Pleasure and pain
Hedonism and anhedonia

How the brain gives rise to pleasure and pain

L.A.B.

Leknes Affective Brain lab

Opioid effects on pleasure and pain

	Agonist	Antagonist
• Reward responsiveness	↑	↓
• Pain, stress	↓	↑
• Mood, euphoria	↑	↓

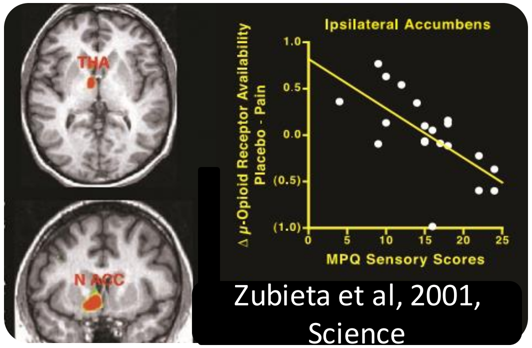
Leknes & Tracey, 2008, Nat Rev Neurosci

Human opioid studies: toolbox

- Endorphin release (blood)
  - Non-informative
- Opioid specific PET studies
  - Correlational
- Acute drug studies
  - Causal
    - Agonists
    - Antagonists
- Chronic drug studies
  - Patients typically self-recruited (to opioids)

Proopiomelanocortin

ACTH + beta-endorphin



Zubieta et al, 2001, Science

Opioid regulation of

HEDONIC TONE / REWARD RESPONSIVENESS

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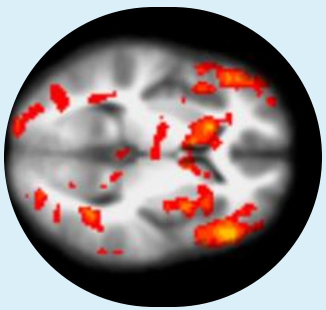
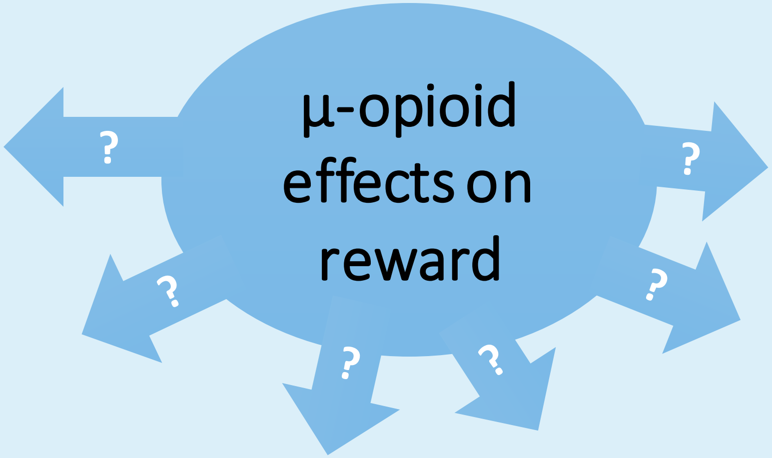
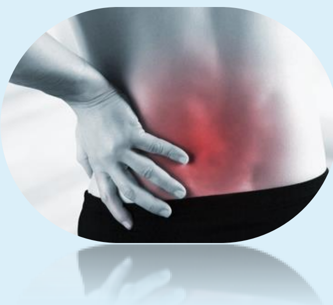
OPIOID REGULATION OF HEDONIC TONE?



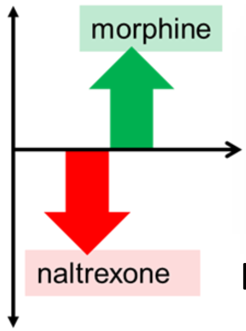




Wins & losses

Agonist & antagonist studies in healthy people

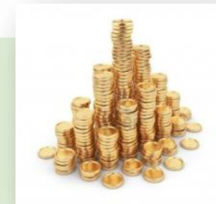
Opioid regulation of reward behaviours

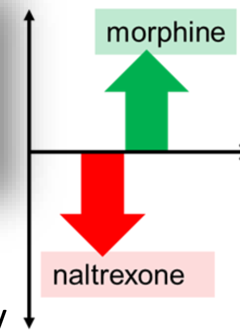


Sweet taste

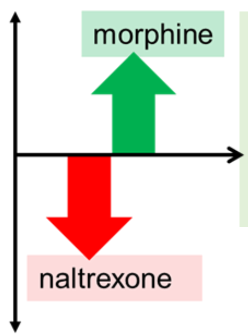
Eikemo et al, 2016, Psychopharmacology

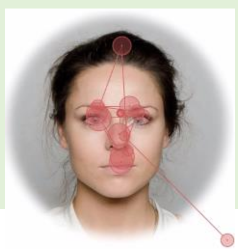
Abstract Reward





Eikemo et al, 2017, Neuropsychopharmacology

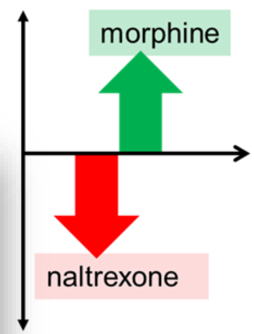




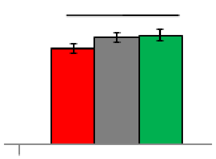
Eye gaze to faces

Chelnokova et al, 2016, SCAN

Face attractiveness

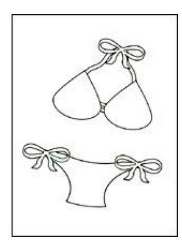


Chelnokova et al, 2014, Molecular Psychiatry

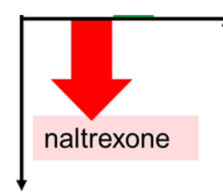


Social touch

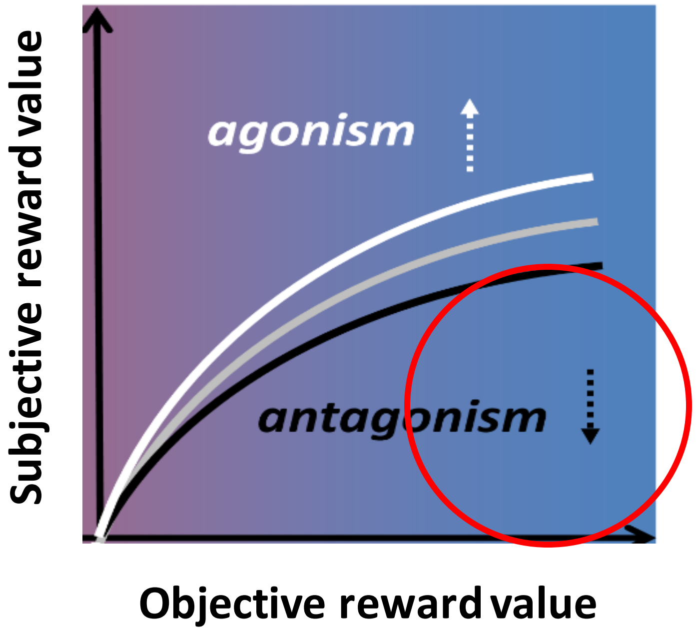
Løseth et al, 2019, SCAN,
See also Korb et al, preprint



See also
Büchel et al, 2018, eLife



Opioid regulation of ‘hedonic gloss’



van Steenbergen*, Eikemo* & Leknes, 2019, CABN

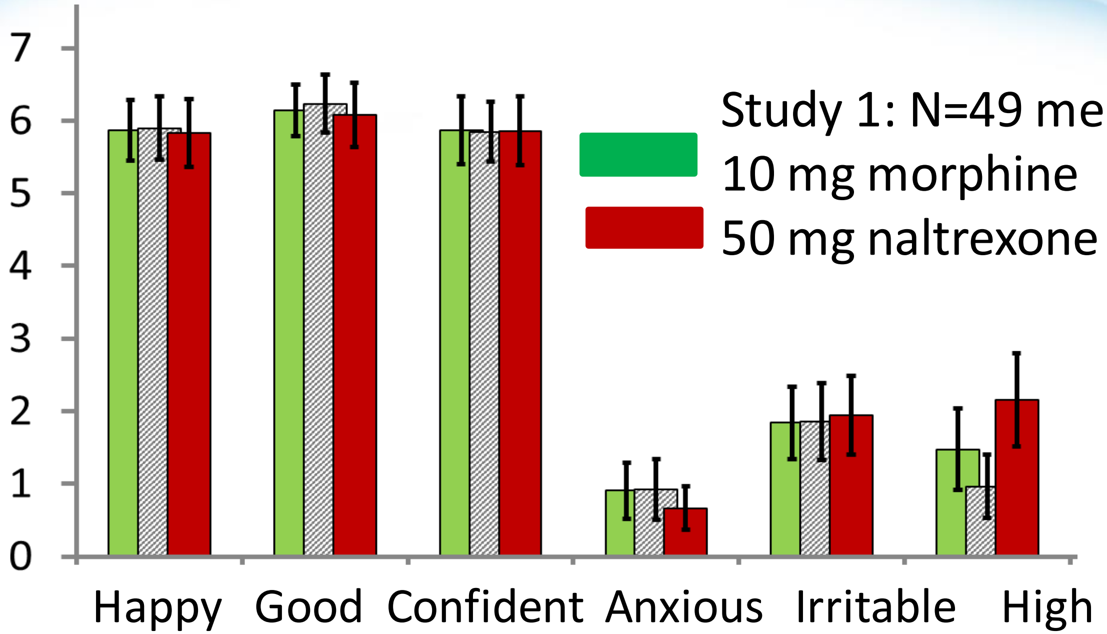
Mu-antagonism in rats

- Intact ‘baseline liking’
- Blocked **reward boost** from hunger or μ-microstimulation

Smith & Berridge, 2007, J Neurosci
Wassum et al, 2009, PNAS

MOOD

Opioid regulation of mood?



Study 1: N=49 men
10 mg morphine
50 mg naltrexone

Study 2: N=20 (10 F)
Full naloxone blockade

Study 3: N=64 (32 F)
10 mg morphine

Eikemo et al 2016, Psychopharmacol
Berna*, Leknes* et al 2018, J Neurosci; Løseth et al 2018, PNEC

E.g. **Oxycodone**: Zacny & de Wit, 2009, PBB; Wardle et al 2014, Psychopharmacol. **Remifentanil**: Wagner et al, 2010, Neuropsychologia; **Naloxone:** Eippert et al, 2009, Neuron

- Antagonist => dysphoria?
- Mu agonist => euphoria?
  - Drug liking + drug disliking

Did people like opioids in 1955?

- 20 'normal' subjects
- HEROIN (4 mg i.m.)
  - (L.E.): I felt irritable, shaky, unsteady, and nauseated. Angry at doctor for making me sick.

20 'normal subjects'

	Eu-phoric	Dys-phoric
Placebo..............	4	..
Amphetamine........	21	..
Pentobarbital......	2	..
Heroin..............	..	9
Morphine...........	..	16

Lasagna, Felsinger, Beecher, 1955, JAMA

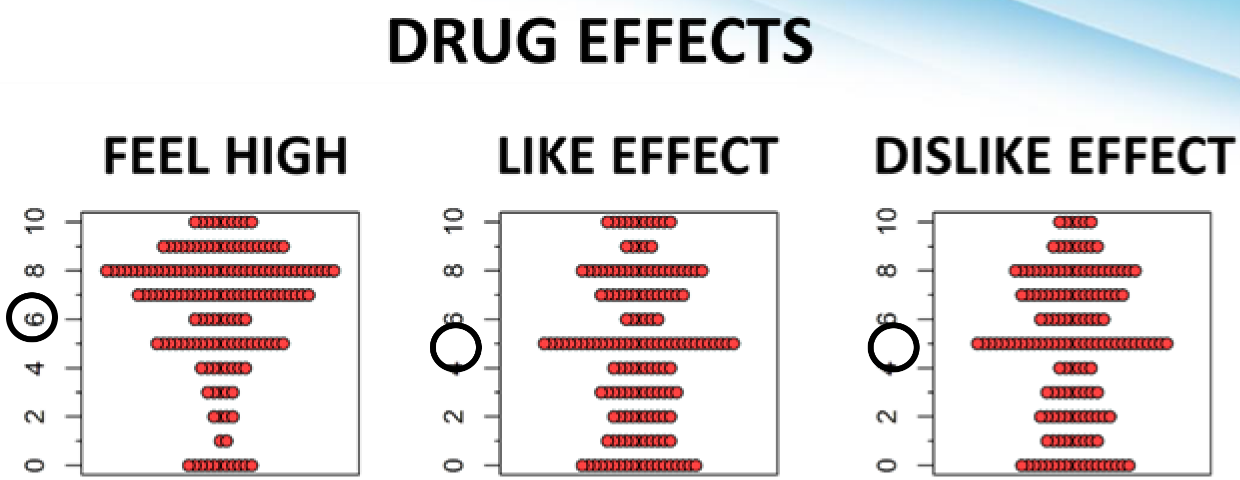
What determines opioid subjective effects?

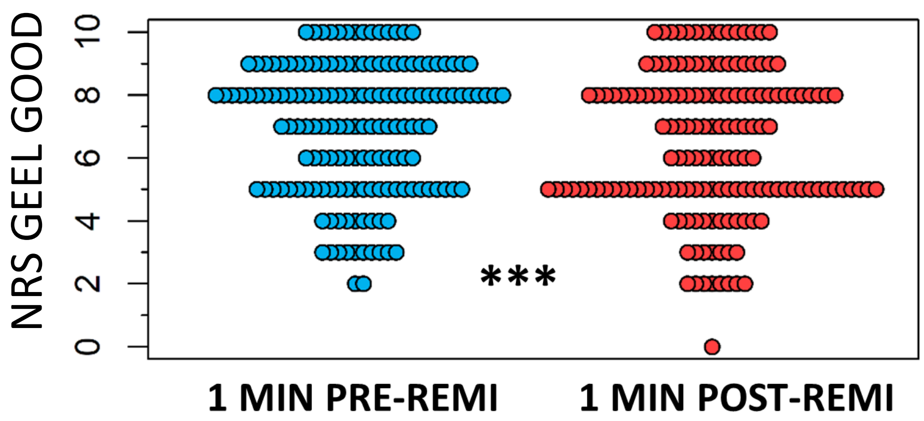
- Drug
- Dose
- Administration method
- CONTEXT + expectations
  - Lab setting
  - Placebo control

Opioid analgesics on operating table

N=160 day surgery patients:

Open-label pre-surgery remifentanil





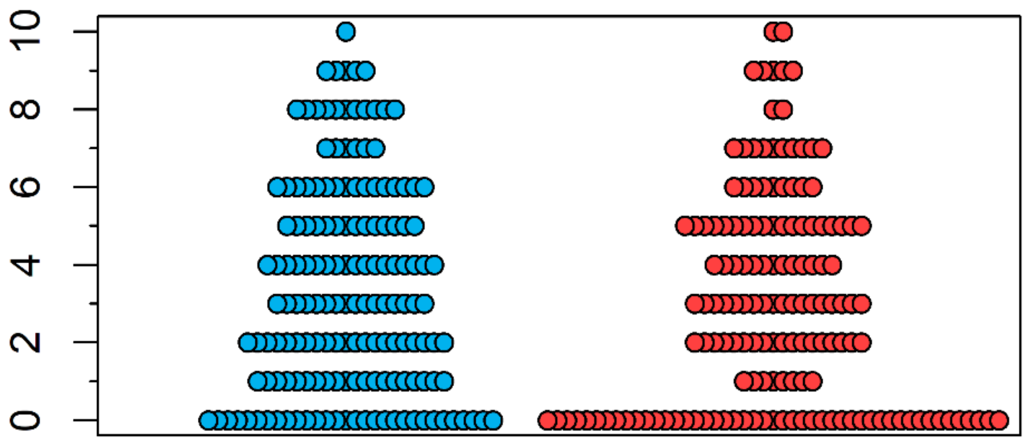
Patients felt 0.5 points LESS good

Leknes, Ernst et al, in preparation

STRESS

Opioid stress reduction on operating table?

DRUG EFFECTS ON ANXIETY



1 MIN PRE-REMI | 1 MIN POST-REMI

0.4 decrease on 11-point scale, d=0.2
BF=2 - inconclusive

N		160 (96 women)
Age		46.5 years (14.2)
Height		1.73 m (0.1)
Weight		80.3 kg (15.5)
Tobacco use		34 (21.3%)
Prior opioid use		103 (64.4%)
Prior pain (weeks before surgery)		73 (45.6%)
Procedure (N)	Surgical	74
	Orthopedic	25
	Gynaecological	52
	Otorhinolaryngological	4

- Cortisol
- Subjective stress (anxiety)

Bershad et al, 2018, Horm B; Bershad et al, 2016, PNEC

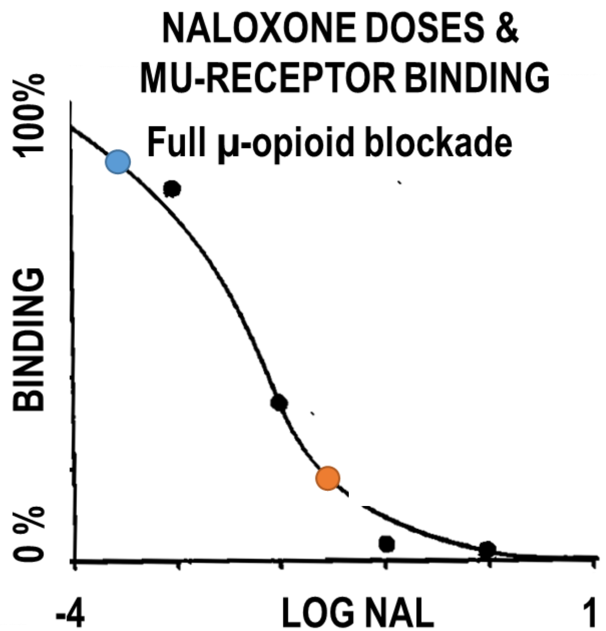
What determines opioid subjective effects?

- Drug
- Dose
- Administration method
- CONTEXT + expectations
- WHO + their experience
  - **Self-selected opioid users** typically like opioids
    - Due to exposure or early trauma/mood disorder?
  - People in pain often **want** opioid analgesia
    - We cannot infer opioid liking from this

PAIN

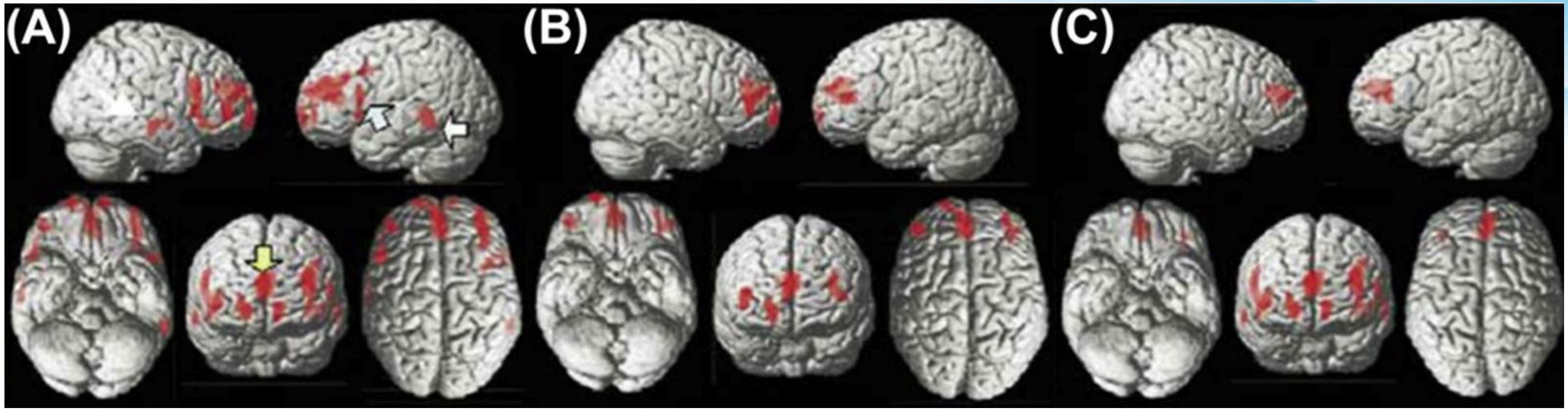
Endogenous opioid regulation of pain?

- Opioid agonists relieve pain
- Stress, pain and reward reduce pain
  - In non-human animals, opioid-dependent
  - In humans, evidence is mixed



Werner et al, 2015, PLoS ONE;
Berna*, Leknes* et al, 2018, J Neurosci

Mayberg & Frost, 1990, *Quantitative Imaging;*
Leknes & Atlas, 2019, British J Anaesthesia

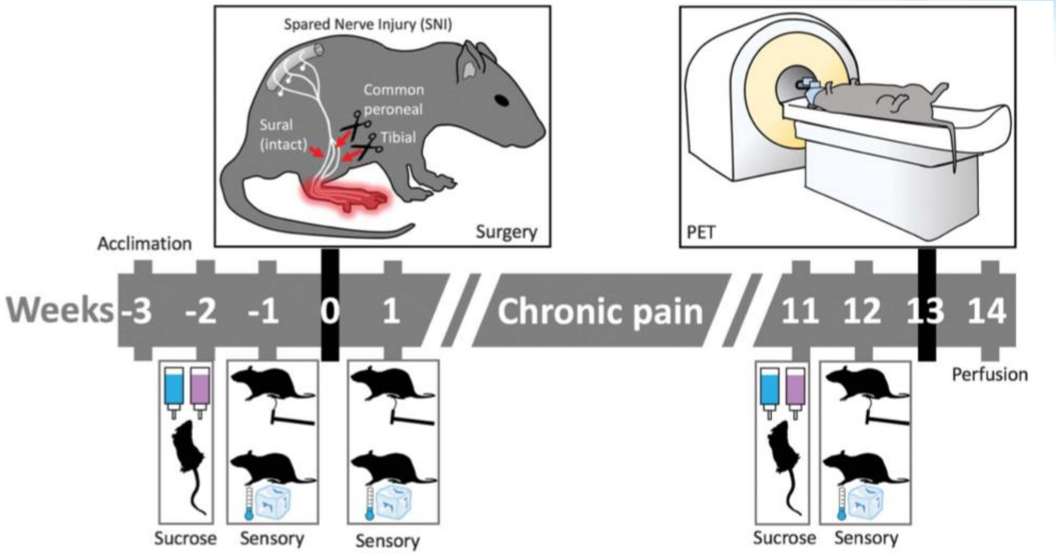


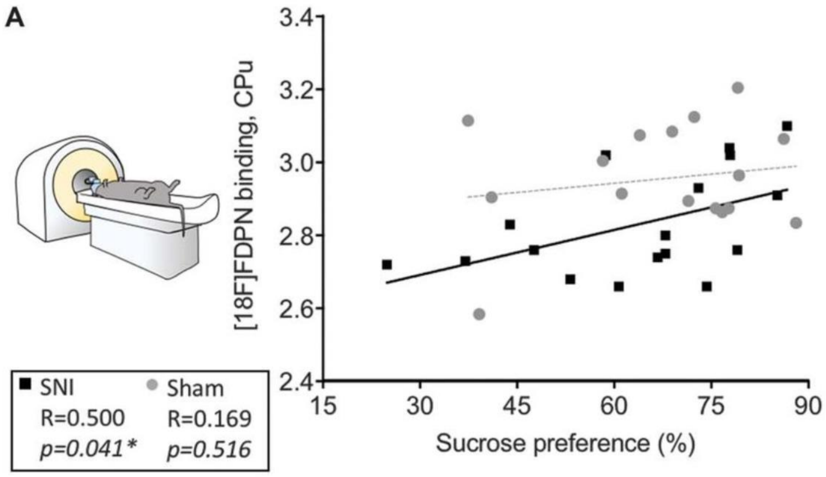
μ-binding in cocaine addiction changes over time,
Image from Colasanti et al, 2013, Biol Res Addiction

Chronic opioid activation alters receptor binding

OPIOID DISRUPTION OF HEDONIC TONE?

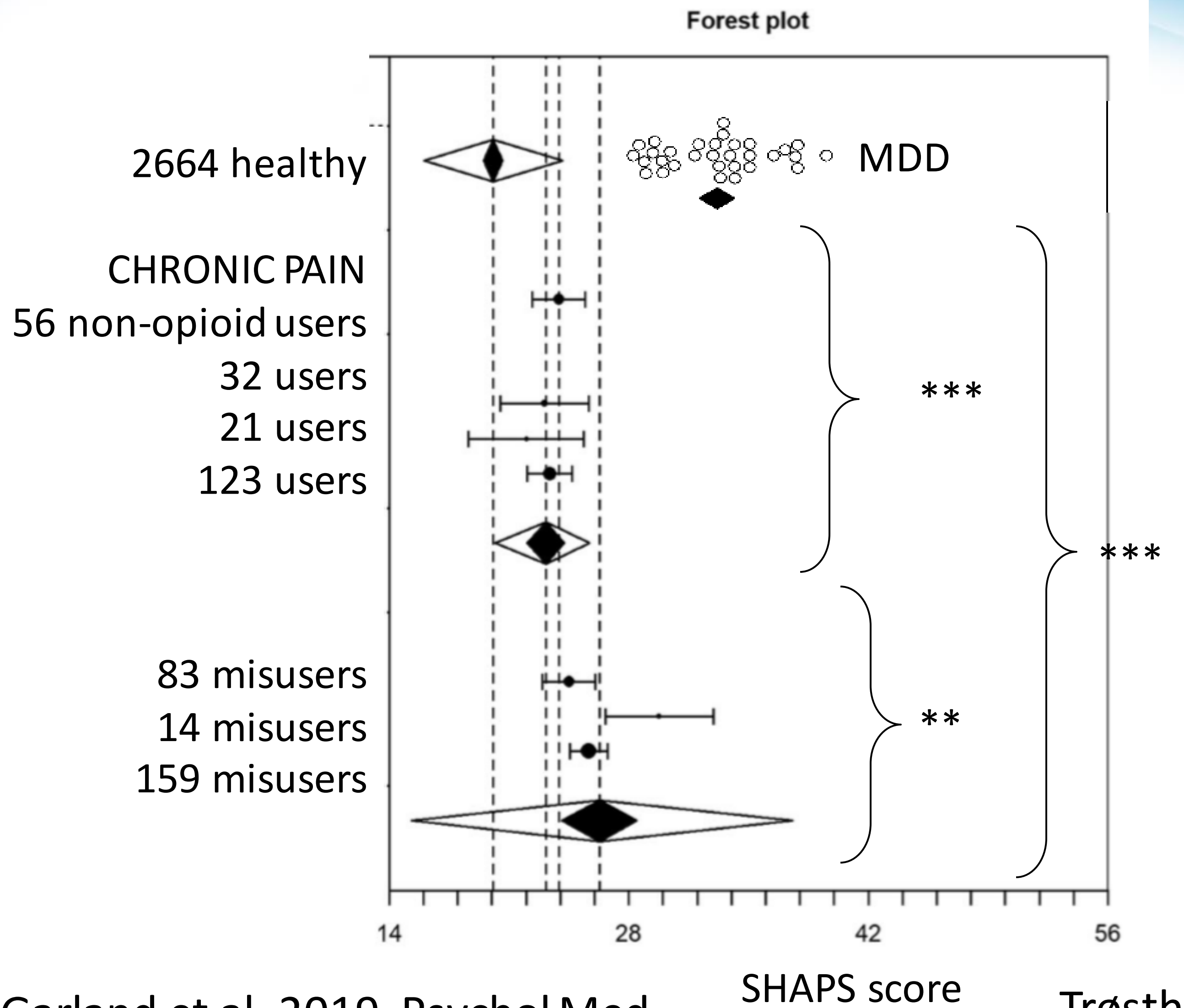
Anhedonia in chronic pain - rodents





Thompson et al, 2018, Pain

Anhedonia in chronic pain - humans



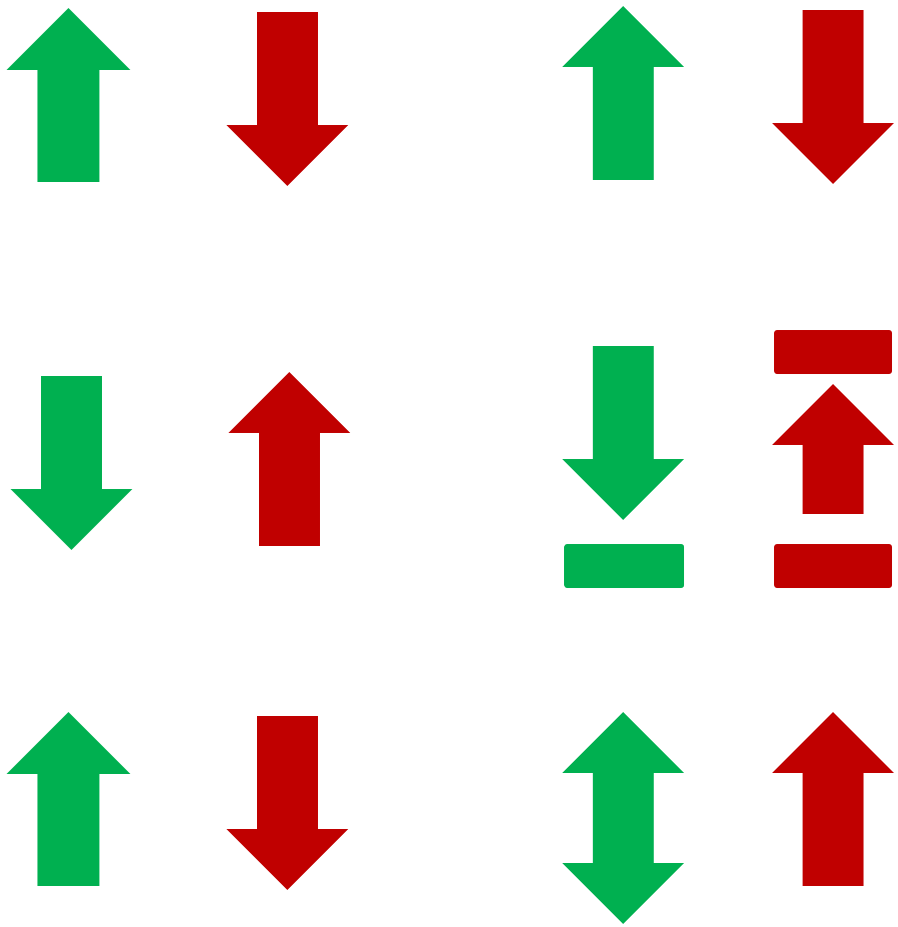
Garland et al, 2019, Psychol Med

Trøstheim et al, in preparation

Opioid effects on pleasure and pain

	OPIOID USERS		HEALTHY NON-USERS	
	Agonist	Antagonist	Agonist	Antagonist

- Reward responsiveness
- Pain, ~~stress~~
  - Cortisol
  - Subjective stress
- Mood, euphoria



Opioids: hedonism or anhedonia?

- Classic opioid effects in **self-selected users**
  - Stress relief
  - Drug liking, euphoria
- Endogenous opioids may yield ‘hedonic gloss’ in healthy humans

- Let’s dismiss hedonism: opioid liking is rare
- Long-term opioid misuse => anhedonia

L.A.B.

Leknes Affective Brain lab

UNIVERSITAS OSLOENSIS MDCCCXI

Current team

Siri Leknes

Professor & PI

Marie Eikemo

Postdoc

Guro Løseth

PhD student

Gernot Ernst

Anesthetist physician

Martin Trøstheim

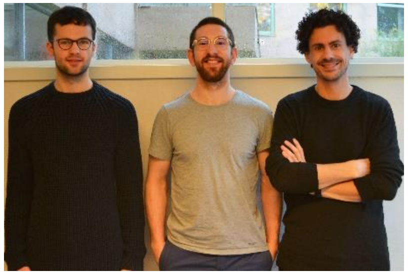
PhD student

Guido Biele

Professor II

Andreas Dahl

MA student



HELSE SØR-ØST

The Research Council of Norway

erc European Research Council

Oslo University Hospital

- How brain creates pleasure and pain
- Start with opioid system
- ACUTE
  - Pain relief
  - Reward behaviours
  - BUT no opioid liking without self-selection
- CHRONIC
  - Opioid liking
  - Anhedonia
- Sum: opioids do some of what we thought, but less

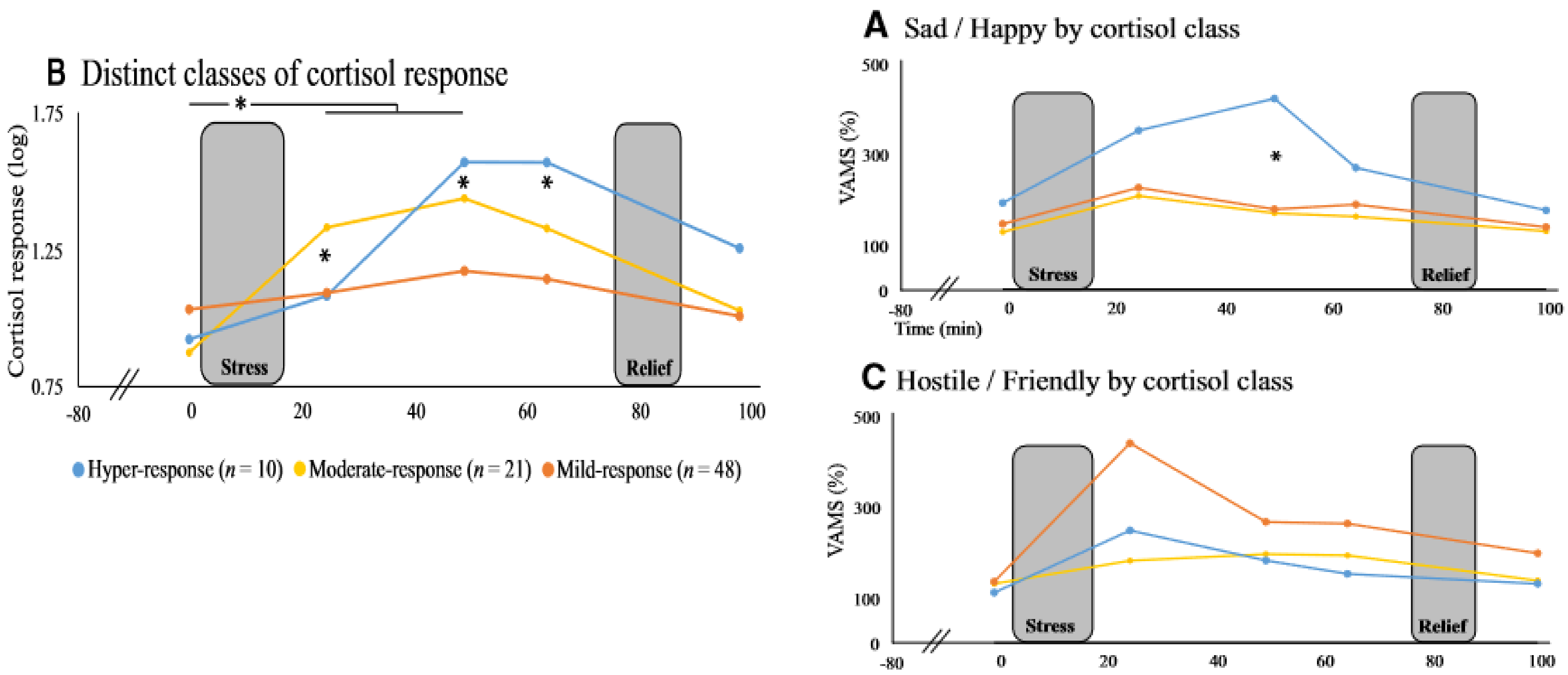
Major neurotransmitters:

- **Amino acids:** glutamate,[6] aspartate, D-serine, γ-aminobutyric acid (GABA),[nb 1] glycine
- **Gasotransmitters:** nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S)
- **Monoamines:** dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine, serotonin (SER, 5-HT)
- **Trace amines**: phenethylamine, *N*-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc.
- **Peptides:** oxytocin, somatostatin, substance P, cocaine and amphetamine regulated transcript, opioid peptides[11]
- **Purines:** adenosine triphosphate (ATP), adenosine
- **Catecholamines**: dopamine, norepinephrine (noradrenaline), epinephrine (adrenaline)
- Others: acetylcholine (ACh), anandamide, etc.

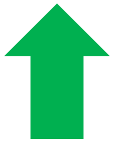
In addition, over 50 neuroactive peptides have been found, and new ones are discovered regularly. Many of these are "co-released" along

Cortisol ≠ subjective stress

- ~25% of stress studies report correlation between cortisol & subjective stress



Who are the ‘opioid likers’?

- Clinicians and former users suggest:
  - A subgroup vulnerable to addiction
  - Recreational and dependent opioid users 

STRESS IN OPIOID USERS

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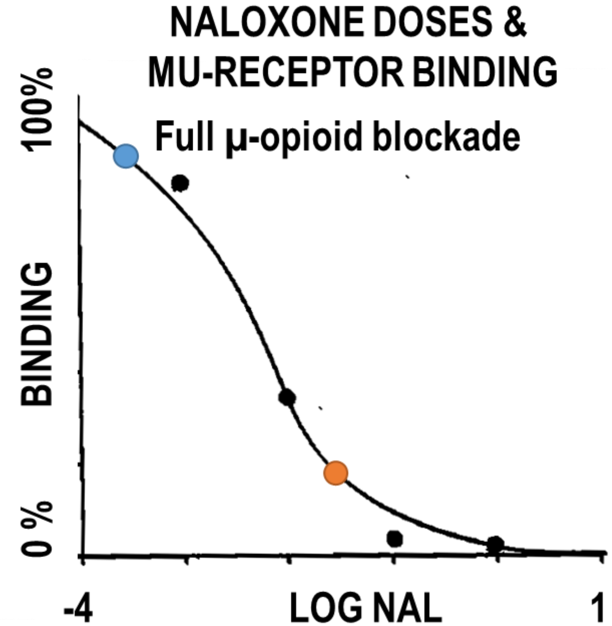
June 2019 Volume 122, Issue 6, Pages e216–e219

The opioid agonist remifentanil increases subjective pleasure

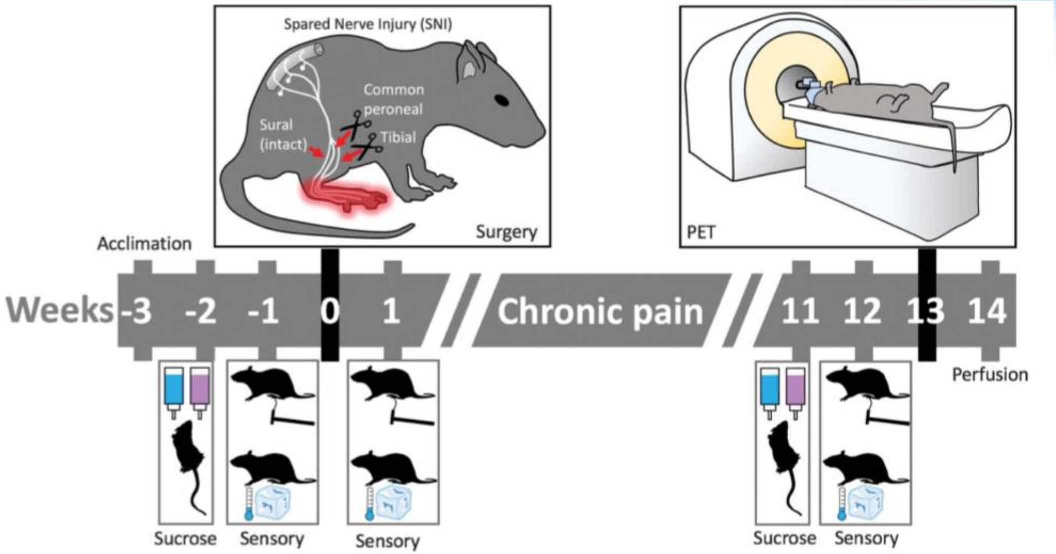
Tarja Heiskanen[1,*], Mika Leppä[2], Juulia Suvilehto[2], Minna Elomaa[1], Ethem Akural[1], Tekla Larinkoski[3], Iiro Jääskeläinen[3], Mikko Sams[3], Lauri Nummenmaa[4], Eija Kalso[1]

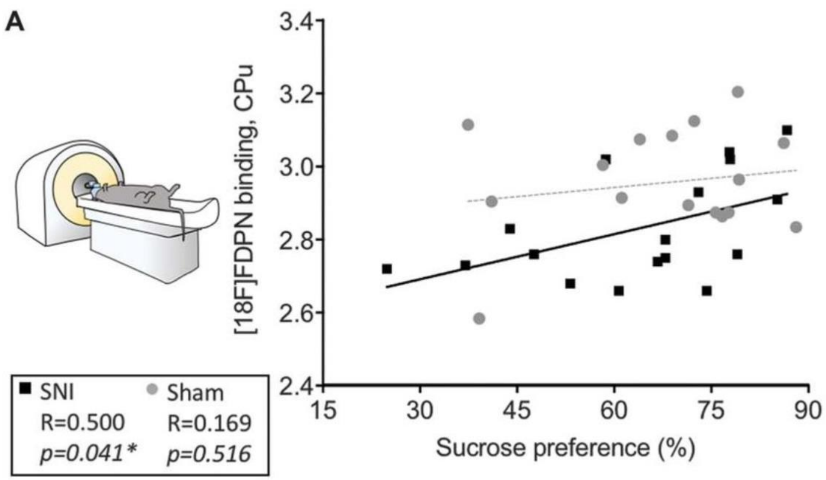
- Single-blind
- Fixed order
- One-session
- Measured valence, not mood



Leknes & Atlas, in review, BJA

Anhedonia in chronic pain - rodents





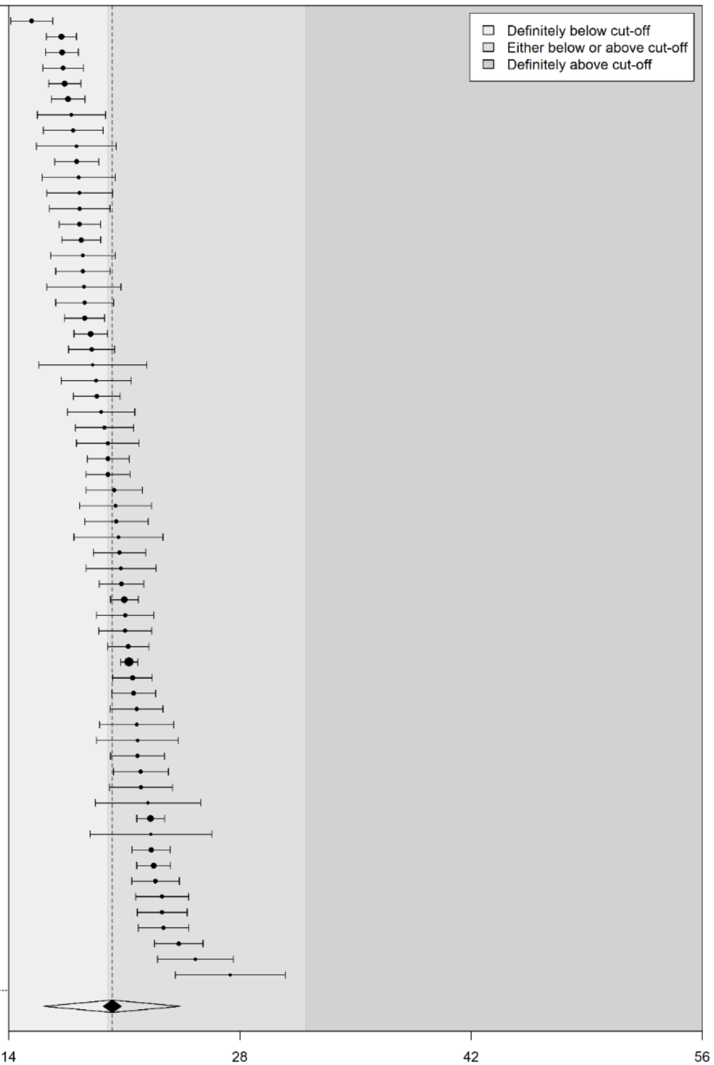
Thompson et al, 2018, Pain

Anhedonia: meta-analysis SHAPS scores – healthy people

Study	N	Female	Age	Depression	Anhedonic	SHAPS [95% CI]
Ricciardi et al. (2016)	20	60%	56.5 (10.8)	12.4 (15.0)	---	15.4 [14.1, 16.7]
Barch et al. (2014)*	39	51%	37.4 (9.2)	4.6 (7.1)	---	17.2 [16.3, 18.1]
Mann et al. (2013)	39	51%	36.5 (9.1)	---	---	17.2 [16.2, 18.2]
Chung & Barch (2015)	27	44%	35.6 (8.6)	3.4 (5.6)	---	17.3 [16.1, 18.5]
Eisenstein et al. (2017)*	59	56%	32.6 (9.2)	---	---	17.4 [16.4, 18.4]
Culbreth, Gold et al. (2016)*	36	47%	36.6 (9.2)	4.8 (7.6)	---	17.6 [16.6, 18.6]
Tudge et al. (2015)*	20	50%	25.4 (4.5)	2.2 (3.6)	---	17.8 [15.7, 19.9]
Vrieze, Ceccarini et al. (2013)*	10	100%	33.3 (8.2)	2.7 (2.5)	---	17.9 [16.1, 19.7]
Steele et al. (2007)	14	50%	43.0 (13.3)	1.7 (3.0)	---	18.1 [15.7, 20.5]
Gradin et al. (2015)*	25	68%	25.4 (5.0)	0.6 (1.2)	---	18.1 [16.8, 19.5]
Young et al. (2013)*	32	69%	34.4 (10.5)	0.7 (2.4)	---	18.2 [16.0, 20.5]
Kumar et al. (2008)*	18	61%	42.0 (12.8)	4.8 (4.4)	---	18.3 [16.3, 20.3]
Sprengelmeyer et al. (2011)	21	57%	42.0 (12.9)	4.9 (4.6)	---	18.3 [16.5, 20.1]
Misaki et al. (2016)	45	27%	32.0 (9.3)	4.7 (4.6)	---	18.3 [17.0, 19.6]
Godlewska et al. (2018)*	50	56%	31.3 (9.9)	1.2 (1.8)	---	18.4 [17.2, 19.6]
Fervaha et al. (2013)*	16	44%	27.5 (4.5)	1.1 (3.0)	---	18.5 [16.5, 20.5]
Nugent et al. (2018)*	26	62%	33.9 (10.4)	2.0 (2.1)	---	18.5 [16.8, 20.2]
Pechtel & Pizzagalli (2013)*	16	100%	30.4 (10.8)	2.7 (2.8)	---	18.6 [16.3, 20.8]
Kumar et al. (2018)*	25	76%	26.1 (8.1)	0.7 (1.5)	---	18.6 [16.8, 20.4]
Lansdall et al. (2017)	50	54%	70.6 (6.5)	6.7 (6.3)	---	18.6 [17.4, 19.8]
Gadeikis et al. (2017)*	99	60%	34.0 (13.8)	8.0 (7.3)	---	19.0 [17.9, 20.0]
Chase et al. (2017)*	52	56%	21.3 (1.8)	17.0 (6.5)	---	19.0 [17.6, 20.4]
Young, Bellgowan et al. (2014)*	16	62%	27.3 (8.0)	0.9 (2.0)	---	19.1 [15.8, 22.4]
Culbreth, Westbrook et al. (2016)*	30	53%	35.9 (8.2)	---	---	19.3 [17.2, 21.4]
Horndasch et al. (2016)*	36	100%	23.9 (8.3)	7.2 (6.7)	---	19.3 [17.9, 20.8]
Szczepanik et al. (2017)	23	43%	31.8 (8.0)	2.7 (4.4)	---	19.6 [17.6, 21.6]
Stevens et al. (2007)	26	0%	28.6 (6.5)	7.6 (2.4)	---	19.8 [18.0, 21.6]
Scheidegger et al. (2012)*	19	53%	40.5 (7.5)	---	---	20.0 [18.1, 21.9]
Auerbach et al. (2017)	50	100%	13.0 (0.8)	10.4 (11.9)	---	20.0 [18.7, 21.3]
Walsh et al. (2018)*	42	69%	30.2 (8.1)	12.2 (7.1)	---	20.0 [18.7, 21.4]
Garfield et al. (2017)	33	24%	36.0 (8.9)	15.3 (15.5)	---	20.4 [18.7, 22.1]
Renfroe et al. (2016)*	15	40%	70.0 (6.9)	4.1 (3.9)	---	20.5 [18.3, 22.6]
Greenberg et al. (2015)*	31	61%	38.4 (15.7)	2.7 (5.0)	---	20.5 [18.6, 22.4]
Dean et al. (2016)*	17	53%	24.0 (4.3)	2.7 (5.0)	---	20.6 [18.0, 23.3]
Ubl et al. (2015)*	28	54%	44.0 (12.8)	2.7 (3.9)	---	20.7 [19.1, 22.3]
Admon & Pizzagalli (2015)*	30	73%	30.2 (11.1)	1.9 (3.3)	---	20.8 [18.7, 22.9]
Liu, Wang, Zhao et al. (2012)	61	49%	26.1 (5.7)	4.3 (3.6)	---	20.8 [19.5, 22.2]
Kirkpatrick et al. (2016)*	97	70%	23.3 (4.1)	7.5 (10.0)	---	21.0 [20.2, 21.8]
Dillon et al. (2015)*	37	62%	36.2 (14.3)	5.4 (4.8)	---	21.1 [19.3, 22.8]
Pechtel et al. (2013)*	36	64%	31.8 (12.5)	2.1 (2.8)	---	21.1 [19.5, 22.7]
Huneke et al. (2017)*	60	50%	23.4 (4.3)	14.0 (6.5)	---	21.2 [20.0, 22.5]
Ang et al. (2017)	479	52%	29.7 (10.7)	17.8 (16.2)	---	21.3 [20.8, 21.8]
Liu, Wang, Zhu et al. (2012)	72	60%	30.9 (10.4)	4.6 (4.6)	---	21.5 [20.3, 22.7]
Lempert & Pizzagalli (2010)	36	56%	26.3 (7.5)	7.6 (8.1)	---	21.6 [20.2, 22.9]
Osuch et al. (2016)*	40	50%	20.1 (1.3)	7.5 (8.7)	---	21.8 [20.2, 23.3]
Yang et al. (2017)	28	46%	28.6 (6.9)	12.6 (8.7)	---	21.8 [19.5, 24.0]
Lawson et al. (2017)*	25	44%	27.4 (8.8)	4.6 (4.8)	---	21.8 [19.3, 24.3]
McCabe et al. (2012)*	25	64%	18.6 (1.6)	5.7 (5.4)	---	21.8 [20.2, 23.4]
Drijgers et al. (2012)*	23	9%	65.4 (9.2)	4.0 (3.6)	---	22.0 [20.3, 23.7]
Admon et al. (2017)*	43	77%	25.9 (6.3)	11.1 (6.6)	---	22.0 [20.1, 23.9]
Liu et al. (2014)	27	56%	34.1 (10.2)	5.4 (10.0)	---	22.4 [19.3, 25.6]
Al Aïn et al. (2013)	107	59%	23.9 (3.4)	6.2 (4.7)	---	22.6 [21.8, 23.4]
Han (2017)*	18	72%	30.1 (9.9)	8.6 (7.0)	---	22.6 [18.9, 26.3]
Liu et al. (2011)	87	52%	26.2 (6.5)	17.0 (6.4)	---	22.6 [21.5, 23.8]
Liu et al. (2016)	107	56%	32.5 (9.3)	8.3 (4.8)	---	22.8 [21.8, 23.8]
Ng et al. (2014)	82	43%	37.0 (12.6)	---	---	22.9 [21.4, 24.3]
Chuang et al. (2014)*	20	20%	34.3 (10.4)	1.3 (2.0)	---	23.3 [21.7, 24.9]
Yoshida et al. (2017)	65	43%	34.8 (13.0)	11.0 (9.4)	---	23.3 [21.8, 24.8]
Arrondo et al. (2015)*	21	19%	34.3 (10.1)	6.8 (7.8)	---	23.4 [21.8, 24.9]
Norbury, et al. (2015)*	45	62%	24.3 (3.5)	---	---	24.3 [22.8, 25.8]
Rzepa & McCabe (2016)*	35	71%	16.5 (1.4)	24.9 (14.8)	---	25.3 [23.0, 27.6]
Ryu (2013)*	24	54%	31.9 (6.7)	---	---	27.4 [24.1, 30.7]
Summary	2835	55%	31.2 (9.2)	9.3 (9.4)	---	20.3 [19.7, 20.8]

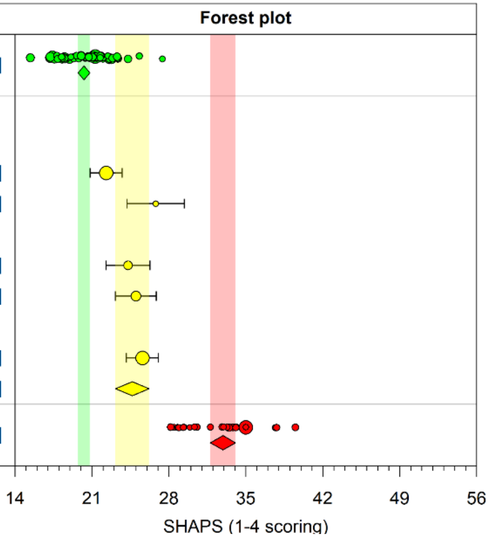
k = 62; Q (df) = 550.5 (61), p < .0001; $T^2 = 4.0$; T = 2.0; $I^2 = 89\%$

Forest plot of individual study effects (healthy)

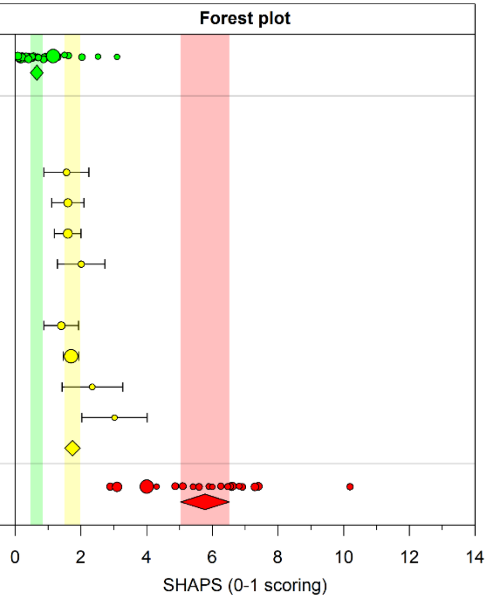


Anhedonia in substance dependence?

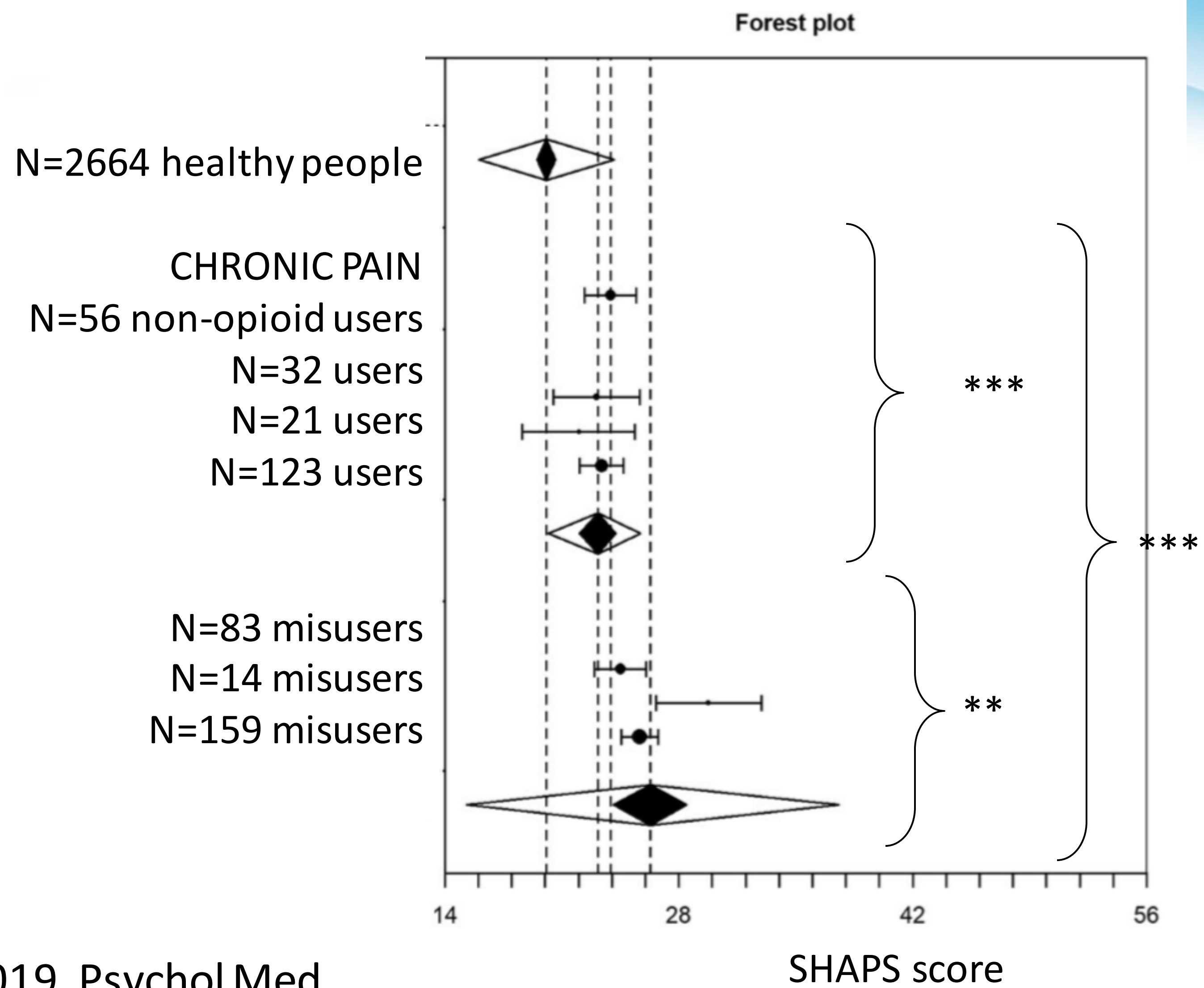
Group or study	Substance	k	N	SHAPS [95% CI]
Healthy		62	2835	20.27 [19.72, 20.81]
Substance use disorders				
Abstinent				
Stevens et al. (2007)	Polydrug		26	22.30 [20.84, 23.76]
Garfield et al. (2017)	Opioids		31	26.80 [24.20, 29.40]
Current use				
Stevens et al. (2007)	Polydrug		25	24.30 [22.30, 26.30]
Wardle et al. (2017)	Stimulants		85	25.00 [23.15, 26.85]
Pharmacotherapy				
Garfield et al. (2017)	Opioids		90	25.60 [24.13, 27.07]
Summary:		5	257	24.67 [23.15, 26.19]
Major depressive disorder (Current)		25	1481	32.91 [31.77, 34.06]



Group or study	Substance	k	N	SHAPS [95% CI]
Healthy		36	3138	0.65 [0.46, 0.85]
Substance use disorders				
Abstinent				
Huhn et al. (2016)	Opioids		36	1.56 [0.87, 2.25]
Janiri et al. (2005)	Various		70	1.60 [1.11, 2.09]
Martinotti et al. (2008b)	Alcohol		102	1.60 [1.19, 2.01]
Martinotti et al. (2008a)	Alcohol/opioids		50	2.01 [1.29, 2.73]
Current use				
Ersche et al. (2012)	Stimulants		50	1.40 [0.87, 1.93]
dela Cruz et al. (2016)	Stimulants		299	1.70 [1.46, 1.94]
Boger et al. (2014)	Various		40	2.35 [1.42, 3.28]
Balducci (2009)	Alcohol		40	3.02 [2.03, 4.02]
Summary:		8	687	1.74 [1.51, 1.98]
Major depressive disorder (Current)		24	1234	5.78 [5.03, 6.52]

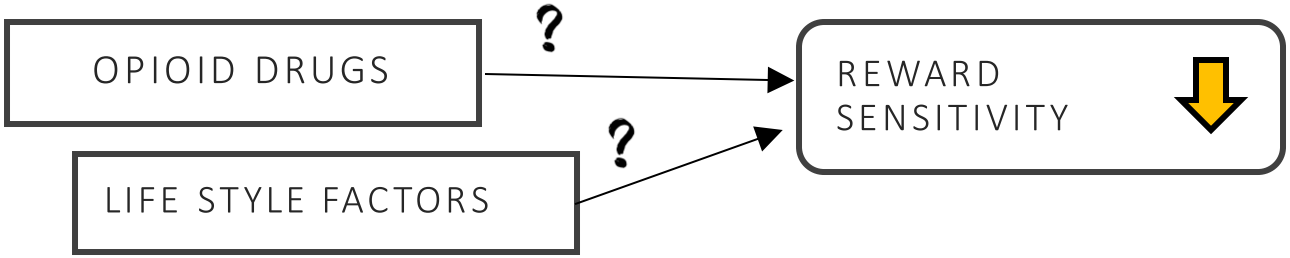


Anhedonia in chronic pain - humans

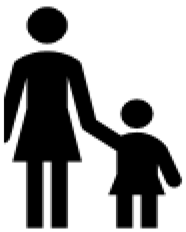


Garland et al, 2019, Psychol Med

Anhedonia in long-term opioid maintenance?



- Unique patient group of mothers in opioid agonist treatment
- Custody of children = fewer life style ‘risk’ factors

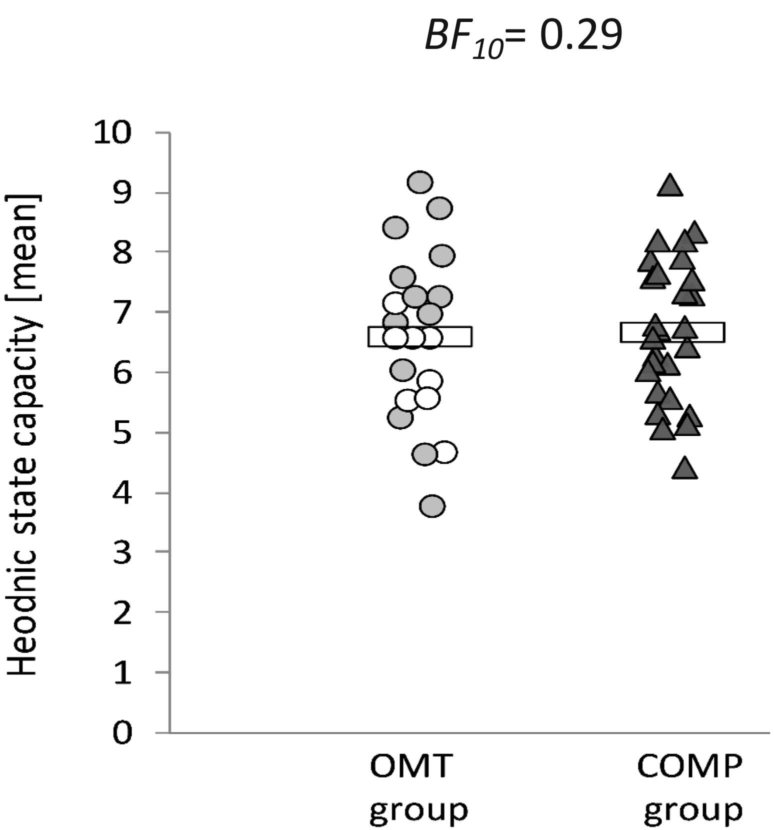


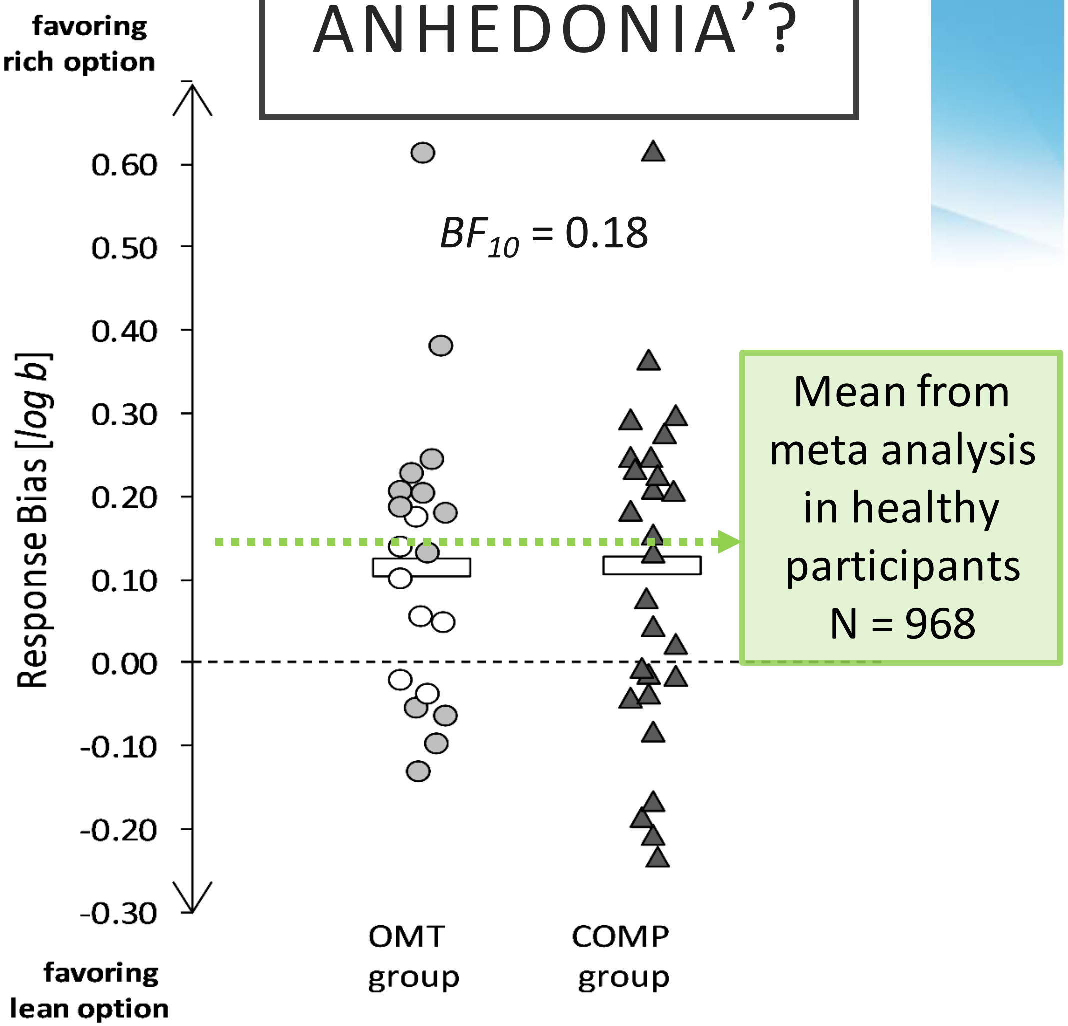
23 patients
29 controls

Eikemo et al, preprint PsyArXiv

SUBJECTIVE ANHEDONIA?

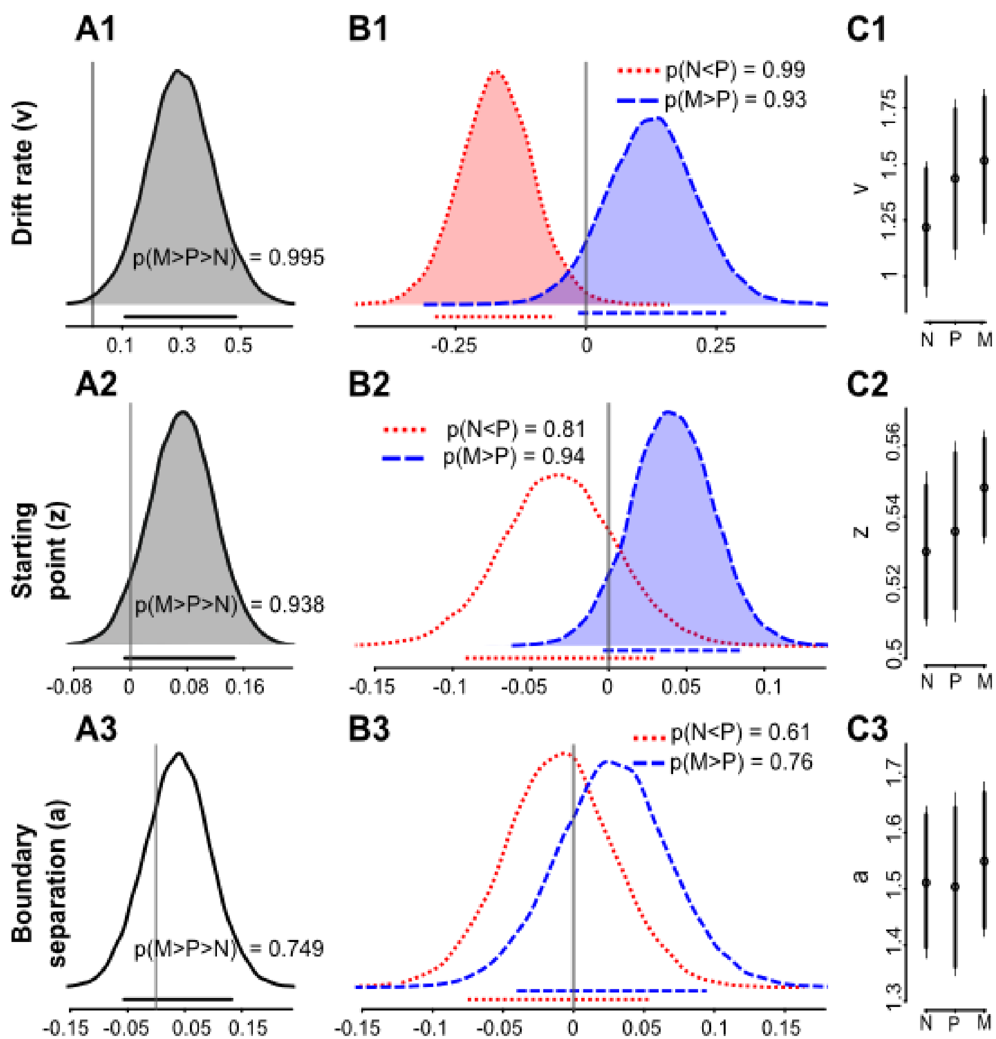
'OBJECTIVE ANHEDONIA'?

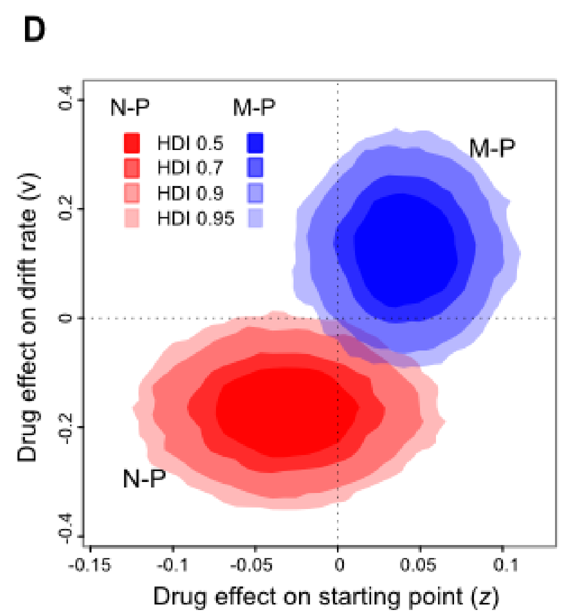




Eikemo et al, 2019, NPP

Opioid modulation of value-based decisions

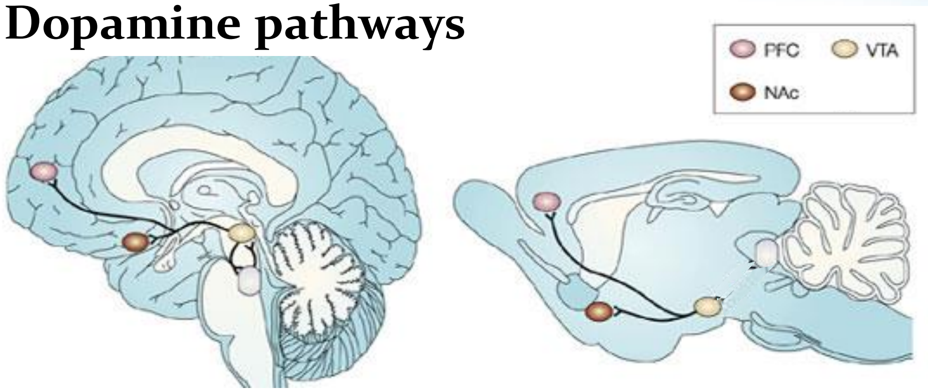




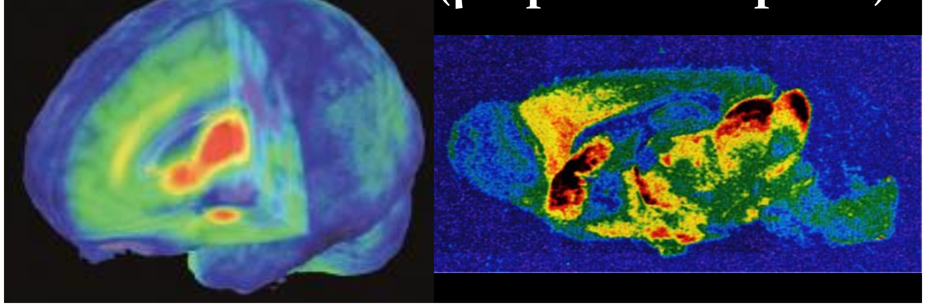
Eikemo et al, in press, Neuropsychopharmacology

Opioids & the neurobiology of addiction

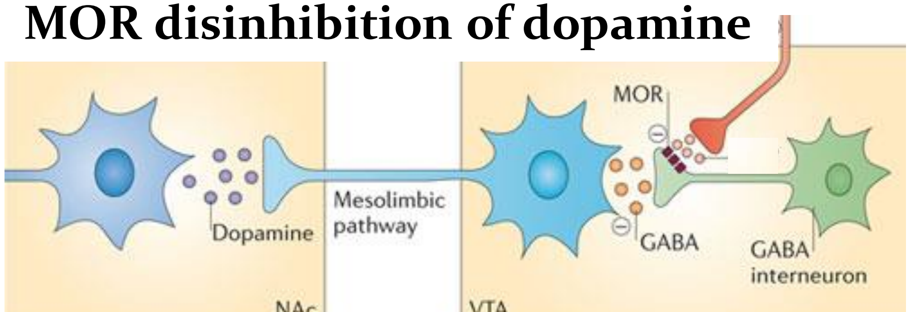
Dopamine pathways



MOR distribution (μ-opioid receptors)



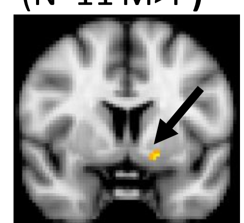
MOR disinhibition of dopamine



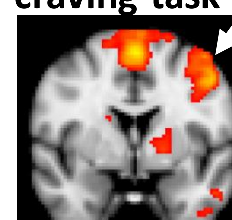
N= 64
Within-subject

Pharmacological fMRI

Reward task
(N=11 M>P)



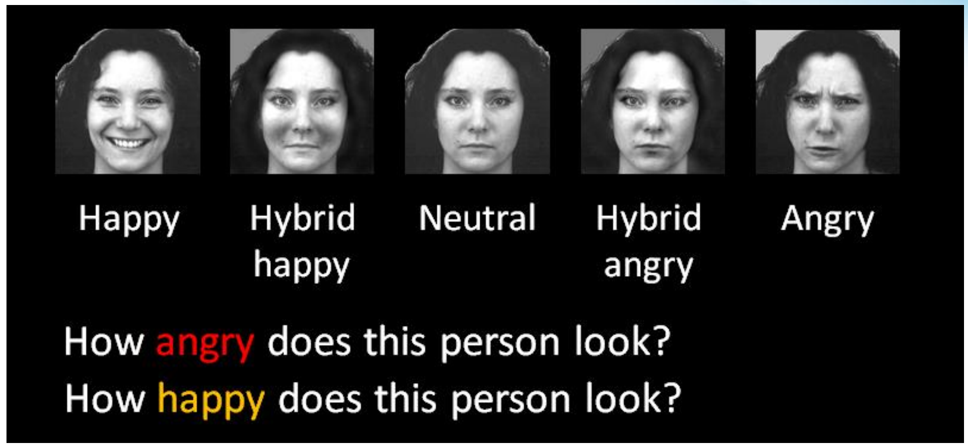
Regulation & craving task

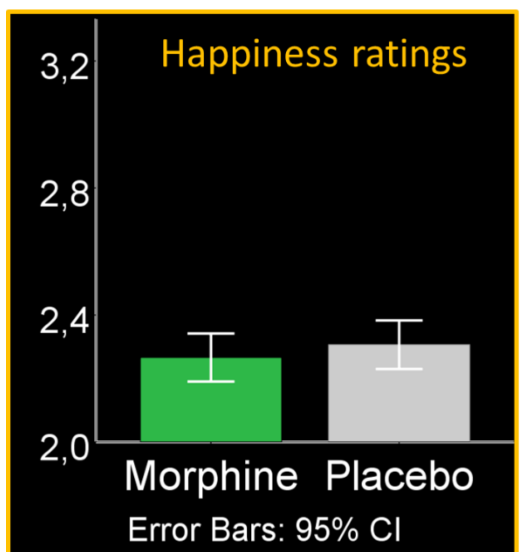


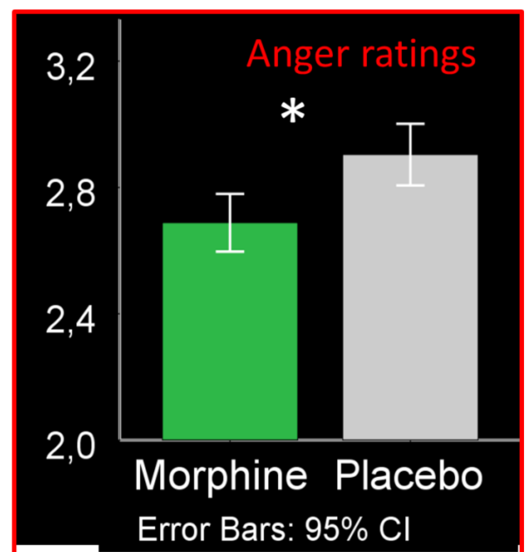
Morphine reduced anger perception

- N=64 (32♀)

cross-over

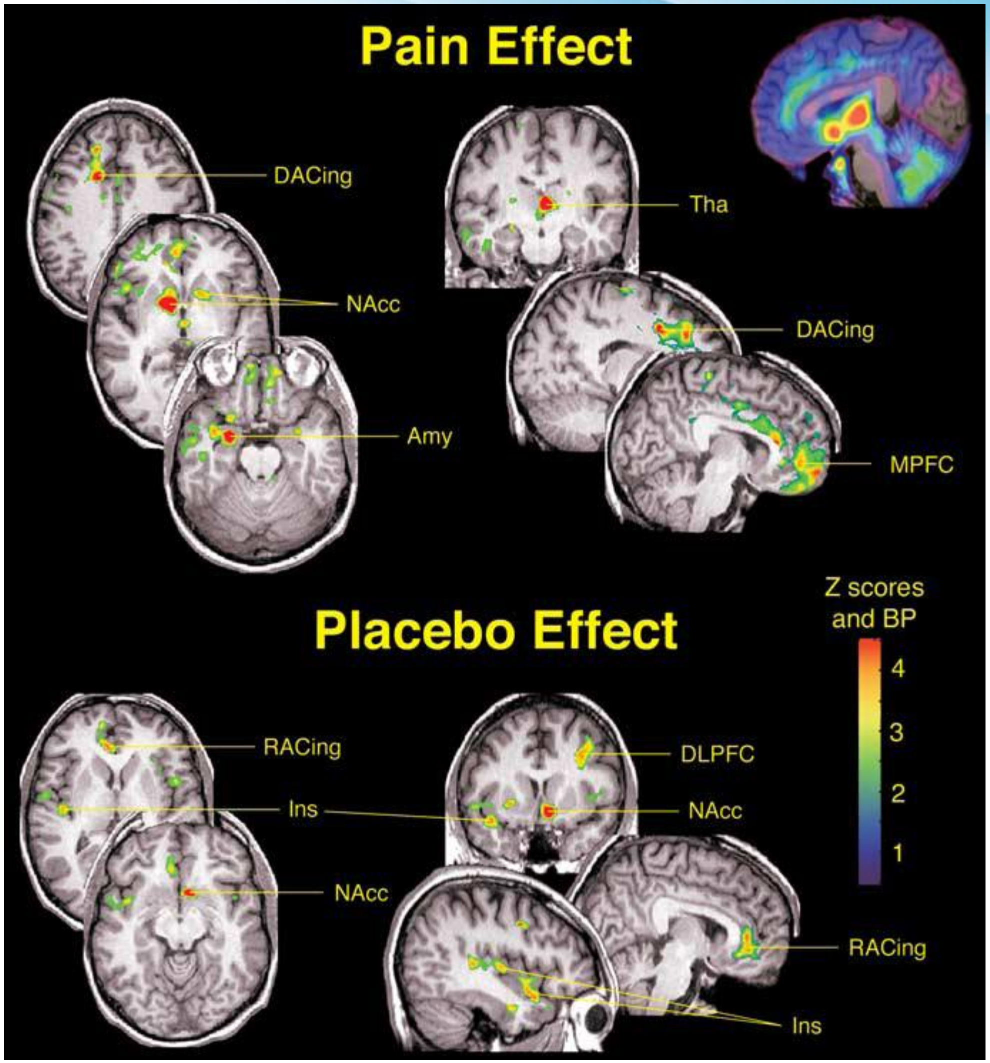






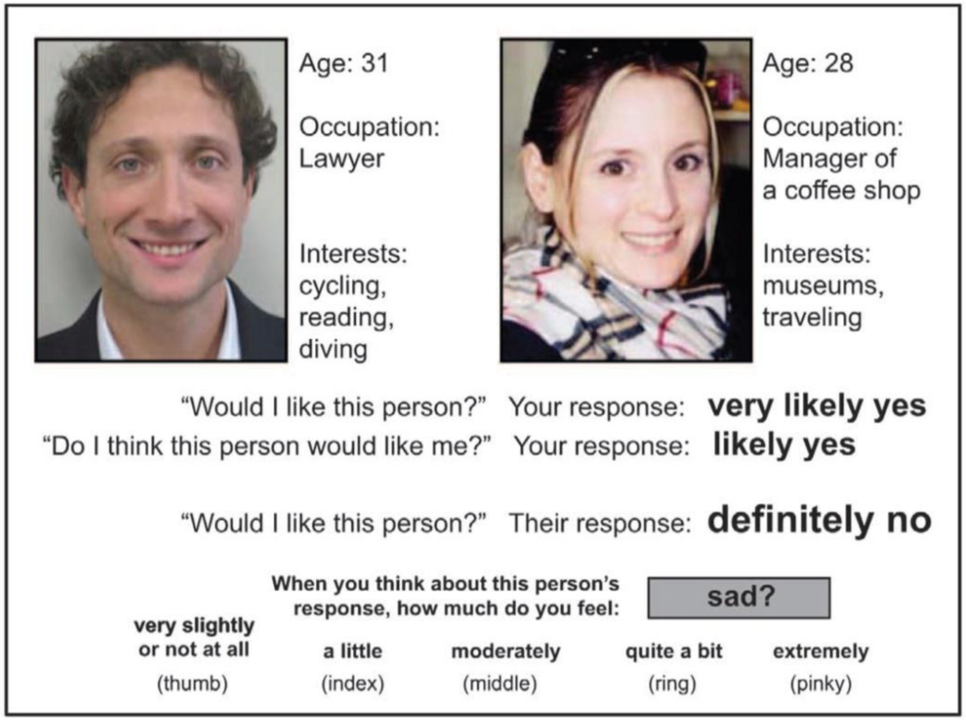
Endogenous μ-opioid relief: placebo

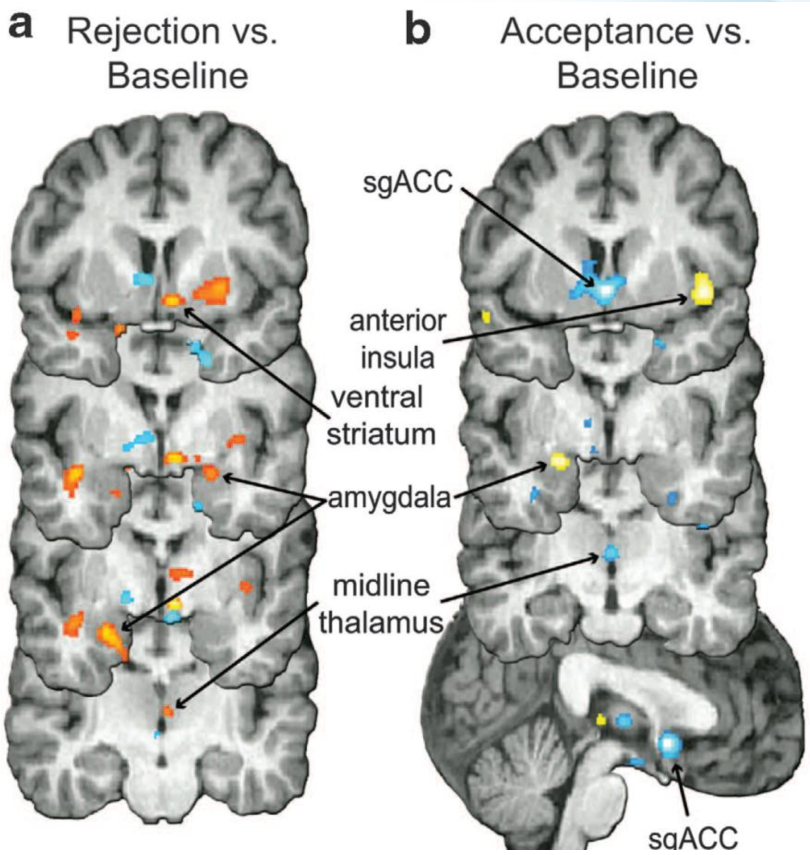
Levine et al, 1978, Lancet



Zubieta et al 2005, J Neurosci

Opioid regulation of social emotions





Hsu et al, 2013, Molecular Psychiatry