Brain Mechanisms of Relapse Prevention Medications for Opioid Use Disorder

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Disclosure Information

Zhenhao Shi, PhD

- No Disclosures

RDoC Domains & Constructs

Positive Valence
Craving
Delay Discounting
Incentive Sensitization

Social Processes
Emotion Recognition
Parental Bonding
Self-Knowledge

Negative Valence
Anhedonia
Negative Reinforcement
Stress

Addiction

Cognitive
Attentional Bias
Inhibitory Control
Performance Monitoring

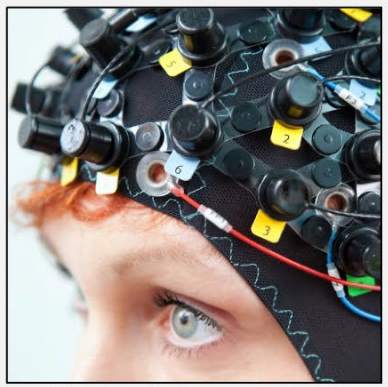
Arousal / Regulatory
Emotional Reactivity
Sleep Disturbance
Motivated Behavior

Sensorimotor
Compulsive Behavior
Habitual Behavior
Response Inhibition

Opioid Use Disorder (OUD)

1. Drug cue-reactivity
2. Inhibitory control
3. Socioaffective processes
4. Interregional connectivity
5. New methods

Functional magnetic resonance imaging (fMRI)

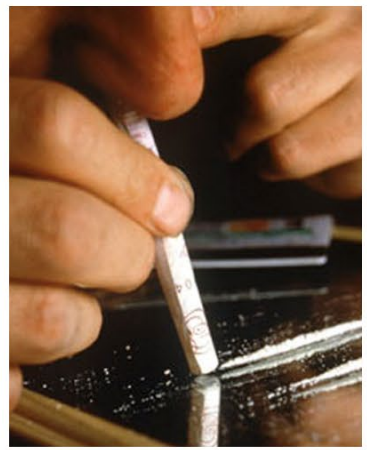


Functional near-infrared spectroscopy (fNIRS)

Event-related potentials (ERP)

1. Drug Cue-Reactivity

Cue-reactivity is a type of learned response which is observed in individuals with an addiction and involves significant physiological and subjective reactions to presentations of drug-related stimuli (i.e., drug cues).



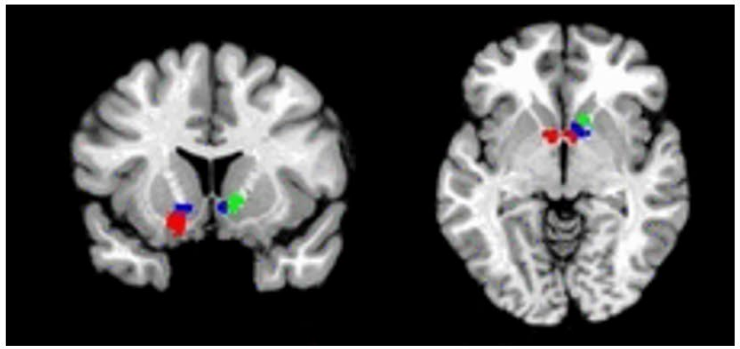
Drug cues

Neutral cues

en.wikipedia.org

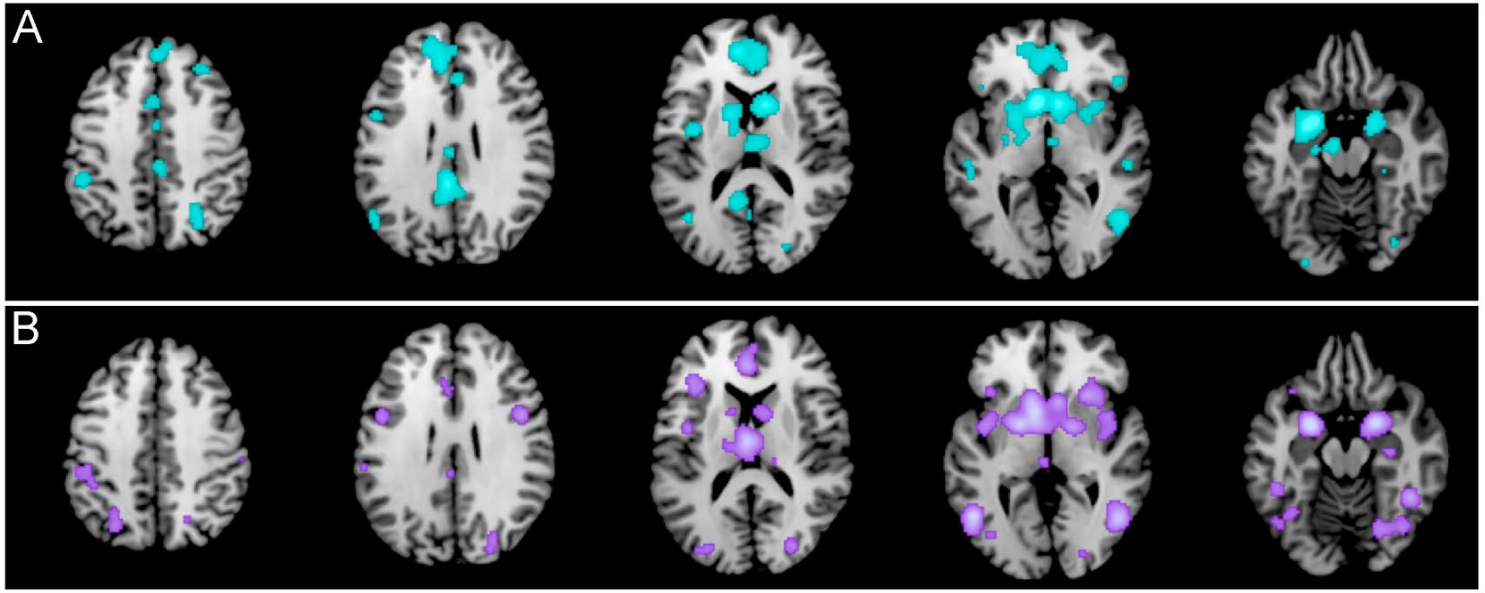
1. Drug Cue-Reactivity

Meta-Analyses of fMRI Findings



Nicotine
Alcohol
Cocaine

Nucleus accumbens (NAcc)

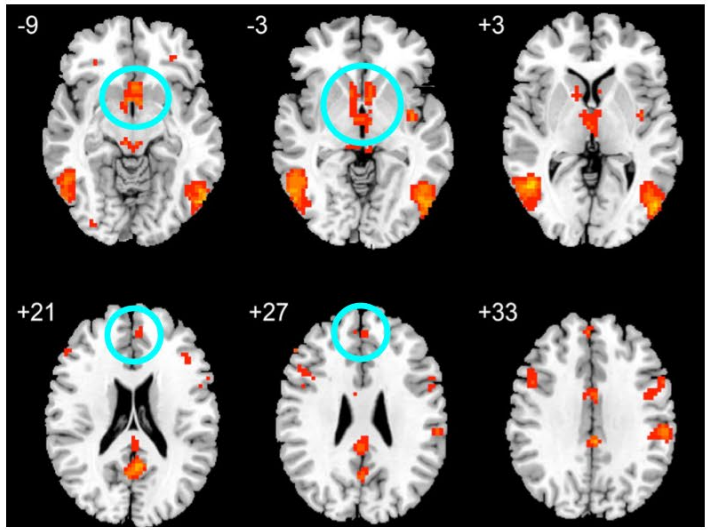


- Drug (alcohol, cannabis, cocaine, heroin, nicotine)
- Natural (food, sex)

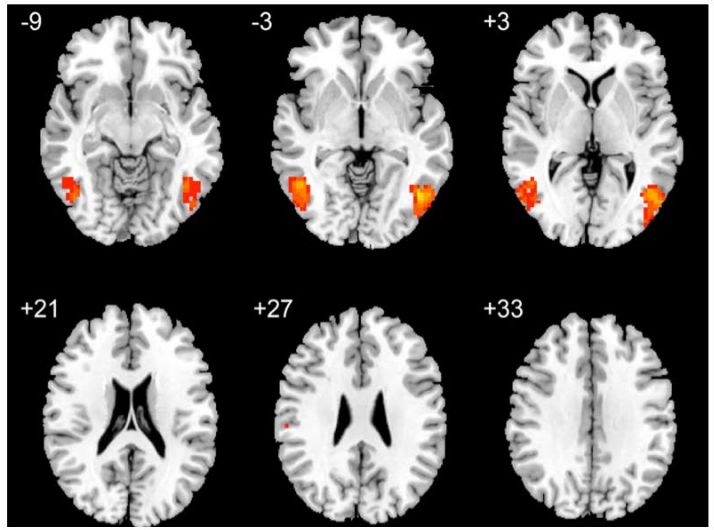
Noori et al. 2016 Eur NPP.
Kuhn & Gallinat 2011 Eur J Neurosci.

1. Drug Cue-Reactivity

Effects of Withdrawal and Abstinence



Short Abstinence

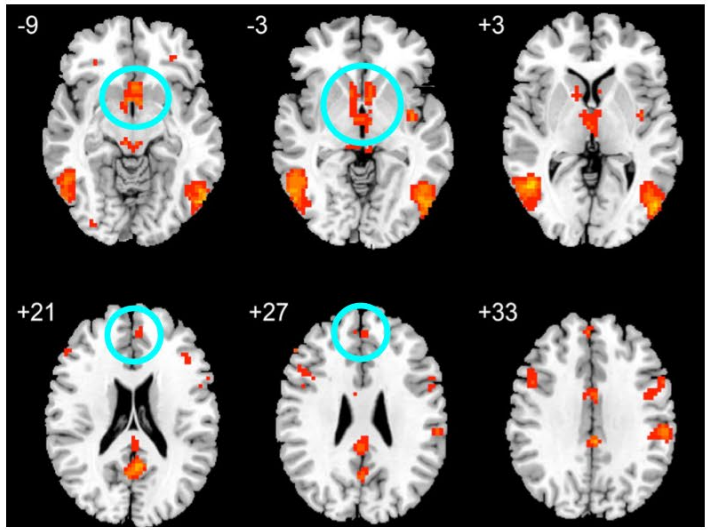


Long Abstinence

Li et al. 2013 PLoS ONE.

1. Drug Cue-Reactivity

Effects of Withdrawal and Abstinence



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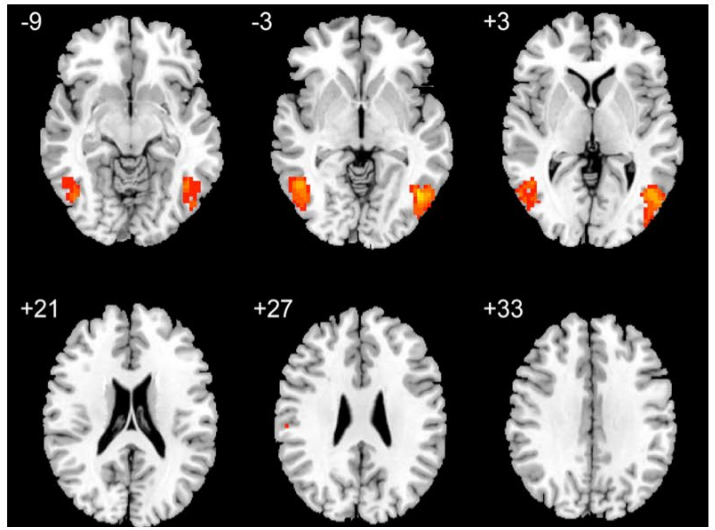

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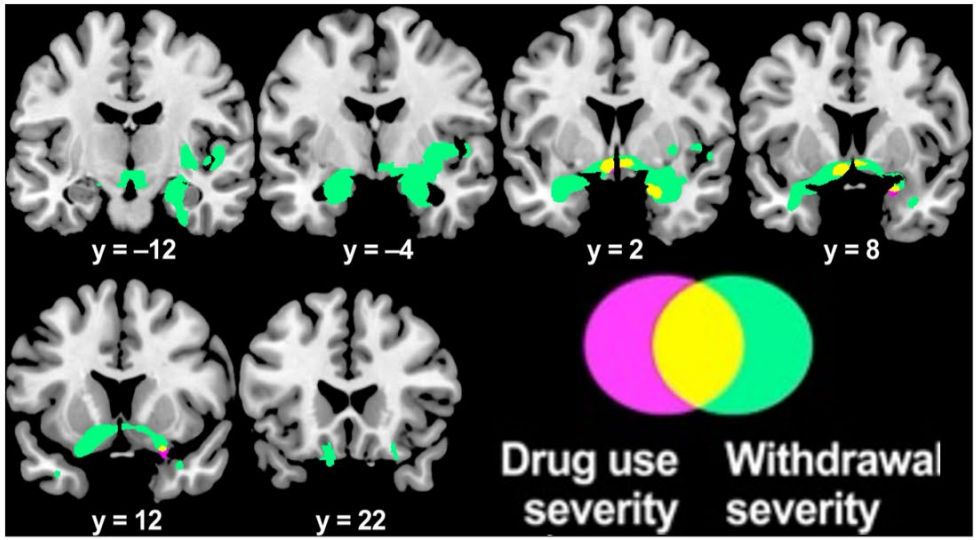
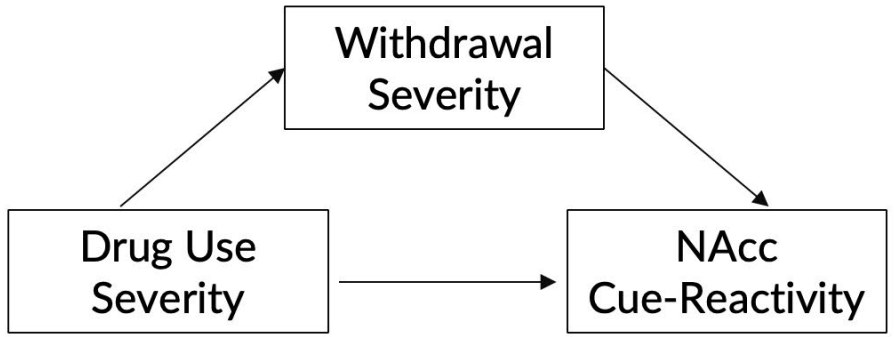




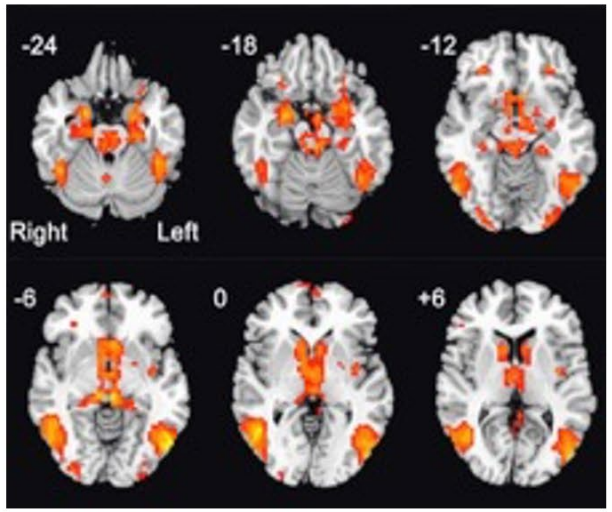
Li et al. 2013 PLoS ONE.
Shi et al. 2021 Addict Biol.

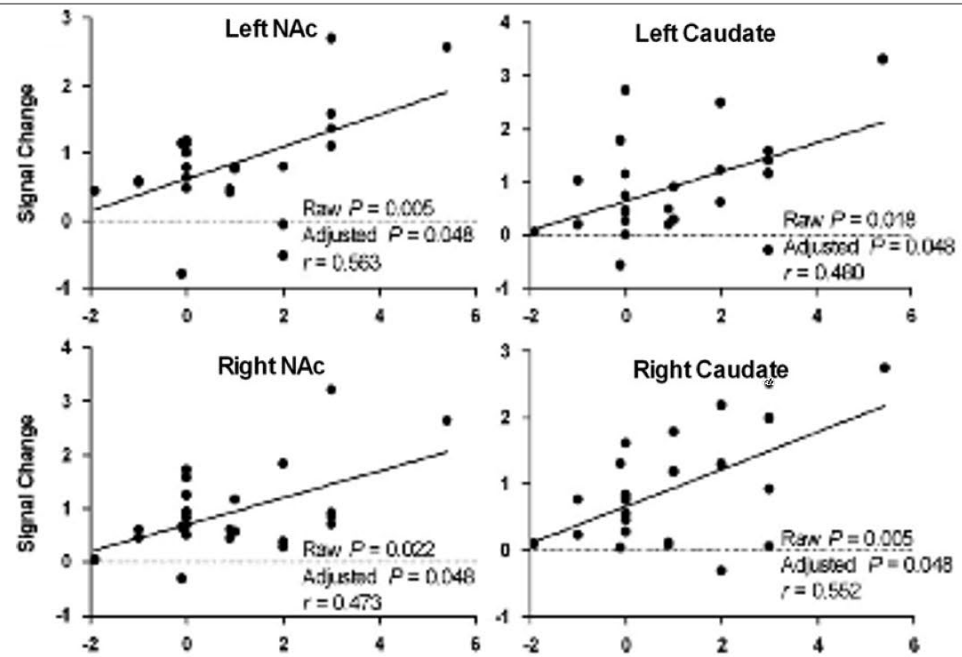
1. Drug Cue-Reactivity

Associations with Self-Reports

Correlation between:

Brain cue-reactivity and cue-induced craving





Li et al. 2012 Brain Res.

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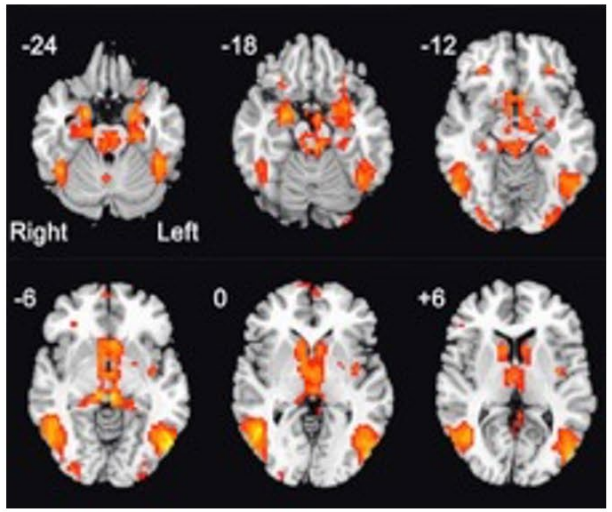
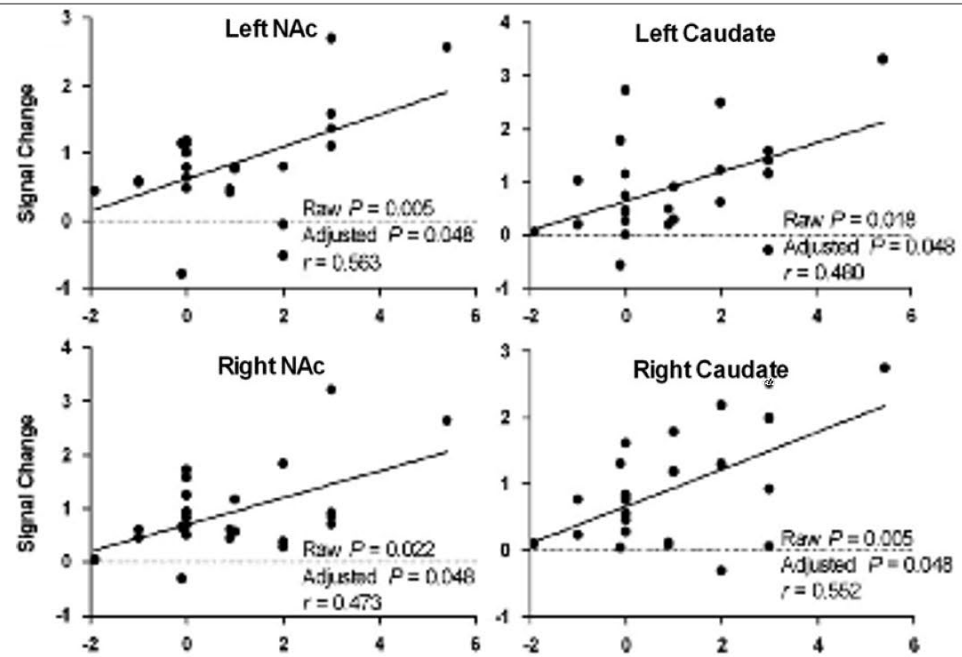
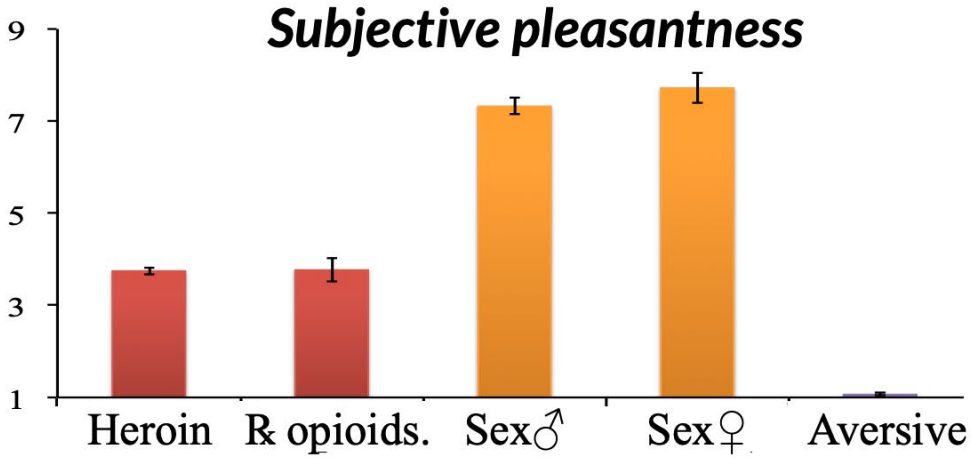
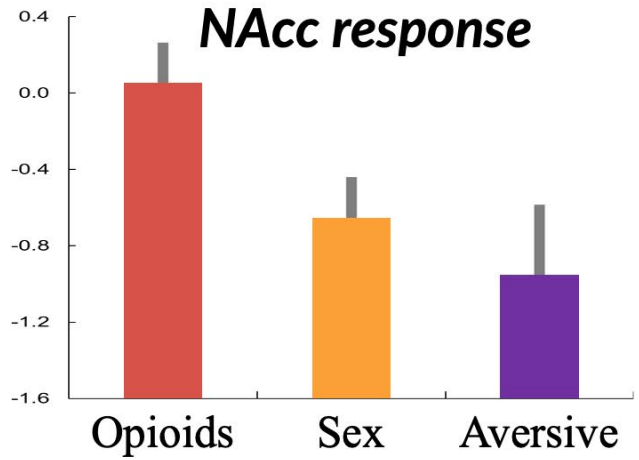






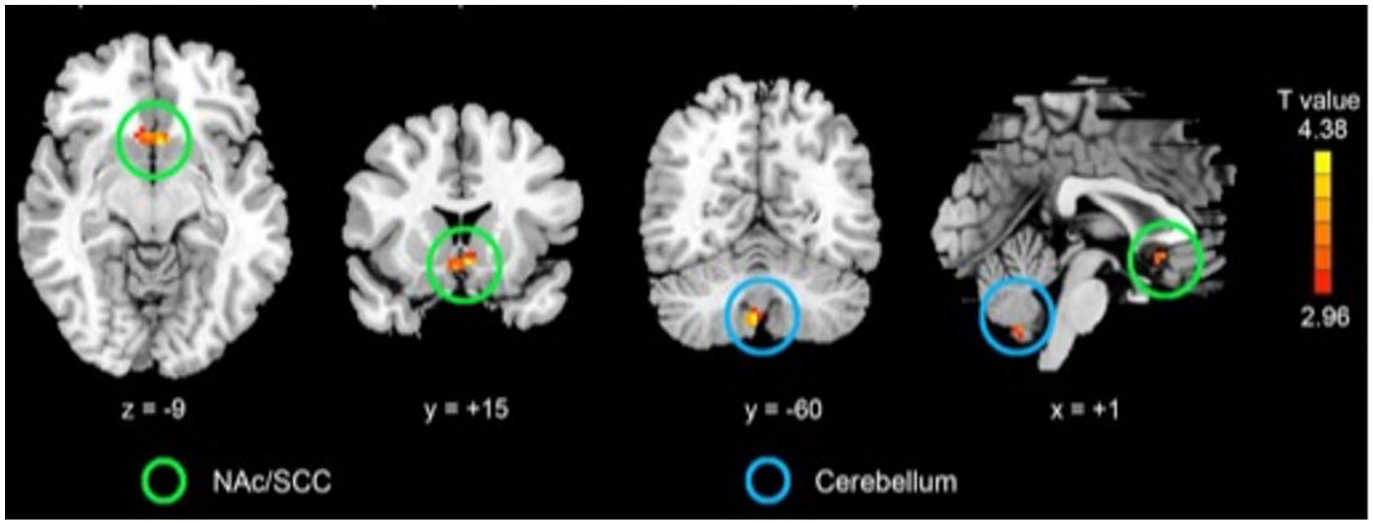


Li et al. 2012 Brain Res.
Shi et al. 2021 Addict Biol.

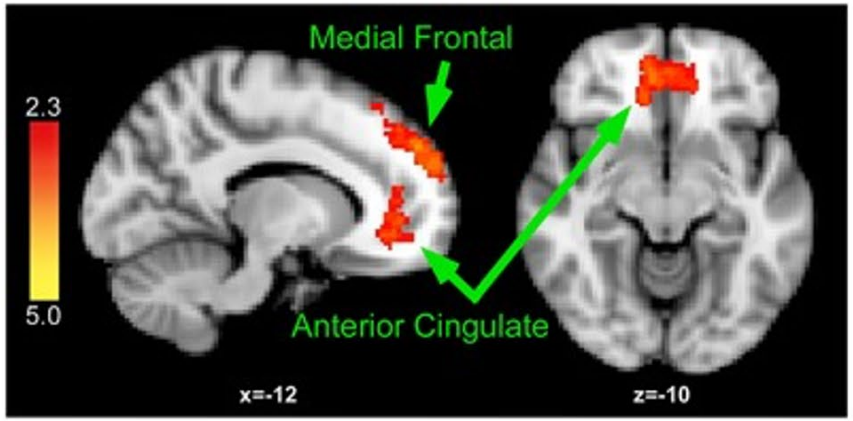
1. Drug Cue-Reactivity

Associations with Outcomes

Methadone maintenance: ***Relapsers > Non-relapsers***



Extended-release naltrexone: ***Treatment adherence***

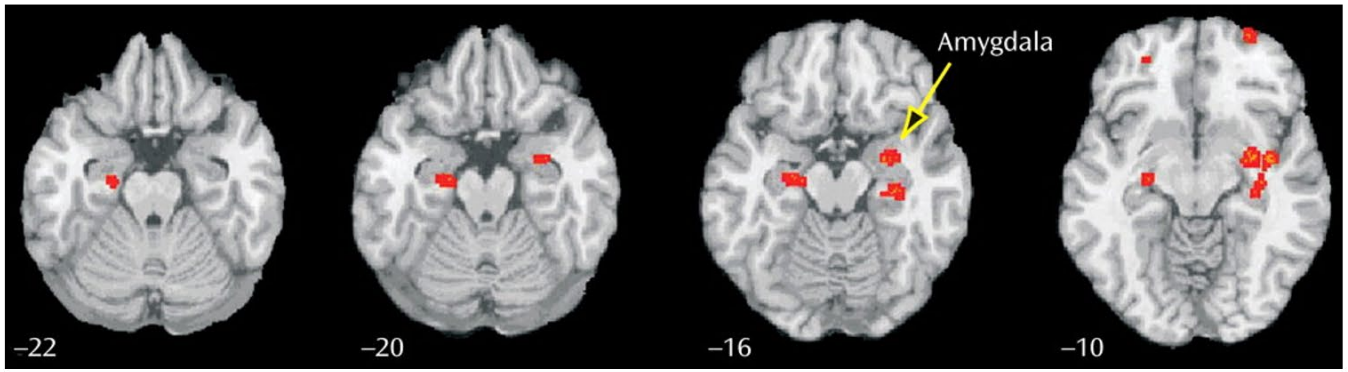


Li et al. 2014 Addict Biol.
Wang et al. 2015 Transl Psychiatry.

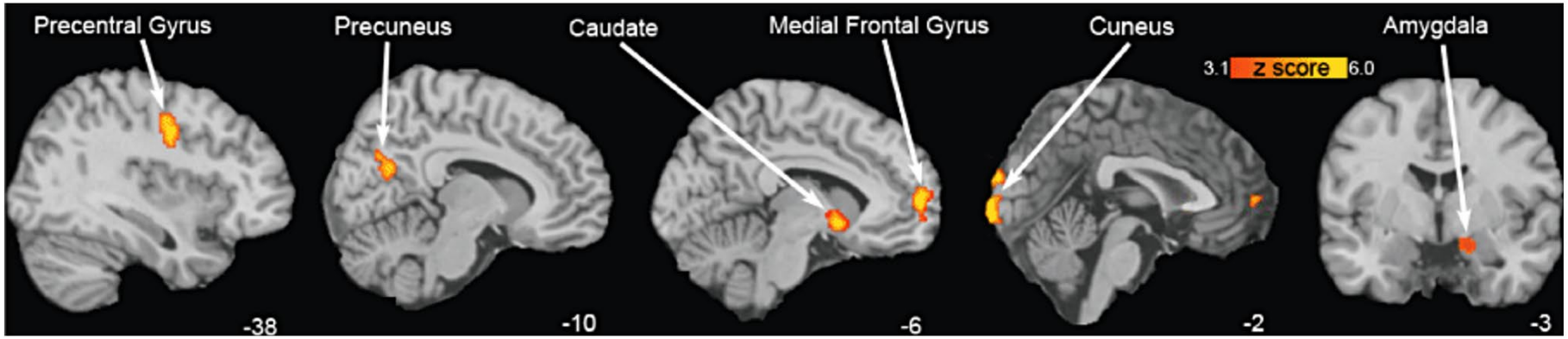
1. Drug Cue-Reactivity

Effects of Treatments

Methadone maintenance: ***Pre-dose > Post-dose***



Extended-release naltrexone: ***Pre-Tx*** *(before first injection)* **> *On-Tx*** *(two weeks after first injection)*

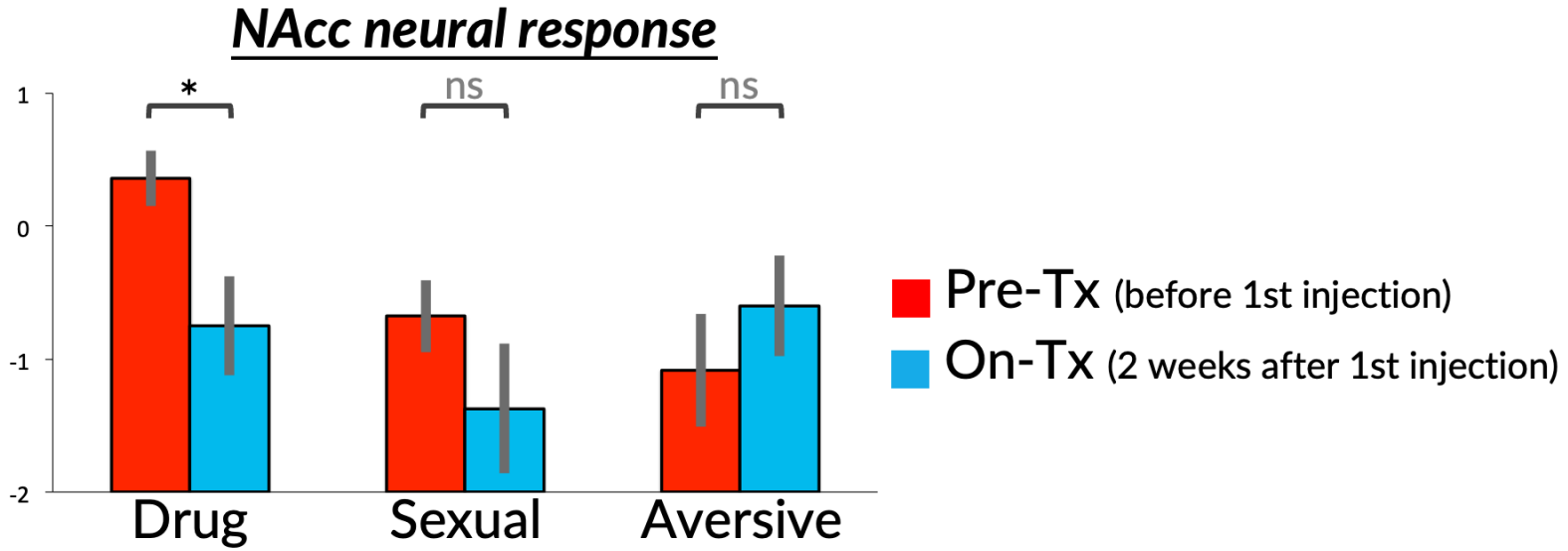


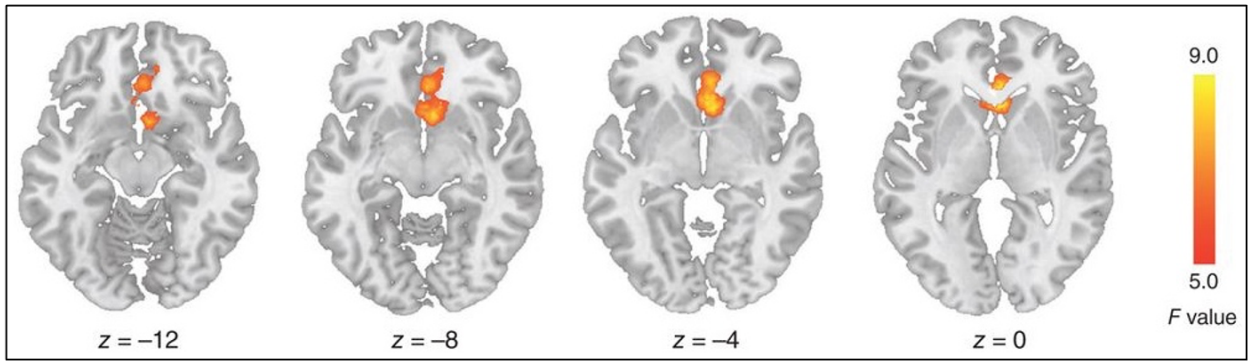
Langleben et al. 2008 Am J Psychiatry.
Langleben et al. 2014 Addict Biol.

1. Drug Cue-Reactivity

Effects of Treatments

Extended-release naltrexone: ***Time x Stimulus Interaction***





Shi et al. 2018 J Psychiatry Neurosci.

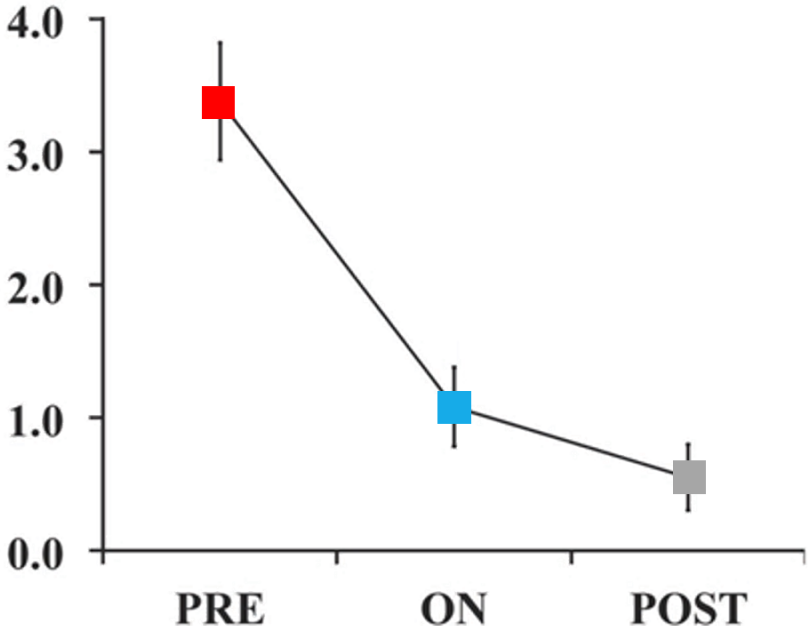
1. Drug Cue-Reactivity

Effects of Treatments

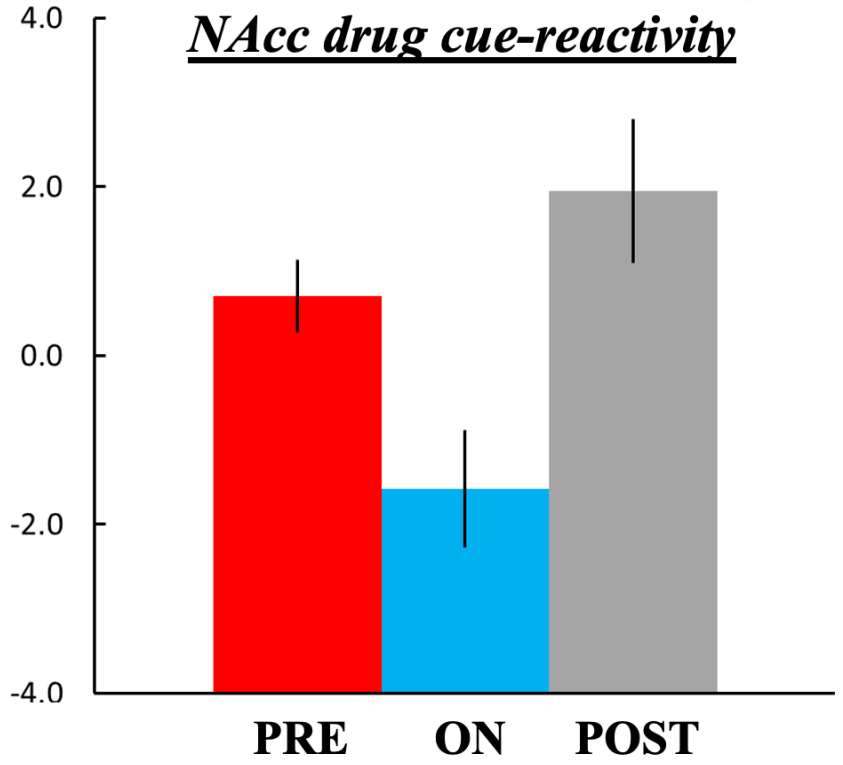
Extended-release naltrexone: ***Pre ➔ On ➔ Post***

PRE = before 1st injection
ON = 2 weeks after 1st injection
POST = 4 weeks after 3rd injection

Self-reported craving



NAcc drug cue-reactivity

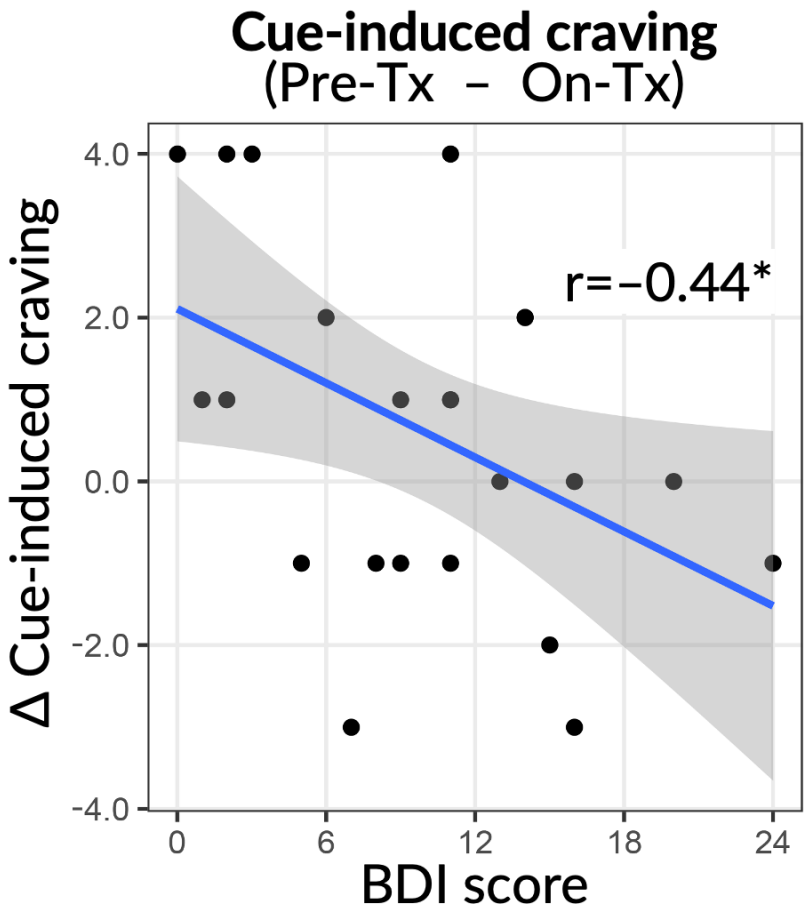


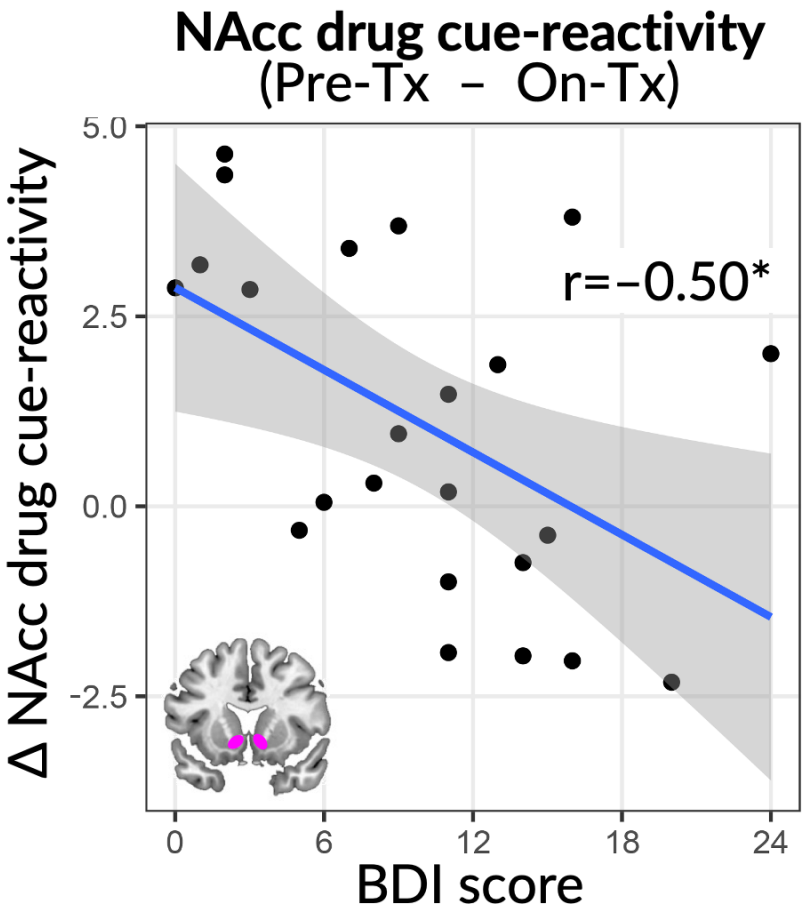
Shi et al. 2018 J Psychiatry Neurosci.

1. Drug Cue-Reactivity

Effects of Treatments

Extended-release naltrexone: ***Role of Depression***





Shi et al. under review.

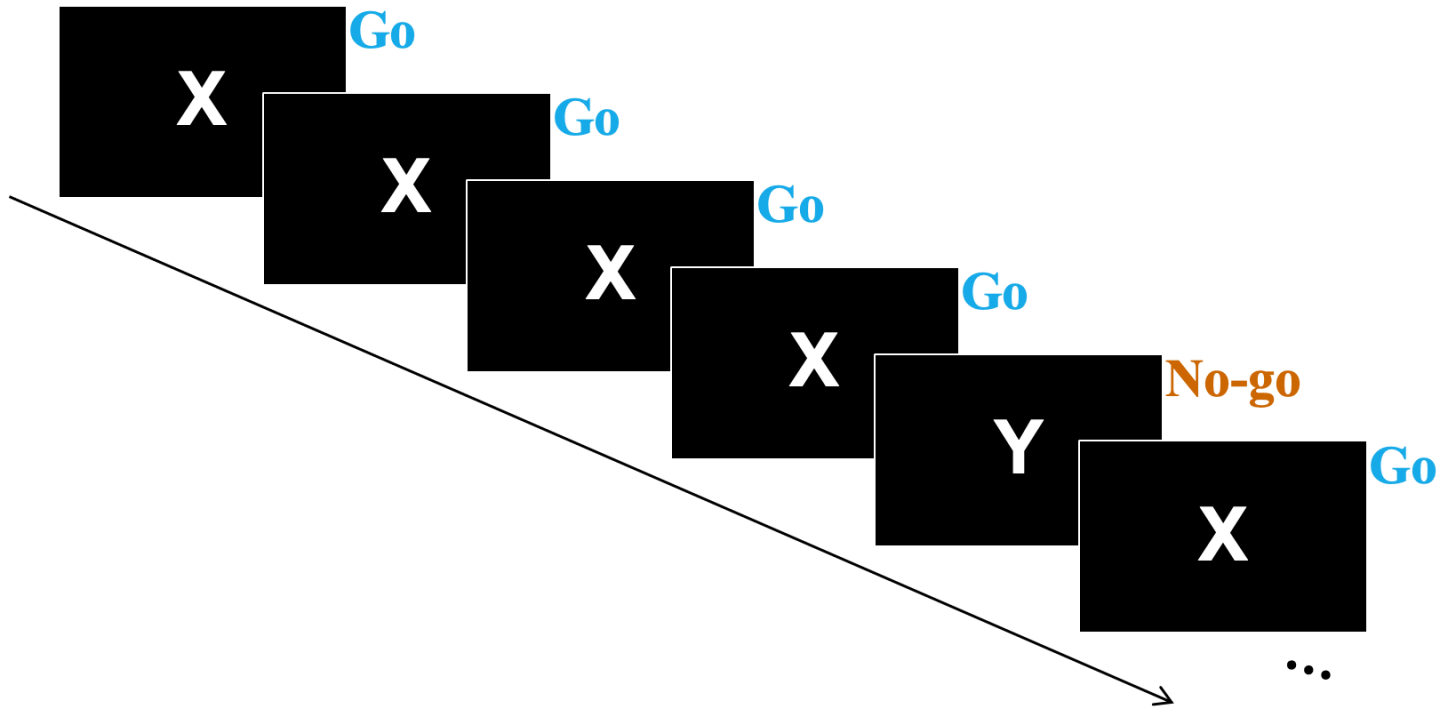
1. Drug Cue-Reactivity

Summary:

- In OUD patients, drug-related cues elicit increased neural response in the brain **reward system** that includes the striatum (NAcc, caudate), amygdala, and PFC.
- Brain cue-reactivity is modulated by **abstinence** duration and severity of **withdrawal** symptoms.
- Brain cue-reactivity is associated with self-reported **craving** for opioids, but not with self-reported **liking** of the cues.
- Brain cue-reactivity may serve as a predictor of **future outcomes**.
- **Treatment** for OUD reduces cue-reactivity, and such reduction may depend on **adherence** and psychiatric **comorbidities**.

2. Inhibitory Control

Inhibitory control is a cognitive process that permits an individual to inhibit their impulses and natural, habitual, or dominant behavioral responses to stimuli in order to select a more appropriate behavior that is consistent with completing their goals.

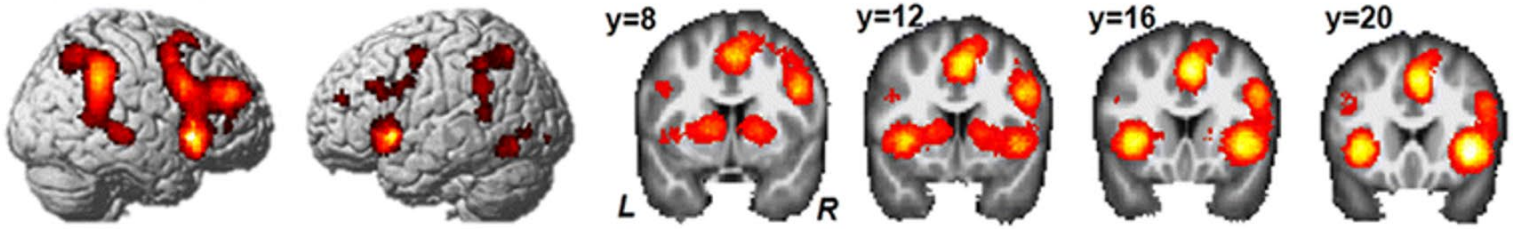


en.wikipedia.org

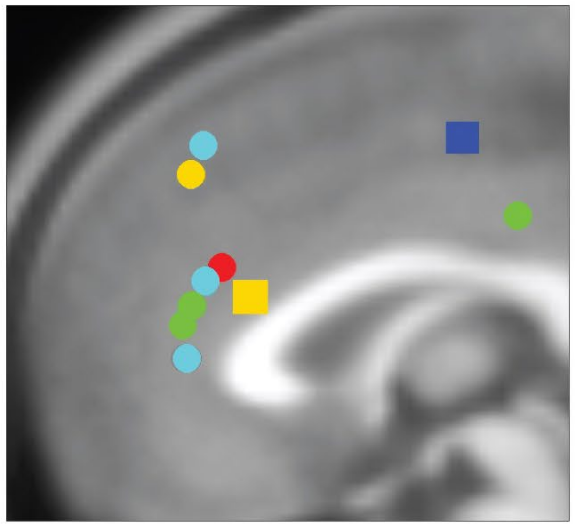
2. Inhibitory Control

Meta-Analyses of fMRI Findings

Healthy population



Patients with addiction vs. Healthy controls



□ Hyperactivity
○ Hypoactivity

Opioid
Cocaine
Cannabis
Nicotine
Behavioral

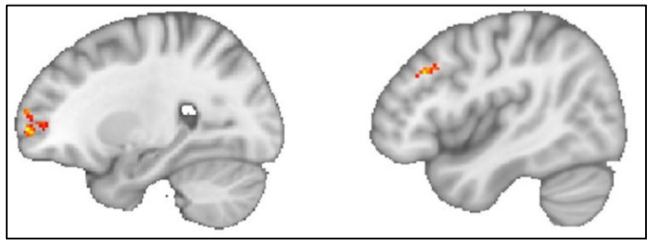
Zhang et al. 2017 Brain Struct Funct.
Luijten et al. 2014 J Psychiatry Neurosci.

2. Inhibitory Control

fMRI and EEG Correlates of Inhibitory Deficit

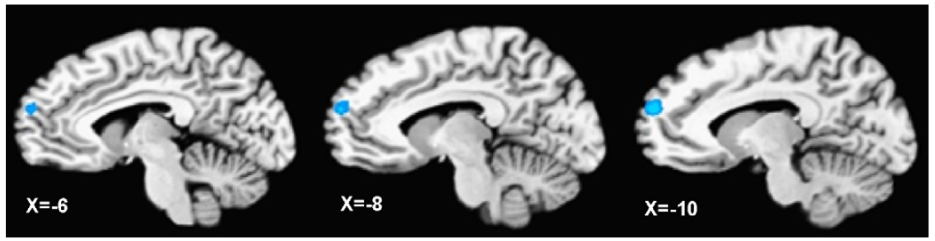
Brain hypoactivity

Heroin users vs. *Healthy controls*



- dorsolateral PFC
- frontal pole

Heroin users vs. *Healthy controls*



- medial PFC
- anterior cingulate cortex (ACC)

Ceceli et al. 2022 medRxiv.
Fu et al. 2008 Neurosci Lett.

2. Inhibitory Control

fMRI and EEG Correlates of Inhibitory Deficit

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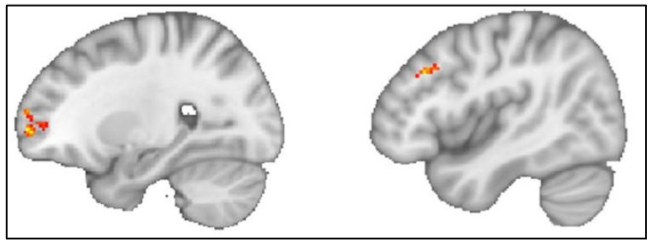

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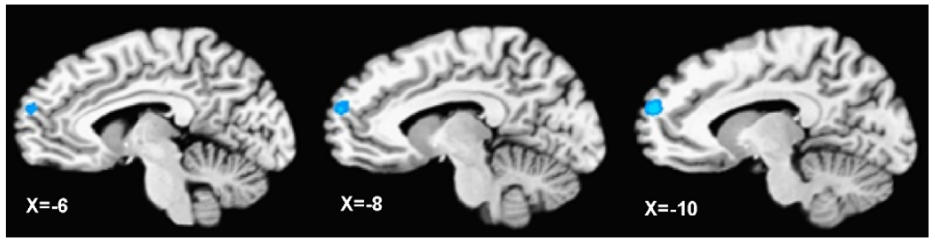
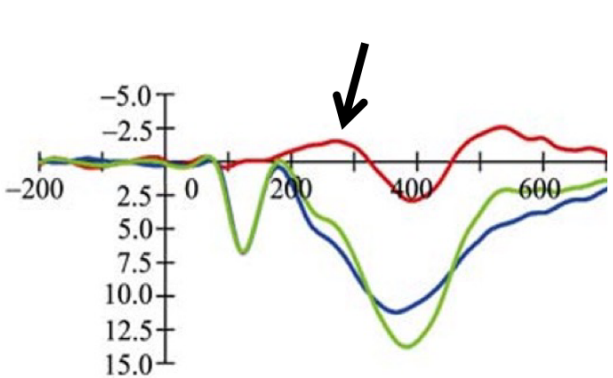


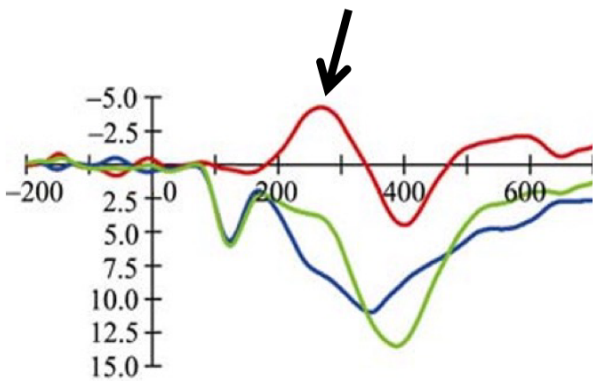
- medial PFC
- anterior cingulate cortex (ACC)

ERP "N2" response
at Fz (medial PFC)

Heroin users



Healthy controls

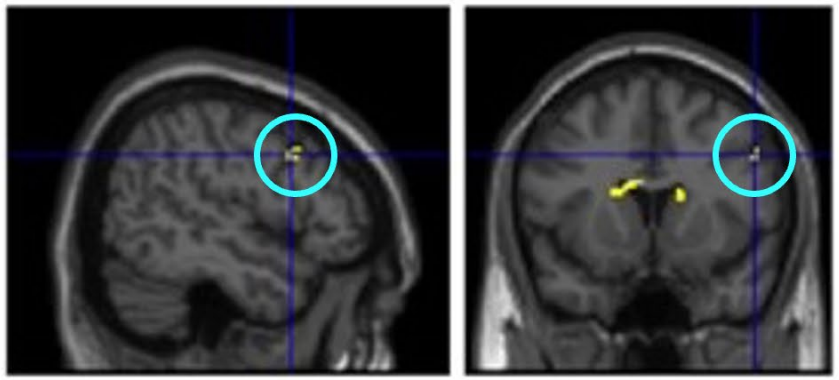


- NoGo
- Go
- Diff (NoGo – Go)

Ceceli et al. 2022 medRxiv.
Fu et al. 2008 Neurosci Lett.
Yang et al. 2009 Sci China C Life Sci.

2. Inhibitory Control

Effects of Treatments



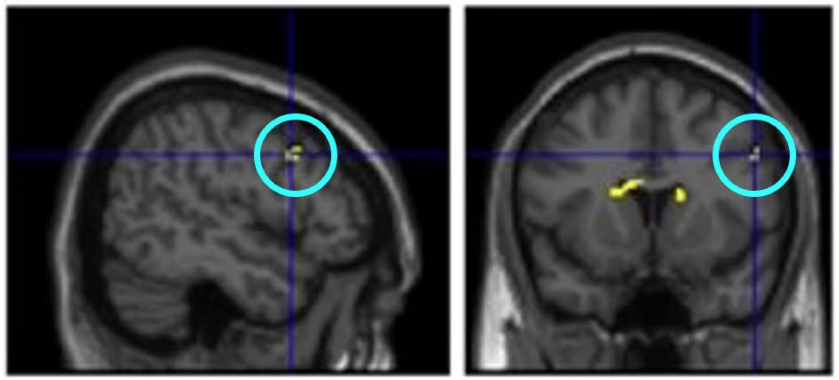
Right inferior frontal gyrus (rIFG):

Acute heroin < Acute saline
in heroin-maintenance treatment

Schmidt et al. 2013 NPP.

2. Inhibitory Control

Effects of Treatments



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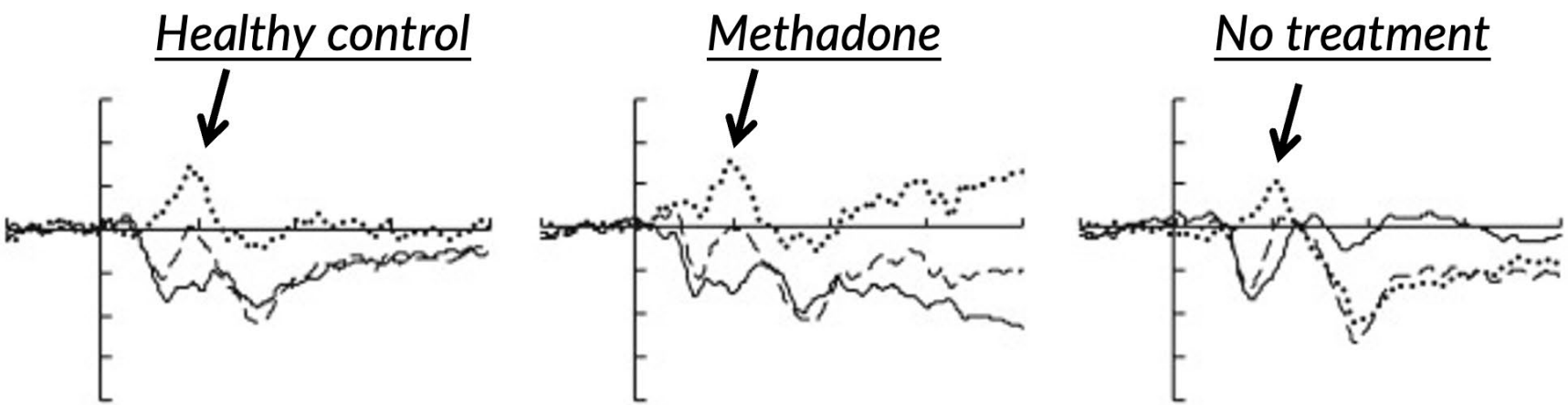


ERP N2 response at Fz (medial PFC):

Control = Methadone > No treatment

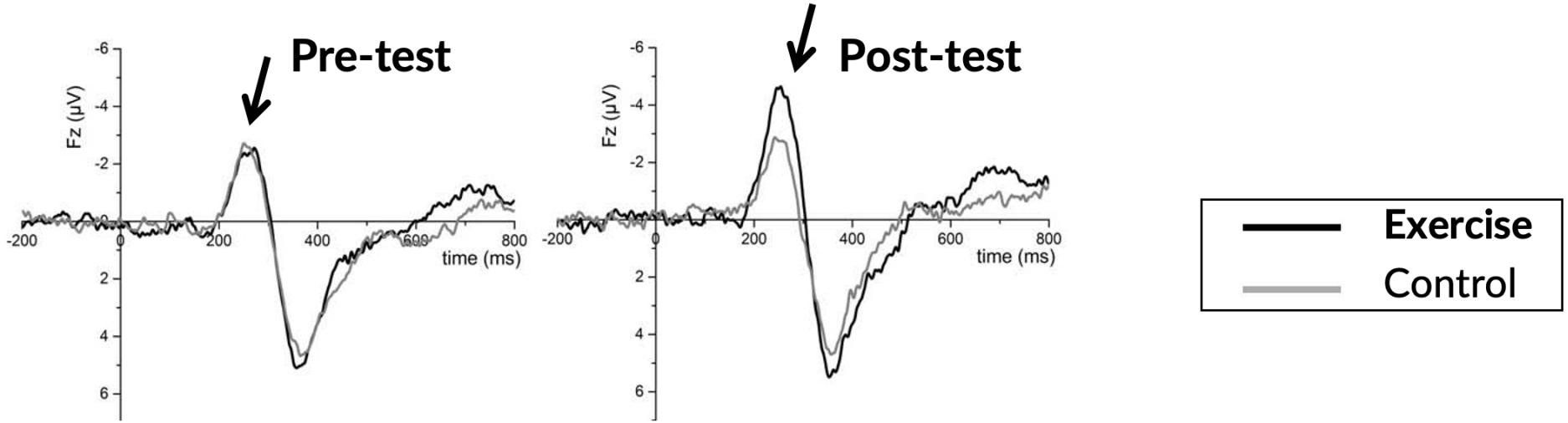
Schmidt et al. 2013 NPP.
Yang et al. 2015 J Food Drug Anal.

2. Inhibitory Control

Effects of Treatments

Aerobic Exercise

N2 diff. wave: NoGo – Go at Fz (medial PFC)



Wang et al. 2020 Front Psychol.

2. Inhibitory Control

Effects of Treatments

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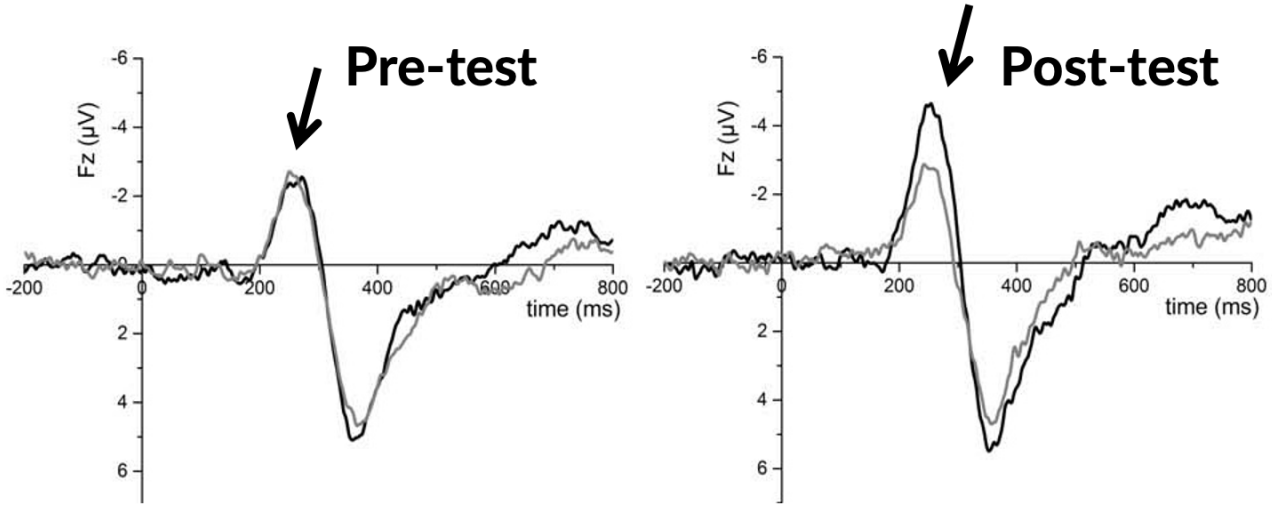
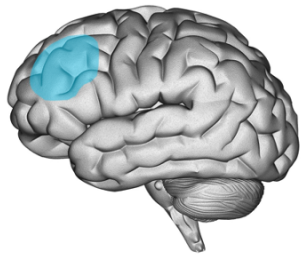
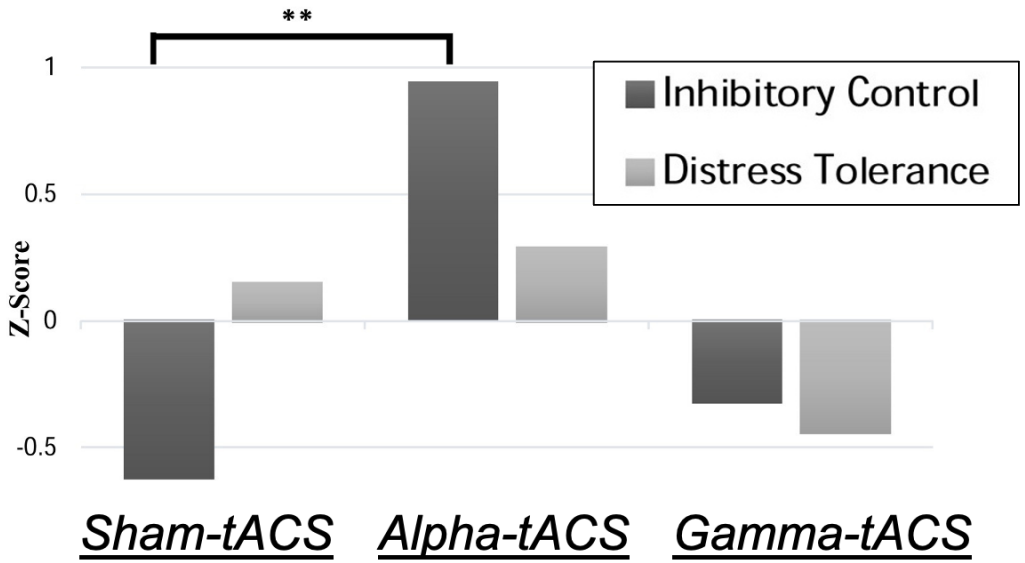


Transcranial alternating current stimulation (tACS)

at *bilateral dorsolateral PFC*

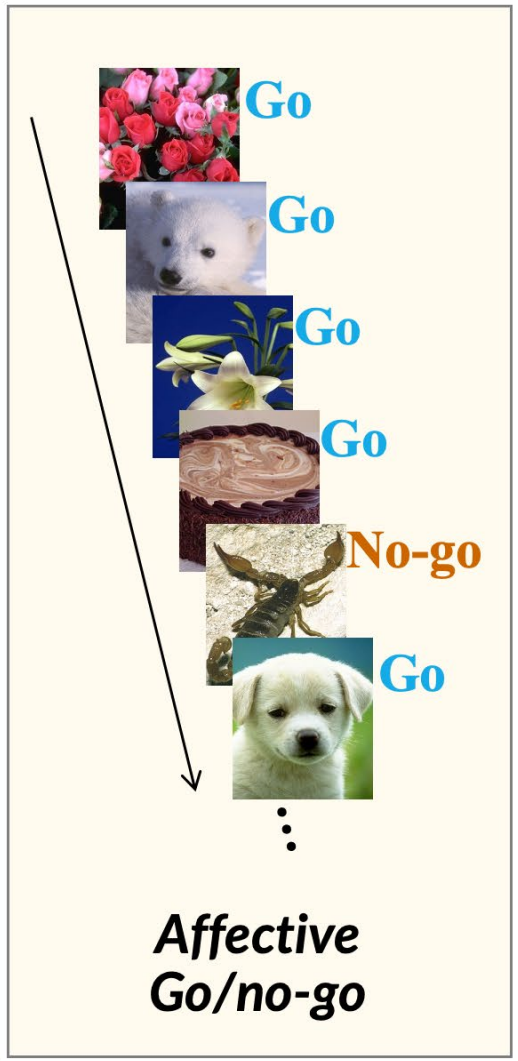


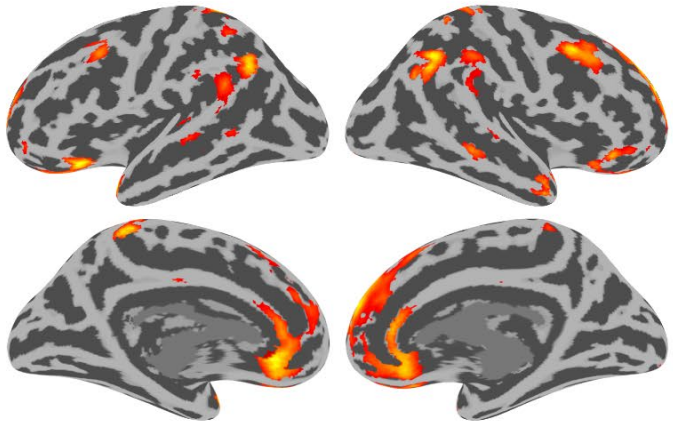


Wang et al. 2020 Front Psychol.
Daughters et al. 2020 DAD.

2. Inhibitory Control

Emotional Inhibitory Control

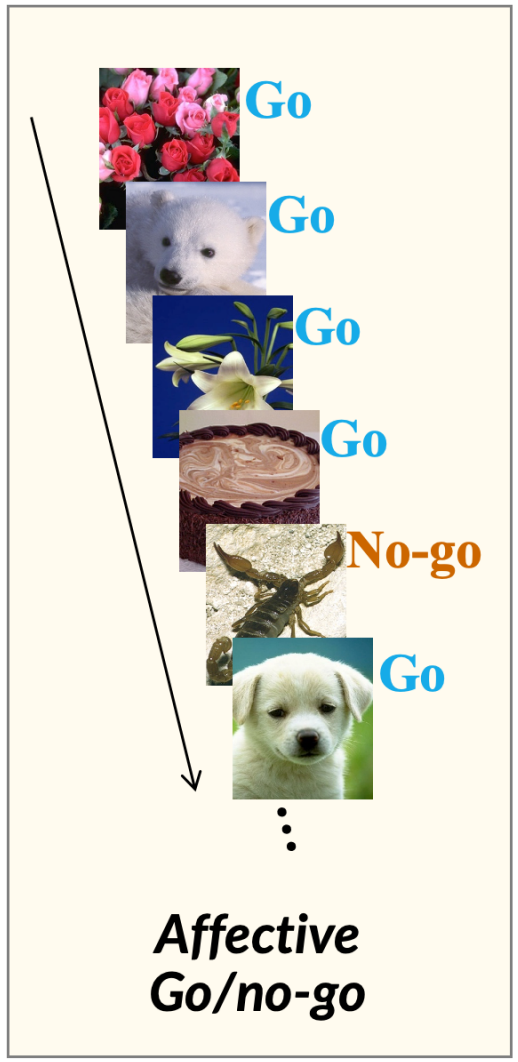


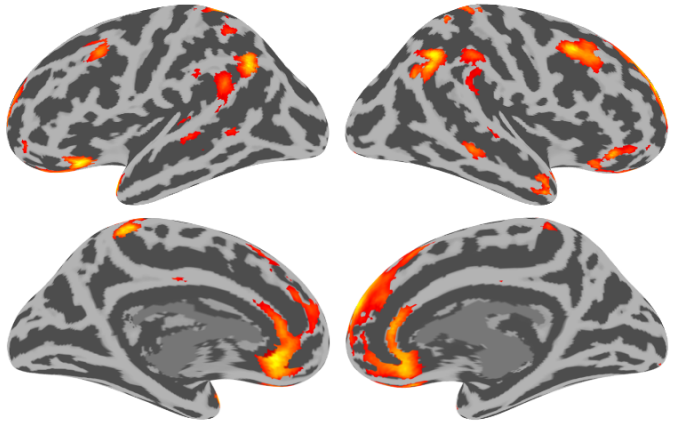


Shi et al. 2019 Int J NPP.

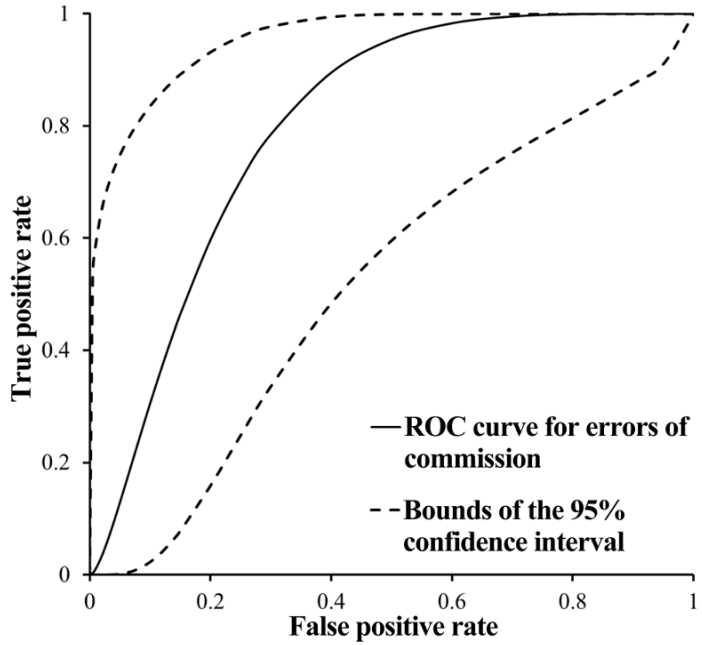
2. Inhibitory Control

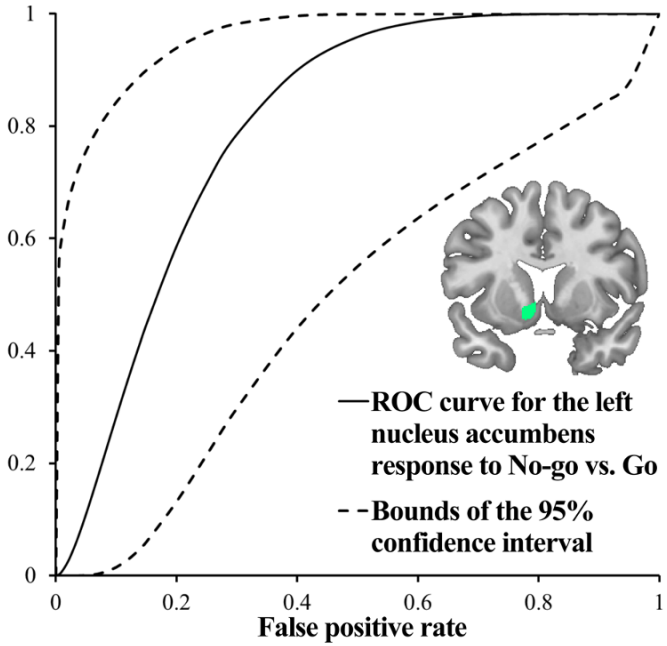
Emotional Inhibitory Control





Prediction of adherence to 3-month extended-release naltrexone

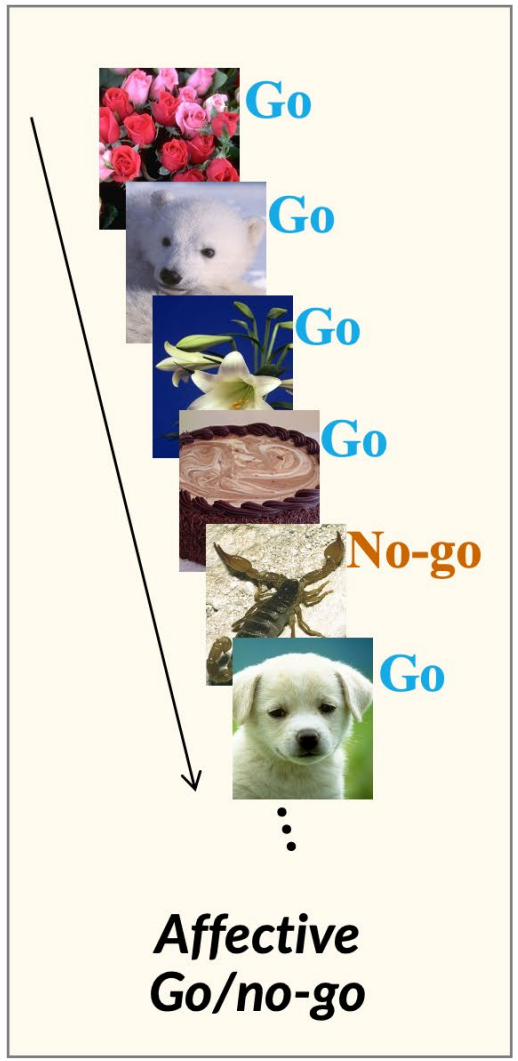




Shi et al. 2019 Int J NPP.

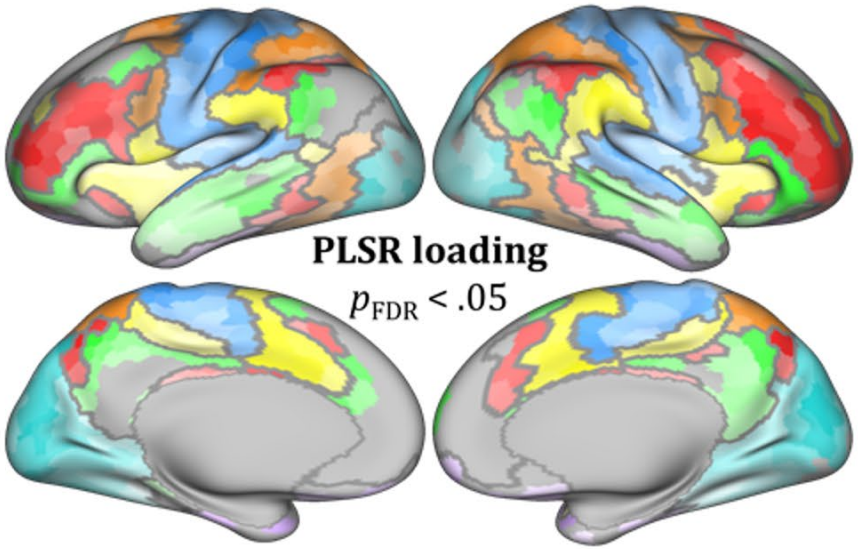
2. Inhibitory Control

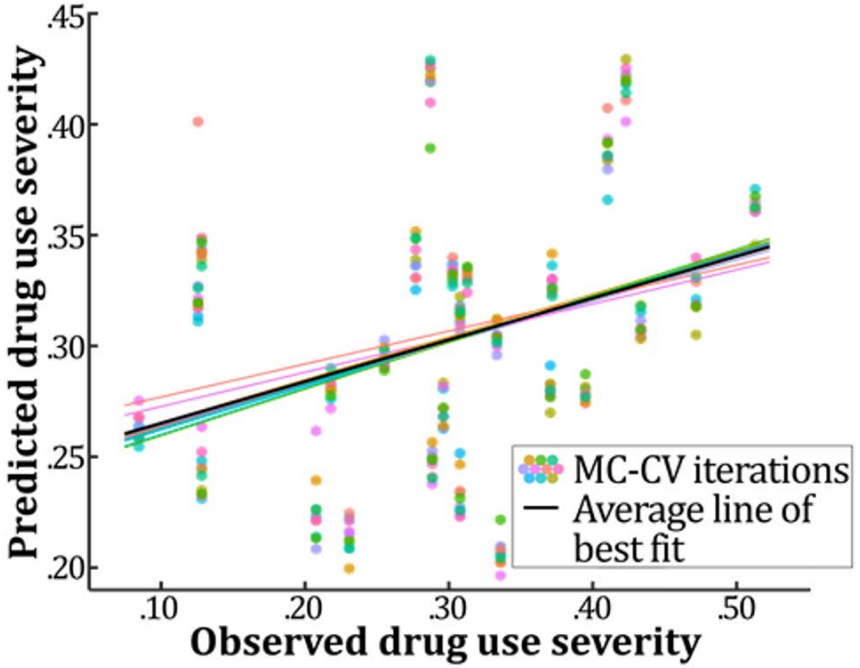
Emotional Inhibitory Control



Imaging marker of drug use severity

[using partial least squares regression (PLSR)]





Shi et al. 2021 Neuroimage Clin.

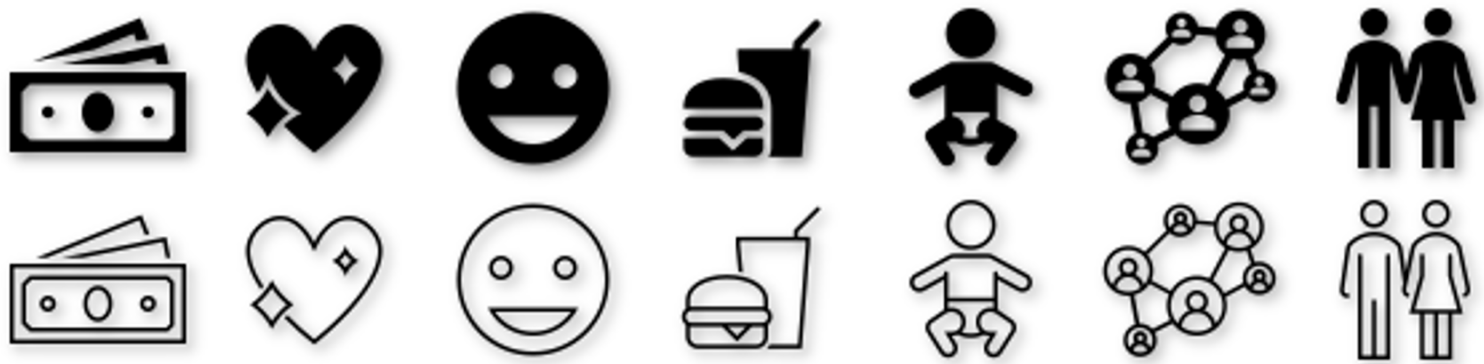
2. Inhibitory Control

Summary:

- OUD patients how reduced **ACC/PFC response** and **N2 amplitude** during inhibitory control.
- **Medications** for OUD (heroin/methadone maintenance) appear to affect the neural correlates of inhibitory control.
- **Aerobic exercise** and **neuromodulation** of the dorsolateral PFC appear to improve inhibitory control.
- fMRI measures of **emotional inhibitory control** may be linked to addiction **severity** and treatment **outcomes**.

3. Socioaffective Processing

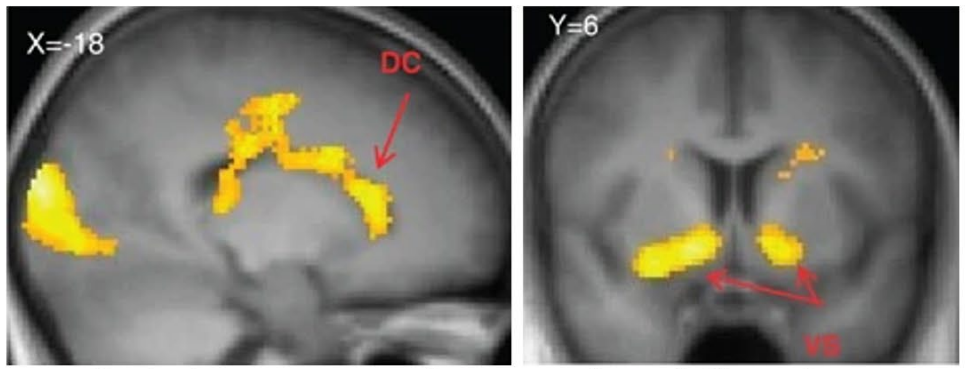
- ***Affective neuroscience*** is the study of the neural mechanisms of emotion.
- ***Social neuroscience*** is an interdisciplinary field devoted to understanding the relationship between social experiences and biological systems.



en.wikipedia.org

3. Socioaffective Processing

Monetary Reward



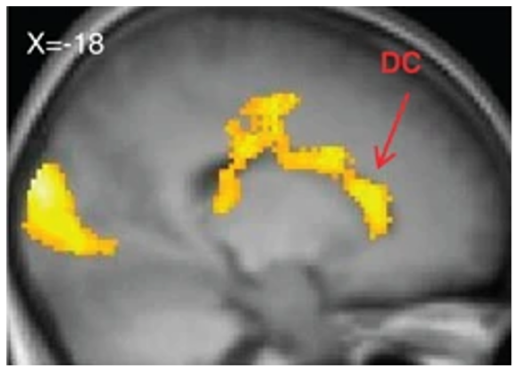
Gaining reward Avoiding loss

Heroin users (MT)
<
Healthy controls

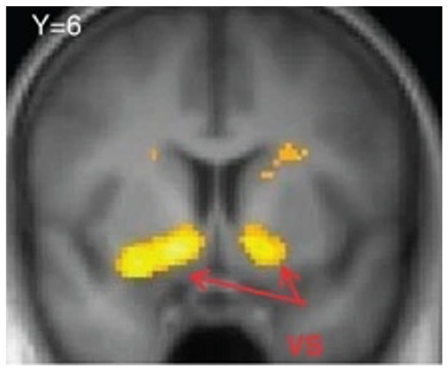
Gradin et al. 2014 NPP.

3. Socioaffective Processing

Monetary Reward

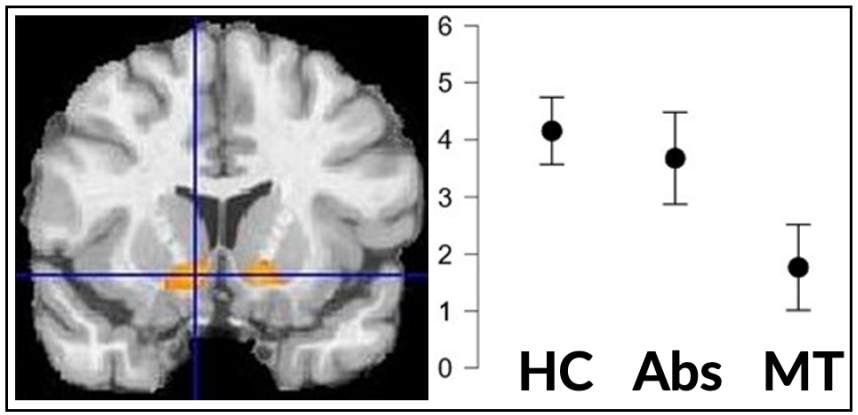


Gaining reward

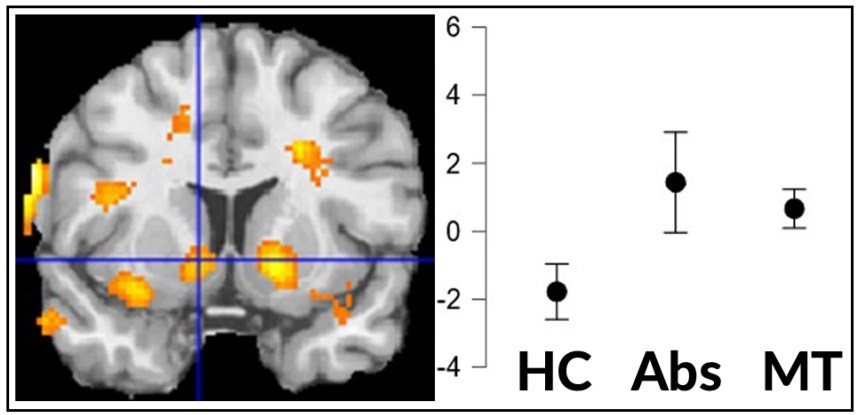


Avoiding loss

Heroin users (MT)
<
Healthy controls



Gaining reward



Failure to avoid loss

HC : healthy control
Abs: abstinent
MT : methadone treatment

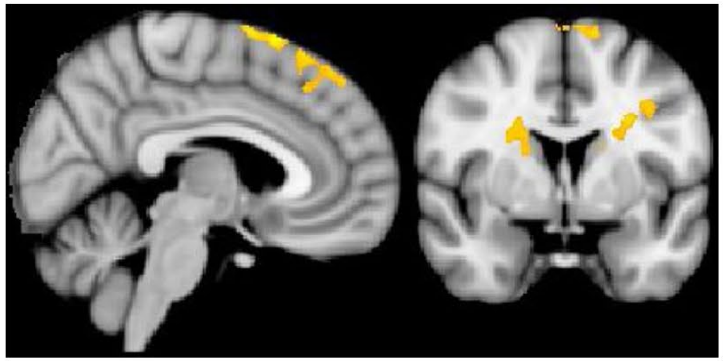
Gradin et al. 2014 NPP.
Tolomeo et al. 2022 Transl Psychiatry.

3. Socioaffective Processing

Natural Reward Cues

Social *vs.* *Non-social*

Depressed OUD < Healthy controls



Yi et al. 2019 DAD.

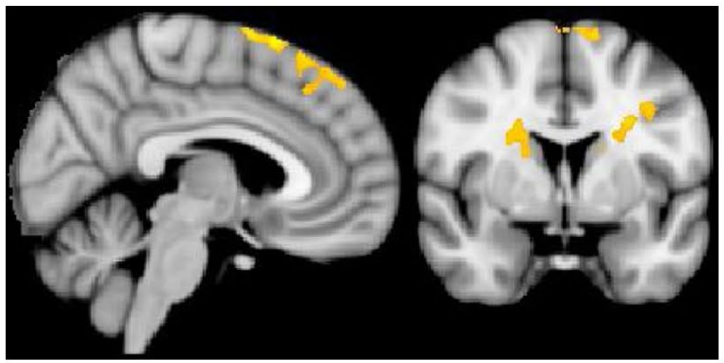
3. Socioaffective Processing

Natural Reward Cues

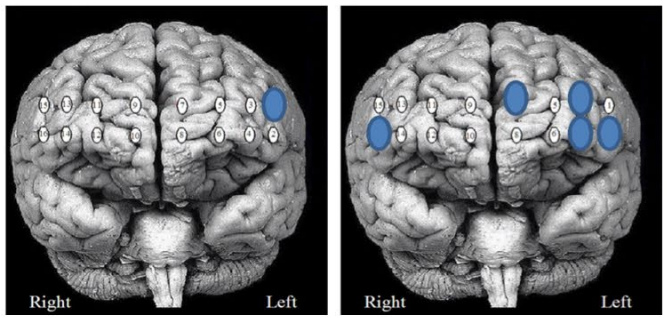
Social *vs.*

Non-social

Depressed OUD < Healthy controls

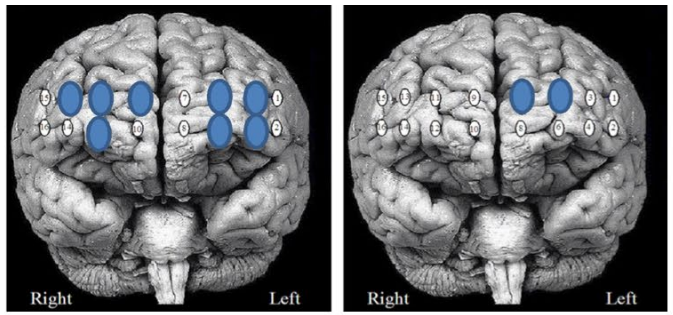


OUD < Control



Social cues Food cues

OUD+Anhedonia < OUD



Social cues Food cues

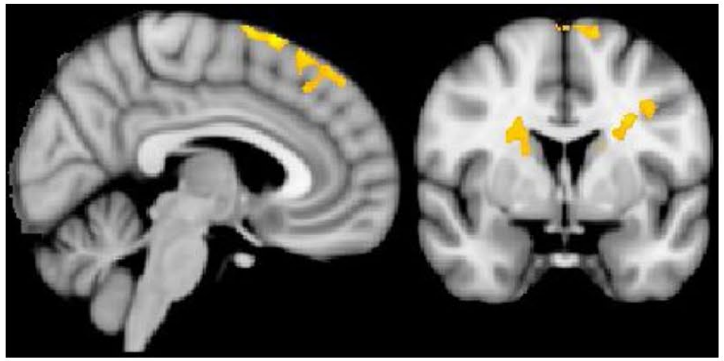
Yi et al. 2019 DAD.
Huhn et al. 2016 Brain Res Bull.

3. Socioaffective Processing

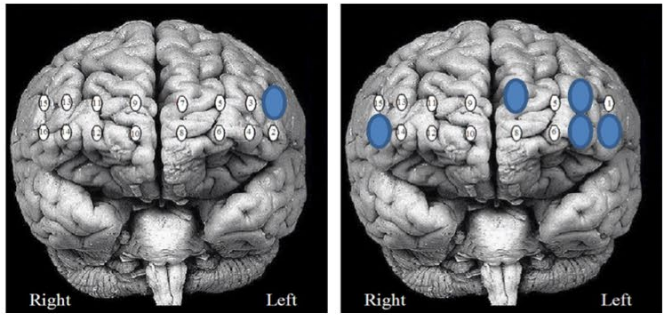
Natural Reward Cues

Social *vs.* *Non-social*

Depressed OUD < Healthy controls

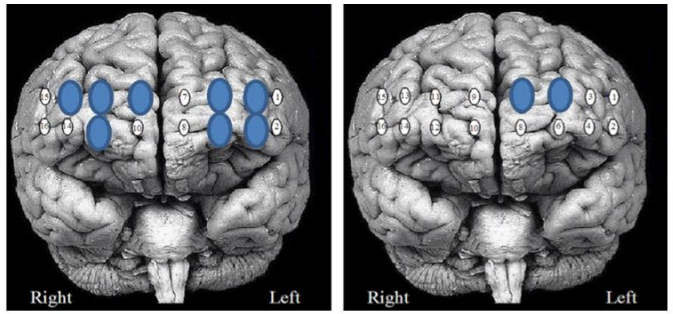


OUD < Control



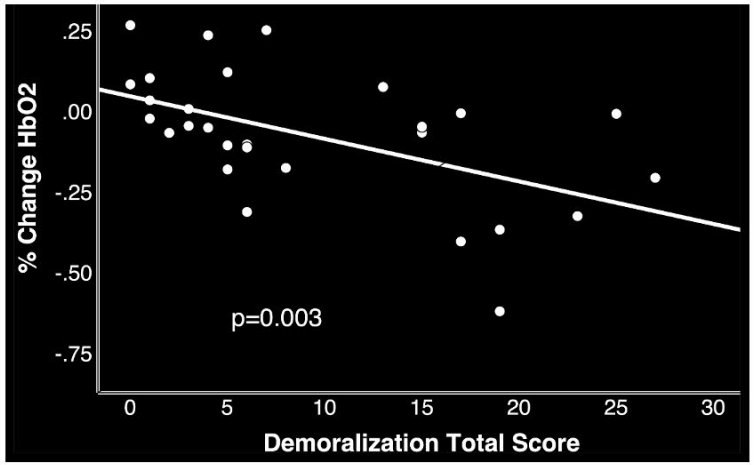
Social cues Food cues

OUD+Anhedonia < OUD



Social cues Food cues

Demoralization ↑, PFC social response ↓

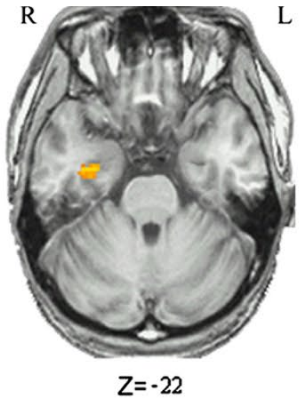


Yi et al. 2019 DAD.
Huhn et al. 2016 Brain Res Bull.
Huhn et al. 2021 Addict Behav.

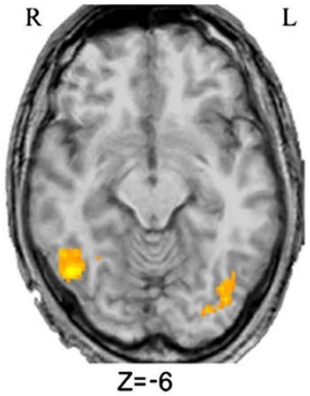
3. Socioaffective Processing

Facial Expressions

Heroin users < controls



Amygdala
emotional - neutral



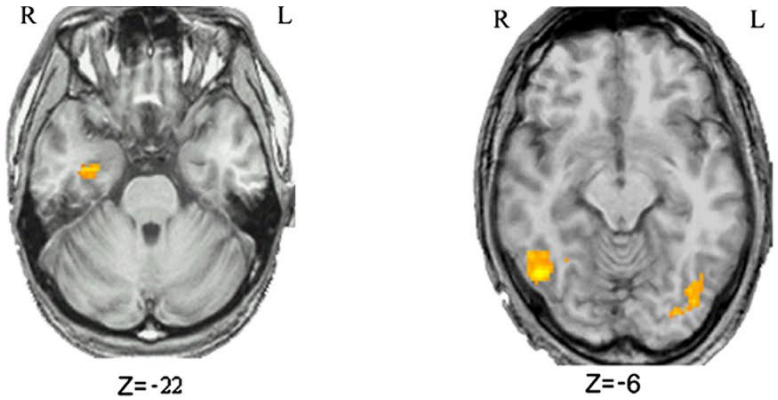
Occipital cortex
positive - negative

Wang et al. 2010 Neuroimage.

3. Socioaffective Processing

Facial Expressions

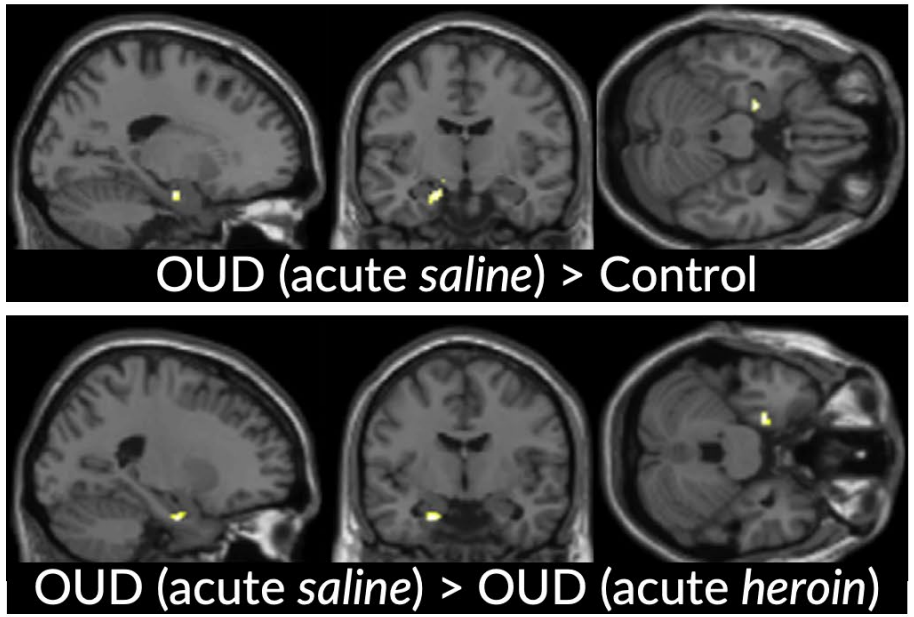
Heroin users < controls



Amygdala
emotional - neutral

Occipital cortex
positive - negative

Amygdala fear response
heroin-maintained and controls

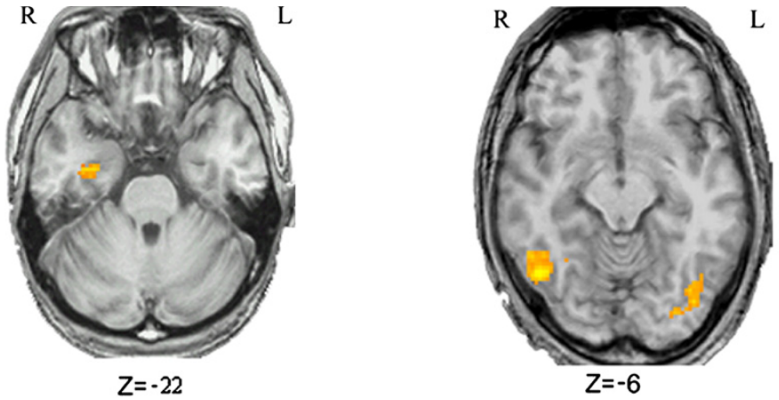


Wang et al. 2010 Neuroimage.
Schmidt et al. 2014 Biol Psychiatry.

3. Socioaffective Processing

Facial Expressions

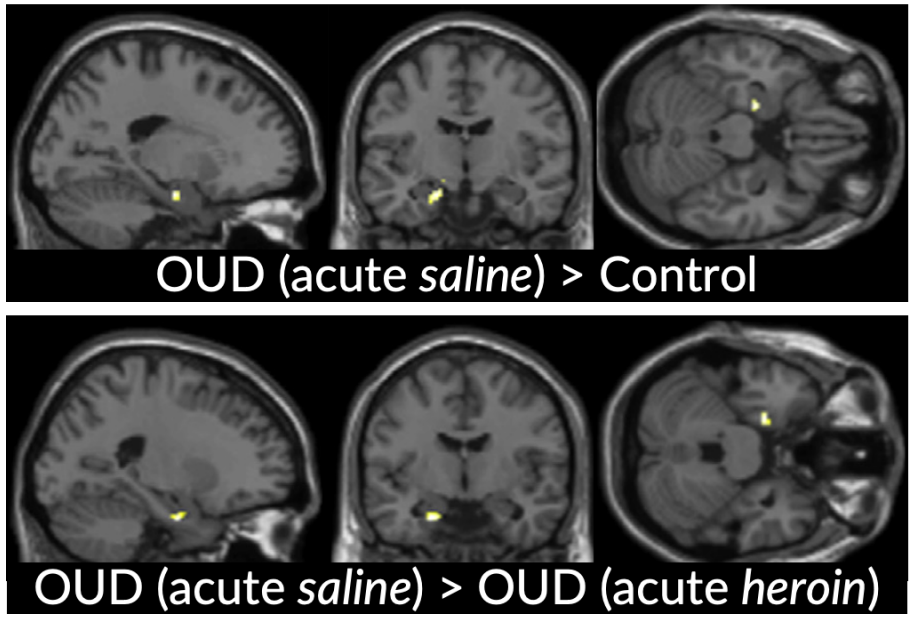
Heroin users < controls

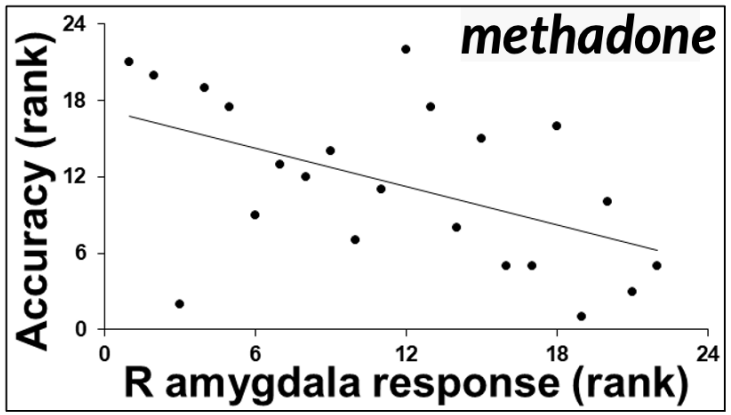


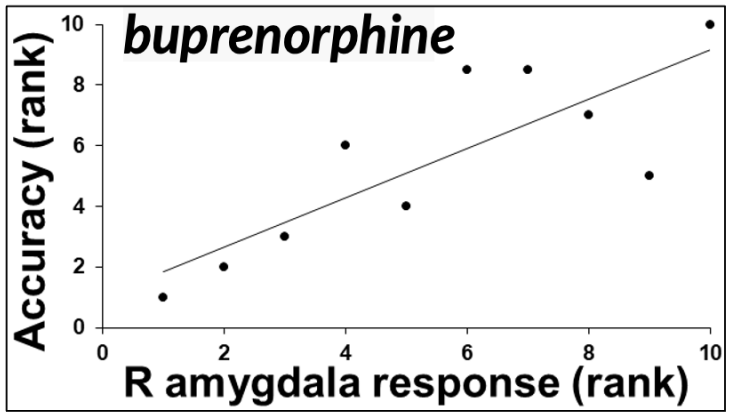
Amygdala
emotional - neutral

Occipital cortex
positive - negative

Amygdala fear response heroin-maintained and controls



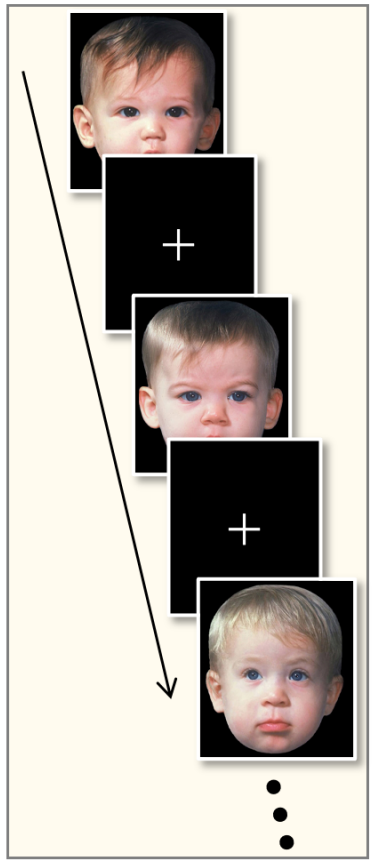


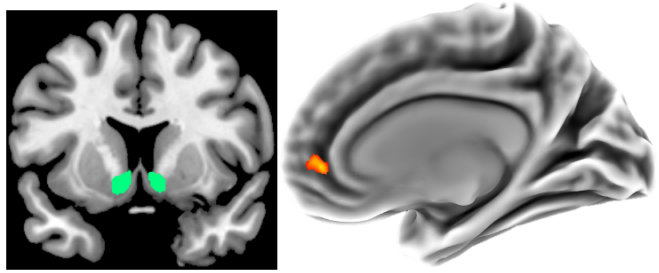


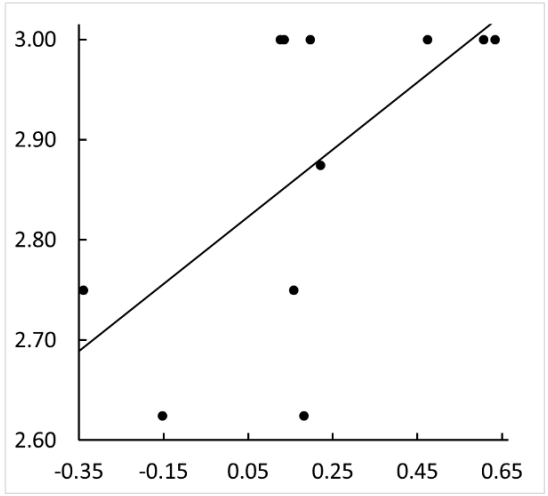
Wang et al. 2010 Neuroimage.
Schmidt et al. 2014 Biol Psychiatry.
Shi et al. in prep.

3. Socioaffective Processing

Caretaking Correlates







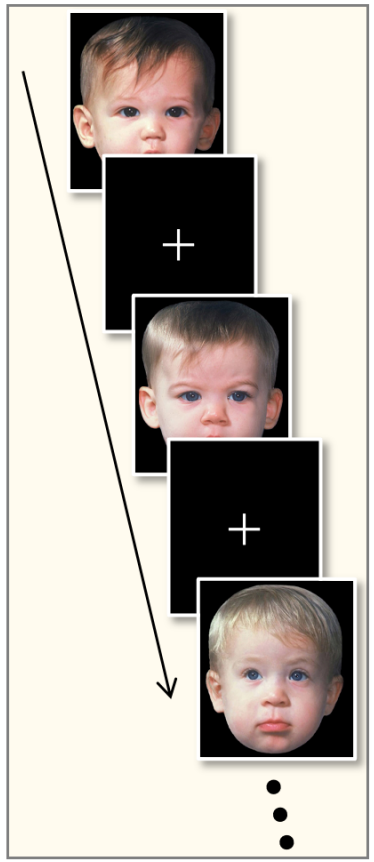
Correlation between
neural response to baby faces
and **<u>mother-infant bonding</u>**

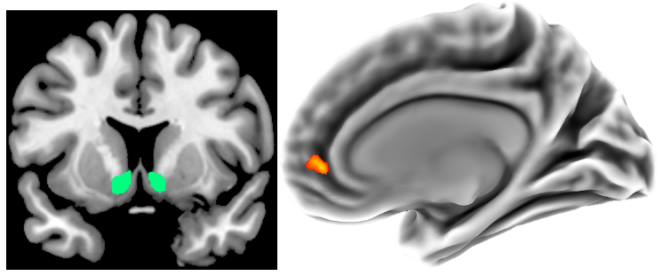
(methadone-maintained mothers)

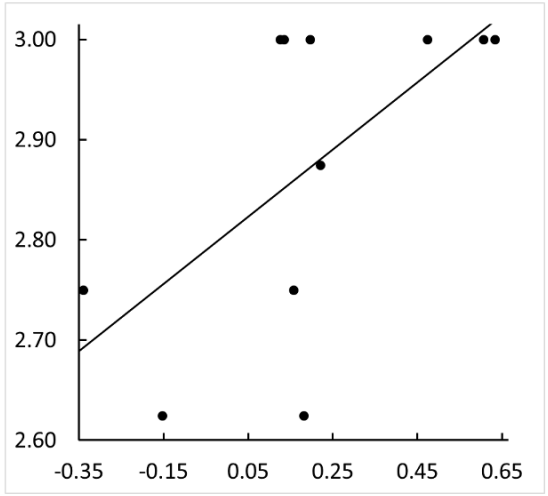
Shi et al. unpublished.

3. Socioaffective Processing

Caretaking Correlates



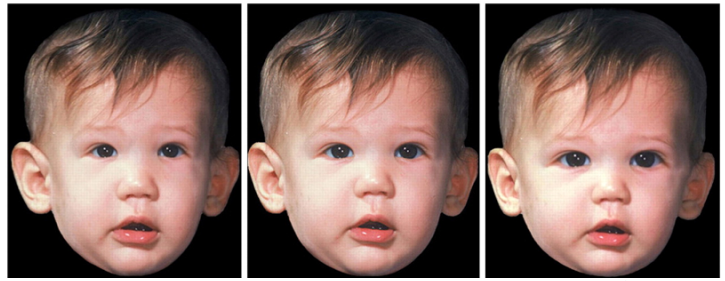




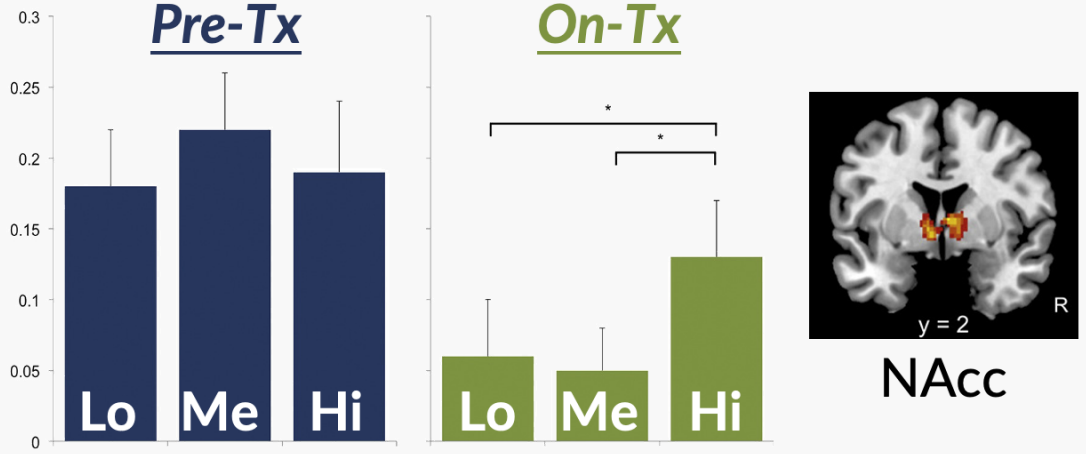
Correlation between
neural response to baby faces
and **mother-infant bonding**

(methadone-maintained mothers)

Levels of cuteness



Effect of extended-release naltrexone



NAcc

Shi et al. unpublished.
Wang et al. 2018 JSAT.

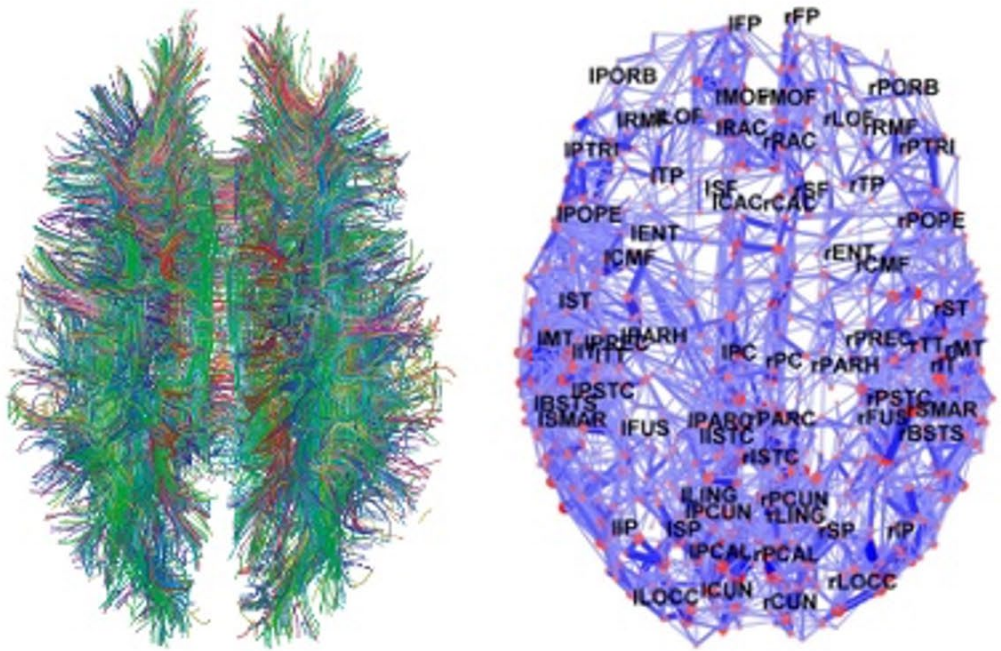
3. Socioaffective Processing

Summary:

- OUD patients show reduced sensitivity to **monetary reward** in the striatum.
- OUD patients show reduced front-striatal neural response to **natural reward cues** that may be associated with clinical and behavioral indices of socioaffective deficits (e.g., anhedonia).
- OUD patients appear to show altered amygdala response to **facial expressions** that may be modulated by treatment status.
- Medications for OUD appear to modulate the neural correlates of **caretaking**.

4. Interregional Connectivity

- ***Structural connectivity*** defines the existence of white matter tracts physically interconnecting brain regions whereas
- ***functional connectivity*** describes the statistical dependencies between neural signals acquired from different brain areas using measures such as correlation and coherence.

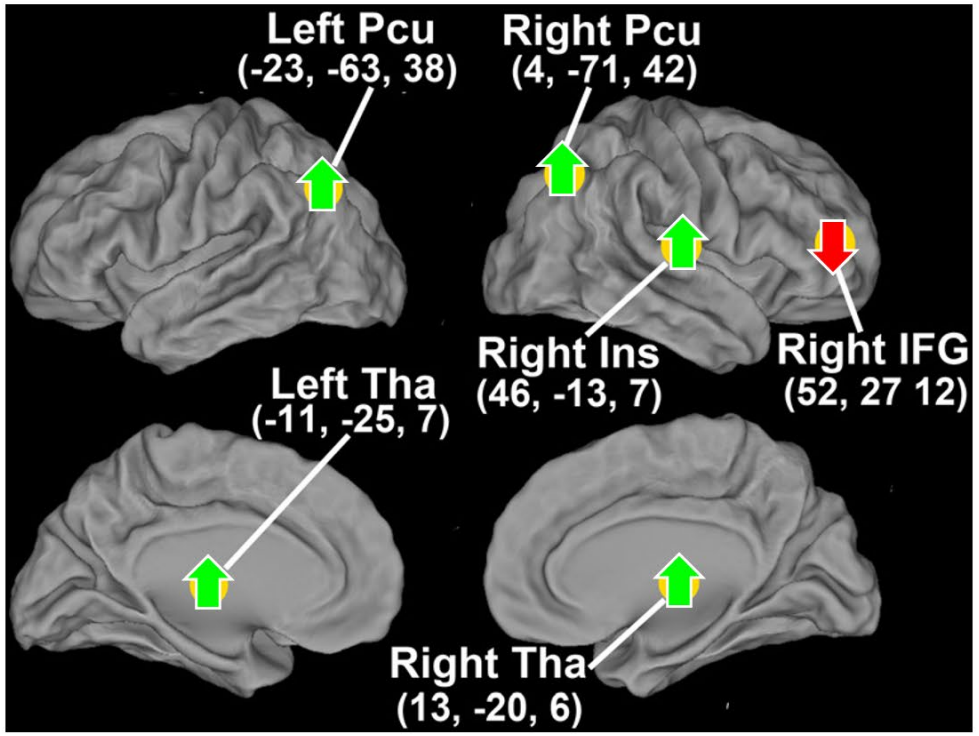


Erol & Hunyadi 2021.
commons.wikipedia.org

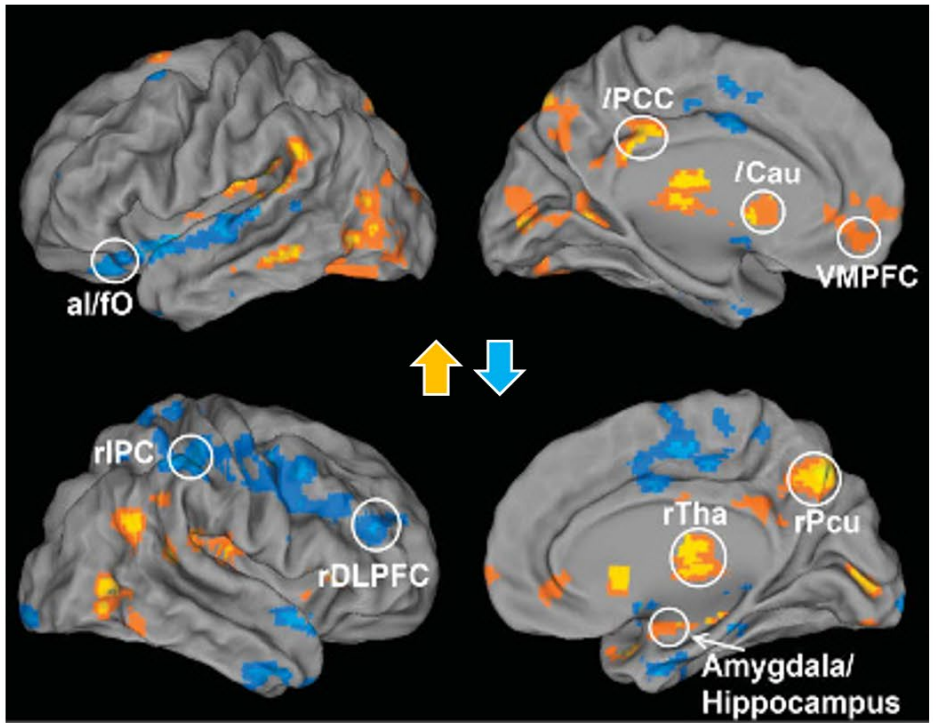
4. Interregional Connectivity

Cortico-Subcortical Connectivity

Amygdala **connectivity**
OUD vs. control



NAcc **connectivity**
OUD vs. control

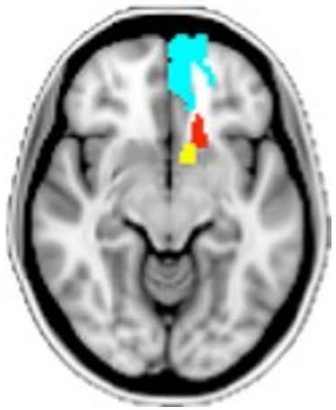


Xie et al. 2011 Behav Brain Res.
Xie et al. 2014 Mol Psychiatry.

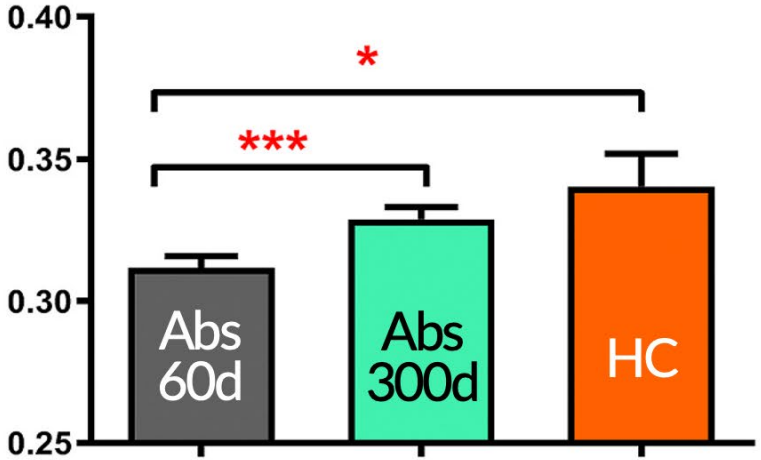
4. Interregional Connectivity

Effect of Abstinence

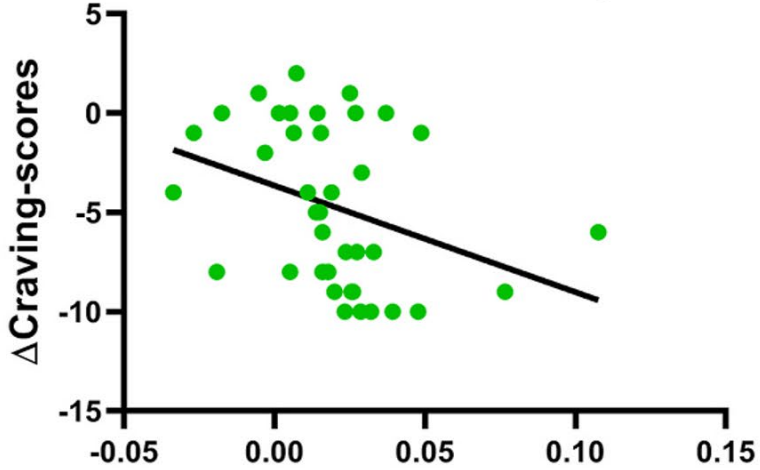
Structural (DTI)



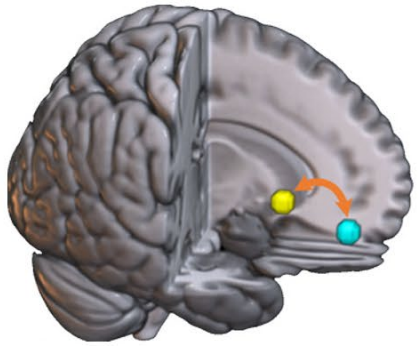
mOFC-NAcc connectivity



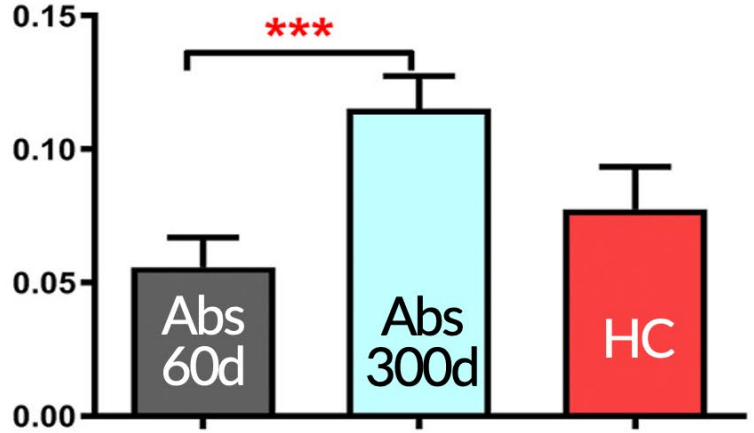
Corr. with Δ craving



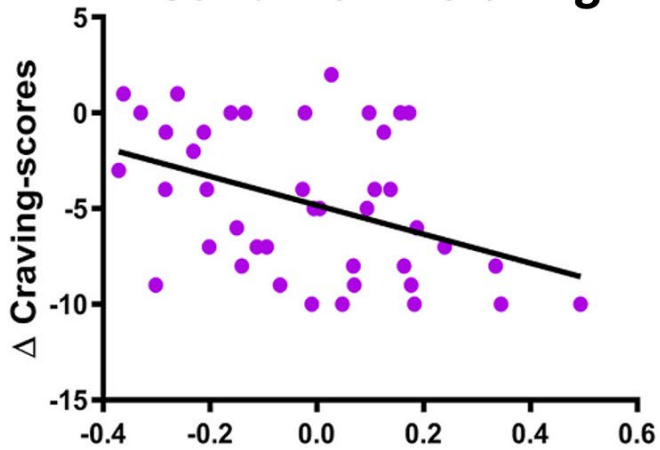
Functional (fMRI)



mOFC-NAcc connectivity



Corr. with Δ craving

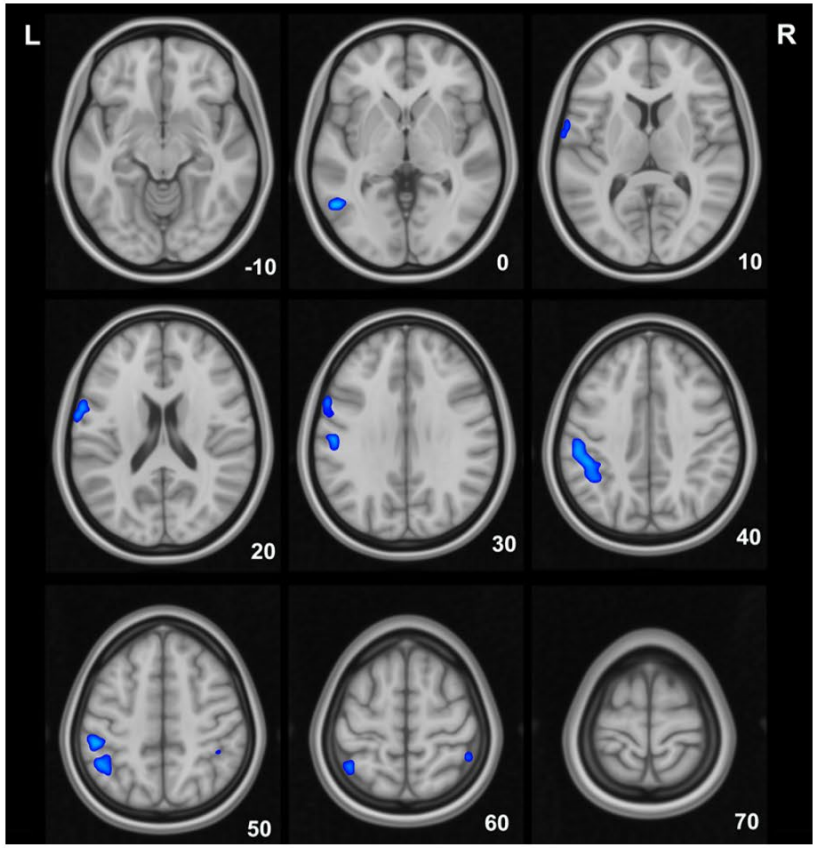


Lu et al. 2022 J Psychiatr Res.

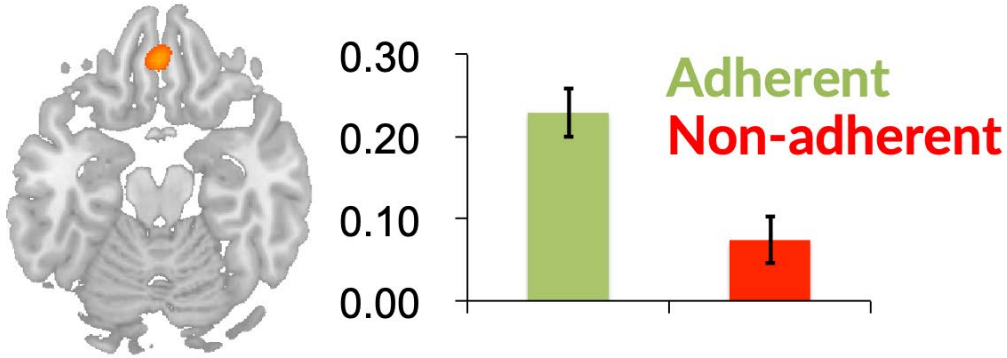
4. Interregional Connectivity

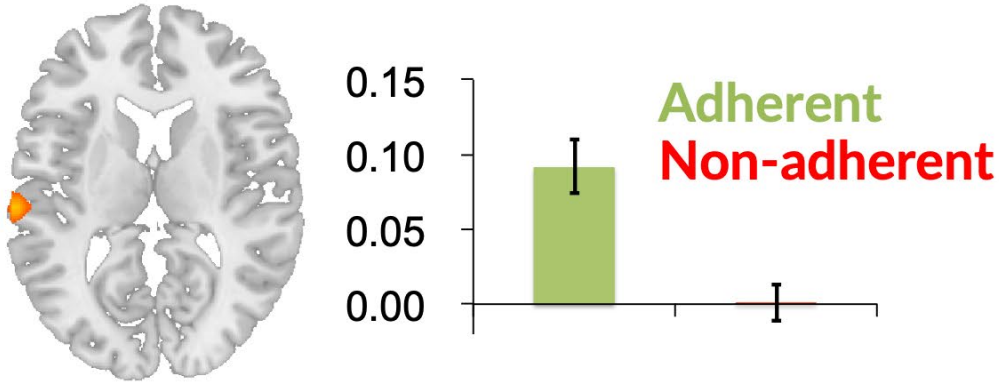
Associations with Outcomes

***NAcc* connectivity**
relapsers < non-relapsers (methadone)



***NAcc* connectivity**
adherence to extended-release naltrexone



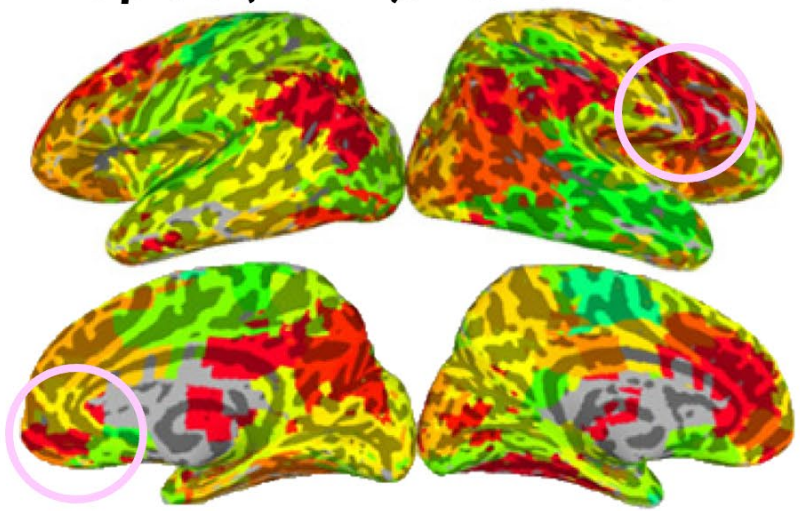


Wang et al. 2021 DAD.
Shi et al. in prep.

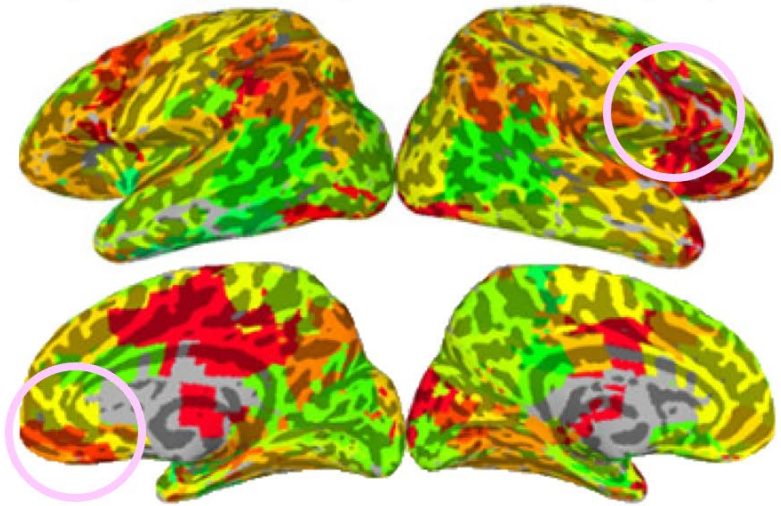
4. Interregional Connectivity

Prenatal Opioid Exposure

Opioid (No Tx). vs. Control



Opioid (No Tx). vs. Opioid (Tx)

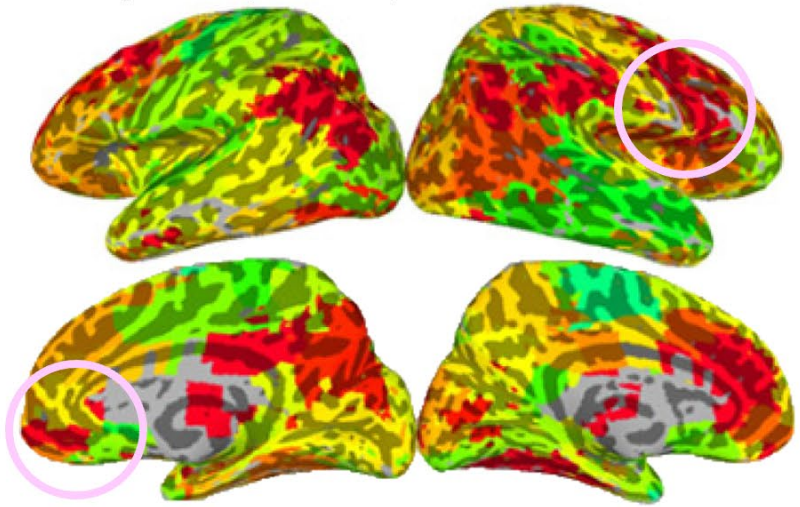


Liu et al. 2022 J Neurosci

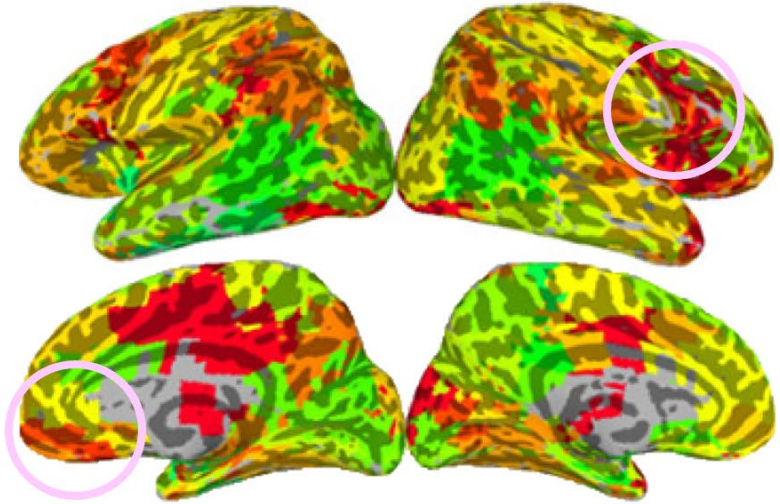
4. Interregional Connectivity

Prenatal Opioid Exposure

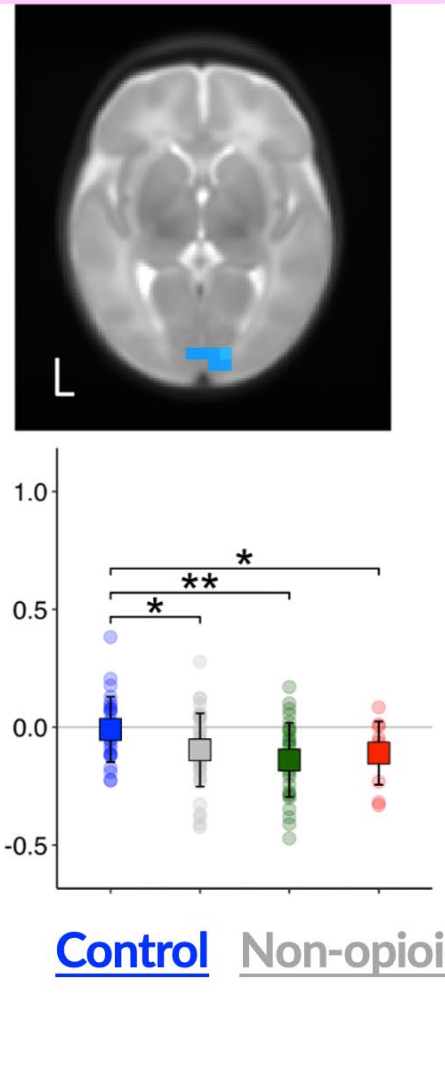
Opioid (No Tx). vs. Control



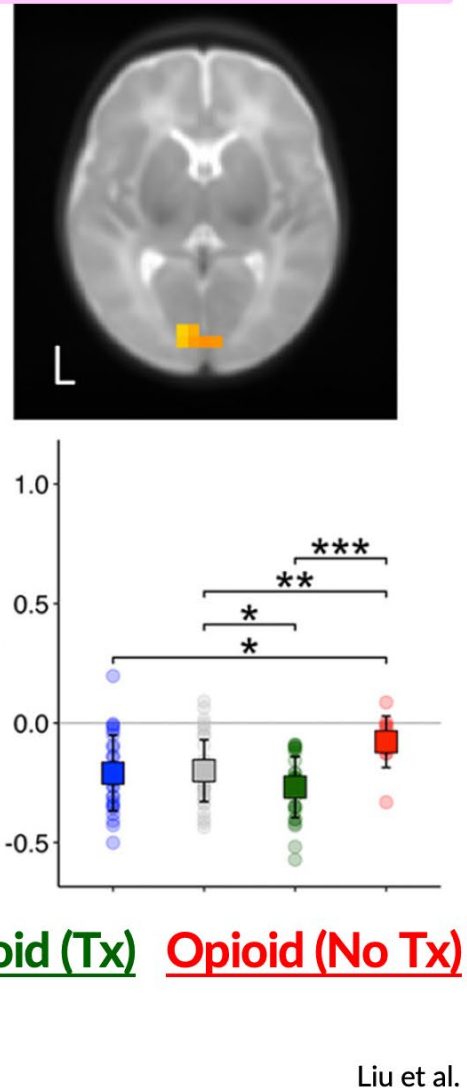
Opioid (No Tx). vs. Opioid (Tx)



medial orbitofrontal



right inferior frontal



Control Non-opioid **Opioid (Tx)** **Opioid (No Tx)**

Liu et al. 2022 J Neurosci

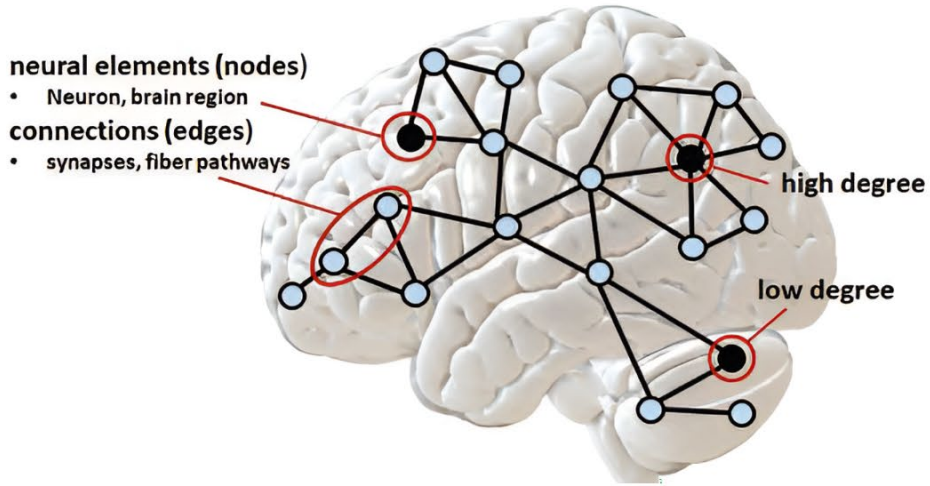
4. Interregional Connectivity

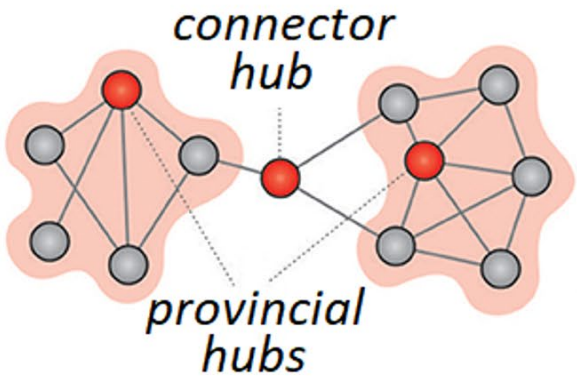
Summary:

- OUD patients show reduced amygdala and NAcc connectivity with the lateral PFC.
- Fronto-striatal connectivity appears to be associated with treatment status and treatment outcomes.
- Medication for OUD during pregnancy appears to modulate neonate fronto-occipital connectivity.

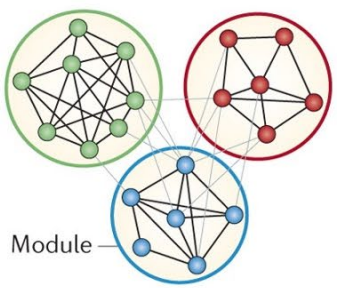
5. New Methods

Graph-Theoretical Analysis of Brain Networks

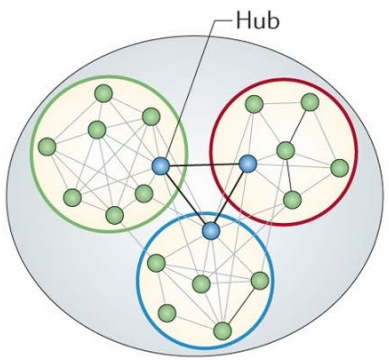




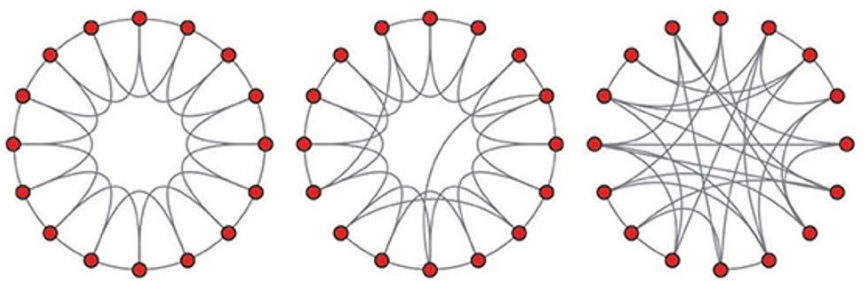
Node centrality



Segregation



Integration

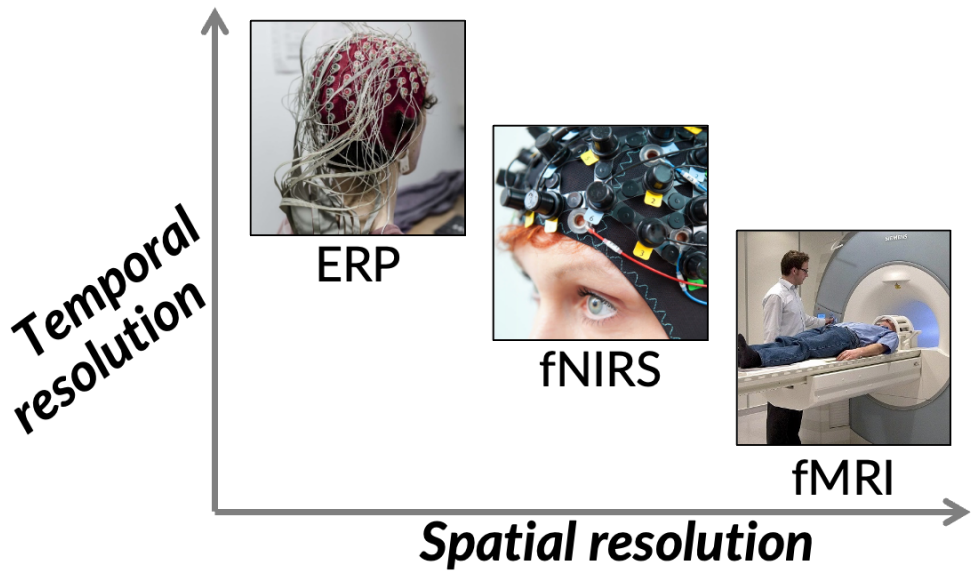


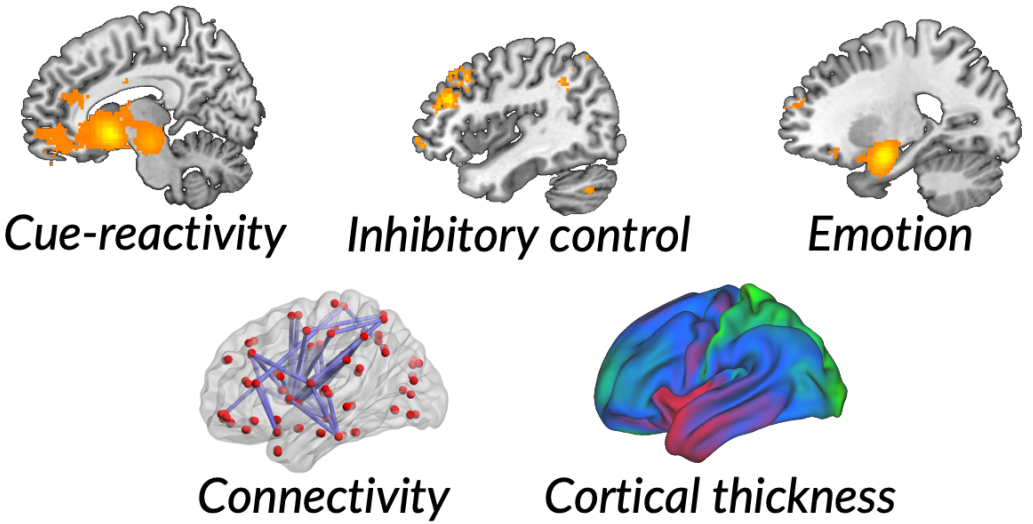
Small-worldness

Ray et al. 2018 ASPCON.
Deco et al. 2015 NRN.
Farahani et al. 2019 Front Neurosci.

5. New Methods

Multimodal Data Fusion





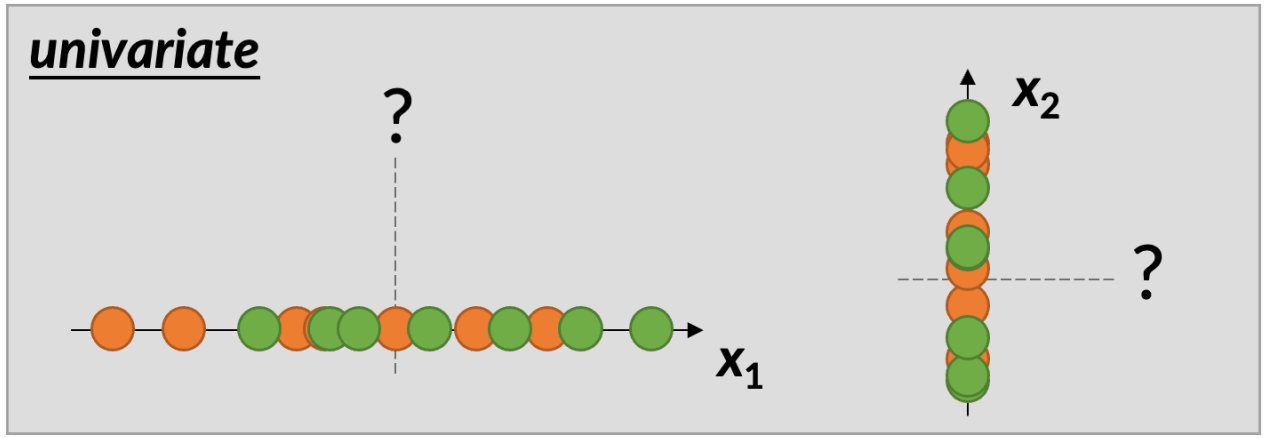
Multivariate approaches to data fusion:

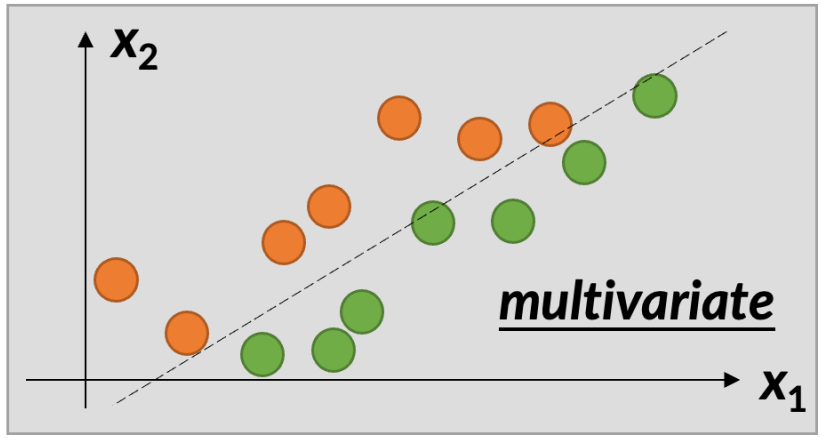
- Independent component analysis (ICA)
- Principle component analysis (PCA)
- Partial least squares regression (PLSR)
- Canonical correlation analysis (CCA)

Calhoun & Sui 2016 Biol Psychiatry CNNI.

5. New Methods

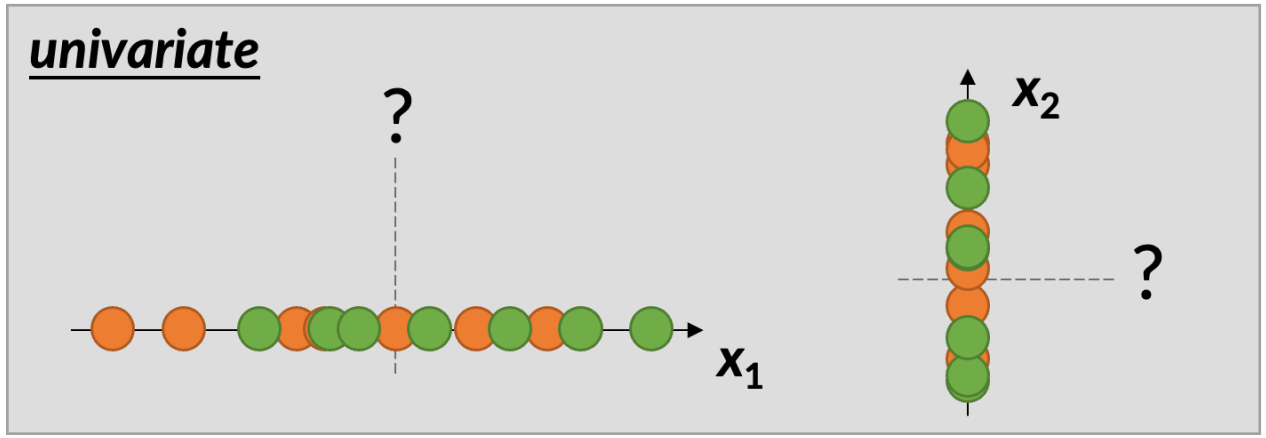
Machine Learning

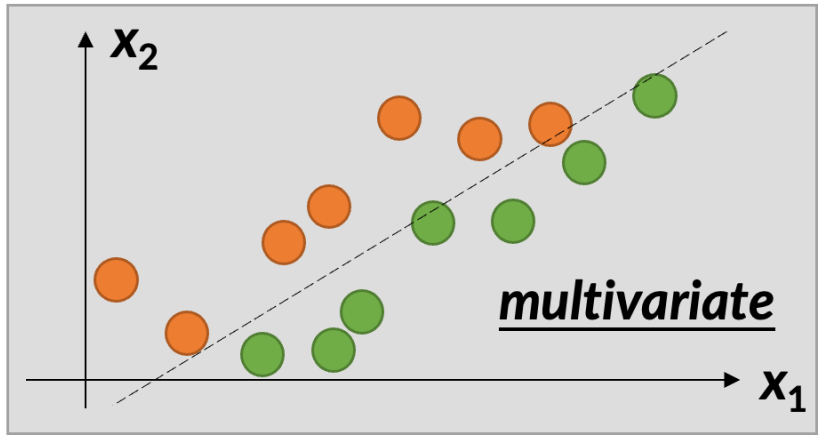


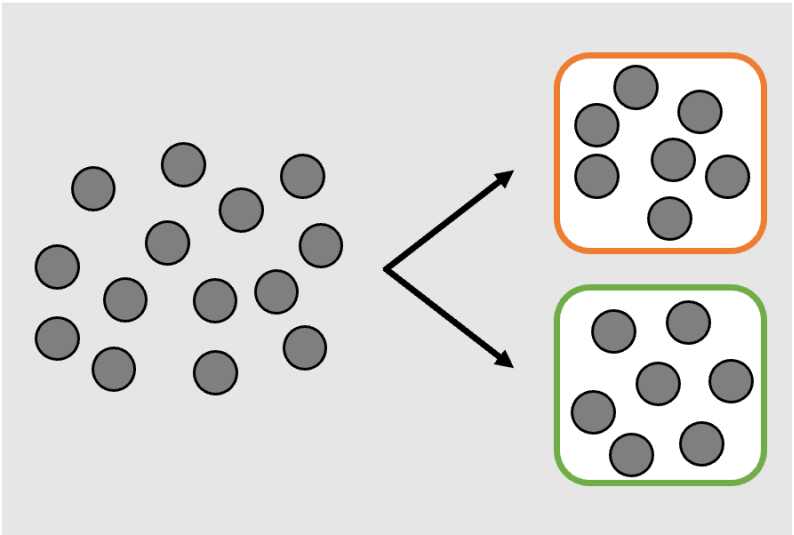


5. New Methods

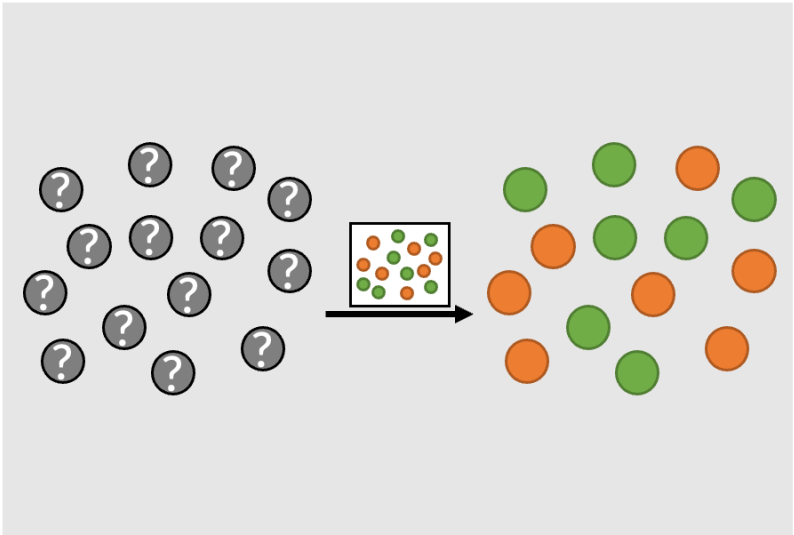
Machine Learning





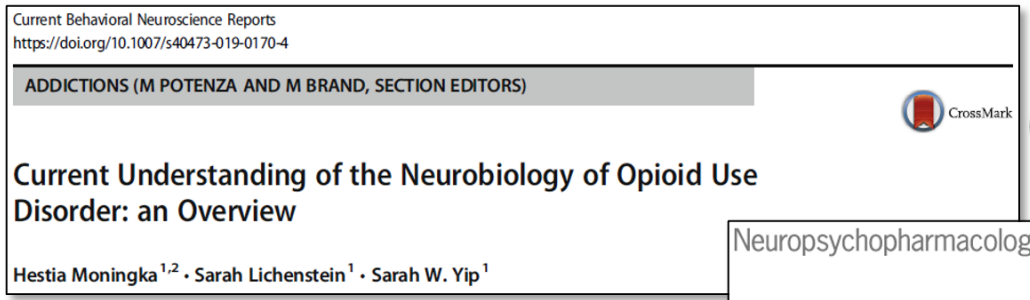


Unsupervised learning
(e.g., identifying biotypes)



Supervised learning
(e.g., predicting outcomes)

Further Readings


Current Behavioral Neuroscience Reports
https://doi.org/10.1007/s40473-019-0170-4

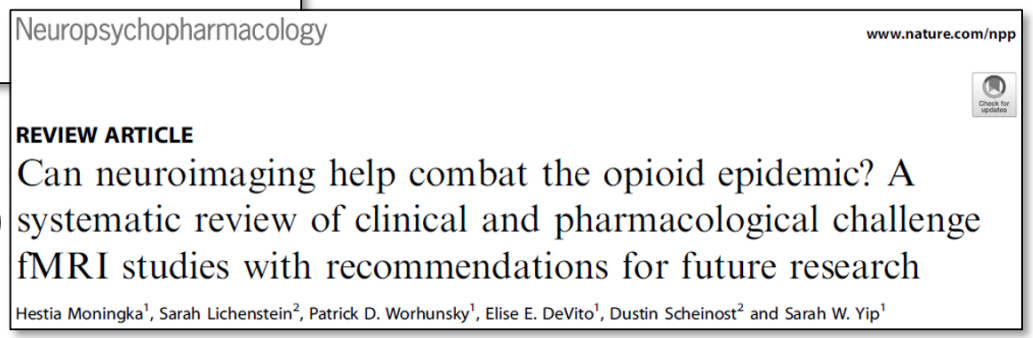
ADDICTIONS (M POTENZA AND M BRAND, SECTION EDITORS)

CrossMark

Current Understanding of the Neurobiology of Opioid Use Disorder: an Overview

Hestia Moningka[1,2] · Sarah Lichenstein[1] · Sarah W. Yip[1]

(Moningka et al. 2019 Curr Behav Neurosci Rep)


Neuropsychopharmacology

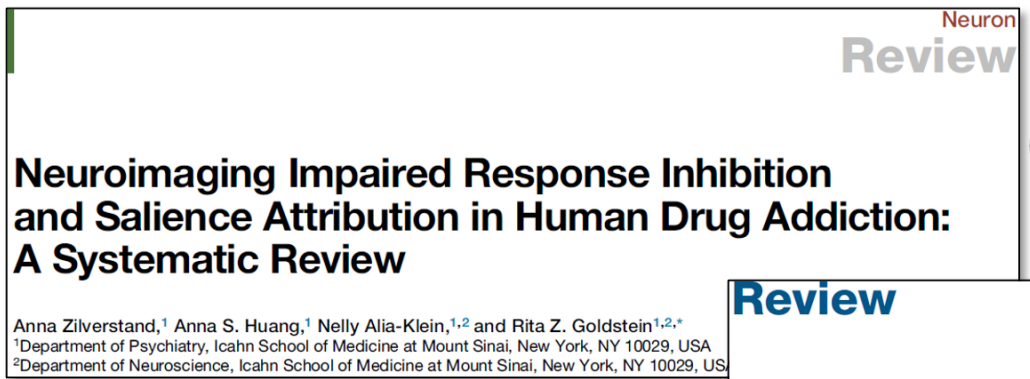
www.nature.com/npp

REVIEW ARTICLE

Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research

Hestia Moningka[1], Sarah Lichenstein[2], Patrick D. Worhunsky[1], Elise E. DeVito[1], Dustin Scheinost[2] and Sarah W. Yip[1]

(Moningka et al. 2019 NPP)

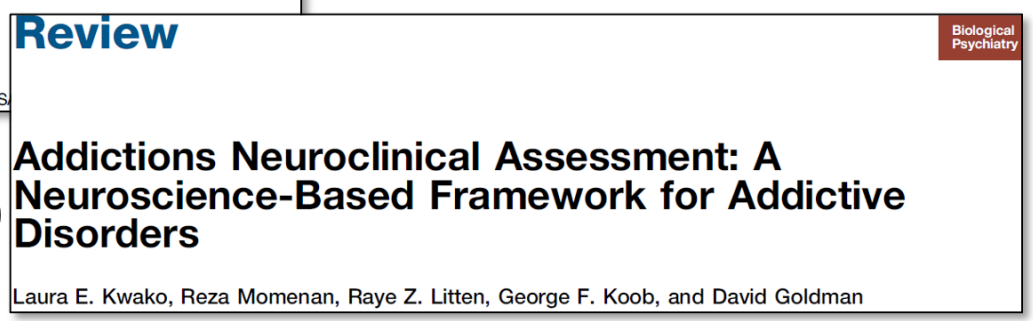

Neuron

Review

Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review

Anna Zilverstand,[1] Anna S. Huang,[1] Nelly Alia-Klein,[1,2] and Rita Z. Goldstein[1,2,*]
[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[2]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, US

(Zilverstand et al. 2018 Neuron)


Review

Biological Psychiatry

Addictions Neuroclinical Assessment: A Neuroscience-Based Framework for Addictive Disorders

Laura E. Kwako, Reza Momenan, Raye Z. Litten, George F. Koob, and David Goldman

(Kwako et al. 2016 Biol Psychiatry)

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Thank You!