michael J.	PM078
Kelly, John	PT151	Knolle, Franziska	PS156
Kelly, John P.	PM019, PT002	Koerling, Anna-Lucia	PT120
Kelly, Rachel	PS089, PM069	Kolk, SM	PM138
Kelly, Simon	PS168, PM005, PT166	Kong, Yazhuo	PS165
Kelly, Simon	PM169, PT006	König, Hans-Georg	PS126
Kelly, Simon P.	PM001	Korkki, Saana	PT030
Kennedy, Niamh	PM054	Koroleva, Annastasia	PT122
Kennelly, Sean	PS090, PT057	Korotkov, Alexander	PT003

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Kenney, Joanne	PS011, PS162, PT153	Koteshwara, Muralidhara	PM107
Kenny, Aidan	PM147	Kouchmeshky, Azita	PS066
Kenny, Paul	PS012	Kozlov, Andrei	PS174
Kenny, Rose Anne	PM070	Krawczyk, Janusz	PT023
Kenyon, Marcus	PT151	Kryzhanovskyi, Sergii	PM095
Keogh, Conor	PT158	Kullmann, Dimitri	PM130, PT105
Keogh, Elaine	PT058	Kullmann, Dimitri	PT140
Keogh, Samuel	PT130	Kumar, Shalini	PS097
Kerr, Daniel M	PM010	Kusek, M	PT123
Kerr, Daniel M.	PM023	Kuznietsov, Illia	PM095

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L. Murray, Carol	PM087	Liewald, David	PS036
Lacey, Austin	PM146	Lightman, Stafford	PM049, PS102, PS106, PM103, PT090, PT138, PT113, PT094, PT095, PT100
Lage-Martinez , Carmen	PT163	Lightman, Stafford	PS007
Lagojda, Lukasz	PM129	Lightman, Stafford L.	PM104
Lahert, Nessa	PM166	Lignani, Gabriele	PM134
Lai, F. Anthony	PS021	Lignani, Gabriele	PT140, PT127
Lai, M-C	PM161	Lim, Chu Hsien	PS074
Lam, Brian	PT091	Lim, Lee Wei	PT164
Lambert, Jeremy	PT074, PT041, PT047	Lim, Wei Ling	PT164
Lane, Jon	PM096	Lim, Wei Ling	PS163
Lanfranco, Renzo	PM170	Lin, Tzu-Chin, E.	PS153
Langa, Elena	PM152	Lin, Tzu-ching	PS154
Langston, Rosamund	PT074, PT041, PM058, PT077, PM061, PT047	Linden, James	PM148
Langston , Ros	PT150	Lindsay, Andrew	PM091
Lanigan, Sinead M	PS122	Lingford-Hughes, Anne R	PT161
Lapsley, Coral R.	PM164	Lingnau, Angelika	PS044
Lapsley, Coral, R	PM151	Linington, Christopher	PS110
Large, Charles	PS041	Linington, Christopher	PS136
Lasbareilles, Camille	PM177	Lipovsek, Marcela	PT114, PT115
Laskowska, Joanna	PT069	Lipovsek, Marcela	PT128
Lass, Geffen	PS102, PS106	Lipp, Ilona	PT015

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Lau E How, Kelvin	PM118	Liss, Birgit	PT008
Lautarescu, Alexandra	PM026	Liu, George	PS135
Lavelle, Ed C	PM087	Lizio, Roberta	PT063
Lawand, Nada	PS060	Llorente-Berzal, Alvaro	PM009, PM173, PM059
Lawrence, Andrew	PS053	LLORENTE-FOLCH, IRENE	PM077
Lawrence, Andrew D.	PT015	Lloyd-Evans, Emyr	PT062
Le Caignec, C	PM138	Loane, Clare	PM046
Le Dieu-Lugon, Bérénice	PS138	Loane , Clare	PT163
LeBeau, Fiona	PS065, PT107	Loehfelm, Aline	PS086
LeBeau, Fiona	PT143	Lolait, Stephen	PS101
Lecointre, Maryline	PS138, PS139	Lombardo, MV	PM161
Lecuyer, Matthieu	PS139	Lomet, Dideir	PS105
Lee, David	PM018	Long, Maeve	PS076
Lee, David	PM016	Long-Smith, Caitriona	PM041
Lee, Min-cheol	PS118	Lopez, Dianne	PT107
Leitch, Beulah	PS015	Lopez, Lorna	PS032
Leite, Marco	PT127	Lopez Rodriguez, Ana Belen	PS113
Lelos, M	PT081	Lopez-Rodriguez, Ana Belen	PM087
Lemay, Alice	PM105	Lopez-Rodriguez, Ana-Belen	PS080
Lemus, Evelyn	PM086	Loughnane, Gerard	PS168
Leng, Gareth	PS104	Love, Seth	PM098
Lenihan, Joan	PM114	Lowery, Madeleine	PM083
Leroux, Philippe	PS138	Lowry, John P.	PS080
Leroux-Nicollet, Isabelle	PS138	Lucas, José J.	PS034
Leu, Tristan	PS124	Lucin, Kurt	PM086
Leung, Brian	PS135	Luckett, Jeni	PM106
Levenstein, Jacob	PS173	Luckman, Simon	PS098
Lewis, Jo	PM106	Ludwig, Mike	PS104
Lewis, Lucy	PS001	Lugarà, Eleonora	PT127
Li, Daqing	PM153	Lukasz, Bartlomiej	PT152
Li, Jennifer	PS145	Lunn, Sharna	PM056
Li, Meng	PS019	Luthi-Carter, Ruth	PM135
Li, Xiaofeng	PS102, PS107	Lynch, Lydia	PT032
Li, Ying	PM153	Lynch, Marina	PS069, PS114
Li, Xiao-Feng	PS106	Lynch, Marina	PT130

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Liadi , Modinat PM153
 Librach, Clifford PS142
 Lieberam, Ivo PM112
 Lieverse, Elizabeth PT113

M

Ma, Marcella PT091

Ma, Yue PS100

Mac Cionnaith, PM105

Conall Eoghan

MacCabe, James PS028

Macdonald, James PT007

Macdonald, Warren PT131

MacDonald, Debra PM144

MacDonald, Hayley PS093

Macedo, Paula PM108

Machenahalli, PM107

Pratibha

MacInnes, Caitlin PT150

Ray

Mackay, Clare PT084

Mackay, Clare PM084

Mackonochie, PS140

Marion

Mackowiak, M PT123

MacLachlan, Robert PM098

Maclatchy, Amy PS144

MacMahon, Jill PT085

MacSweeney, PM166

Niamh

Madasu, Manish PS006

Kumar

Madder, Annemieke PS105

Madi, Gulden PS016

Magalhães, Daniela PS002

Magloire, Vincent PM130, PT105

Mahmood, Abda PT084

Mahmood, Abda PM084

Mahmood, Ayisha PT037

Major, Ian PT146

Lynch, Marina A. PS068

Lynch, Sally PT023

Lyons, Declan PT057

Medvedev, PT003

Svyatoslav

Mee, Joe PS143

Meftah, Soraya PM085

Mehraram, Ramtin PS081, PS082

Meijer, Dies PT129

Mela, Virginia PS068

Mellor, Jack PS134, PM030,

PM039, PM044

Méndez, Raúl PS034

Mendl, Michael PS004

Mequinion, M PT073

Mercer, Ella PT129

Merces, George O.T. PM057

Mercier, Marion PM130, PT105

Mereuta, Oana PT136

Madalina

Metzler-Baddeley, PS063

Claudia

Michaelevski, Izhak PM034

Michels, Monique PS072

Michels Orben, PS071

Monique

Micioni Di PS012

Bonaventura, Maria

V.

Mikkelsen, Mark PT015

Mill, Jonathan PS028

Mills, Edouard PS103, PM107

Mills, Edouard GA PM140

Milner, Mark PS068

Milton, Amy PM035

Milton, Fraser PT028

Mink, Jonathon W. PT026

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Makropoulos, Antonios	PS024	Minkley, Lucy	PM075
Malijauskaite, Sigita	PT156	Minogue, Aedin	PM125
Maltsev, Alexander	PM040	Minogue, Eleanor	PT139
Mampay, Myrthe	PS002	Mirza, Zainab	PS100
Manchishi, Stephen	PM109	Modebadze, Tamara	PT107
M			
Mannikko, Roope	PM134	Modi, Manish	PM140
Mannion, Orlaith	PT168	Mohamed-Ali, Nada	PS150
Mannion, Orlaith	PS166	Mohr, Kieran	PT166
Manuel, Martine	PT027	Moldzio, Rudolf	PM080
Maravita, Angelo	PM167, PT172	Molholm, Sophie	PM155, PT165, PT009
Marchant, Nicky	PM104, PT138	Molhom, Sophie	PT036
Marcos, Tiago	PT027	Mollet, Inês Guerra	PM108
Marini, Pietro	PS146	Molloy, Ciara	PT001
Marioni, Riccardo	PS035, PS036	Molloy, Eleanor	PM024, PT155
Marks, Lydia	PT043	Mongan, David	PS161
Marks, Lydia C.	PM043, PT032	Mongan, David	PT154
Marret, Stéphane	PS138, PS139	Monnier, Chloe	PM106
Marsh, Alexander	PS140, PT050	Monsefi, Naser	PT066
Marson, Tony	PT137	Montagnese, Marcella	PS156
Marston, Hugh	PS007, PS145	Monteiro, Olivia	PT074, PT041, PT047
Martens, GJ	PM138	Montgomery, Therese	PT146, PM154
Martens, GJ	PM138	Montgomery, Therese	PT146, PM154
Martin Alonso, Aldara	PM110	Moody, Anna	PS122
Martinez Gonzalez, Cristina	PT119	Carlene	
Martinez Rodriguez, L. Alexandra	PM001	Moolla, Siddiq	PS142
Martinez-Pernia, David	PM170	Mooney, Catherine	PS030
Martins, Manuella	PM094	Mooney, Catherine	PM152
Martyn, FionaM	PM048	Moore, Gerald	PM063
Marzolo, María Paz	PT118	Moore, Gerald	PT088
Mason, Rob	PS045	Moore, Katrina	PT055
Mathew, Ryan K	PS143	Moore, Lauren	PT163
Mathiasen, Mathias	PS061	Moorhouse, Pamela	PM125
L		Mora, Joshua	PT004
Mathiasen, Mathias	PT035	Morales, Juan Pablo	PM170
L.			

Mathis, Victor	PS012	Moran, Catherine	PS011
Mattimoe, Darragh	PM011	Moran, Paula M.	PM028
Mazurek, Kevin	PM175, PT068	Moran, Rosalyn	PT138
Mazziotti, Raffaele	PM094	Morgan, A	PT081
Mc Veigh, Conor	PT103	Morgan, AH	PT073, PT079
James			
McArthur, Simon	PS144	Morgan, Alan	PS029, PT137
McCaffery, Peter	PS120	Morgan, Alwena	PM121, PT106
McCaffery, Peter	PS146, PS037	Morgan, James	PT110
McCaffery, Peter J.	PS066	Morgan, Peter	PS120
McCall, Jordan	PM060	Moriarty, Fiona	PS114
McCall, Jordan G.	PS006	Moriarty, Niamh	PS089, PM139, PM076, PM082
McCandless, Conor	PS162	Morisaki, Mizuki	PS077
McCandless, Conor	PT153	Morris, Chris	PM081
McCann, Bryony	PM078	Morris, Derek	PS031
McCartney, Daniel	PS035, PS036	Morris, Derek	PT151
McClellan, Paula	PT083	Morris, Derek W	PS088
McClellan, Paula L	PT072	Morris, Gareth	PM145
McCombe, Niamh	PT072	Mortensen, Erik	PT159
		Lykke	
McComish, Sarah	PM096	Moss, Jonathan	PT056
McCutcheon, James	PM014	Mota, Bibiana C.	PS068
E.			
McDaid, Liam	PS130	Mothershill, David	PS031
McDermott, Barry	PM139	Mothersill, David	PT151
McDonagh, Katya	PT023	Moutoussis, Michael	PS156
McDonnell, Lisa	PT058, PT029	Moyron-Quiroz, Juan	PM133
McGee, Aaron	PS167	Muhammad, MS	PS079
McGinnity, T. M.	PM164	Muhlert, Nils	PS048, PT015
McGonigle, John	PT161	Muilu, Juha	PM145
McGourty, Kieran	PT156	Muletier, Camille	PS107
McGovern, Andrew	PM119	Mullins, PaulG	PM048
J.			
McGovern, David	PS011, PM169, PM176	Munafo, Marcus	PT138
Mcgrady, Laura	PT040	Munafo, Marcus R.	PM104
McGrath, Jane	PS159	Muralidhar, Venkiteswaran	PM051
McGrath, Ryan	PT017	Murphy, Anna	PT161
McGrory, Claire	PM123	Murphy, Brian	PT075
McGuinness, Bernadette	PT075	Murphy, Brona	PT132
McGuire, Brian E.	PT168		
		Murphy, Daniel	PS009

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Mchugh, Stephen	PM045	Murphy, David	PT094
McHugh, Patrick	PS137, PS119	Murphy, Keith	PT058, PT029
McInerney, Veronia	PT023	Murphy, Keith J	PM165
McIntosh, Andrew	PS035	Murphy, Keith J.	PT152
McIntyre, Caitlin	PS107	Murphy, Kevin G.	PM110
Mckernan, Declan	PM082	Murphy, Patrick	PM104
McKernan, Declan	PM069, PT151	Murphy, Robert	PT058
McKinley, John	PT075	Murphy, Susannah	PM141
McLafferty, Margaret	PM164	Murphy, Susannah	PM163
McLean, Fiona	PT074, PT041, PM058, PT047	Murray, Carol	PS080
McLoughlin, Declan	PM123	Murray, Carol	PS113, PT069
McMahon, Jill	PT104	Murray, Carol L.	PM097
McMahon, Siobhan	PM116	Murray, Elaine	PM148
Mcmanus, Elizabeth	PS048	Murray, Elaine K.	PM164
McManus, Roisin	PM090	Murray, Graham K	PS156
McPhilemy, Genevieve	PM048	Murray, James	PM122
McRae, Allan	PS036	Murray, Elaine, K	PM151
Mechelli, Andrea	PM159	Musicco, Massimo	PT071
Meddle, Simone	PS109	Muyderman, Hakan	PS091
Medina, Miguel	PM147	Myers, Evan	PS020
N			
Nabulsi, Leila	PM048	Nicholson, Janet	PT052
Nagel, David	PT122, PT125	Nicholson, Timothy	PT134
Nalberczak-Skóra, Maria	PS152	Nicke, Annette	PT110
Nan, Xincheng	PM017	Nicolas, Sarah	PM033
Naneix, Fabien	PM014	Nieto-Rostro, Manuela	PS172
Nanou, Sophia	PT089	Nikolaev, Anton	PM038
Nardo, Giovanni	PT066	Nillesen, WM	PM138
Nasrallah, Gheyath	PS021	Nilsson, Simon R. O.	PT052
Nassini, Romina	PT171	Nissen, Wiebke	PT008
Nazarpour, Kianoush	PT070	Niu, Meiqi	PT033
Nazmi, Arshed	PM087, PM097	Nolan, Matthew	PM029
Neill, Joanna	PM157, PM162	Nolan, Matthew	PT119
Nelken, Israel	PT082	Nolan, Yvonne	PT060
Nelson, Andrew	PS047, PM012	Nolan, Yvonne M.	PM119, PM033, PM041

Nettekoven, Caroline	PS173	Nomikos, Michail	PS021
Netty, Alexa	PM035	Nord, Camilla	PS157
Ng, Li Fang	PS074	Noreika, Valdas	PM170
Nguyen, Ngoc	PS033	Norton, Mariana	PS100
Nguyen, Ngoc	PM152	Novak, Ondrej	PM065
Nguyen, Ngoc Thanh	PM118	Nunn, Nicolas	PS098
Ni Bhroin, Megan	PM024	Nurdal, Volkan	PM079, PM037
Ní Ghrálaigh, Fiana	PS032	Nutt, David	PT159, PT161
Nicholas, Eric	PS020, PT009	Nutt, David	PT157
Nicholas, Eric	PT026	Nuvvula, Sri	PT165
Nicholas , Eric	PT020	Nygart, Victoria	PT159

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O' Callaghan, Claire	PS155	O'Leary, James D.	PM119, PM043
O' Connell, Redmond	PS168	O'Leary, Olivia	PT060, PM149
O Conner, Gerard	PS112	O'Leary, Olivia F.	PM119
O Hanlon, Erik	PT153	Ollà, Ivana	PS034
O' Hanlon, Erik	PT024	Olsen, Laura	PM082
O'Neill, Cora	PM041	Olusanya, Adedunni	PT097, PT080
Oakes, Leona	PT020	O'Mara, Shane	PM031
O'Boyle, Conor	PM097	O'Mara, Shane M	PS008, PS014, PM027, PM006
O'Brien, Timothy	PT023	O'Muircheartaigh, Jonathan	PS024
O'Byrne, Kevin	PS102, PS107	Ondrejcek, Tomas	PM067
O'Byrne , Kevin	PS106	O'Neill, Aisling	PM159
O'Carroll, Anne- Marie	PS101	O'Neill, Amie	PT152
O'Carroll, Ross	PM057	O'Neill, Cora	PM091, PT060, PT062, PT087
O'Connell, Redmond	PM005, PM169, PM176, PT006	O'Neill, Eoin	PS084
O'Connor, John J	PS122	O'Neill, Nathanael	PM117
O'Connor, Richard M.	PS012	O'Neill, Siobhan	PM164
O'Dea, Reuben	PS056	Ong, Bee Eng	PM137
Odell, Mark	PS144	Ong, Charlie	PT075
Odi, Tuamoru	PS116	Opitz, Bertram	PS147
Odoka, Juliet	PT097	O'Rahilly, Stephen	PT091
O'Donnell, Cian	PT049	Orban, Csaba	PT161
O'Donoghue, Catherine	PT151	O'Riordan, Kenneth	PM052

O'Donovan, Sarah M	PT060	Orlate Sánchez, Cristian	PS120
O'Driscoll, Tara M.	PT037	Orpwood, Roger	PM002
Oelschlegel, Anja M	PS127	Ortega-de San Luis, Clara	PM043, PT032, PT043, PT045
Oghene, Okikiade	PT097	Osbourne, James	PT077
O'Gorman, Denise M.	PM041		
Ogunrinade, Folashade	PS067	O'Shea, Donal	PS159
Ogunsola, Oluseyi	PT097	O'Shea, Sean	PT058
O'Halloran, Martin	PM139	Osorio, Daniel	PT169
O'Halloran, Philip	PT132	O'Sullivan, Josiah	PM165
O'Keefe, Gerard	PT078	O'Sullivan, Matthew	PT023
Okine, Bright	PM009	O'Sullivan, Niamh	PS075, PS076, PS087
Okolo, Adaobi	PT104	O'Sullivan, Orla	PT060
Okolo, Adaobi	PM131	O'Sullivan, Sinead	PS073
OLAJIDE, OLUMAYOKUN	PS067	Owen, Michael	PS156
O'Leary, James	PT043, PT045		

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Ó Gráiligh, Rónán	PS011	Ó Léime, Ciarán S.	PM033
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P

Palace, Jacqueline	PS165	Phylactou, Maria	PM140, PM107
Palacios, Jon	PM030	Pick, Susannah	PT134
Paller, Ken	PT087	Pickering, Mark	PT058, PM057
Pallmann, Philip	PM150	Pickering, Tony	PM039
Palomero-Gallagher, Nicola	PT033	Pienaar, Abigail	PM007
Panayi, Marios C	PT160	Piet, Richard	PM100
Pandareesh, Mirazkar	PM074	Pietsch, Maximillian	PS024
Pandit, Abhay	PS089, PM116, PS171, PM076, PT136	Piggins, Hugh	PM007
Pantall, Annette	PT070	Piilgaard, Louise	PT048
Papadopoulou, Deborah	PM140, PM107	Pineda , Rafael	PT102
Park, Rebecca	PT144	Pingen, Marieke	PS136
Parker, Matthew	PM003, PS149	Pinhasov, Albert	PM034
Parker, Matthew	PT046	Pini, Giorgio	PT158

Parmar, Jassleen	PM167	Pinki, Farhana	PM092
Parras, Alberto	PS034	Pizzorusso, Tommaso	PM094
Parri, Rhein	PT122, PT125	Plate, Mathilda	PM099
Parri, Rheinallt	PT124	Pletzer, Belinda	PS005
Parthier, Daniel	PS121	Plumptre, Isabella	PM140
Passmore, Peter	PT075	Poelmans, Geert	PT145
Pasterkamp, Jereon	PM145	Polis, Baruh	PS064
Paterson, Louise M	PT161	Pomeroy, Valerie	PM054
Patil, Vaibhav	PM116	Pommerencke, Lis Marie	PT159
Paton, Julian	PS101	Poobalasingam, Thurka	PM133
Patterson, Alex	PT094	Popa, Traian	PS157
Patterson, Dillon	PS026	Postans, Mark	PS053
Patterson, Michael	PT099	Power, Emer	PS166
Pau, Ashni	PT131	Power, Emer	PT168
Paul, Susana	PT090	Power, Ruth	PT069
Paulsen, Ole	PT120, PM047	Power, Sarah D.	PM043
Pawley, Lauren C.	PM119	Prado, Seigfred	PT038
Pecheva, Diliana	PM026	Prague, Julia K	PS103
Pedersen, Sigrid C.M.	PT032	Pragulbickaite, Gabi	PM032
Peeters, Hilde	PT023	Prasad, Girijesh	PT072
Pekcec, Anton	PT008	Praschberger, Roman	PM134
Peraza Rodriguez, Luis	PS081, PS082	Prehn, Jochen	PS030, PT066
Perez, Jonathan	PS109	Prehn, Jochen H. M.	PS126, PM128
Perez, Omar	PM035	Prehn, Jochen HM	PM145
Perkins, Alan	PM106	PREHN, JOCHEN H.M.	PM077
Perkinton, Michael	PM067	Prendergast, James	PM131, PT104
Perriman , Adam	PM056	Price, Anthony	PS024
Peters, Kate Z.	PM014	Price, David	PT027
Petrini, Karin	PM160	Probert, Fay	PM158
Pezzoli, Maurizio	PT043	Procyshyn, Tanya L	PM161
Pfalzgraf, Hadley	PT087	Pulcu, Erdem	PS009
Pfaus, James	PM105	Purugganan, Kate	PM140
Pfundt , R	PM138	Purves, Alistair	PT134
Q			
Qi, Yingjie	PM071	Quines, Caroline B.	PT121

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Qi, Yingjie PM073
 Qiu, Yichen PT140
 Quarrell, Tom PT120
 Quent, Jörn PS043
 Alexander

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Rabiner, Eugenii, A PS103
 Rabona, Alberto PM147
 Raby-Smith, Will PS052
 Radad, Khaled PM080
 Radford-Smith, Daniel PM158
 Radwańska, Kasia PS152
 Radyushkin, Konstantin PM137
 Rae, Mark G. PT065
 Rafailov, Edik PT122
 Rai, Laura PM032
 Raisman, Geoffrey PM153
 Ramgoolam, Krishma PS172
 Ramirez, Valerie PT111
 Randall, Andrew PS062
 Ranson, Daniel C PT013
 Raoof, Rana PS030
 Rastle, Kathy PS044
 Ratnasabapathy, Risheka PS100
 Ratto, Federica PT071
 Rausch, Wolf-Dieter PM080
 Rawlins, J. Nicholas PM097
 Rayner, Megan PT066
 Reckner, Erin PS095
 Reedman, Edward G PM022
 Rees, D PT079

Quinlan, Leo PM139, PT023
 Quinting, Theresa PS125
 Quraishie, Shmma PS129

Roca-Fernandez, Adriana PM046, PT163
 Rocha Abatti, Mariane PS071, PS072
 Roche, Michelle PS166, PS171, PM009, PM010, PM011, PM023, PM172, PM059
 Roche, Michelle PM131
 Roche, Richard PT040
 Roche, Richard PM171
 Roche, Richard A.P. PT086
 Roche, Michelle PT002
 Rochefort, Nathalie PT119
 Rochester, Lynn PT070
 Rodrigues, Frederico PS117
 Rodriguez, Eugenio PM170
 Rodríguez, Ana Belén PT102
 Rodriguez Luis, Alejandro PT129
 Rogers, Jake PT038
 Rogers, Mark PT094
 Rohrer, Jonathan PT055
 Roiser, Jonathan PT162
 Rojo, Francisca PT118
 Rolfe, Vivien PS140
 Rolls, Edmund PS057
 Roman, Andrey PM066
 Romano, Daniele PT172
 Romer, Daniel PM055
 Romero-Ruíz, Antonio PT102

Reeve, Amy	PM081	Roseboom, Warrick	PT014
Reeves, Sue	PT099	Roseman, Leor	PT157
Reilly, Jamie	PT023	Rosenow, Felix	PS030, PM128, PM145
Reilly, Richard	PT158	Rosser, Anne	PS019, PM150
Reis, Renata	PM087	Rossi, Rosanna	PT136
Rennie, Joseph	PM020	Rothaermel, Harris	PT142
Rentzos, Alexandros	PT136	Rothwell, John	PS157
Reschke, Cristina	PM126, PM145	Rouine, Jennifer	PS008, PS014, PM027, PM006
Resler, Alexa	PT066	Roversi, Karine	PT012
Reynolds, James	PS116	Rowan, Michael	PM067, PM068, PM071
Rhodes, Adam	PS094	Rowan, Michael	PM073
Rice, Hannah	PM032	Rowe, James	PS070
Richards, Alex	PS156	Roy, Ranjan	PS099
Richardson, David	PM175, PT068	Royes, Luiz F.	PT121
Richardson, Errol	PS100	Rubio-Araiz, Ana	PT130
Richardson, Magnus	PT064	Ruddy, Kathy	PS010
Richardson, Pippa	PM036, PM042	Ruddy, Kathy R.	PM015
Richardson, Thomas	PM056	Rudenko, Svetlana	PM171
Richter, Franziska	PT030	Rueckert, Daniel	PS024
Rickards, Hugh	PT077	Rueda-Delgado, Laura	PS010
Ridgeway, Samuel	PS053	Rueda-Delgado, Laura	PT061
Rimmington, Debra	PT091	Rueda-Delgado, Laura M	PM070
Risler, Thomas	PS174	Rueda-Delgado, Laura M.	PM015
Ritchie, Craig	PS036	Ruedell Reschke, Cristina	PS030
Rivera-Rei, Alvaro	PM170	Ruedell Reschke, Cristina	PM152
Rivers, Caroline	PT090	Rump, P	PM138
Rivest-Beauregard, Marjolaine	PM105	Rusakov, Dmitri	PS116
Rizwan, Mohammed	PS108	Rushdie, Abuhamdah	PM063
Rizzello, Emanuela	PM027	Russell, Georgina	PM104, PT138
Rizzo, Rossella	PM070	Russell, Georgina	PT100
Robbins, Trevor	PS155	Russell, Lucy	PT055
Robbins, Trevor W	PT161	Rutherford, Mary	PS024
Robbins, Trevor W.	PT048, PT052	Ryan, Christina	PM139
Robert, Vincent	PS105	Ryan, Karen	PM123

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Roberts, Luke	PM121	Ryan, Niamh M	PS032
Roberts, Timothy	PM055	Ryan, Tomás	PT043, PT045
Robertson, Ian H	PM070	Ryan, Tomás J.	PM043, PT032
Robinson, Emma	PS001, PS134, PS003, PS007, PS024	Rybnicek, Jonas	PT074, PM058
Robinson, Emma SJ	PS004	Rys, Wouter	PT006
Robinson, Oliver	PT162		

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Saade , Charbel	PS060	Siano, Giacomo	PM094
Safieh-Garabedian, Bared	PS021	Sibilia, Francesca	PT057, PT155
Saha, Orthis	PM114	Siddiqui, Fyyaz	PS142
Sahakian, Barbara	PS155	Sieradzan, Kasia	PT049
Sala-Bayo, Júlia	PT052	Siligardi, Giuliano	PT109
Saleh, Alaaeldin	PS021	Sills, Graeme	PS029, PT137
Salem, Victoria	PM110	Silverman, Jill	PM162
Salim, Rehan	PM140	Simons, Jon	PT030
Salvetti, Beatrice	PS030, PM145	Sin, Wai Wai	PS122
Salvucci, Manuela	PT132	Sinclair, Lindsey	PM098
SALVUCCI, MANUELA	PM077	Singh , Tanya	PM056
Samborska, Veronika	PT160	Singh-Manoux, Archana	PT084
Sammons, Rosanna	PS121	Singh-Manoux, Archana	PM084
Samms, Ricardo	PM106	Siugzdaite, Roma	PT022
Sampedro	PM134	Siwiec, Marcin	PT123
Castaneda, Marisol		Skelly, Donal T.	PM097
Sampietro, Sara	PM133	Slioussar, Natalia	PT003
Samra, Kiran	PT134	Smeaton, Alan	PS011
Samson, Abraham	PS064	Smirnovova, Diana	PM128
Sancesario, Giulia Maria	PT071	Smith, Chris George Severin	PT112
Sanchez, Connie	PS008, PS014, PM006, PM172, PM149	Smith, Dana G	PT161
Sanchez, Connie	PT002	Smith, Emma	PS157
Sanchez, Stephanie	PT142	Smith, Jessica	PS041
Sankarasubramanian, Subbulakshmi	PT044	Smith, Jonathon	PT108, PT067
Sankarasubramanian , Subbulakshmi	PT042	Smith, Karen	PM172
Santiago-Lopez, Angel	PT142		

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Santos, Andreia	PT136	Smith, Stephen	PS024
Sanz Rodriguez, Amaya	PM145	Snoeren, Eelke M. S.	PM014
Sarigiannidis, Ioannis	PT162	Sokolovsky, Sergei	PT122
Sarker, Satyajit D	PS067	Sokolowska, Ewa	PM072
Sartori, Gláubia	PT121	Somogyi, Aleksandra	PT062
Sassi, Martina	PT073	Soubramanian, S	PM161
Sauer, Ann Katrin	PT156	Southworth , Richard	PS128
Saunders-Jennings, Esther	PM078, PM037	Sowa, JE	PT123
Sautreuil, Camille	PS139	Sowa, Joanna Ewa	PS175
Saville, Joanna	PM137	Stack, Gary	PM154
Scaife, Jessica	PM141, PM163, PT144	Stagg, Charlotte	PT173, PS173
Scharer, Christopher	PS026	Stagg, Charlotte J	PT170
Schatz, Paul Marie	PS069	Stahr, Layla B	PT160
Schene, Aart	PS160	Stan, Georgiana	PM120
Schiantarelli, Julia	PT082	Stanton, Biba	PT134
Schieving, J	PM138	Stanton, Catherine	PT111
Schmitz, Dietmar	PS121	Stark, Rudolf	PS022
Schnitzler, Daniela	PS096	Stathi, Afroditi	PM093
Schoen, Ingmar	PM142	Stavreva, Diana A.	PT094
Schorge, Stephanie	PM145, PM134	Stavropoulos, Ioannis	PT134
Schorge , Stephanie	PT140	Steele-Perkins, Peter	PT008
Schreiber, Timm	PS124, PS125	Stefan, Melanie I.	PT037
Schuh, Andreas	PS024	Steinbeck, Fabian	PM168
Schultz, Simon	PT038, PM063	Stern, Yaakov	PM070
Schulz, Stefanie	PT008	Sterr, Annette	PS147
Schumacher, Julia	PS082	Sterratt, David C.	PT037
Schwenke, Daryl	PS099	Stevens, Beth	PM133
Scully, Michael	PT168	Stephenson, Alice	PT007
Seager, Poppy	PM093	Stevenson, Anna	PS036
Seaton, Adam	PS045, PM028	Stevenson, Carl	PS041
Seaton, Natasha	PM035	Stevenson, Carl W.	PS040
Sebastião, Ana M	PS002	Stevenson, Tyler	PS109, PS037
Seckl, Johanathan	PS100	Stevenson , Carl	PM004
Seeboth, Anne	PS036	Stewart, Gavin	PM092
Seifert, Marvin	PT169	Stolp, Helen	PT025
Selwood, James	PT051	Story, Gina M	PS006
Semenoff, Tiia	PS136	Stothart, George	PM079
Sernagor, Evelyne	PS018	Strom , T	PM138
Seth, Anil	PT014	Stuart, Sarah	PM030

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Sethw Hassan, Ilda	PS133	Stubbendorff, Christine	PS040, PS041
Sewell, Bernadette	PM150	Stubbs, Felicity	PT113
Sexton, Claire	PM084, PM093	Stuczynska, Anna	PS119
Seymour, Alexander	PM101	Stumpf, Alexander	PS121
Sharma, Kapil	PS158	Stylianou, Myrto	PS065
Sharma, Rupali	PT101	Suckling, John	PT161
Sharouf, Feras	PM150	Sule, A	PM161
Sharp, Trevor	PT164	Sullivan, Aideen	PT060, PT078
Shaw, Lisa	PT112	Sullivan, Aideen M.	PM091
Shaw, Luke	PT026	Sumbayev, Vadim	PT109
Sheahan, Tayler D	PS006	Suri, Sana	PS070, PM084, PT084
Shearer, Jennifer	PT104	Susai, Subash raj	PT154
Shearer, Jennifer	PM131	Susai, Subash Raj	PS161
Sheinin, Anton	PM034	Susdalzew, Sergej	PT066
Shekh-Ahmad , Tawfeeq	PT140	Svent, Masa	PM136
Shen, Sanbing	PT023	Svobodova, Barbora	PM065
Shepherd, Peter	PS108	Sweeney, Aoife	PT075
Sheridan, Graham K	PS002, PS111	Syed, Yasir	PM056
Shi, Xiaohong	PS136	Sykes, Lucy	PS153
Shimoda, Yoshiteru	PT105	Sykes, Mark	PS103
Shnayder, Alexey	PM034	Sylantyev, Sergiy	PM117
Shpenkov, Oleksiy	PM095	Szank, Tomasz	PM154
Shukuroglou, Melissa	PT157	Sze, Ying	PS096, PS017

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Tabakow , Pawel	PM153	Toffolo, Kathryn	PT020
Tackley, George	PS165	Tokarski, K	PT123
Taghibiglou, Changiz	PM088	Tokarski, Krzysztof	PS175
Tajsic, Tamara	PT133	Toledo-Rivera, Sandra	PM038
Talmi, Deborah	PS048	Toledo-Rodriguez, Maria	PS016
Tam, Eric	PM045	Tolla, Elisabetta	PS109, PS037
Tam, Miguel	PM133	Tolwinski, Nicholas	PS074
Tams, Daniel	PM050	Toman, Marinus	PS130
Tams, Daniel Mark	PS143	Toniolo, Sofia	PT071
Tan, Kyle BC	PM148	Torok, Agoston	PM177
Tarrit, Katy	PT165	Torres , Encarnación	PT102
Tasker, R Andrew	PM144	Tortorelli, Lucas	PM087, PM097
Tatlisumak, Turgut	PT136	Tortorelli, Lucas Silva	PS080
Taylor, Bradley K.	PS166	Tosi, Giorgia	PM167, PT172

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Taylor, Eleanor	PT161	Toulouse, Andre	PM124
Taylor, Joanne	PS044	Town, Terrence	PS135
Taylor, John-Paul	PS081, PS082	Towns, Clodagh	PS113
Taylor, Peggy	PM133	Townsend, Liam	PS090
Teipel, Stefan	PT063	Tracey, Irene	PS165
Teixeira, Rui Pedro	PS024	Tran, Stephanie	PT035
AG			
Temel, Yasin	PT164	Travers, Eoin	PT175
Temel, Yasin	PS163	Trevelyan, Andrew	PT143
Tena-Sempere, Manuel	PT102	Trevisan, Gabriela	PT171
Tendolkar, Indira	PS160	Trezise, Del	PM050
Terstege, Dylan	PM144	Trigo, Margarida	PM162
Tessereau, Charline	PS056	Trillingsgaard Veno, Morten	PM128
		Trolese, Maria Chiara	PT066
Teterina, Ekaterina	PM066	Tropea, Daniela	PT158
		Trotier, Alexandre	PT117, PT085
Thai, Jade	PT138	Tsaneva-Atanasova, Kirasimira	PS106
Thai, Ngoc J.	PM104	Tsimpolis, Alexandros	PT148
Thakrar, Jamini	PM104, PT138	Tsintzas, Kostas	PM106
		Tsipouras, Markos	PT148
Thakur, Vikram	PM035		
		Tsivos, Demitra	PM078
Thal, Serge	PM137	Tucci, Valter	PS038
Thimmalapura Marulappa, Vishwanatha	PS105	Tufo, Candida	PT128
Thomas, Kerrie	PS153, PS154	Tups, Alexander	PS086, PS108
Thomasse, Lisa	PM105	Turner, Bradley	PS091
Thornton, Aoife	PT002	Turner, Thomas	PT140
Thornton, Aoife M	PM010	Turton, Sam	PT161
Thornton, Aoife M.	PM023	Tweedy, Jane	PT107
Thornton, Claire	PS128	Tyler, Lorraine	PS070
Thornton, John	PT136	Tzallas, Alexandros	PT148
Tibon, Roni	PS051		
Tigaret, Cezar, M.	PS153		
Timmons, Suzanne	PT060, PT087		
Todd, Stephen	PT072, PT083		

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ter Horst, Judith PT152

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Udakis, Matt PM044
Uh, Stepheni PT018

Ulzheimer, Norah PT112
Elisa

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Valdes, Joaquin PM170
Valente, Cláudia A PS002
Valeo, Flavia PM137
Vandrey, Brianna PM029
Vangoor, Vamshi PM145
Vann, Seralynne PS063
Vannecke, Willem PS105
Vaughan, Michael B. PT065
Veenstra-Knol, HE PM138
Velasco , Inmaculada PT102
Velasco-Estevez, PS111
Maria
Veldsman, Michele PM064
Veno, Morten PM145
Ventura-Silva , Paula PM052
Vercillo, Tiziana PT036
Verdi, Serena PT161

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van Bakel, NH PM138

van den Berg, PT066
Leonard
van der Meer, PT041
Matthijs
van der Veen, PT008
Bastiaan
van Dongen, L PM138

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W. Griffin, Eadaoin PM087
Wade, John J. PS130

Wakim, Kathryn- PT001
Mary

Upton, Thomas PM049
Urrutia Ruiz, PM156
Carolina
Ushkaryov, Yuri PT109

Verkaik, D PM138
Vertes, Petra PS156
Victor, Suresh PM026
Vieira, Andriele PS071, PS072
Vieyto, Nicole PT011
Vimalan, V PT073
Vincent, M PM138
Visscher, Peter PS036
Visser , JE PM138
Viziteu, Andrei PM177
Voisin, Caroline PS138

Volianskis, Arturas PS132
Voliotis, Margaritis PS106
Voon, Valerie PS157
Vrijnsen, Janna PS160

van Eijndhoven, PS160
Philip
van Es, Michael PT066

van Hulten , JA PM138

van Ravenswaaij- PM138
Arts, CM
van Rossum, Mark PS056

West, Steven PM053
Whelan, Robert PS010, PM015,
PM070, PM032,
PT153, PT061
Whitcomb, Daniel PS058

Wakim , Kathryn- Mary	PT011	White, Robin	PM016, PM018
Walker, Jamie J	PT093	Whiting, Andrew	PS146
Walker, Matthew	PT127	Wilkinson, Lawrence	PS153, PS154
Wall, Mark	PT064	Wilkinson, Matthew	PS134
Wall, Mathew B	PS103	Willcox, Alexandra	PT176
Wall, Matthew	PT157	Willemsen, MH	PM138
Wallace, Rachel	PM102	Williams, Angharad	PS053
Wallbank, David	PS143	Williams, Anna	PT056
Wallington, Francis	PT005	Williams, Rob	PS117
Walsh, Callum	PS062	Williams, Stuart	PS045, PM004
Walsh, Dominic	PM067, PM089	Williams, Stuart	PM028, PS127
Walsh, Kevin	PM176	Wilson, Aileen	PM104, PT138
Walshe, Elizabeth A	PM055	Wilson, Robin	PM159
Walton, Mark E	PT160	Wing, Victoria	PT161
Wang, Xiao-Jing	PT033	Winston, Flaura K	PM055
Wang, Yanqin	PT023	Winter, Carla	PM116
Wang, Yujiang	PT143	Wisden , William	PT098
Warburton, E. Clea	PT034, PT035	Withall, Janet	PM093
Ward, Hannah	PT099	Witteveen, JS	PM138
Ward, Jamie	PT016	Witton, Jonathan	PM085
Wardlaw, Joanna M.	PT056	Wong, Victoria	PT126
Warren, Greta	PS011	Wong-Lin, Kongfatt	PT083
Wassink-Ruiter, JS	PM138	Wong-Lin, KongFatt	PT072
Water , Elaine	PS112	Wood, Will	PS117
Watters, Orla	PS126	Woodhams, Stephen	PS055
Watterson, Steven	PM148, PM151	Woods, Conor	PS090
Wearn, Alfie	PM078, PM037, PT051	Woods, Ina	PT066
Webber, Lisa	PM140	Woollacott, Ione	PT055
Wegmann, Susanne	PT082	Wray, Naomi	PS036
Weidacker, Kathrin	PS157	Wren, Jonathan	PS137
Weightman, Matthew	PS170	Wright, Ingram	PT050
Wells, T	PT081	Wright, Michael	PS169
Wen, Zhexing	PS026	Wu, Qing-Feng	PT089
Werner, Mads U.	PS166	Wurdak, Heiko	PS143

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Xu, Xiangmin PS167

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Yan, Yan PM145

YEO, Shel-Hwa PM111

Yang, Elissa	PT010	Yonis, Amina	PT131
Yang, Lisa	PS103, PM140, PM107	Yoshimatsu, Takeshi	PM174
Yener, Gorsev	PT061	Yoshimura, Mitsuhiro	PT095
Yener, Görsev G	PM070	Young, Leanne	PT052
Yeo, Giles	PT091	Young, Paul	PM114
Yeo, Shel-Hwa	PS102	Yssel, Justin	PS073

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Zaaimi, Boubker	PT143	Zhu, Lan	PM129
Zahova, Simona	PM008	Zhuravlov, Oleksandr	PM095
Zargarán, David	PS103	Zickus, Vytautas	PT119
Zelenka, Ondrej	PM065	Zilles, Karl	PT033
Zhang, Cheng Fei	PT164	Zimmermann, Kirstin	PS022
Zhang, Hong	PM133	Zimmermann, Maxime	PM174
Zhang, Mengya	PM020	Zink , AM	PM138
Zhang, Qian	PS036	Ziolkowski, Luke	PM060
Zhao, Zidong	PT095	Zirpel, Florian	PT088
Zhelyazkov, Nikolay	PM035	Zou, Jiaqi	PS052
Zhou, Ying	PS026	Zsoldos, Eniko	PT084
Zhu, Bangfu	PS029	Zsoldos, Enikő	PM084
Zhu, Fangchen	PS074	Zyma, Ihor	PM095