UNDERSTANDING AND TARGETING NEURAL REWARD SYSTEMS AS A MECHANISM IN ADOLESCENT DEPRESSION

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2025 WISCONSIN SYMPOSIUM ON EMOTION

Article

Regional Patterns of Brain Activity in Adults With a History of Childhood-Onset Depression: Gender Differences and Clinical Variability

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Nathan A. Fox, Ph.D.
Jeffrey F. Cohn, Ph.D.
Erika E. Forbes, M.S.
Joel T. Sherrill, Ph.D.
Maria Kovacs, Ph.D.

Objective: The study investigated t
pothesis that EEG asymmetry score
cating higher right and lower left f
brain activity) are associated with v
ability to negative mood states a
pressive disorders. Gender and c
history variables were examined
tors that may influence the relati
tween EEG and depression.

Method: EEG measures of asymm
alpha frequency (7.5–12.5 Hz) su
sion were analyzed in 55 young
with a documented clinical hist
childhood-onset depression and 5
parison subjects with no history of
psychopathology. EEG patterns we
amined in relation to operationa
noses of mental disorders during
hood and adulthood.

Results: Differences in EEG asym
between childhood depression pro

PSYCHOPHYSIOLOGY
SPR

Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style

ROBERT E. WHEELER, RICHARD J. DAVIDSON, ANDREW J. TOMARKEN

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Biological Psychology 71 (2006) 264–277

BIOLOGICAL PSYCHOLOGY

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Children's affect regulation during a disappointment: Psychophysiological responses and relation to parent history of depression

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Abstract

Psychophysiological responses during affect regulation were examined in 57 children ages 3–9 years
childhood-onset depression (COD). During a structured laboratory task, children were given first a disa
Frontal electroencephalogram (EEG) asymmetry, respiratory sinus arrhythmia (RSA), heart period
measured during resting and task conditions. Affective and self-regulatory behaviors were coded from
relative right frontal activity was associated with withdrawal behavior. High heart period was associate
with children of psychiatrically healthy parents, children of parents with COD exhibited poor heart perio
children of parents with COD, greater relative left frontal activity was related to concurrent internalizing
resting RSA was related to internalizing problems. Physiological responses associated with affect regulat
for depression.

Keywords: Affect regulation; Depression; Frontal EEG asymmetry; RSA; Heart period

Journal of Child Psychology and Psychiatry 47:1 (2006), pp 79–87 doi:10.1111/j.1469-7610.2005.01442.x

Maternal depression, child frontal asymmetry, and child affective behavior as factors in child behavior problems

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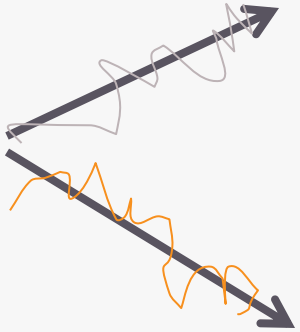
[1]University of Pittsburgh, USA; [2]University of Maryland, USA

Background: Despite findings that parent depression increases children's risk for internalizing and externalizing problems, little is known about other factors that combine with parent depression to contribute to behavior problems. **Methods:** As part of a longitudinal, interdisciplinary study on childhood-onset depression (COD), we examined the association of mother history of COD, child frontal electroencephalogram asymmetry, and affective behavior with children's concurrent behavior problems. **Results:** Children in the COD group had higher anxious/depressed and aggressive problems than did children in the control group, but this was qualified by a COD-by-asymmetry interaction effect. For COD but not control children, left frontal asymmetry was associated with both anxious/depressed and aggressive child problems. Children with left frontal asymmetry and low affect regulation behavior had higher anxious/depressed problems than did those with high affect regulation behavior. Boys with left frontal asymmetry had higher aggressive problems than did those with right frontal asymmetry. **Conclusions:** In children of mothers with COD, physiological and behavioral indices of affect regulation may constitute risks for behavior problems. **Keywords:** Maternal depression, behavior problems, affect regulation, psychophysiology, parent–child interaction. **Abbreviations:** COD: childhood-onset depression.

Roadmap

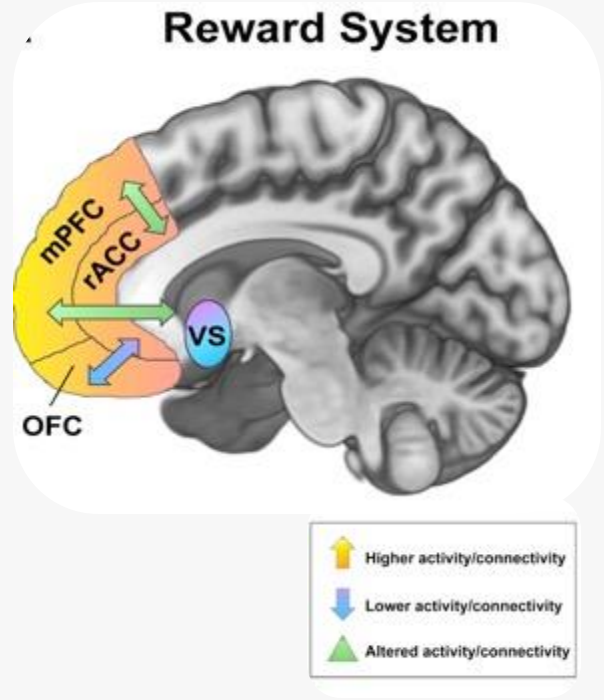
1. Why Neural Reward Circuitry?
2. Methods
3. Our Key Finding
4. Development and Treatment Response
5. Anhedonia
6. Neuromodulation

Disrupted Positive Affect and Reward Function in Depression



Negative Affect

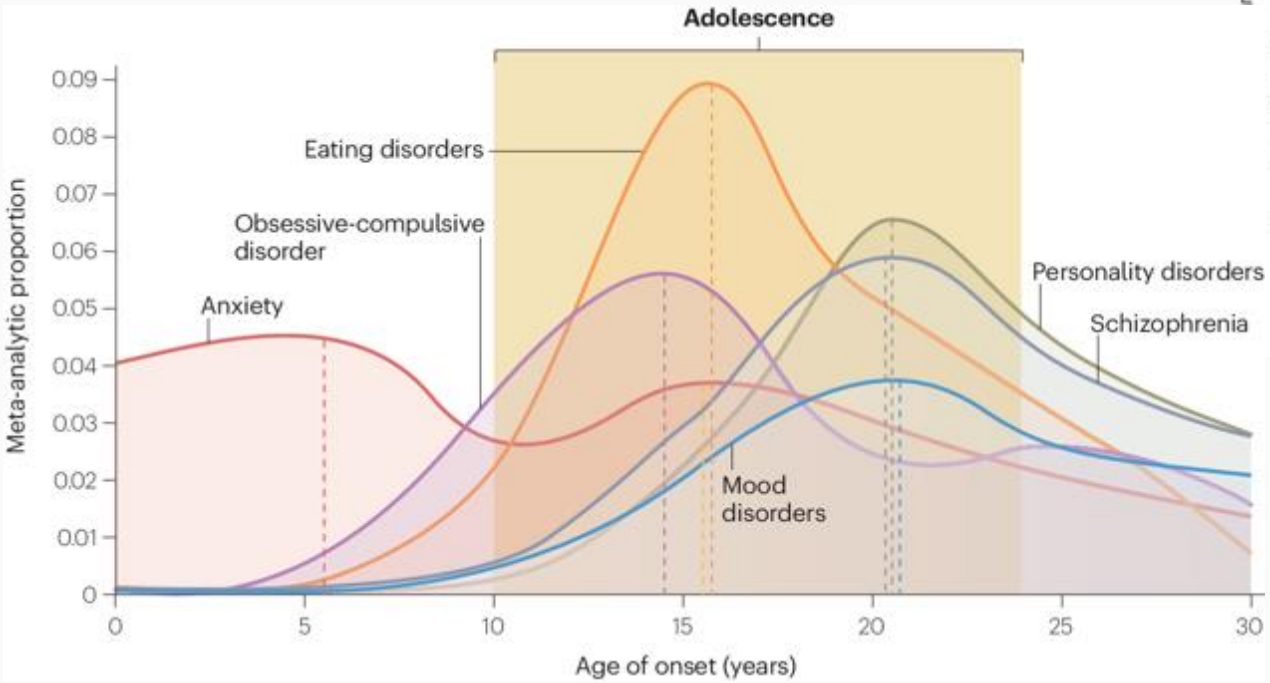
Positive Affect



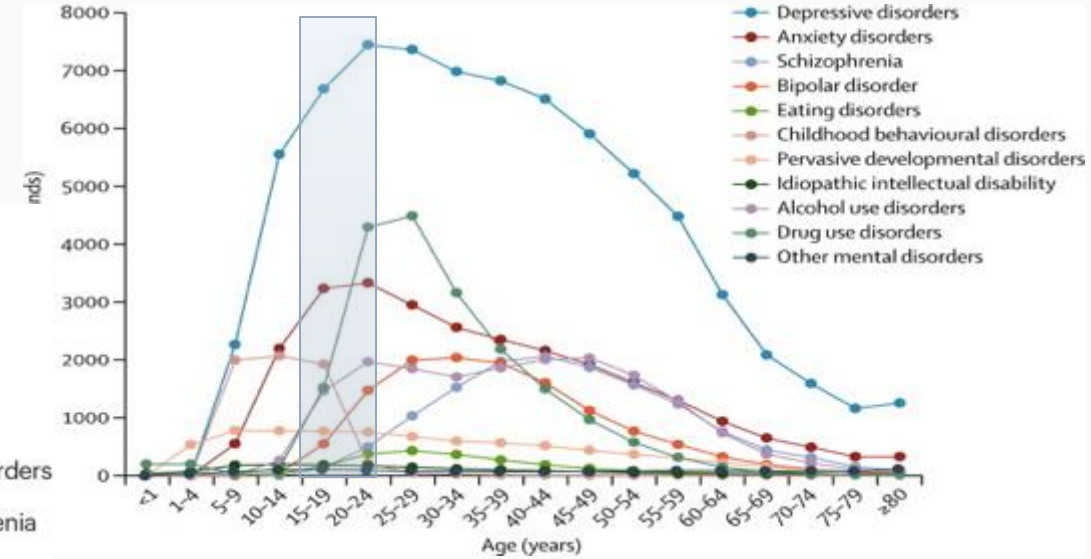
- anhedonia
- low motivation, fatigue, social withdrawal
- experience, behavior, physiology

Forbes & Dahl, 2005, *Development and Psychopathology*
Forbes & Dahl, 2012, *JCPP*
Forbes, Eckstrand, Rofey, & Silk, 2020, *Biol Psychiatry CNNI*

Adolescence and Mental Health

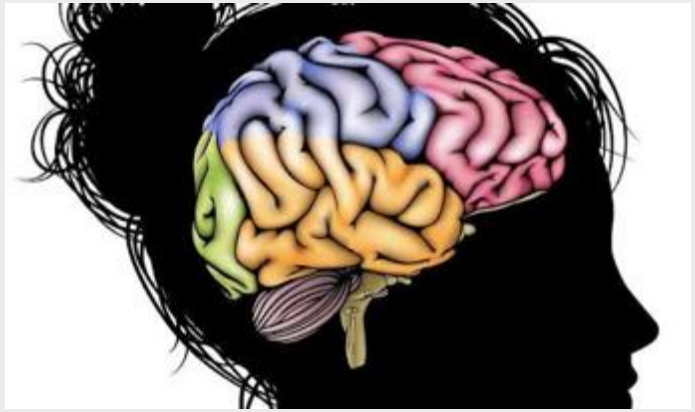


Orben et al., (2024), *Nat Rev Psych*

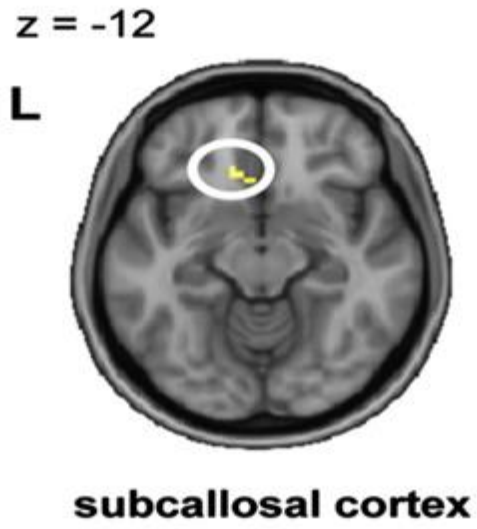


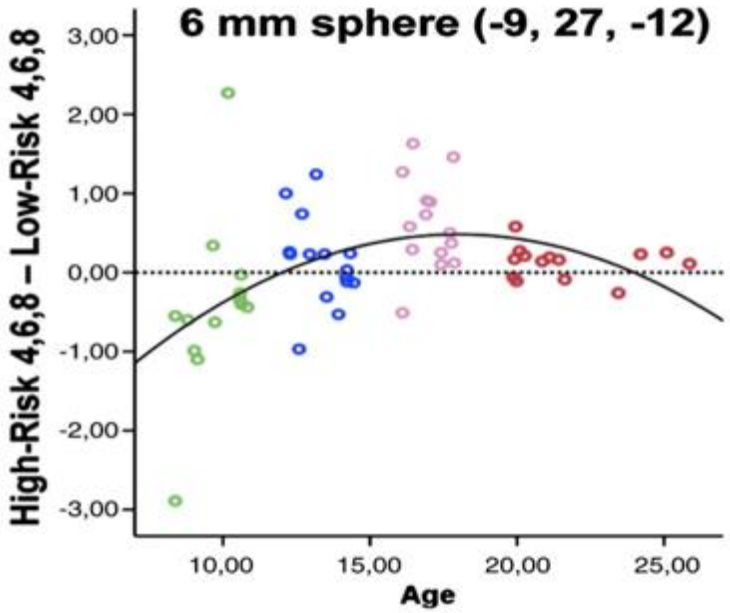
Whiteford et al., 2015, *Lancet*

ADOLESCENCE

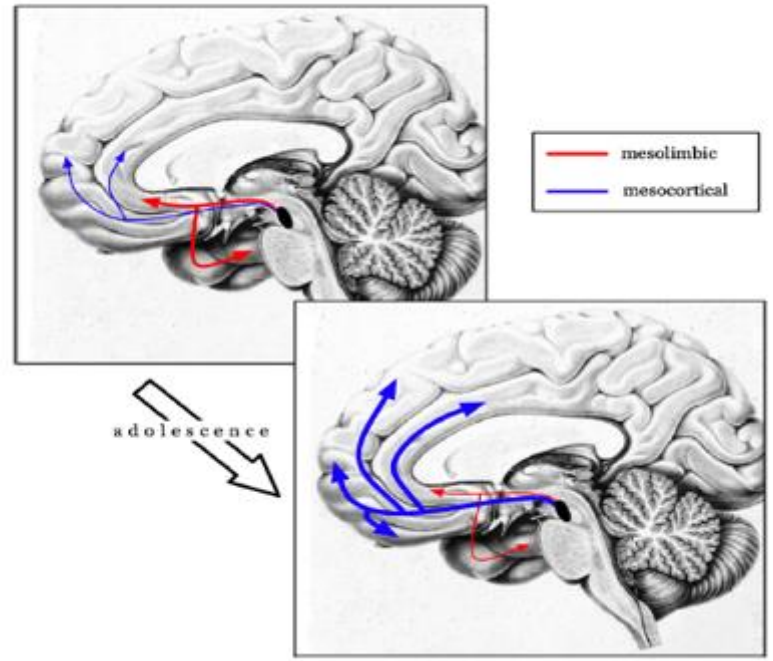


Adolescence and Reward

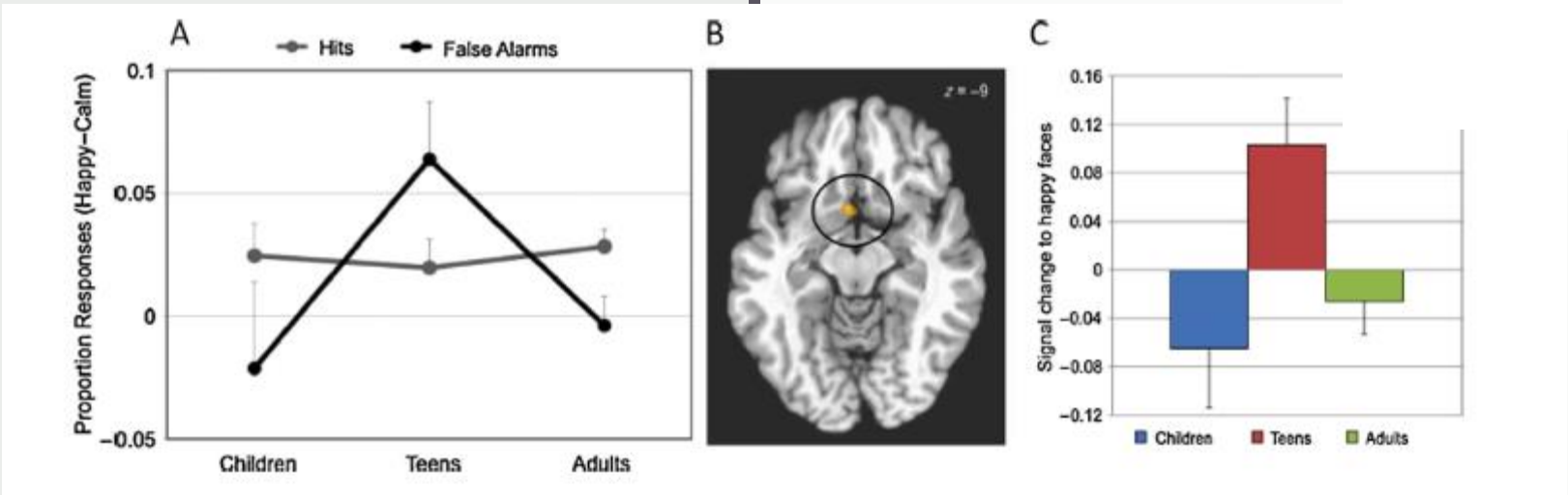




Van Leijenhorst et al., 2010



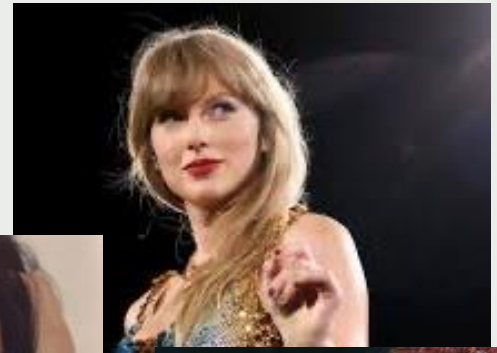
Davey, Yücel, & Allen (2008), *NBBR*

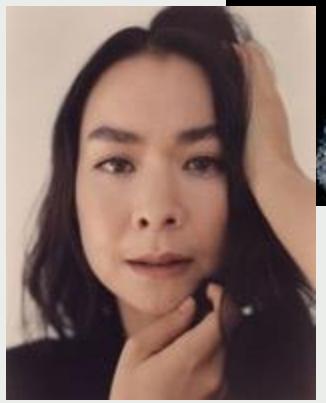


Somerville, Hare, & Casey, 2011

METHODS

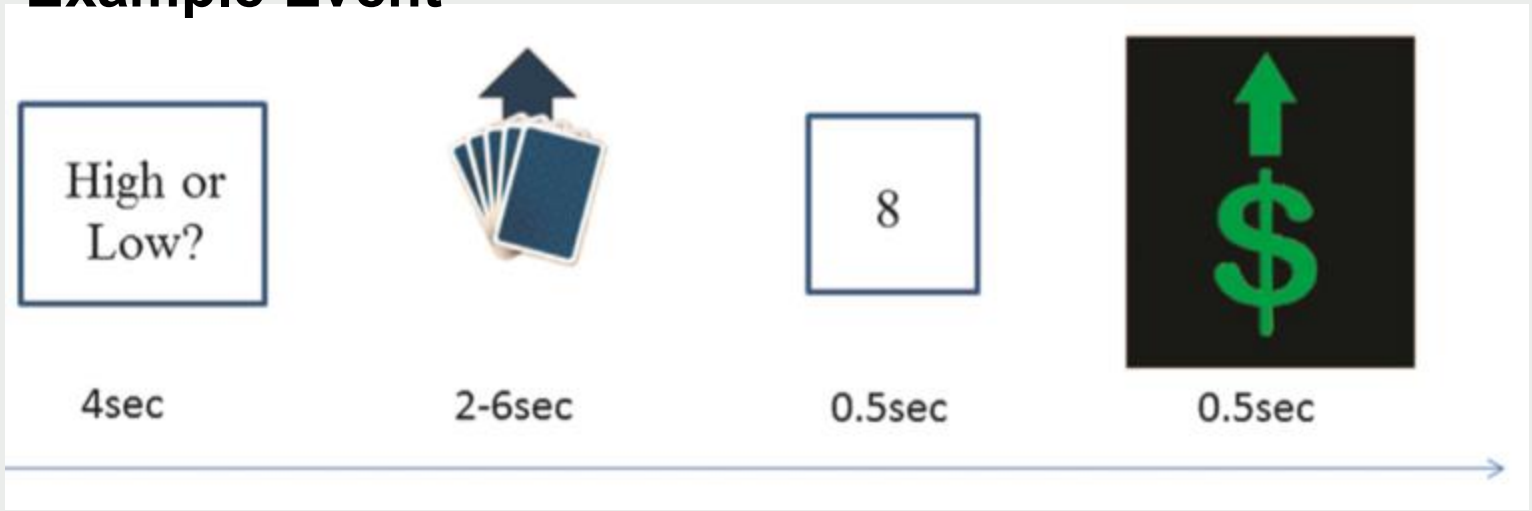
What's Rewarding?

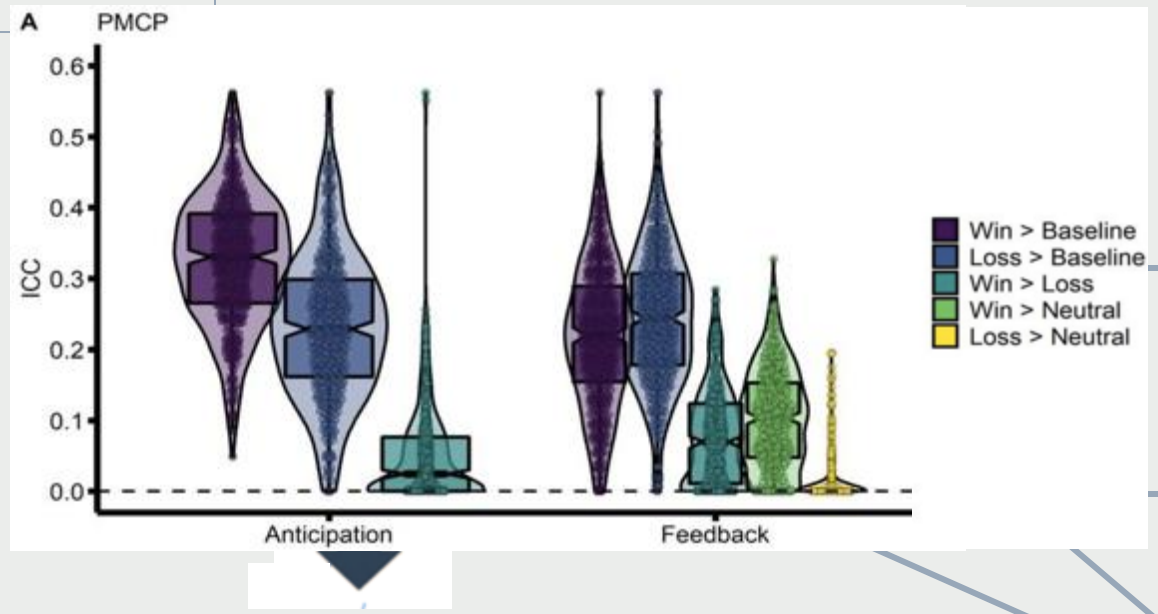




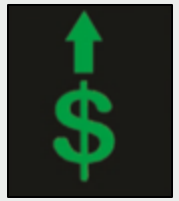
Monetary Reward fMRI

Example Event



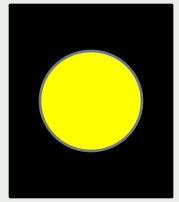


Outcome Conditions



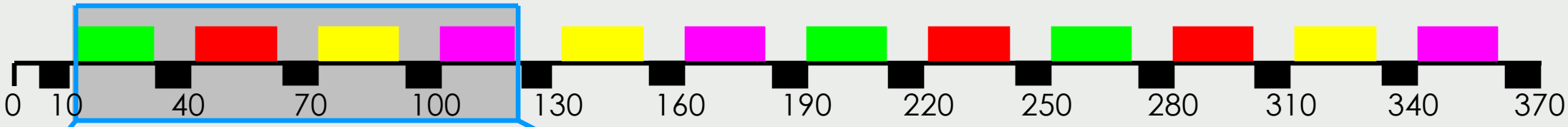
Win (+$1.00)

Loss (-$0.50)



Neutral ($0)

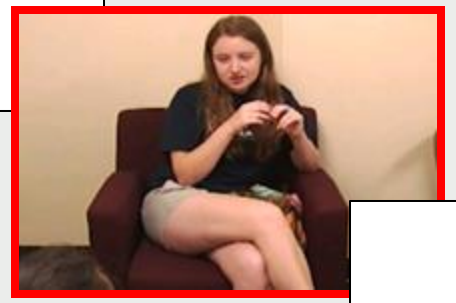
The BFF fMRI Task: Personally Relevant Social Reward



Friend Positive

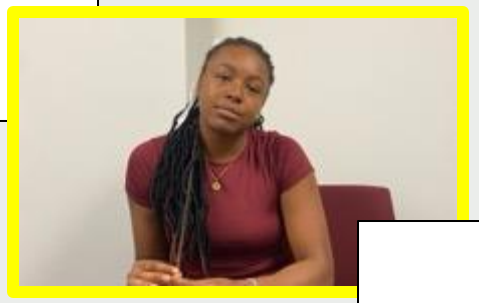
+

Unfamiliar Peer Neutral



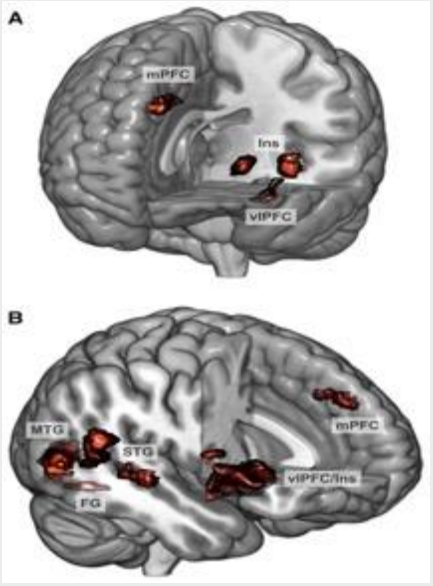
+

Friend Neutral



+

Unfamiliar Peer Positive

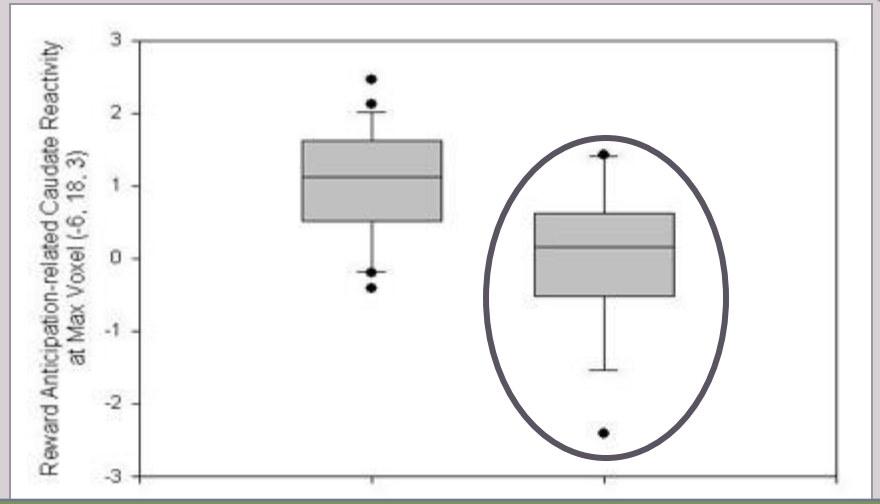


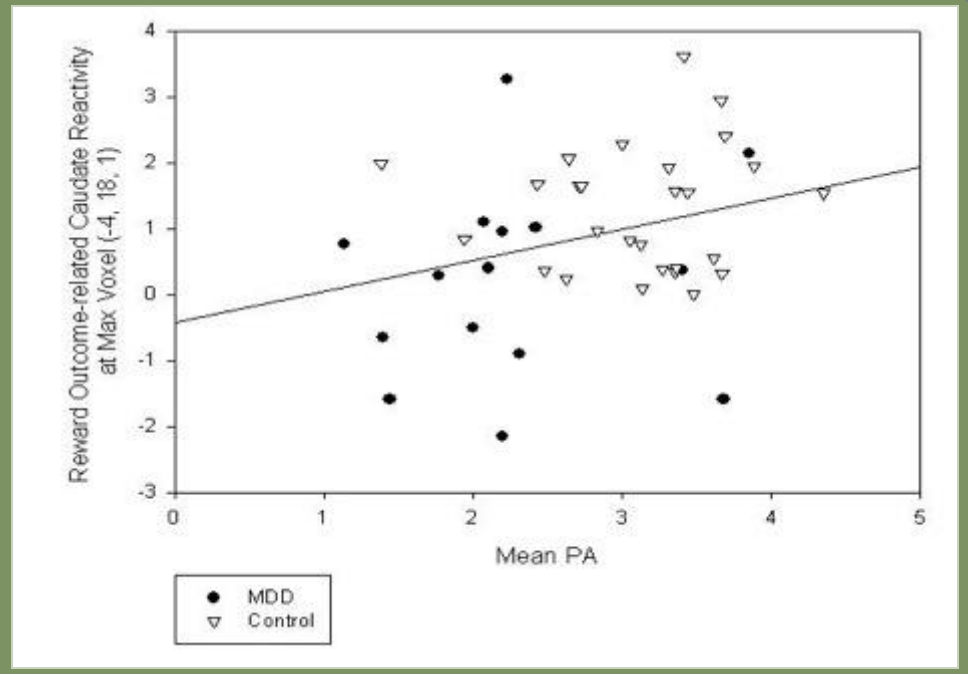
Ambrosia et al., 2018

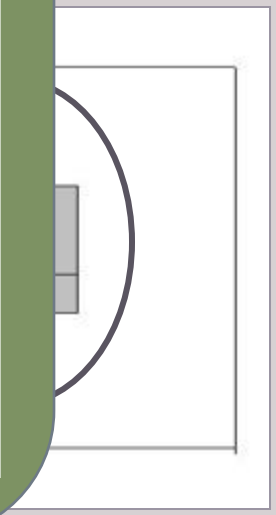
BFF fMRI Task

KEY FINDING

ADOLESCENTS WITH DEPRESSION EXHIBIT *LESS VS* AND *MORE MPFC* RESPONSE TO REWARD





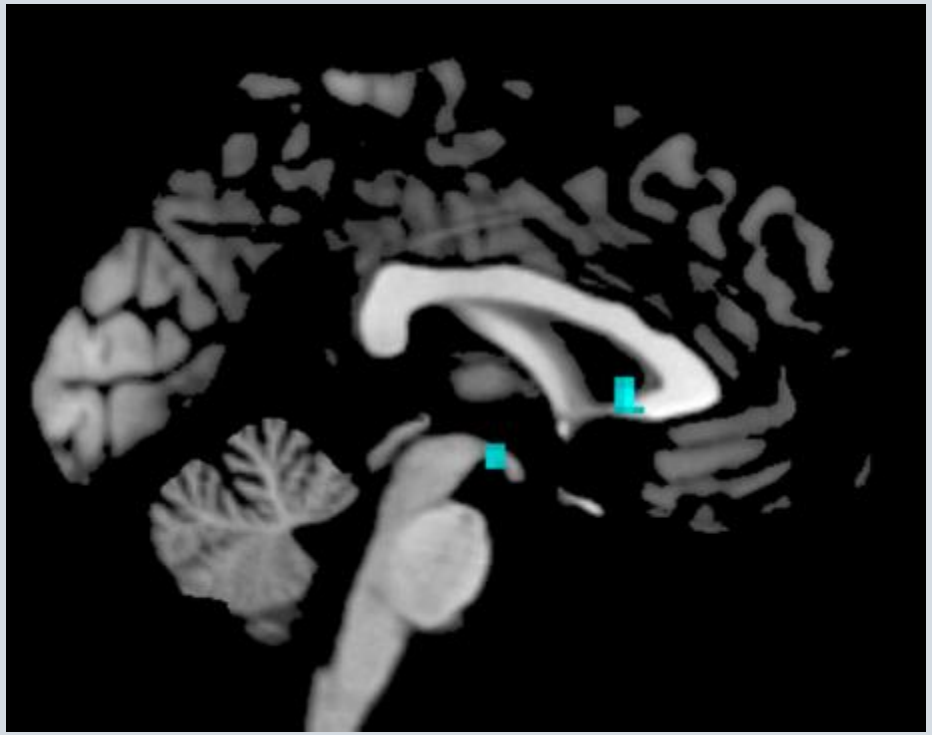


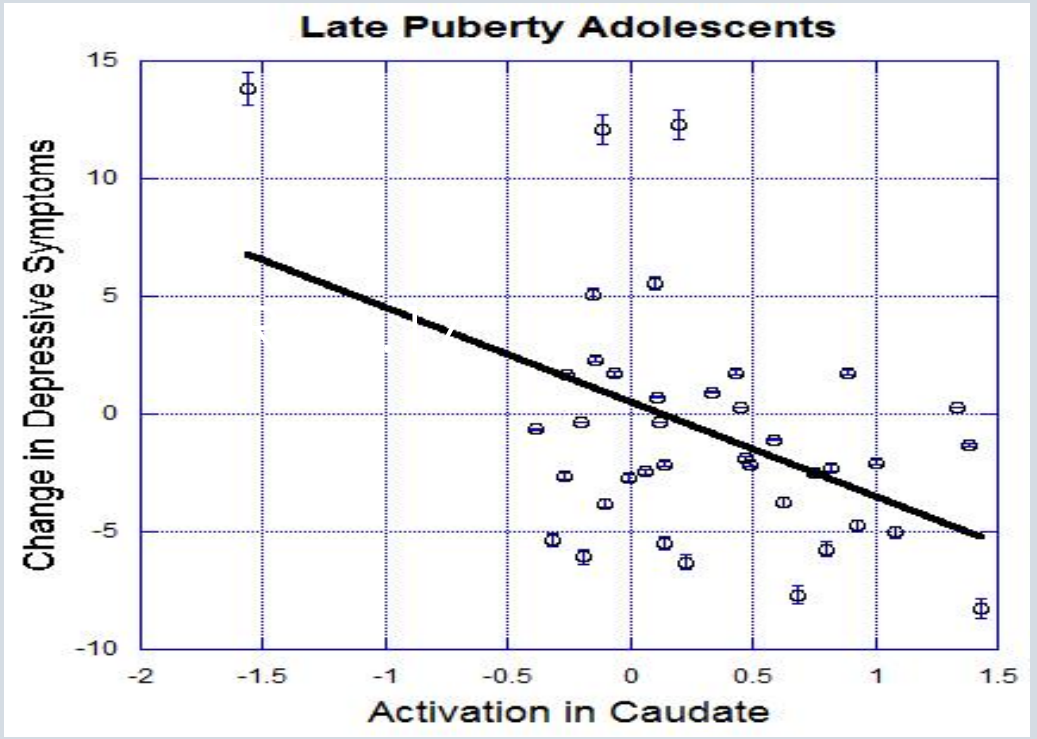
Forbes et al., 2009, *Am J Psychiatry*

DEVELOPMENT OF DEPRESSION AND SUICIDALITY

DEVELOPMENT
Pubertal Maturation X VS Response Predicts Depressive Symptom Increase over 2 Years

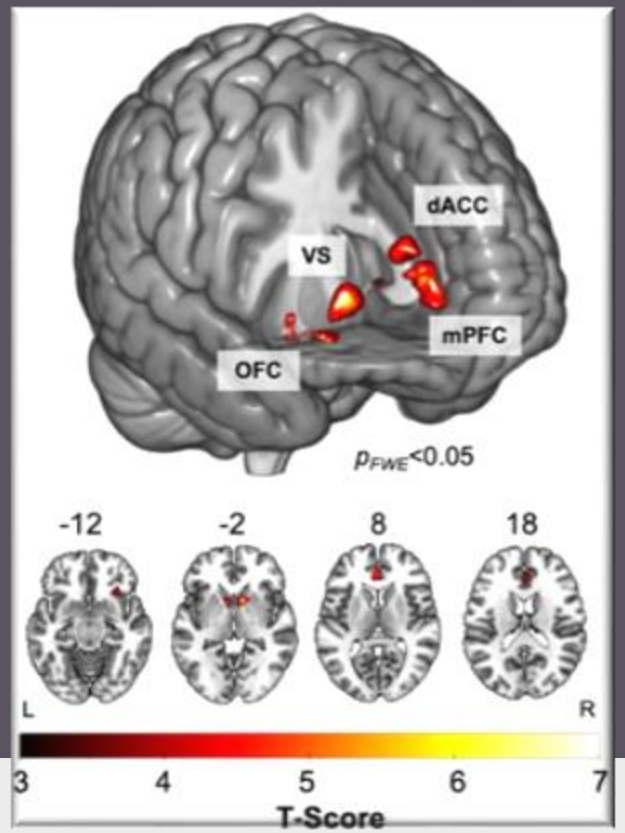
- 72 adolescents
- typically developing
- 11-13 years

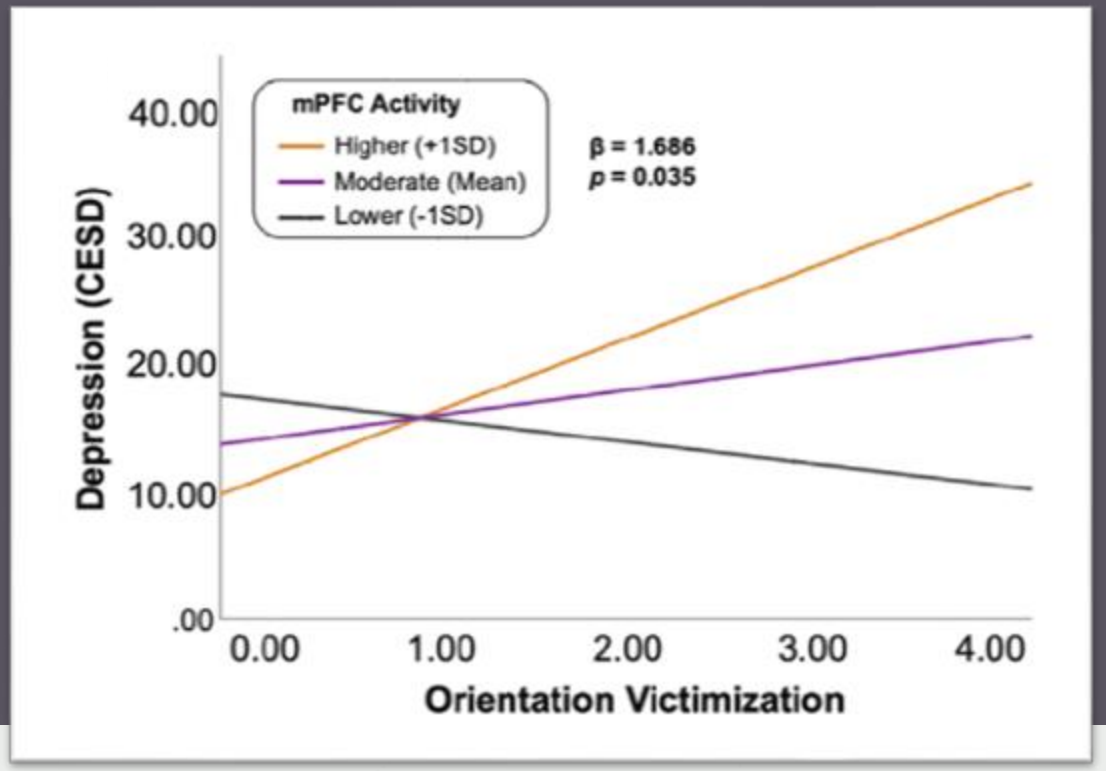




Morgan et al., 2013, *Neurobiology of Disease*

MH DISPARITIES
mPFC Moderates Association between Victimization and Depression in Sexual Minority Adolescents





Model R^2 = 0.38
p < 0.001

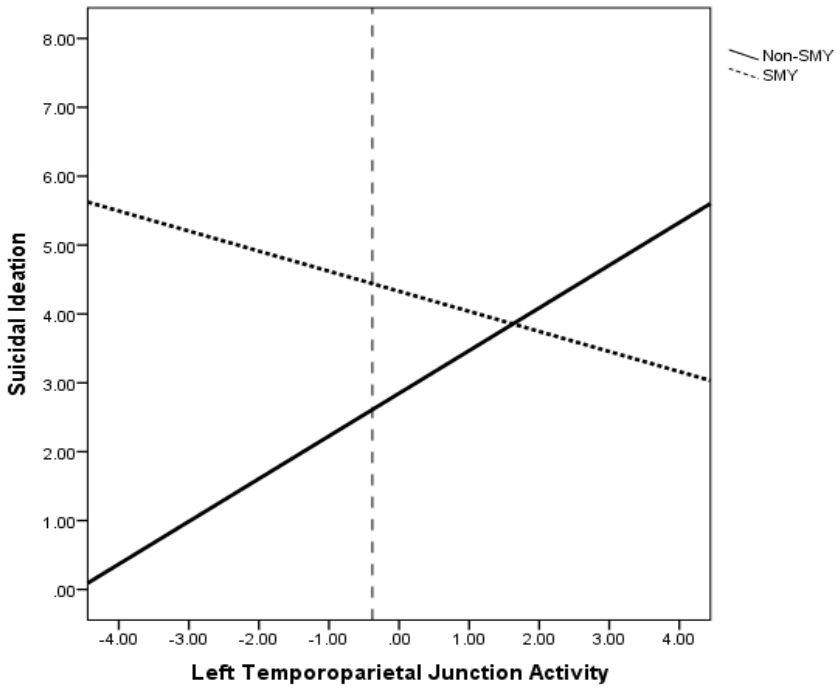
Age (p=0.014)

SO (p<0.001)

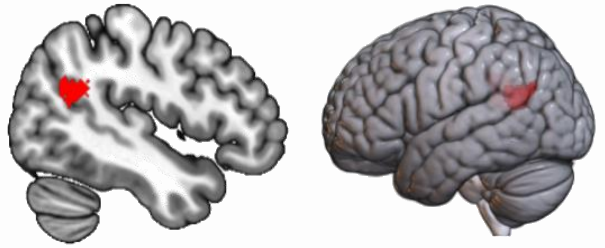
Eckstrand et al., 2022

MH DISPARITIES

Sexual Minority Identity Is Associated with Suicidal Ideation in Adolescents with Low TPJ Response to Social Reward



Neural Activation during Rewarding > Baseline			MNI Coordinates		
Brain Region	Hemisphere	Voxels	X	Y	Z
Temporoparietal Junction	Left	304	-46	-52	28

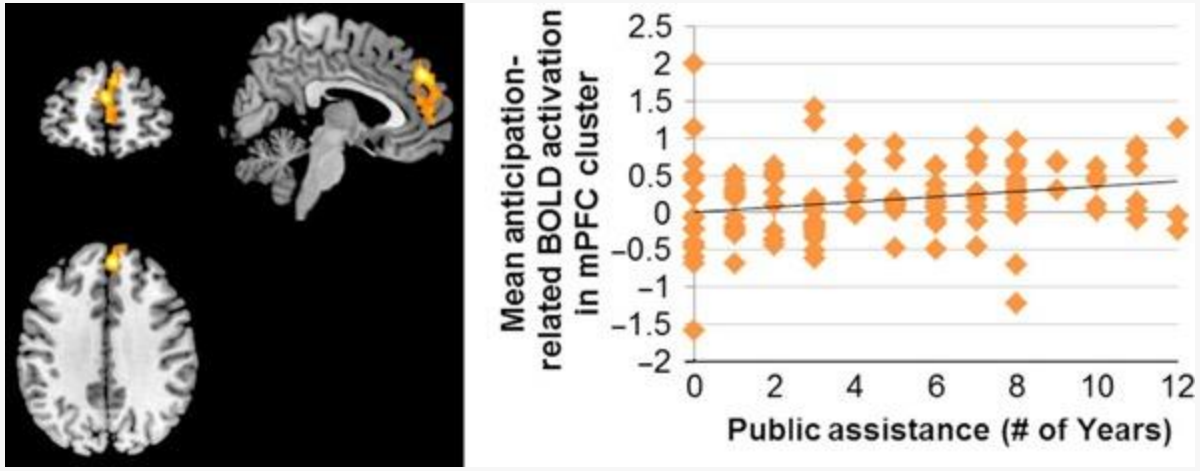


Left Temporoparietal Junction (shaded in red)

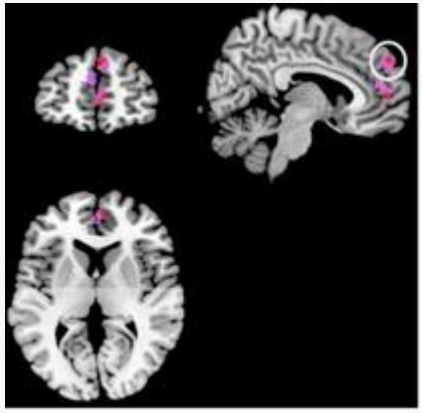
Seah et al., under review

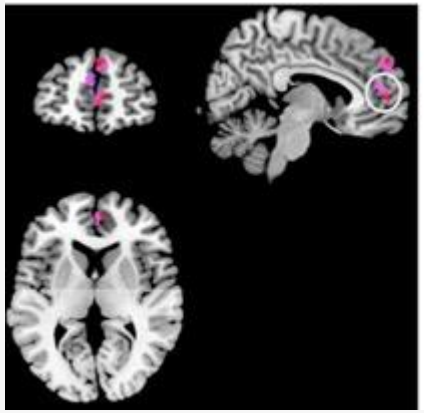
SOCIAL CONTEXT AND DEPRESSION

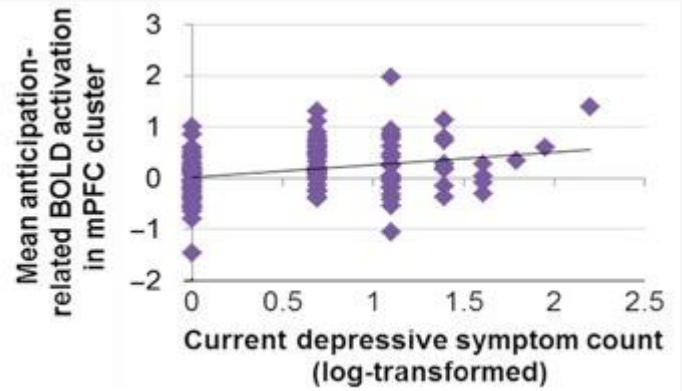
mPFC Response to Reward Mediates Association between Socioeconomic Disadvantage and Depression in Adolescent Girls

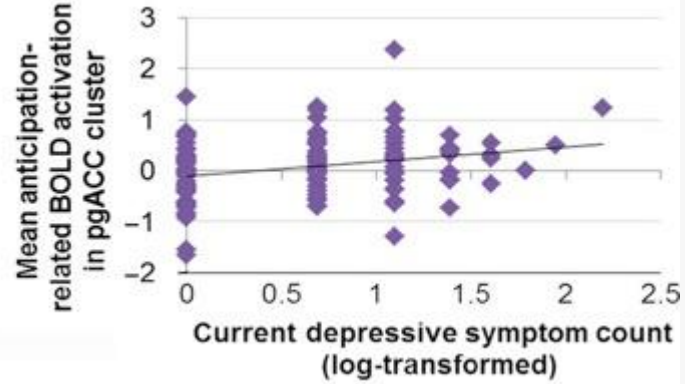


N = 123
public assistance: age 5-16
mPFC response: age 16 (beta = 0.03, R^2 = 0.05)
depression: age 16
bootstrap tests: full mediation









dmPFC (BA 6/8/9, BA 9/10/32):
beta = 0.24, R^2 = 0.07
pgACC: beta = 0.28, R^2 = 0.06

Romens et al., 2015, *JCPP*

TREATMENT RESPONSE

TREATMENT RESPONSE

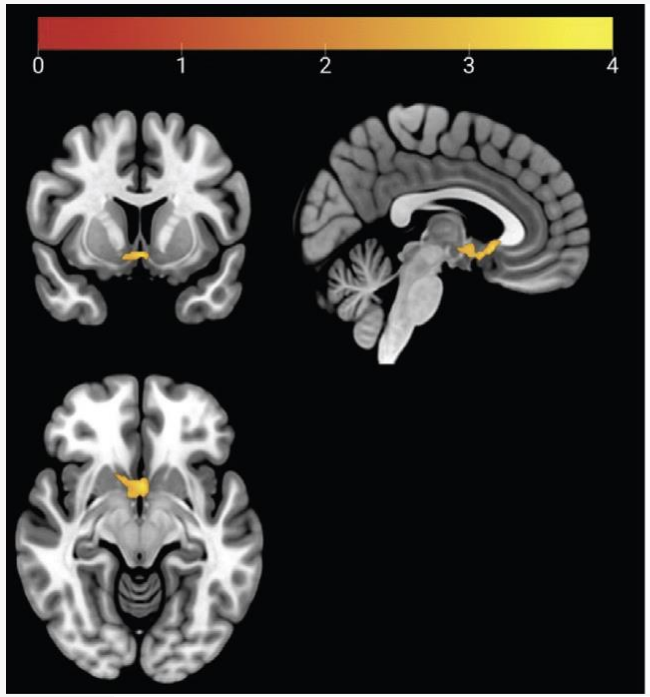
More Typical Ventral Striatum Function Predicts Response to CBT in Adolescents with Anxiety

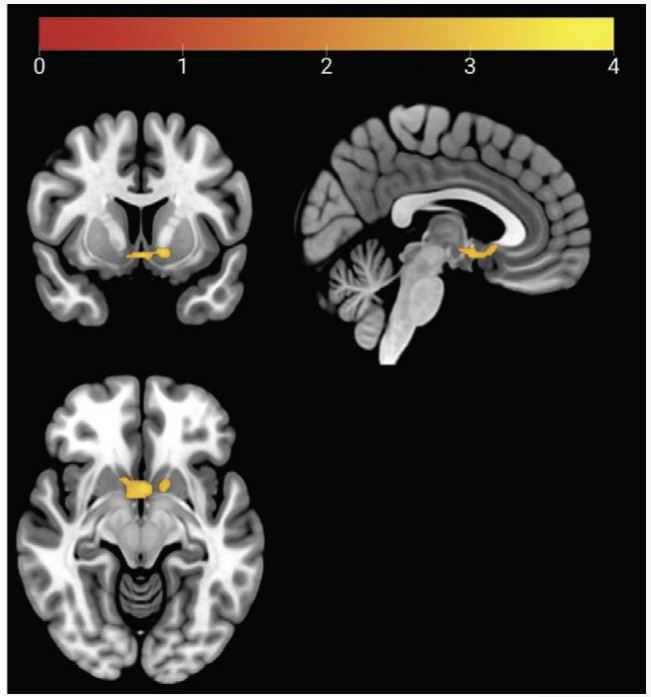
fMRI task & questionnaires

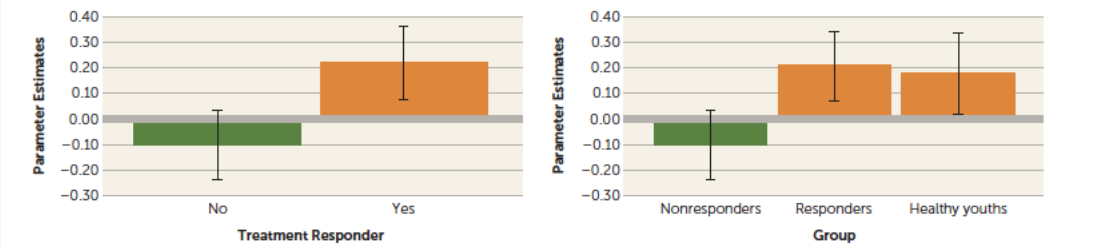
16 weeks

CBT or CCT

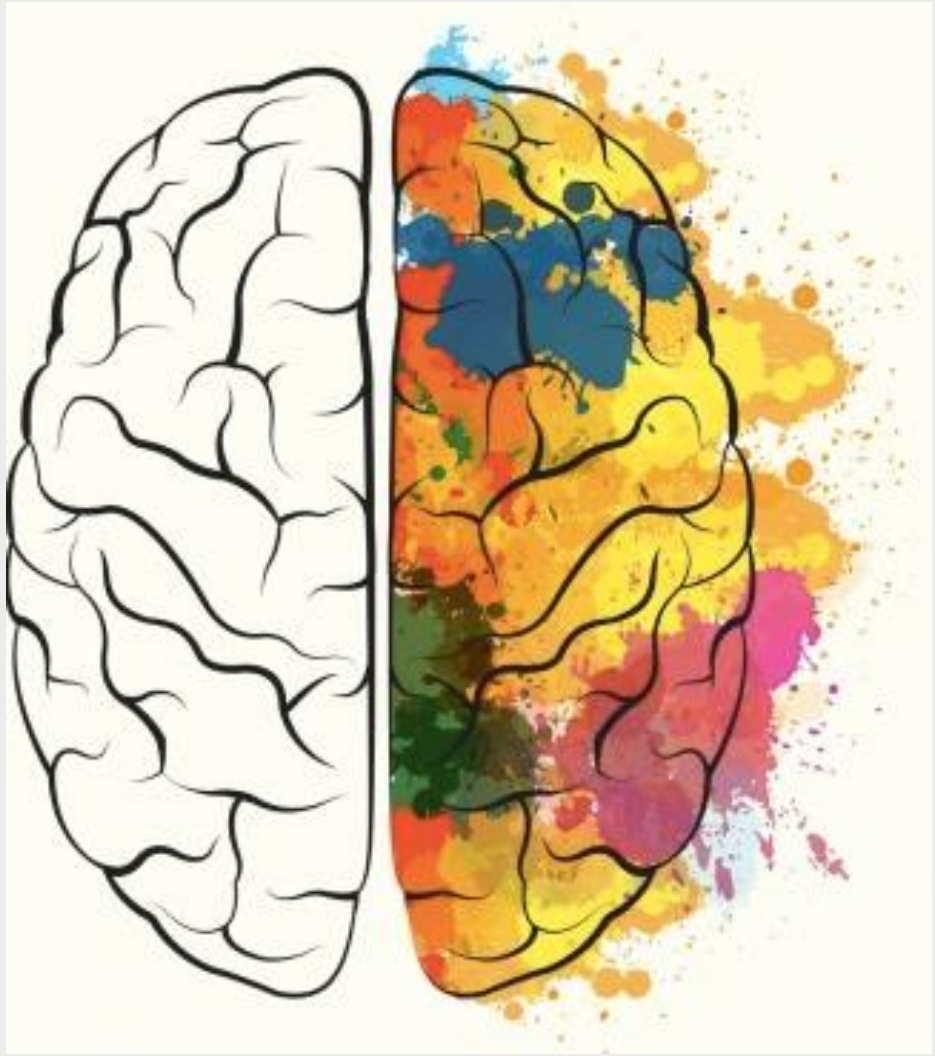
interview, ratings, questionnaires







Sequeira et al., 2021, *Am J Psychiatry*

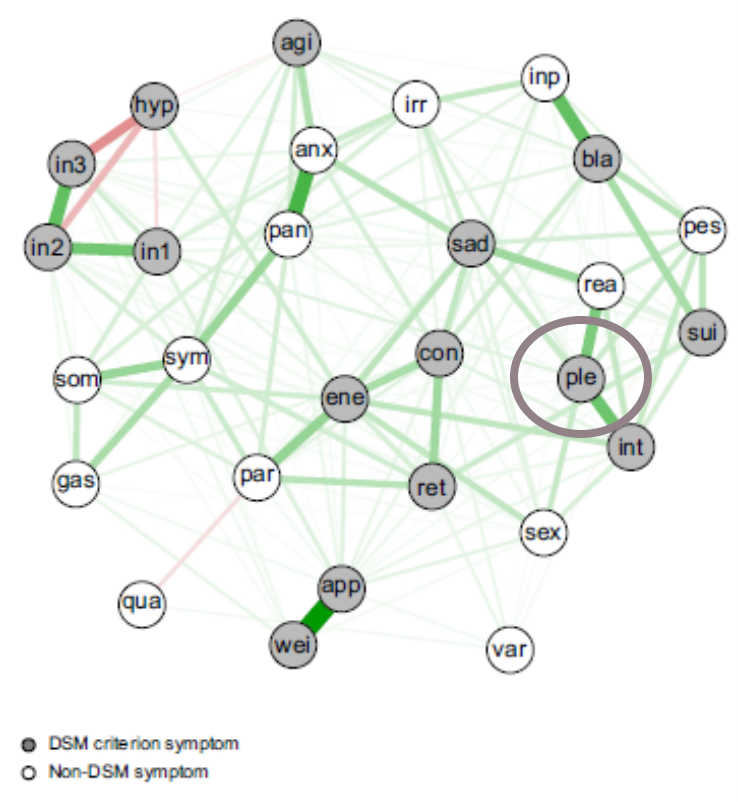


Frontostriatal Response to Reward Is Related to

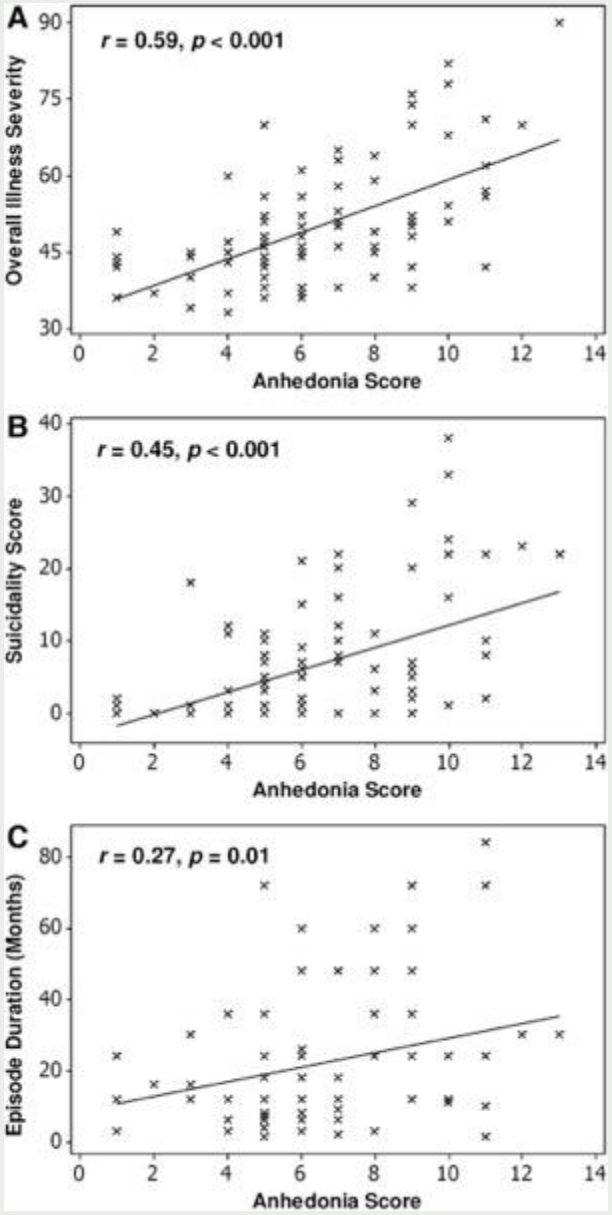
- Adolescent depression
- Development of depression
- Treatment response

ANHEDONIA

Anhedonia is a central symptom of depression



Fried et al., 2016



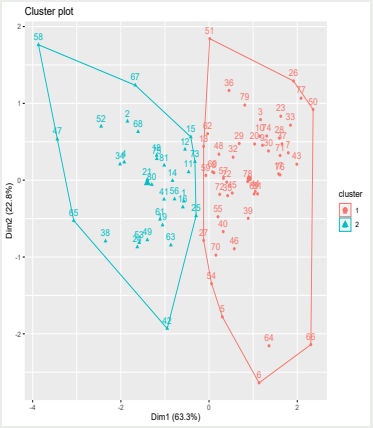
Gabbay et al., 2015

Anhedonia predicts pernicious course in depression

TABLE 1. Chi-Square Statistics for the Kruskal-Wallis ANOVA of Ranks for 954 Patients With Major Affective Disorder Who Did or Did Not Commit Suicide

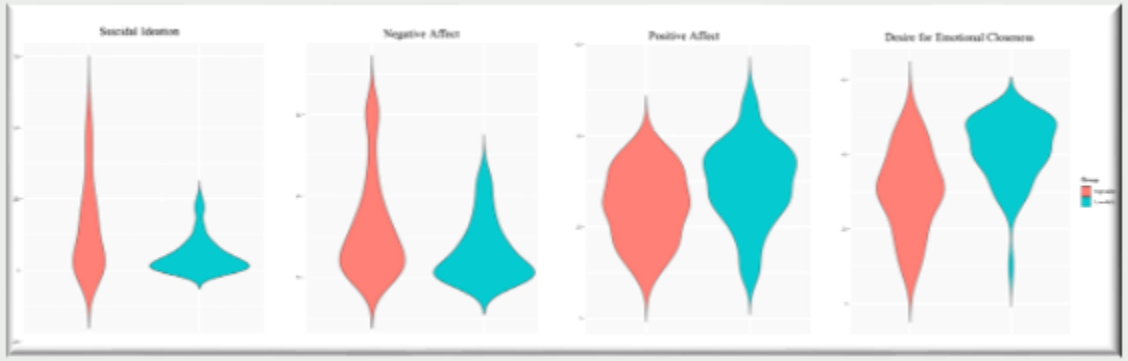
	Chi-Square		ANOVA	
Symptom	χ^2 (df=2)	p	F (df=2, 951)[a]	p
Hopelessness	7.79	0.020	2.34	0.097
Alcohol abuse	5.73	0.057	2.43	0.089
Loss of interest or pleasure (anhedonia)	8.79	0.012	3.74	0.035
Psychic anxiety	6.36	0.042	3.27	0.038
Suicidal ideation	4.48	0.106	2.10	0.123
Suicide attempts	3.03	0.220	1.90	0.150
Obsessive-compulsive features	4.57	0.102	2.97	0.052
Indecisiveness	6.34	0.042	3.57	0.029
Diminished concentration	7.84	0.020	3.11	0.045
Global insomnia	6.58	0.037	2.39	0.096

Anhedonia and suicidality in high-risk youth

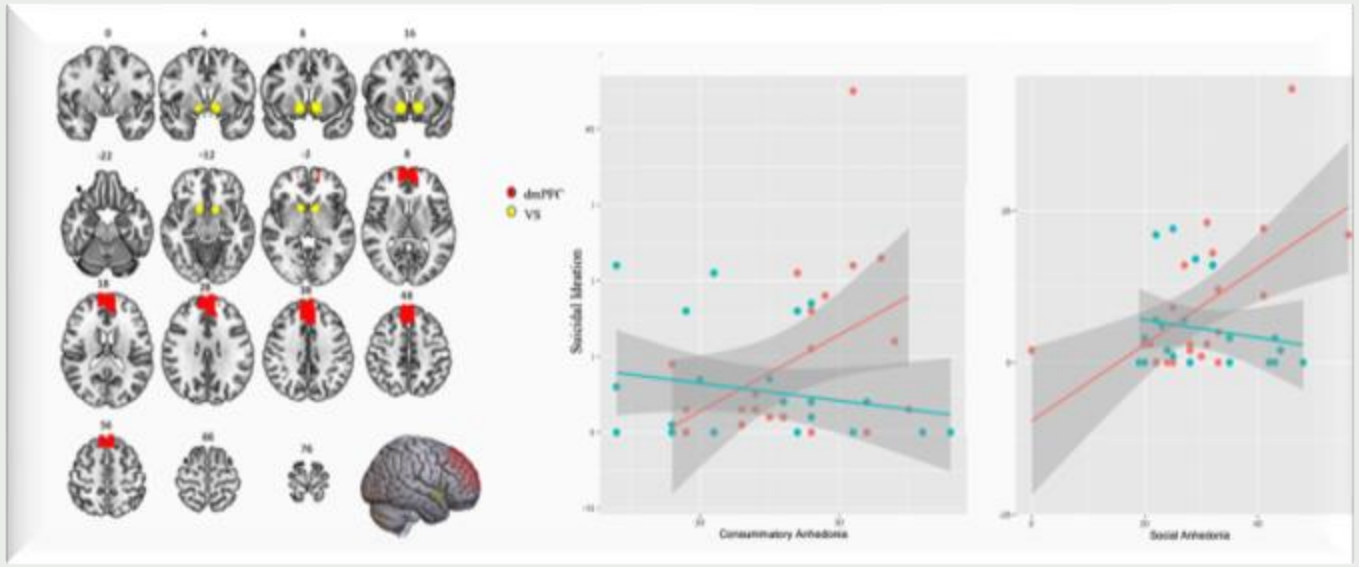


Profile	Familial high-risk	Familial low-risk
Low-Anhedonia	23	26
High-Anhedonia	23	9

k means clustering with 3 aspects of anhedonia



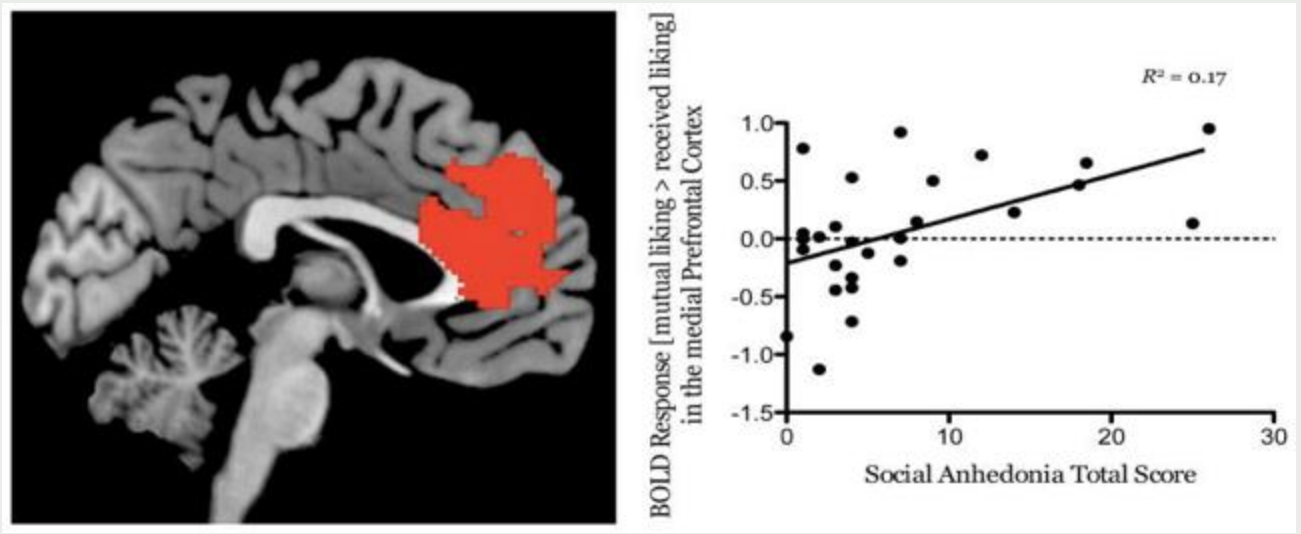
high-anhedonia profile: higher suicidal ideation and negative affect, lower positive affect and desire for emotional closeness

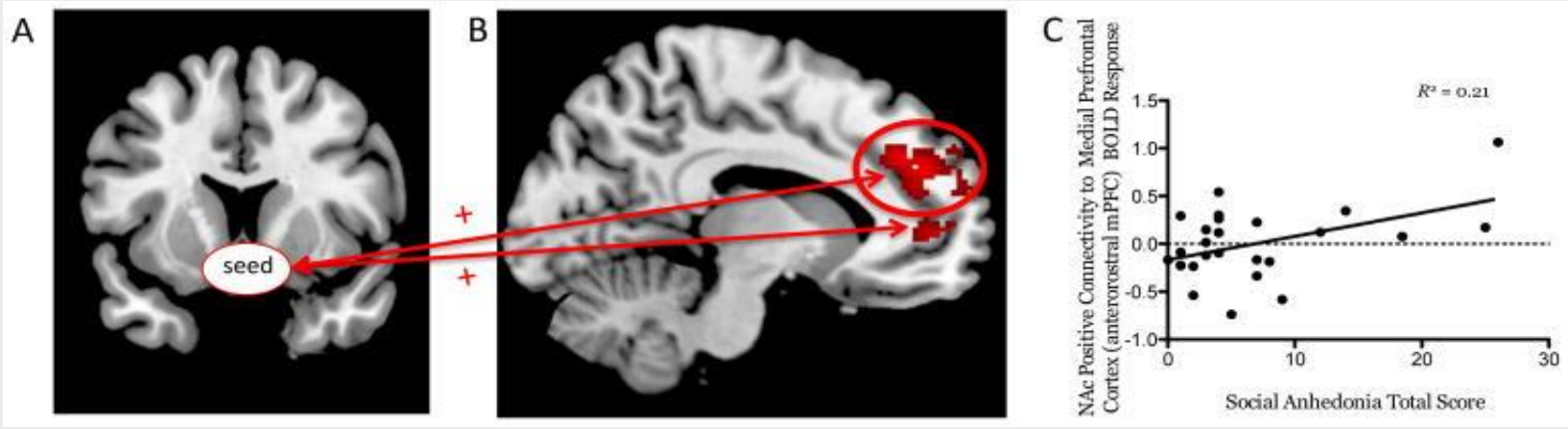


across profiles: higher suicidal ideation in adolescents with high anhedonia (any) and high dmPFC response to reward

Gupta et al., 2024

Adolescent Anhedonia: Higher dmPFC Response, Stronger VS-dmPFC Connectivity



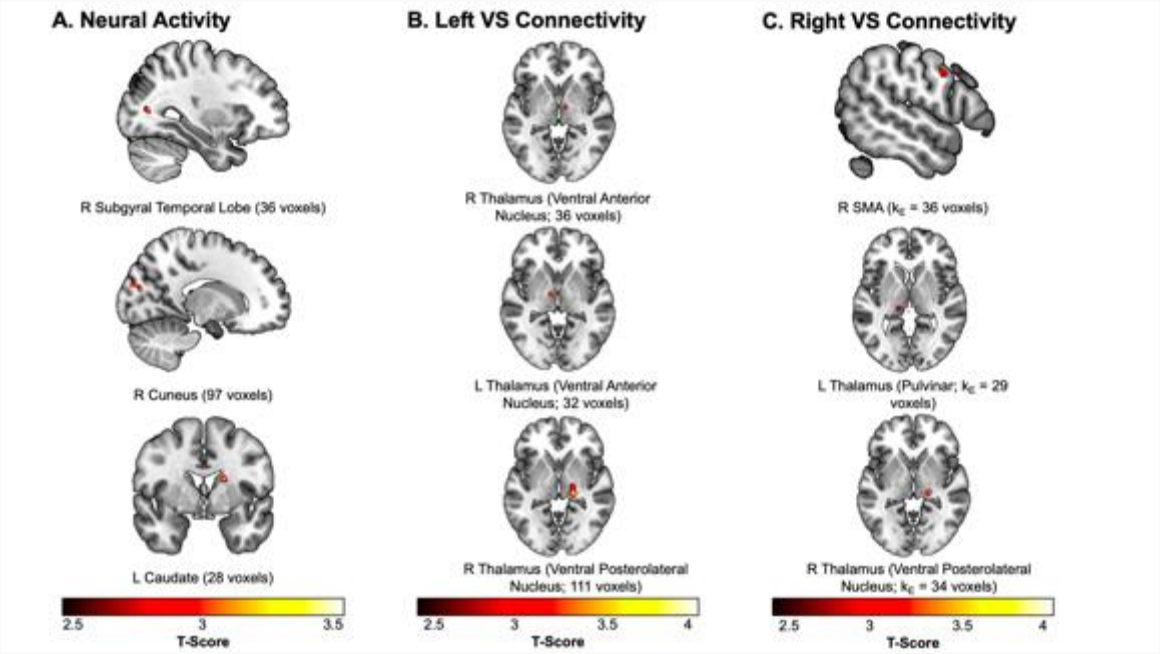


Healey et al., 2014

Neural Factors Predict Peak Anhedonia in High-risk Adolescents, Even When Considering Demographic and Clinical Factors

N = 73, 53% girls
13-17 years
3 time points over 2 years

Reddy et al., In press!



Variable	LASSO Derived Coefficient
Clinical Variables	
Impulsivity	.088
Neural Variables	
Caudate Body Activation	.095
Sub-Gyral Temporal Lobe Activation	.022
Cuneus Activation	.037
Left VS-Thalamus (Ventral Posteolateral) Negative FC	.131
Left VS-Thalamus (Left Ventral Anterior Nucleus) Negative FC	.03
Left VS- Thalamus (Right Ventral Anterior Nucleus) Negative FC	.02
Right VS-Thalamus (Ventral Posterolateral Nucleus) Negative FC	.015
Right VS-SMA Negative FC	.0004
Right VS-Thalamus (Pulvinar) Negative FC	.0303

10% of variance

Additional 40% of variance

FROM PATHOPHYSIOLOGY TO INTERVENTION: BRAIN-BASED TREATMENT

mPFC Subregions

•dmPFC

• BA 9, 24 (pregenual anterior cingulate cortex), and 32 (anterior midcingulate cortex): deliberative decision-making and the evaluation of external information and social situations. Predicting and resolving conflicts between internal valuations and external cues.

•rmPFC

•BA 10 and the anterior cingulate cortex (BA 24, 32): modulating internal valuations based on external factors and situational contexts. Strategic decision-making, particularly in social settings where external cues influence internal judgments.

• dmPFC: Projections to striatum to enhance cognitive control and inhibit reward-seeking

What is important in being “cured” from depression?

Discordance between physicians and patients

Demyttenaere et al., 2015

Table 3a
Rank order: 10 most important DEsCRIBE™ items scored by the physicians (baseline).

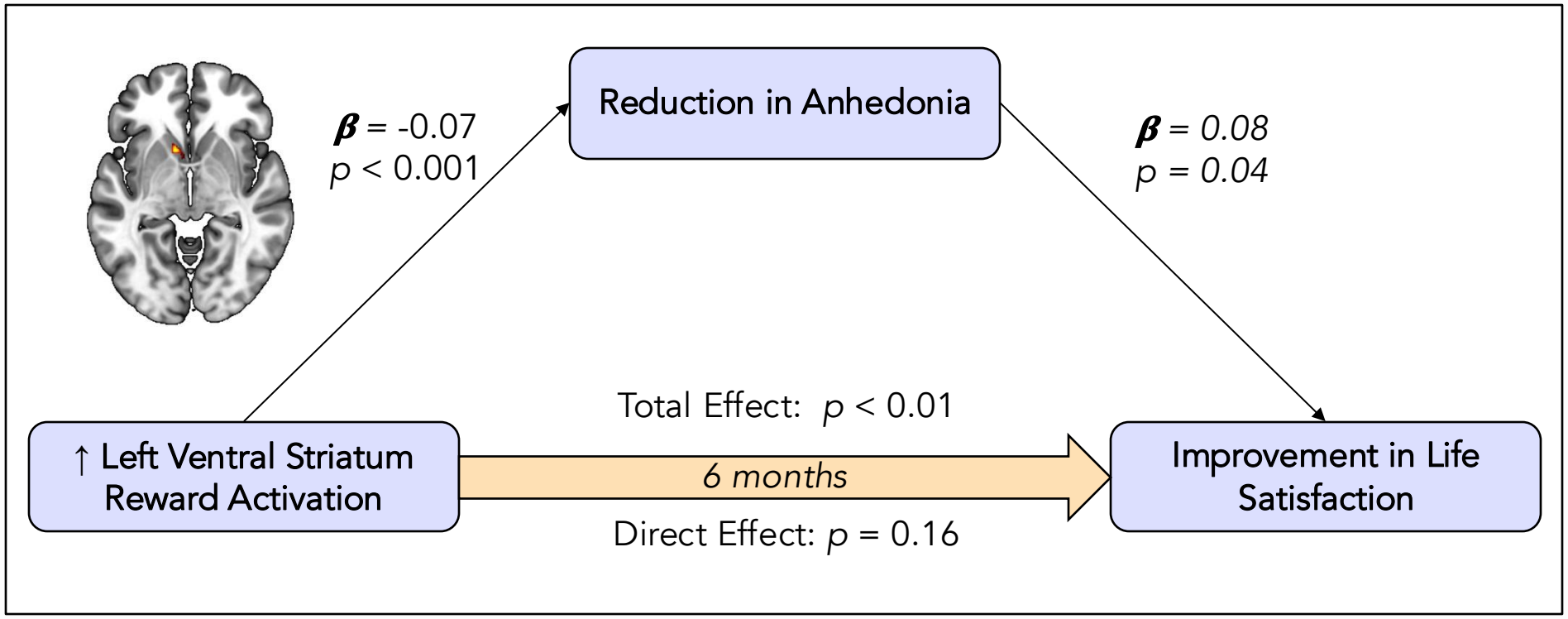
Rank	Scale item	*N*	Mean ± SD	Item description
1	WHOQOL-BREF	422	4.10 ± 1.13	Negative feelings: blue mood, despair, anxiety, depression
2	PHQ-depressive	418	4.09 ± 1.16	Feeling down, depressed or hopeless
3	PHQ9-depressive	421	4.00 ± 1.18	Little interest or pleasure in doing things
4	SDS	421	3.99 ± 1.13	Symptoms disrupted social life/ leisure activities
5	PHQ-depressive	421	3.99 ± 1.15	Feeling tired or having little energy
6	WHOQOL-BREF	423	3.92 ± 1.13	How satisfied are you with yourself
7	WHOQOL-BREF	421	3.87 ± 1.12	How much are you enjoying life
8	SDS	401	3.78 ± 1.30	Symptoms have disrupted your work
9	WHOQOL-BREF	426	3.73 ± 1.20	To what extent life is meaningful
10	WHOQOL-BREF	424	3.73 ± 1.13	How satisfied are you with your personal relationships

Table 3b
Rank order: 10 most important DEsCRIBE™ items scored by the patients (baseline).

Rank	Scale item	*N*	Mean ± SD	Item description
1	WHOQOL-BREF	426	4.35 ± 0.98	To what extent life is meaningful
2	WHOQOL-BREF	421	4.35 ± 0.99	How much do you enjoy life
3	WHOQOL-BREF	423	4.22 ± 1.11	How satisfied are you with yourself
4	WHOQOL-BREF	422	4.13 ± 1.05	How able are you to concentrate
5	WHOQOL-BREF	422	4.08 ± 1.31	Negative feelings: blue mood, despair, anxiety
6	PHQ-depression	421	4.07 ± 1.25	Feeling tired or having little energy
7	PHQ-depression	418	4.07 ± 1.31	Feeling down, depressed or hopeless
8	PANAS-positive	423	4.05 ± 1.09	Feeling strong
9	WHOQOL-BREF	424	4.04 ± 1.10	How satisfied are you with your personal relationships
10	PANAS-positive	426	4.04 ± 1.09	Feeling active

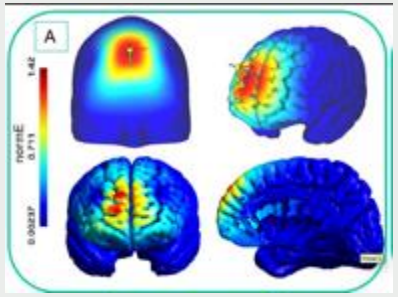
Anhedonia Reduction Mediates Association between Left VS and Life Satisfaction

DIAMOND Study
N=52
Young Adults with High Distress



Eckstrand et al. (2019). *JAMA Psychiatry*.

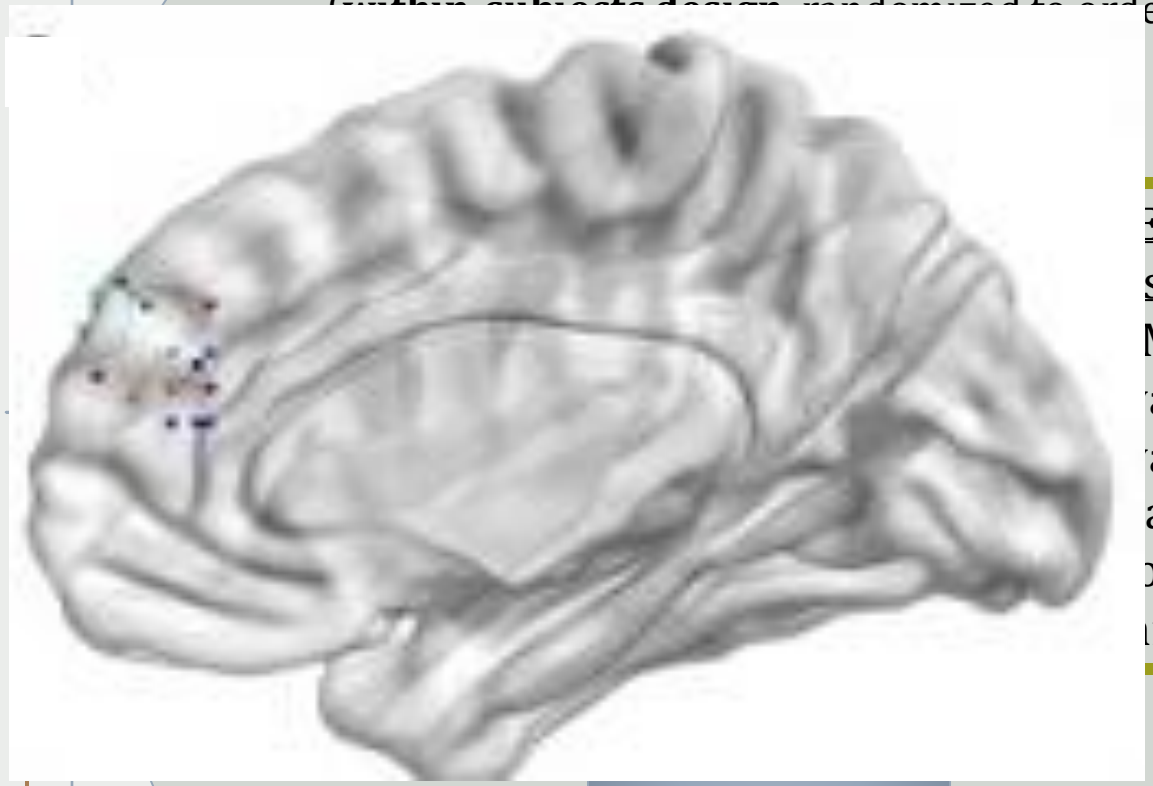
Theta Burst Stimulation of Frontostriatal Reward Circuitry in Young Adults with Depression



29 Youth with Depressive Disorder

- 18-25 years (*M* =21.4)
- 79% female
- Range of anhedonia
- No bipolar disorder, psychosis history, mod-severe SUD, serious neurological disorder, SNRIs or stimulants
- Randomized while accounting for dmPFC response and gender
- 2 sham types

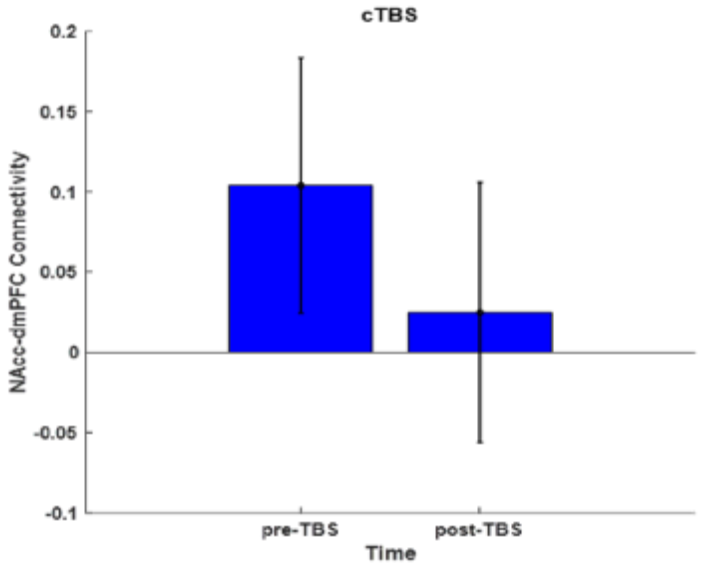
3 sessions of TBS to right dmPFC
(within-subjects design, randomized to order)



Each TBS
ssion
MRI
ard fMRI
ard
avior
od
in total)

Before 1st Session: MRI for neuronavigation

Targeting dmPFC with cTBS—a Brief Form of TMS Thought to Reduce Cortical Activity—Decreased Connectivity between VS and dmPFC

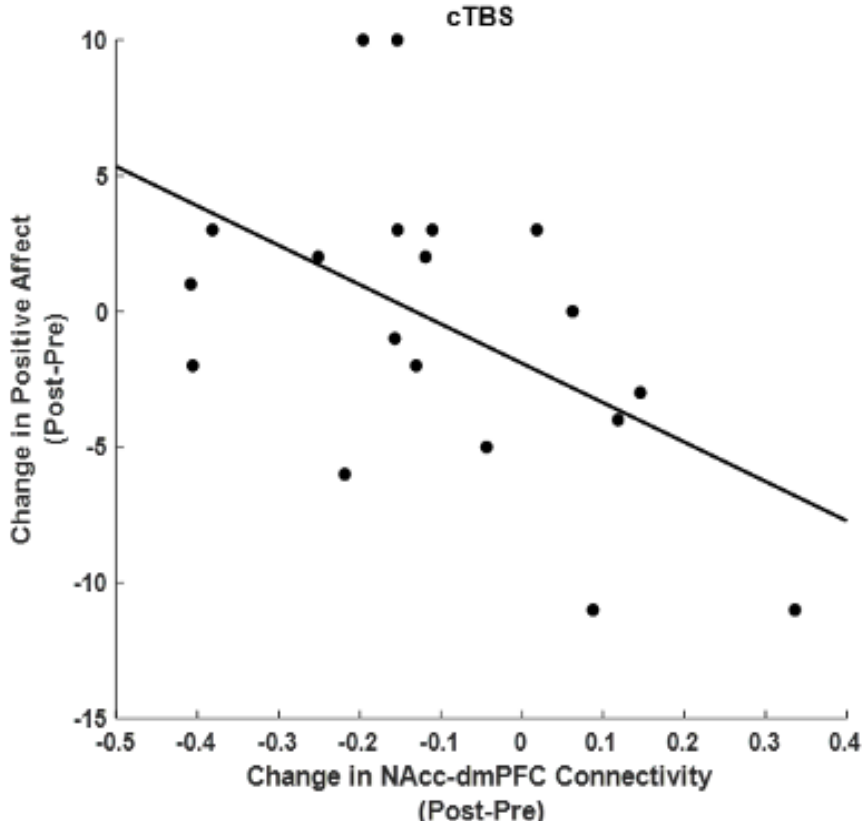


Time * Condition $F(2,28) = 3.9$, $p < 0.05$

Time effect for cTBS: pooled $t(24) = 2.1$, $p < 0.05$

Helmet Karim, PhD

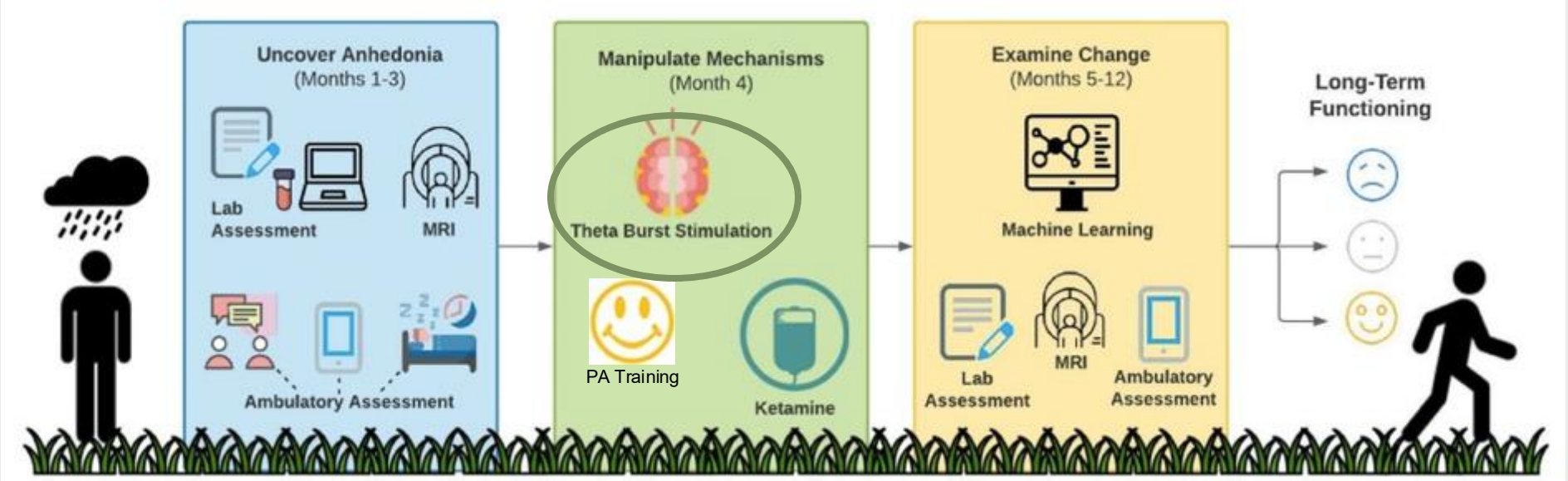
Tina Gupta, PhD



…and Youth Who Had Greater Decreases in VS-dmPFC Had *Greater Increases in Positive Mood*

Change score analysis: $r(18) = -0.5$, $p < 0.05$

Gupta et al., 2024



Month	Mode	Procedures
1, 4, 5, 12 months	Lab/Remote	• Clinical interview (K-SADS) at 0, 3, 12 months • Behavior tasks • Questionnaires • Ambulatory assessment orientation or reminder
1, 4, 5, 12 months	MRI	• Multi-echo turbo-spin echo for striatal tissue iron • Neuromelanin MRI • [illegible] • Reward task fMRI
1, 4, 5, 12 months	Lab	• Blood sampling for inflammatory [illegible]
4	TBS	• 2 sessions/day, 5 days/week, 2 weeks • Continuous TBS
5	Ketamine	• TBS non-responders only • Single infusion
1-6, 10-12 (9-day burst/ month)	Ambulatory	• EMA of positive affect, reward anticipation, reward-seeking, anhedonia • Passive sensing of [illegible], location, phone/ text activity, social media use, sleep/wake

MCPsych

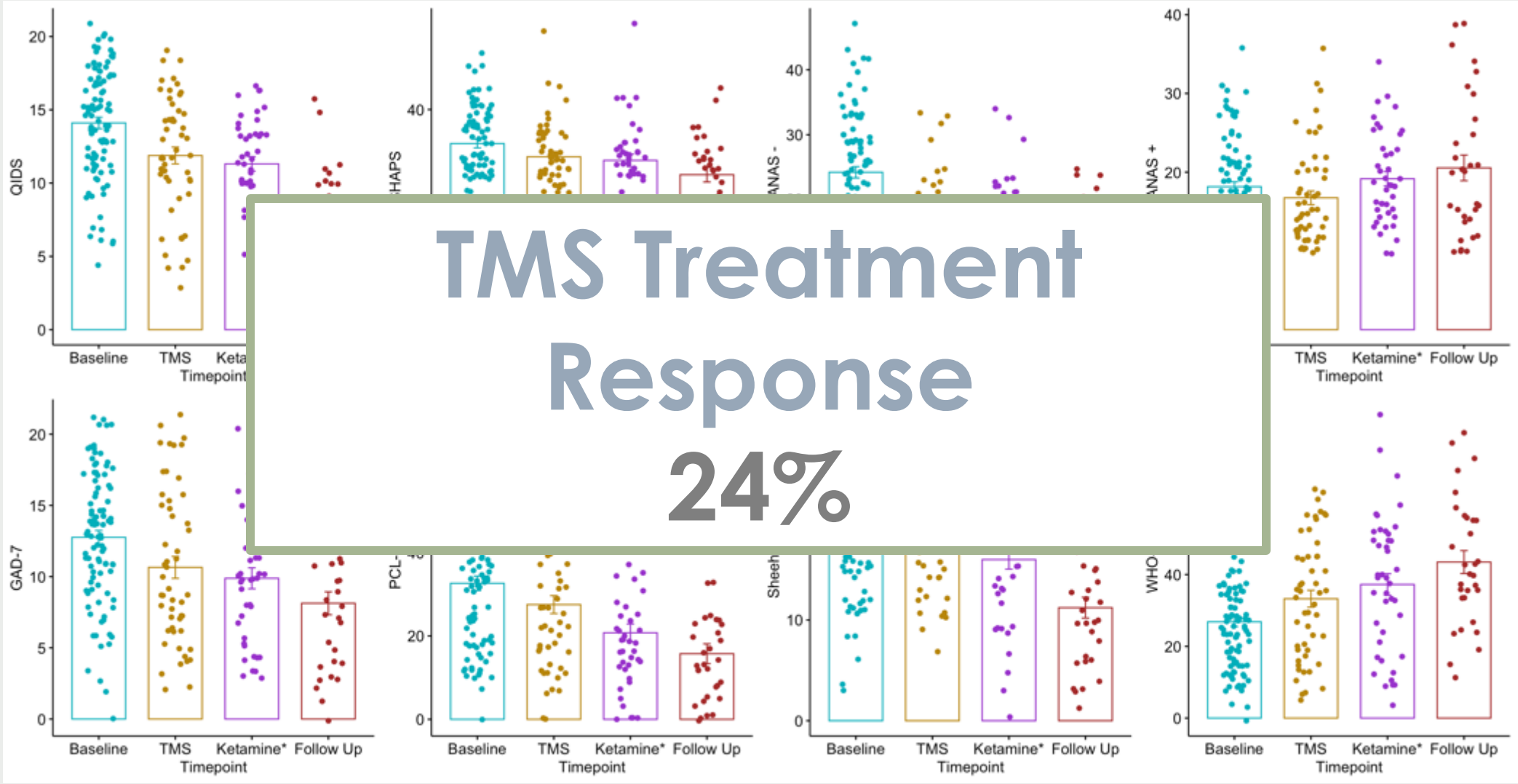
leap | wellcomeleap.org

- *N* = 100, 50 with TMS
- age 15-25
- all with depression, varying in anhedonia
- 1 year/person

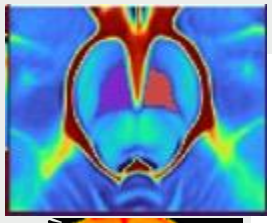
TMS Protocol

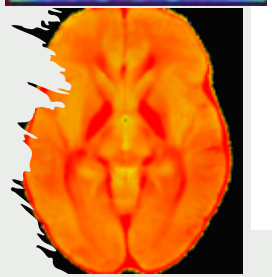
- **cTBS to dmPFC**
- Reward/PA system
- (Not left DLPFC!)
- Goal: enable PA flexibility
  - reduce dmPFC response
  - reduce dmPFC-VS functional connectivity
- Personalized target from resting fMRI
- 20x: 2x/day, 5 days/week, 2 weeks
- PA Training between sessions (Craske)
- Pre: MADRS, MRI, Qs; post: MADRS, Qs

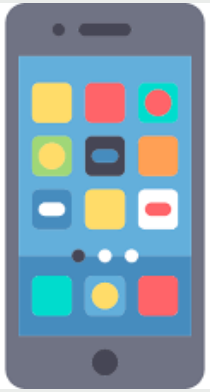
Symptom Change



Do EMA *and* MRI proxies for DA predict decrease in anhedonia?





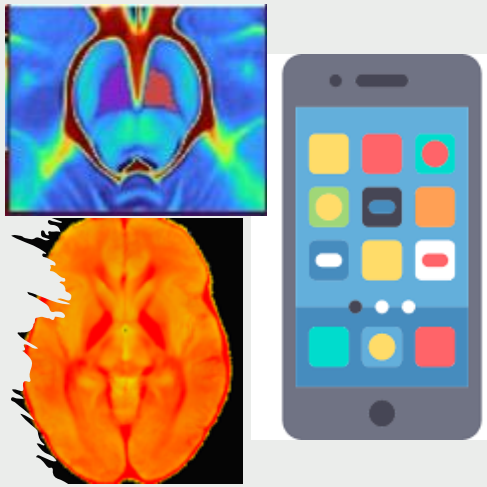


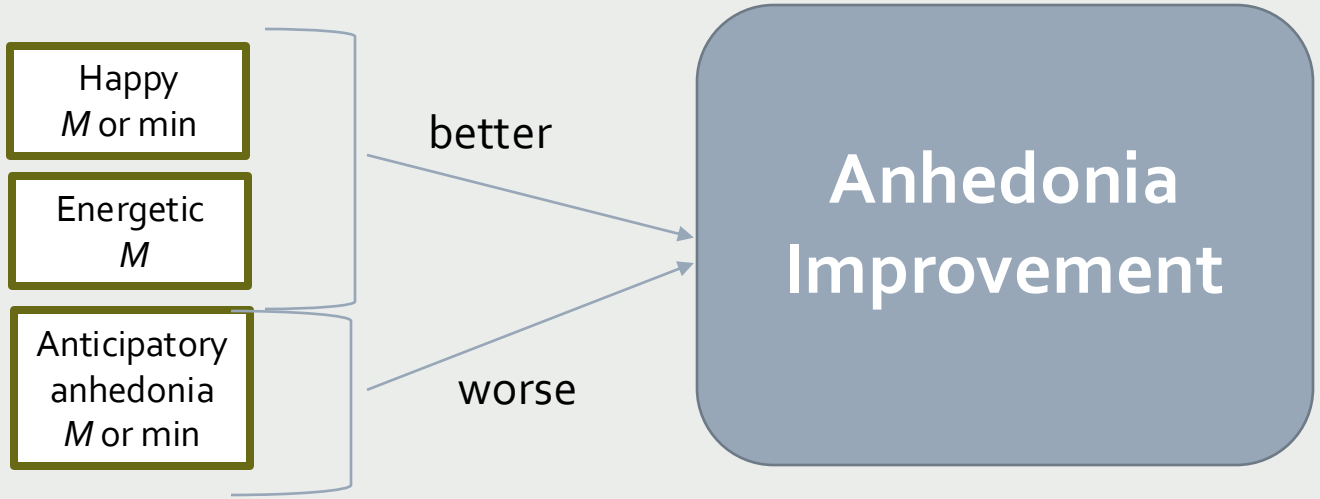
- Happy *M*
- Happy min
- Energetic *M*
- Anticipatory anhedonia *M*
- Anticipatory anhedonia min

Anhedonia Improvement

Brain DA variables not selected

Do EMA *and* MRI proxies for DA predict decrease in anhedonia?





Brain DA variables not selected

Does neural response to reward predict **TMS responder status**?

dmPFC anticipation

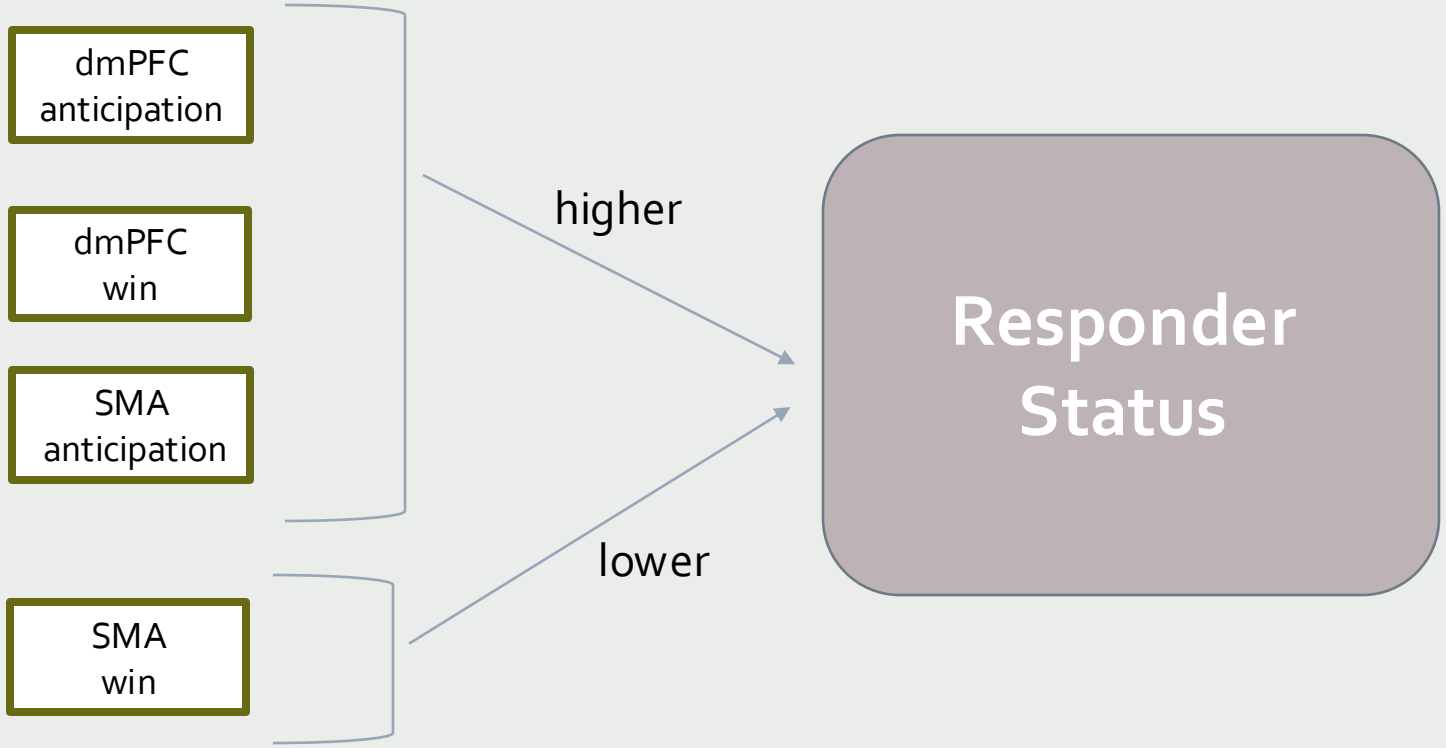
dmPFC win

SMA anticipation

SMA win

Responder Status

Does neural response to reward predict **TMS response**?



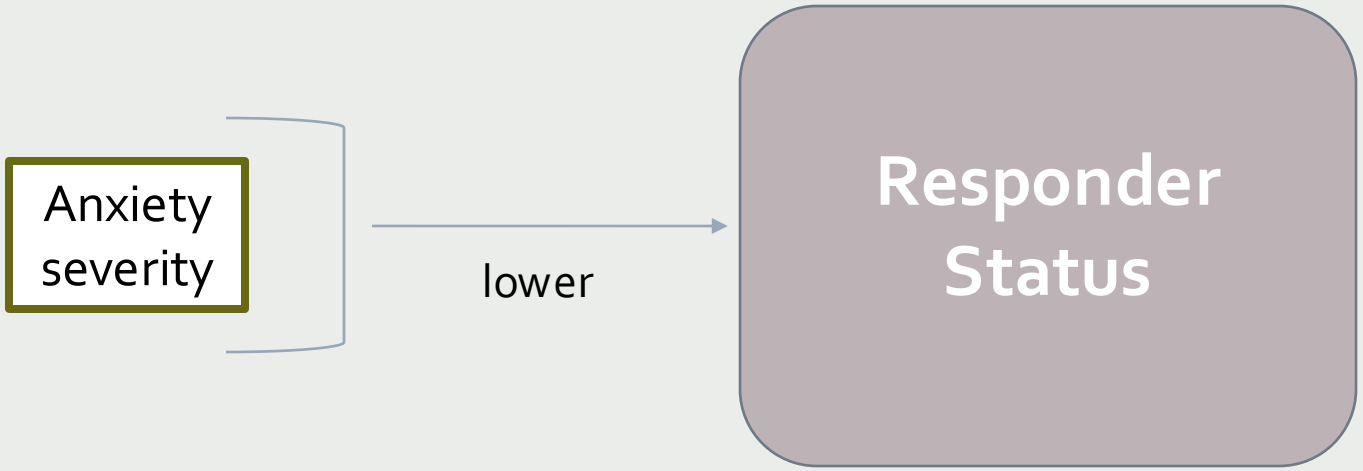
Do baseline symptoms predict **TMS response**?

Anxiety severity

Responder Status

Anhedonia not selected

Do baseline symptoms predict **TMS responder status**?



Anhedonia not selected

Predictors of TMS Response

Is TMS to frontostriatal reward system more likely to work in those with depression-like disruptions?

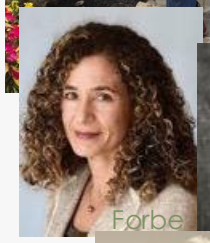
- Compensation? Contrary to capitalization findings with CBT and SSRI
- Treatments that target disruptions more likely to work for those with disruptions?

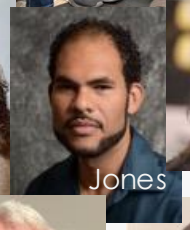
Perhaps reflecting appropriateness to anhedonic subtype, lower anxiety severity was related to higher likelihood of treatment response

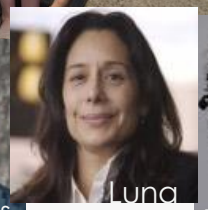
Findings on Pathophysiology Have Motivated Brain-Based Treatment, with Ongoing Focus on Development

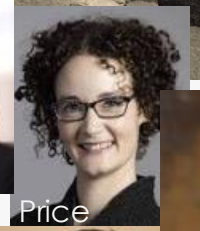
1. Why Neural Reward Circuitry?
2. Methods
3. Our Key Finding
4. Development and Treatment Response
5. Anhedonia
6. Neuromodulation

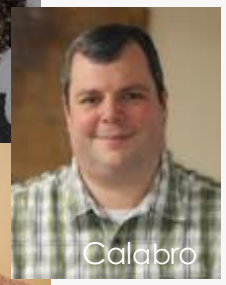
Thanks!

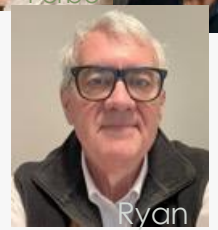


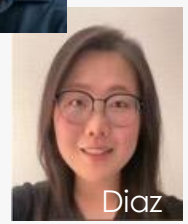


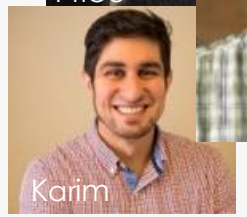












Participants and families

NIMH
National Institute of Mental Health

MCPsych

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Current ANDP Team

- Ashley Pogue
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- Kate Hart
- Colin Rutenbar
- Anvi Kumar
- Megan Julien
- Zach Brodnick
- Chloe Horter
- Kate Hart
- Ola Owodunni
- Tina Gupta
- MDs and PhDs
  - Kristen Eckstrand
  - Tina Gupta
  - Stanley Seah
  - Manny Rengasamy

Affective Neuroscience and Developmental Psychopathology Lab
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Is this how it is?

Is this how it's always been?

To exist in the face of suffering and death

And somehow still keep singing

Free, Florence & the Machine