



# *Developing new treatments for mania using brain-based risk markers*

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***No disclosures***

# Bipolar Disorder



In U.S., **2.6% 12-month, 4.5% lifetime prevalence in adults,** and 1% prevalence in adolescents

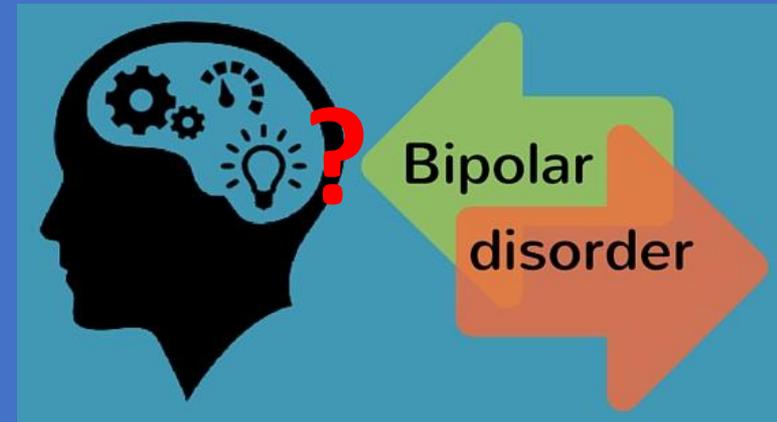
*Characterized by elevated mood (mania), low mood (depression), and mood swings*

*Mania is characteristic symptom of Bipolar Disorder*

*Fourth leading cause of disability* in the world (World Health Organization)

9.2 years reduction in expected life span, 20-30 times greater suicide risk than general population

***No objective biomarkers of risk for BD to guide treatments***



# Treatments for Bipolar Disorder

Multiple medications often used

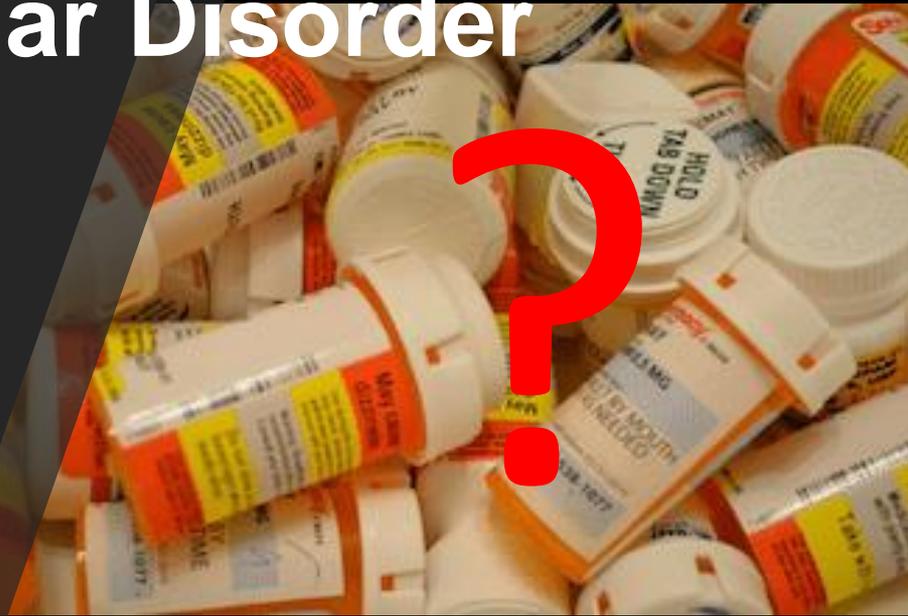
Can have unpleasant side effects

Not all medications are tolerated

Not all medications work

Often difficult to prevent relapse of mania and depression

*Mood switching:* Reducing mania risk to prevent future depression risk - - target for new treatments



# ***High Reward sensitivity and expectation of reward***

## ***High Impulsivity:***

behavior characterized by little or no forethought, reflection, or consideration of the consequences



## ***High sensation seeking:***

tendency and willingness to seek, and take risks for, novel and intense sensations and experiences



***All evident in adults with bipolar disorder***

*(Alloy et al., 2008; Johnson et al., 2012)*

***Predispose to hypo/mania in young adults***

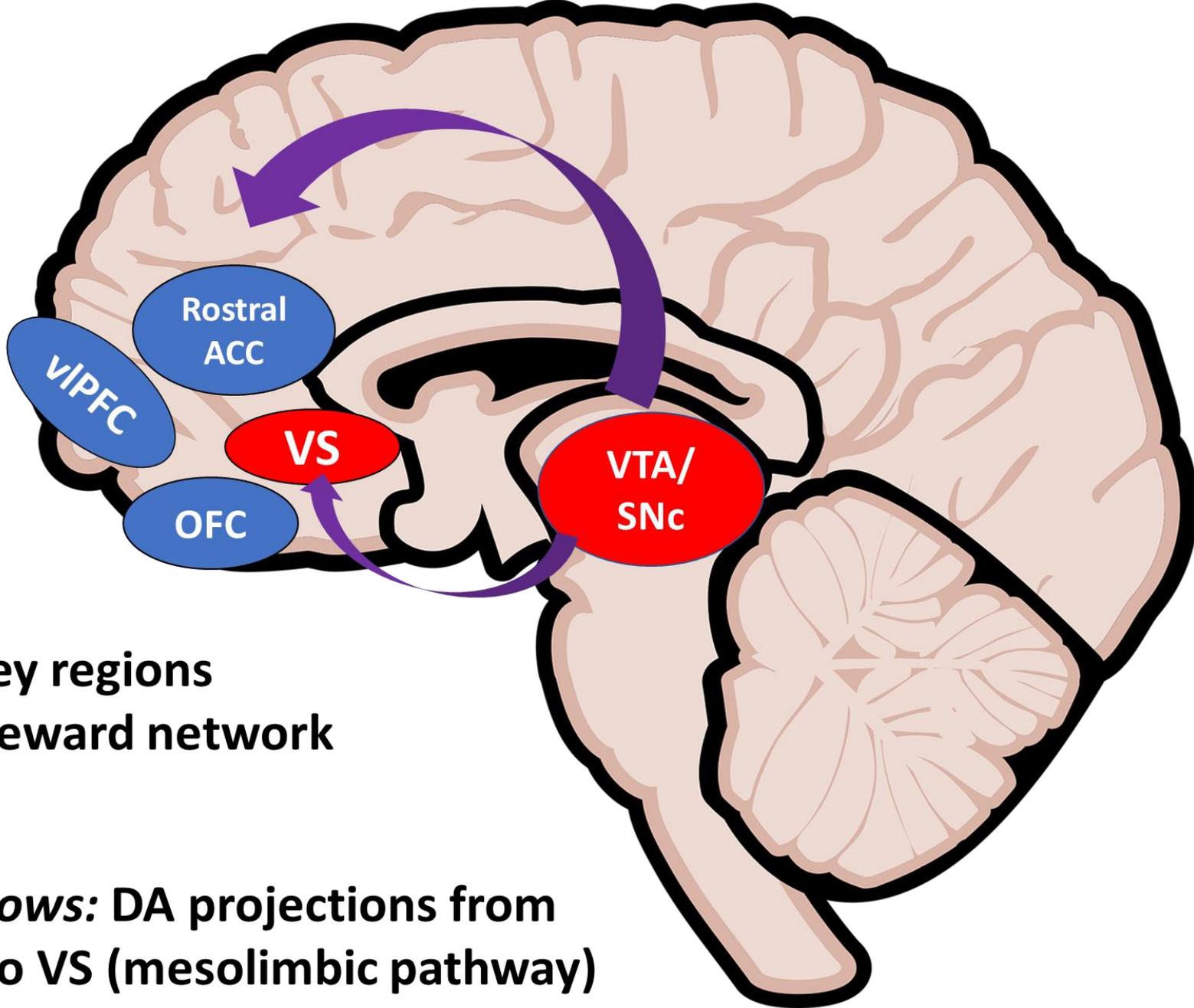
*(Alloy et al., 2012; Giovanelli et al., 2013; Meyer et al., 1999)*

# Overview



***Multimodal examination*** of neural networks conferring risk for mania and future Bipolar Disorder

***New treatment developments*** for Bipolar Disorder based on understanding neural network abnormalities that predispose to impulsive sensation seeking and mania



**Key regions  
in the reward network**

***Purple arrows:* DA projections from  
VTA/SNc to VS (mesolimbic pathway)  
and prefrontal cortex (mesocortical pathway)**

**Multimodal examination of  
Neural networks conferring  
risk for future Bipolar  
Disorder**

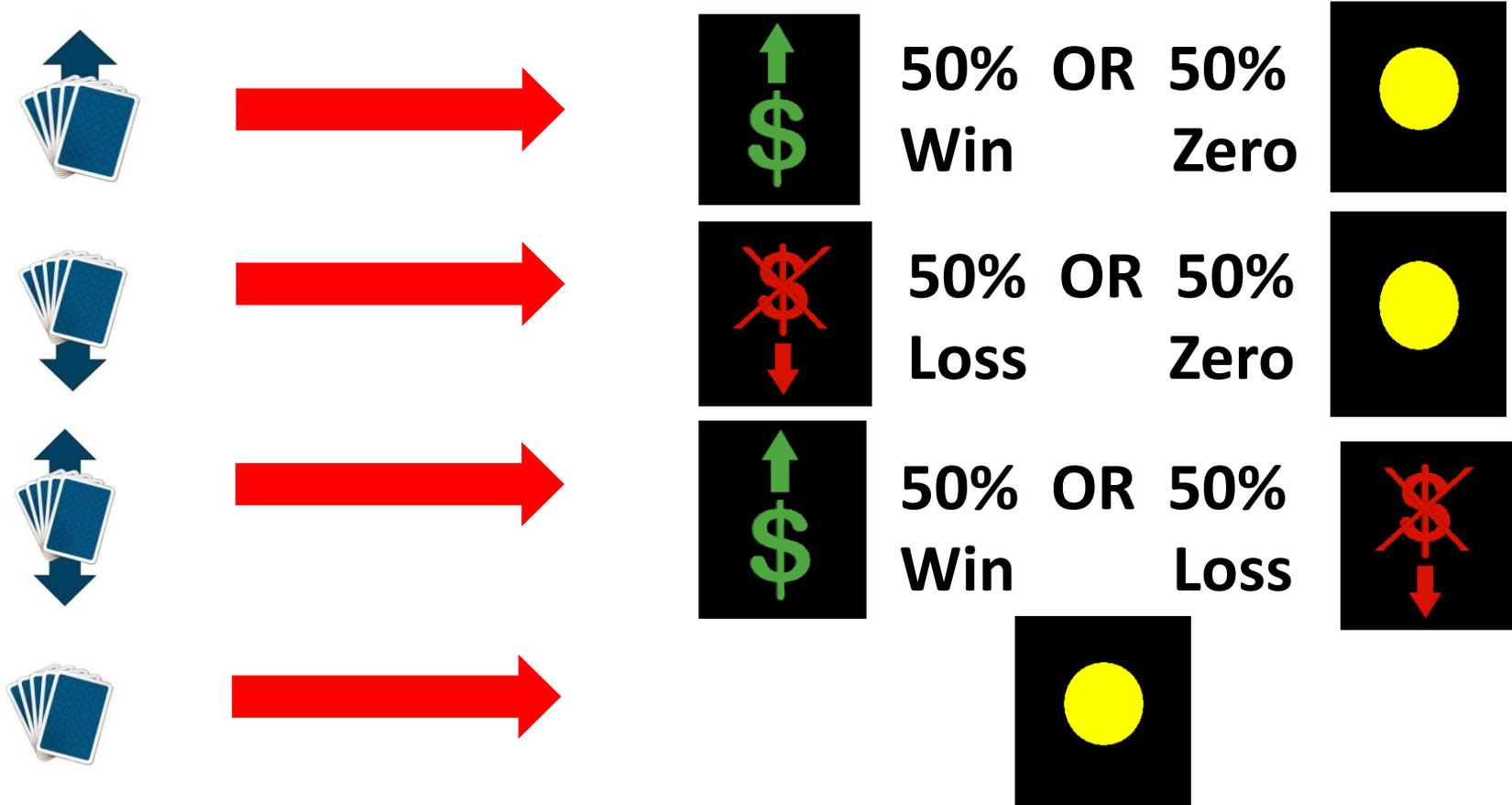
# Reward task

## *Expectation followed by outcome*

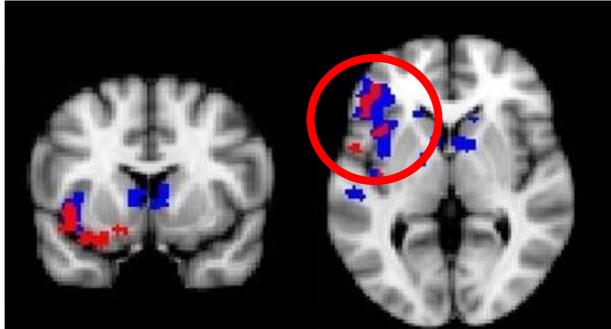
*Erika Forbes, Henry Chase, Mary Phillips*

*Potential reward expectation can trigger frustration in more impulsive and reward sensitive individuals*

### *4 Expectation trial types*



# BD findings: uncertain RE/ outcome expectancy: Left ventrolateral prefrontal cortex

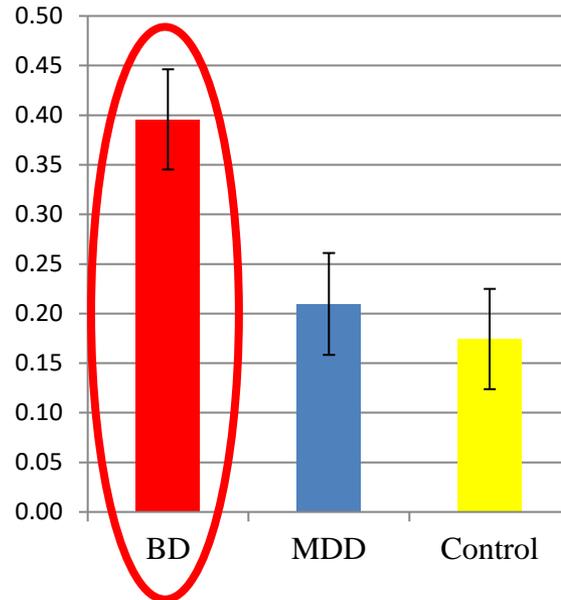
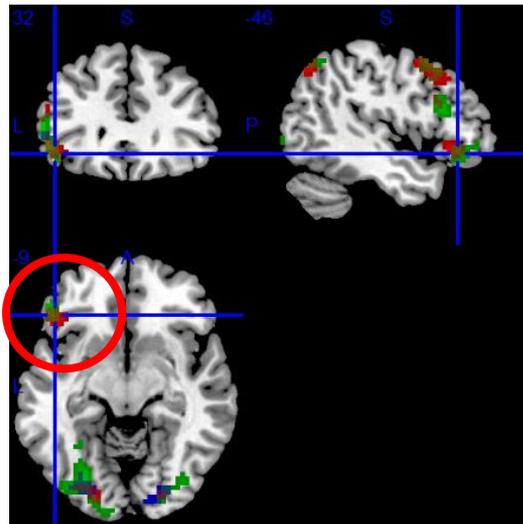


Euthymic Bipolar  
Disorder Type I  
and Type II  
Healthy controls

BPII>HC (blue)

BPII>BPI (red)

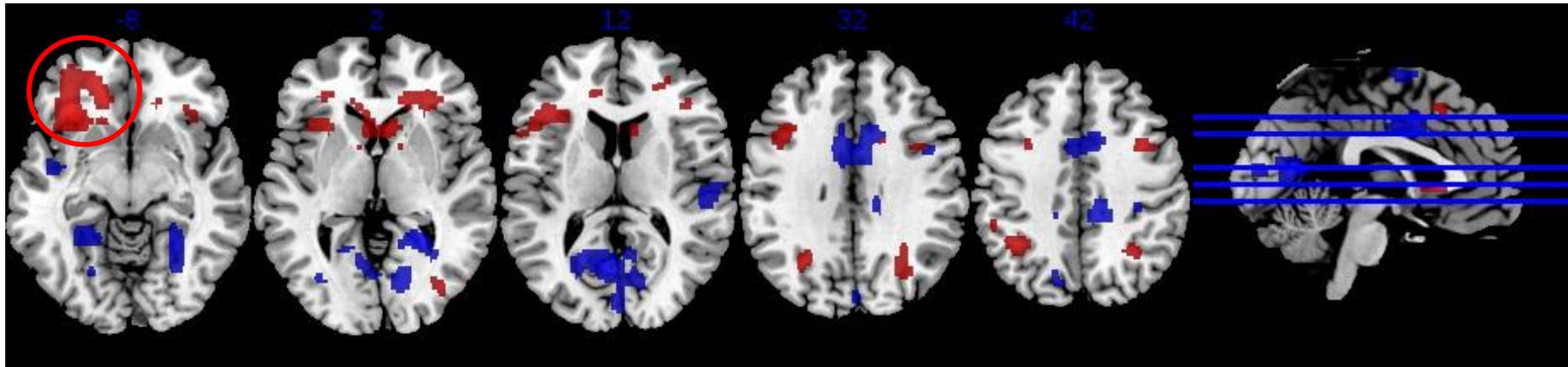
*1. Caseras et al., 2013.  
American Journal  
of Psychiatry*



Depressed Bipolar Disorder  
Depressed Major  
Depressive Disorder  
Healthy controls

*2. Chase et al., 2013.  
Bipolar Disorders*

# Greater impulsive sensation seeking in at-risk young adults is associated with greater left vIPFC activity during reward expectancy

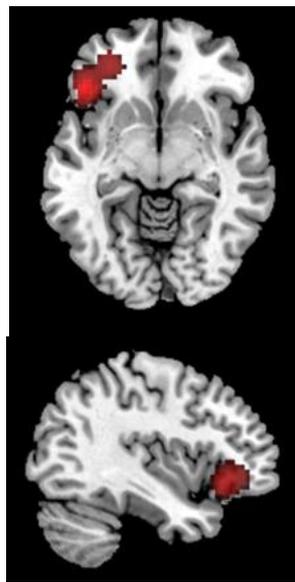


**Red clusters:** Positive relationship between greater impulsive sensation seeking (fun seeking, impulsivity) and greater activity in left vIPFC and striatum

*Chase et al., Translational Psychiatry 2017*

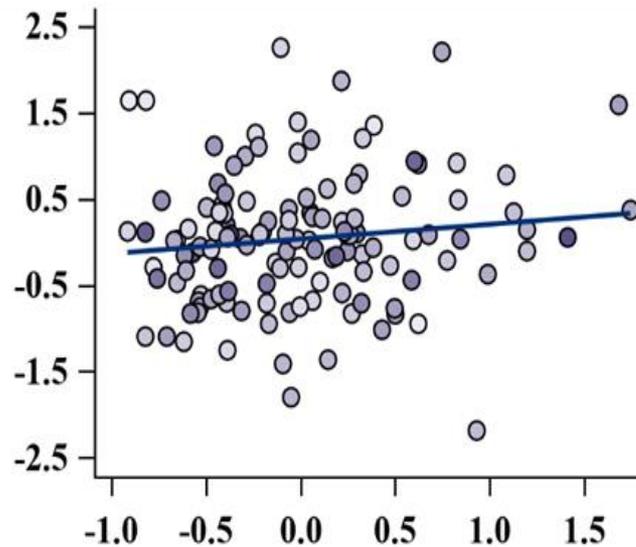
*voxelwise:  $p < 0.001$ , peak level FWE  $p < 0.05$*

# Replication of impulsive sensation seeking results



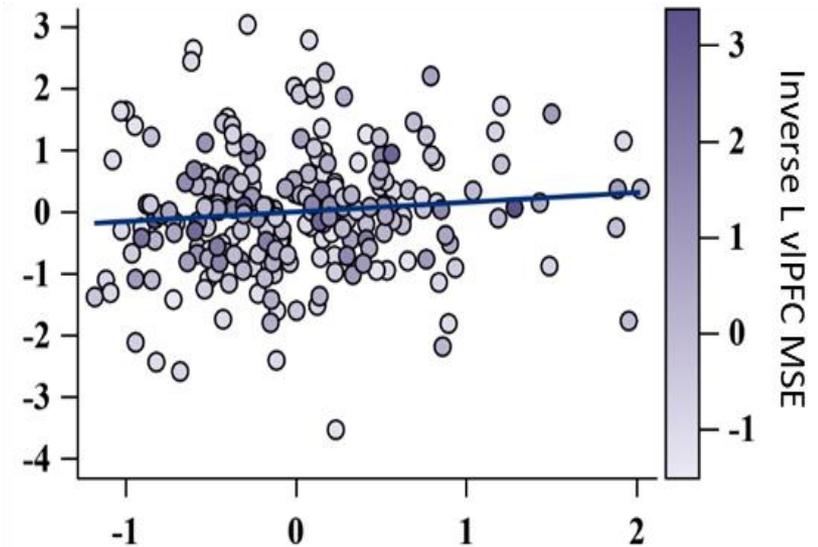
L VIPFC Parameter Estimates

Replication Sample  $N=127$



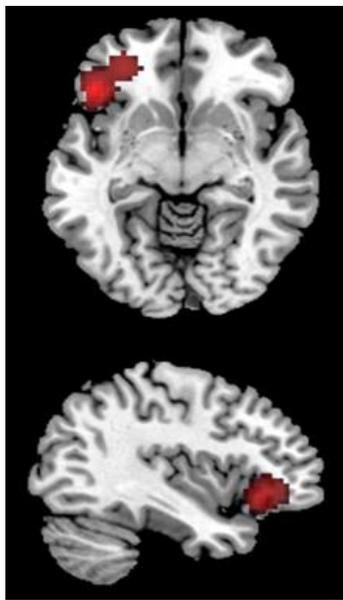
$\beta=0.28, t=2.44, p=0.0169$

Combined Sample  $N=227$



$\beta=0.27, t=2.41, p=0.0184$

*Edmiston et al., 2019. Biological Psychiatry: CNI*



$a=0.187^{**}$



UPPS-P Negative Urgency



*Impulsivity –  
Negative urgency  
Links between left vlPFC  
activity to RE and  
future BD risk*

$b=1.79^{***}$

*Risk for future BD*



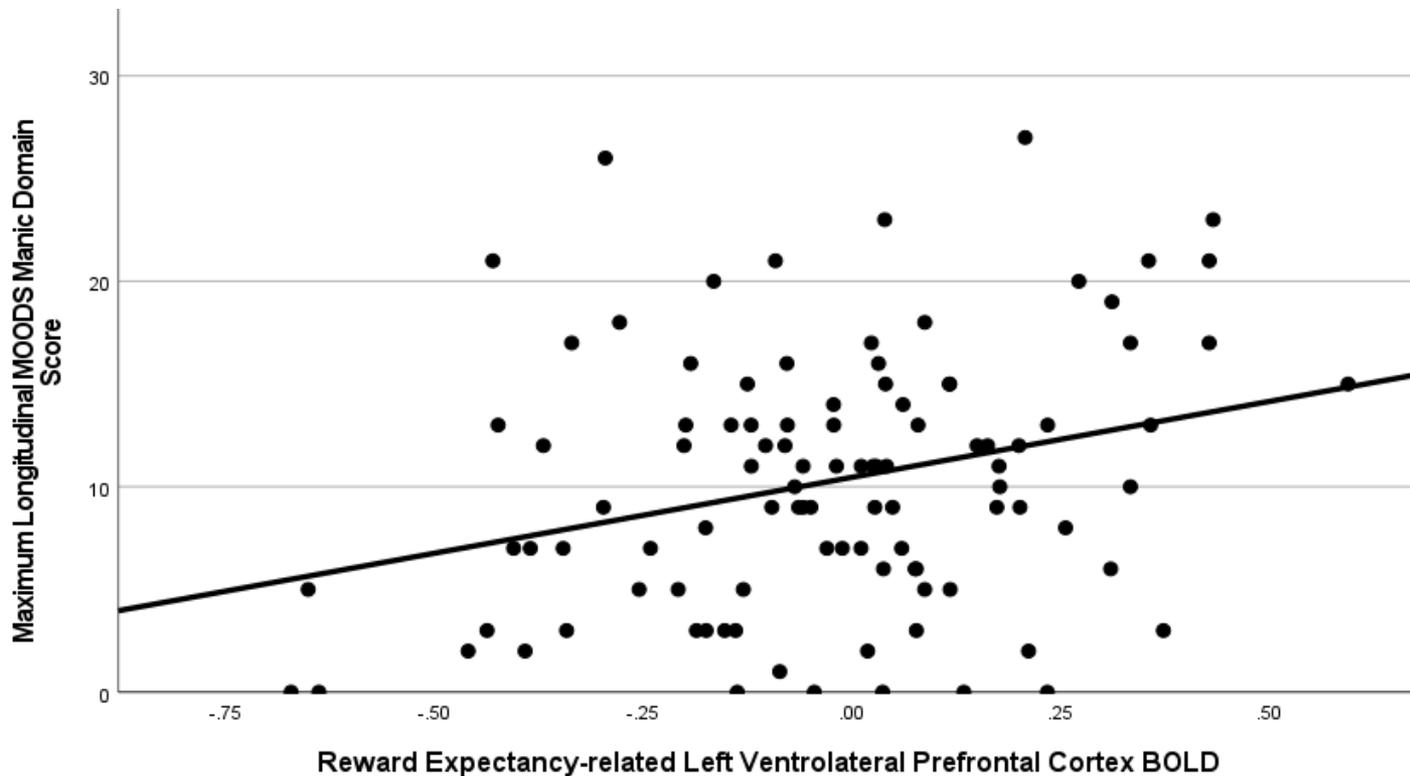
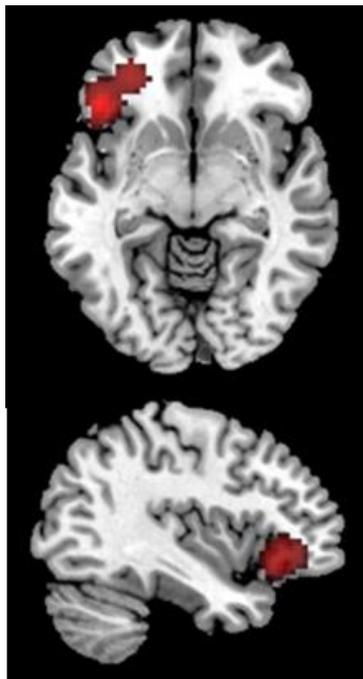
L vlPFC Reward  
Expectancy-related Activity

$c=1.23^{*}$   
 $c^1=1.04$

MOODS Mixed Instability

*Edmiston et al., 2019. Biological Psychiatry: CNNI*

# Left vIPFC activity to RE predicts longitudinally-measured mania risk over 1 year



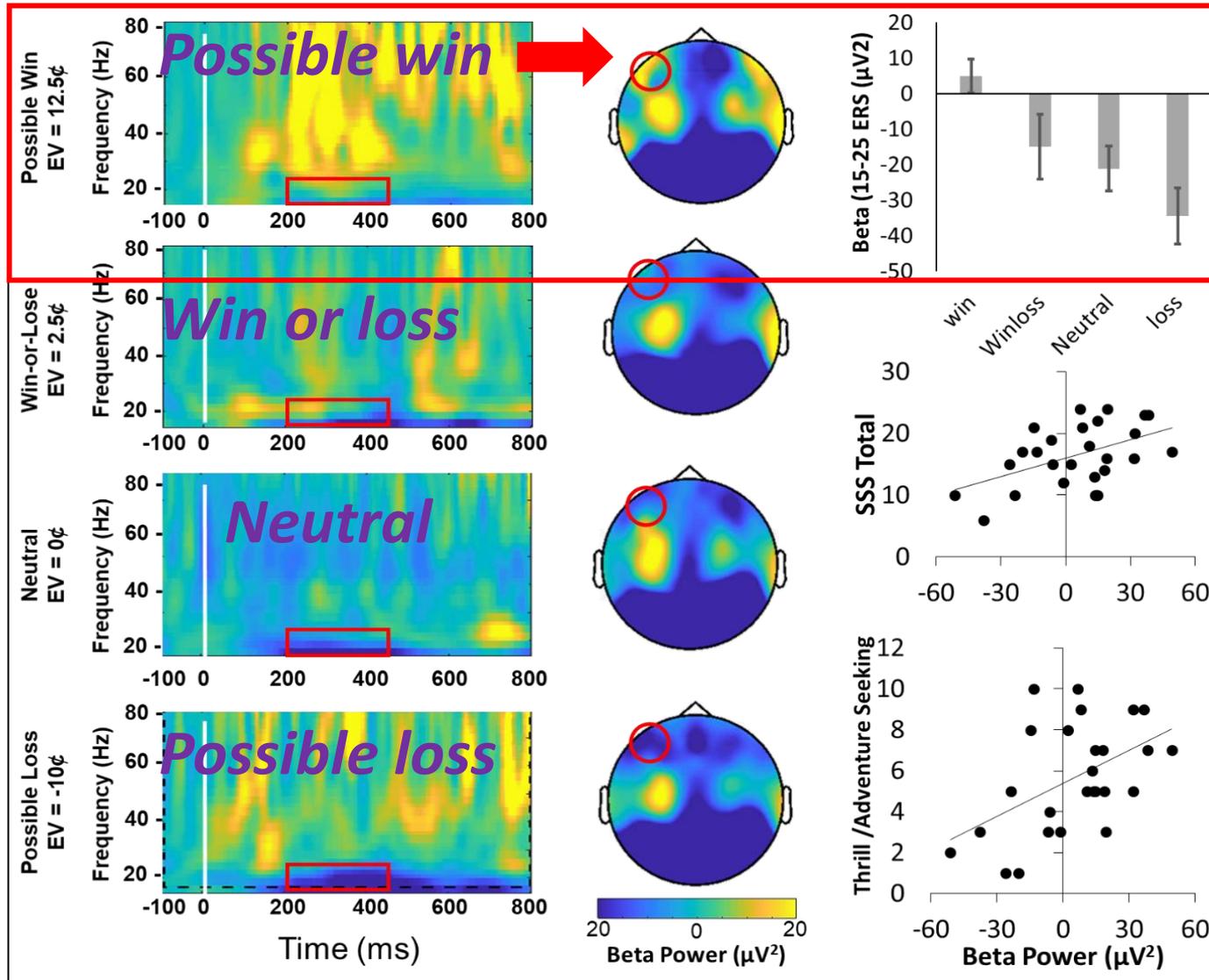
***n=103***

***B=4.995, p=0.037***

*Edmiston et al., in preparation*

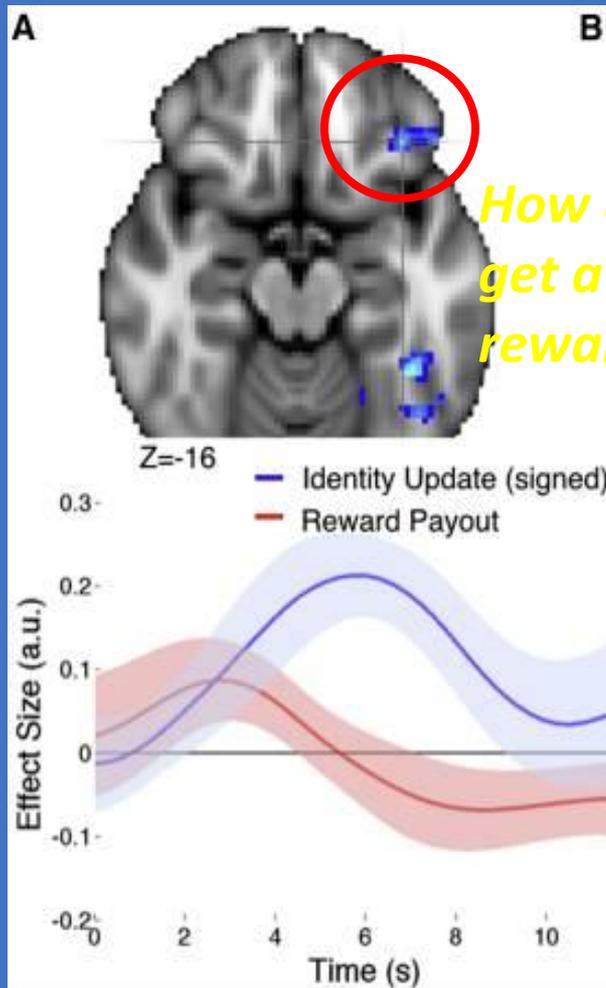


# Reward expectancy-related beta power is positively associated with sensation seeking

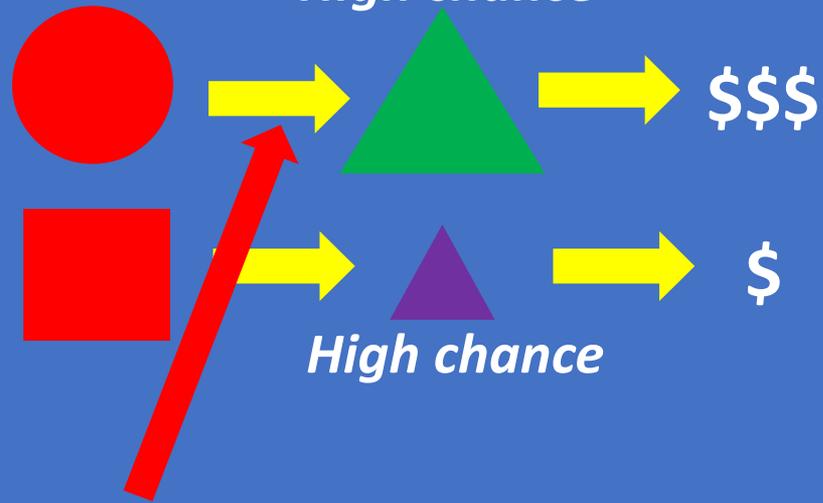


**N=26 (16 female)**  
**Young adults**  
**(22.3 +/- 1.7 yrs)**

# What does the left vIPFC do?



?



**Left vIPFC** guides decision-making about links between stimuli and outcomes to optimize future reward

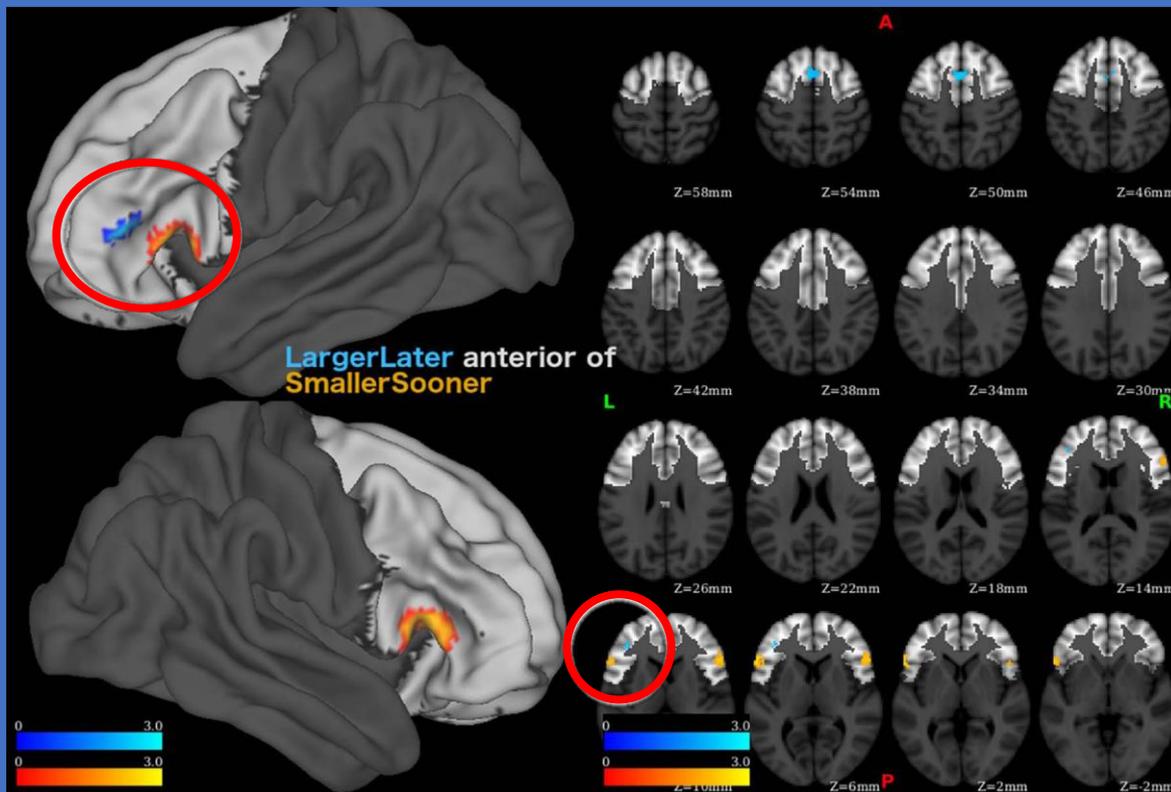
*Boorman et al., 2016*

**Left vIPFC: reward valuation to optimize future rewards**

# Left vIPFC also supports impulsive choices



*Individuals with Bipolar Disorder tend to make more impulsive choices*

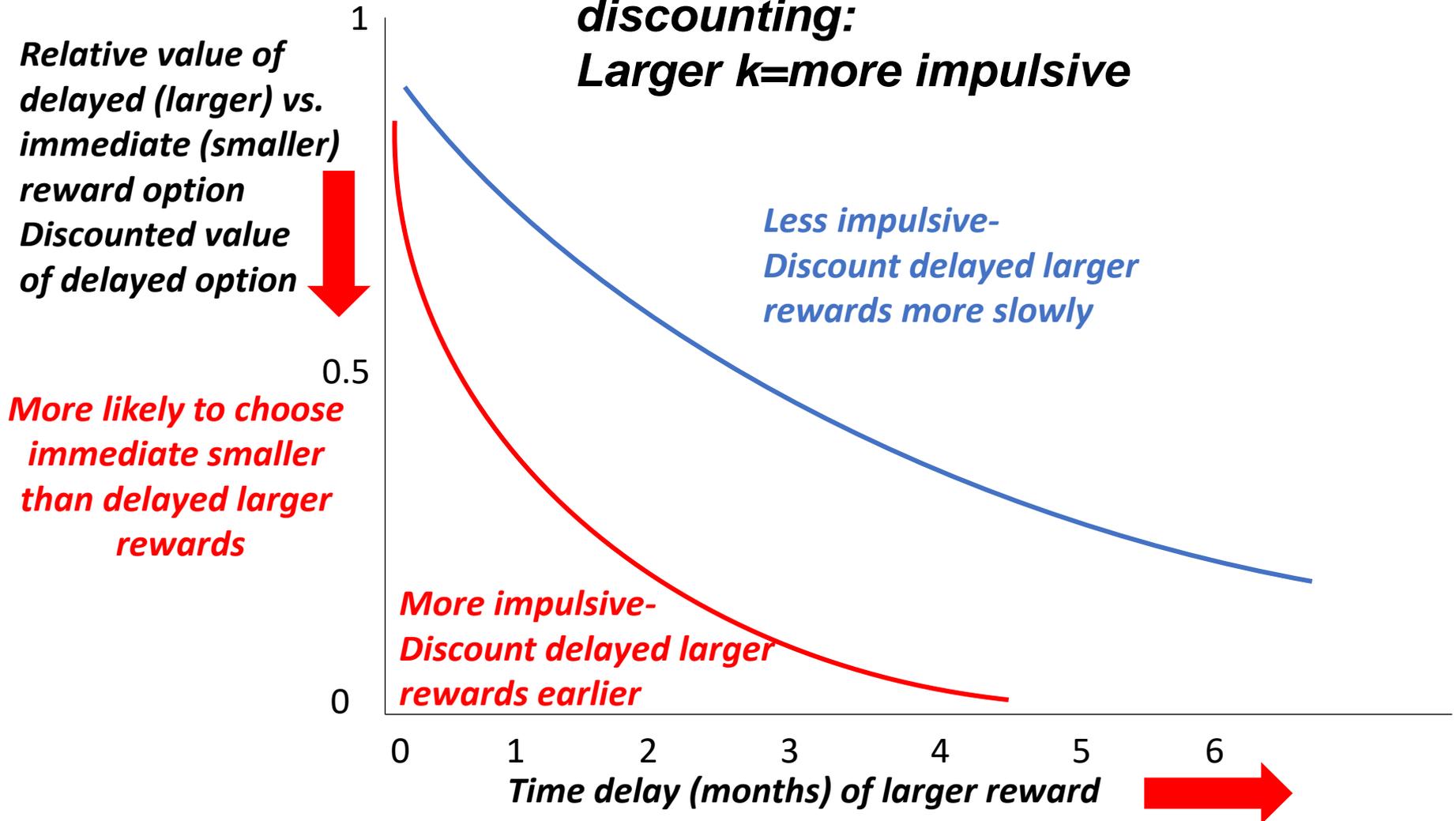


Left vIPFC promotes choice of immediate smaller rewards over later larger rewards

*Smith et al., 2018*

# How is impulsive choice measured?

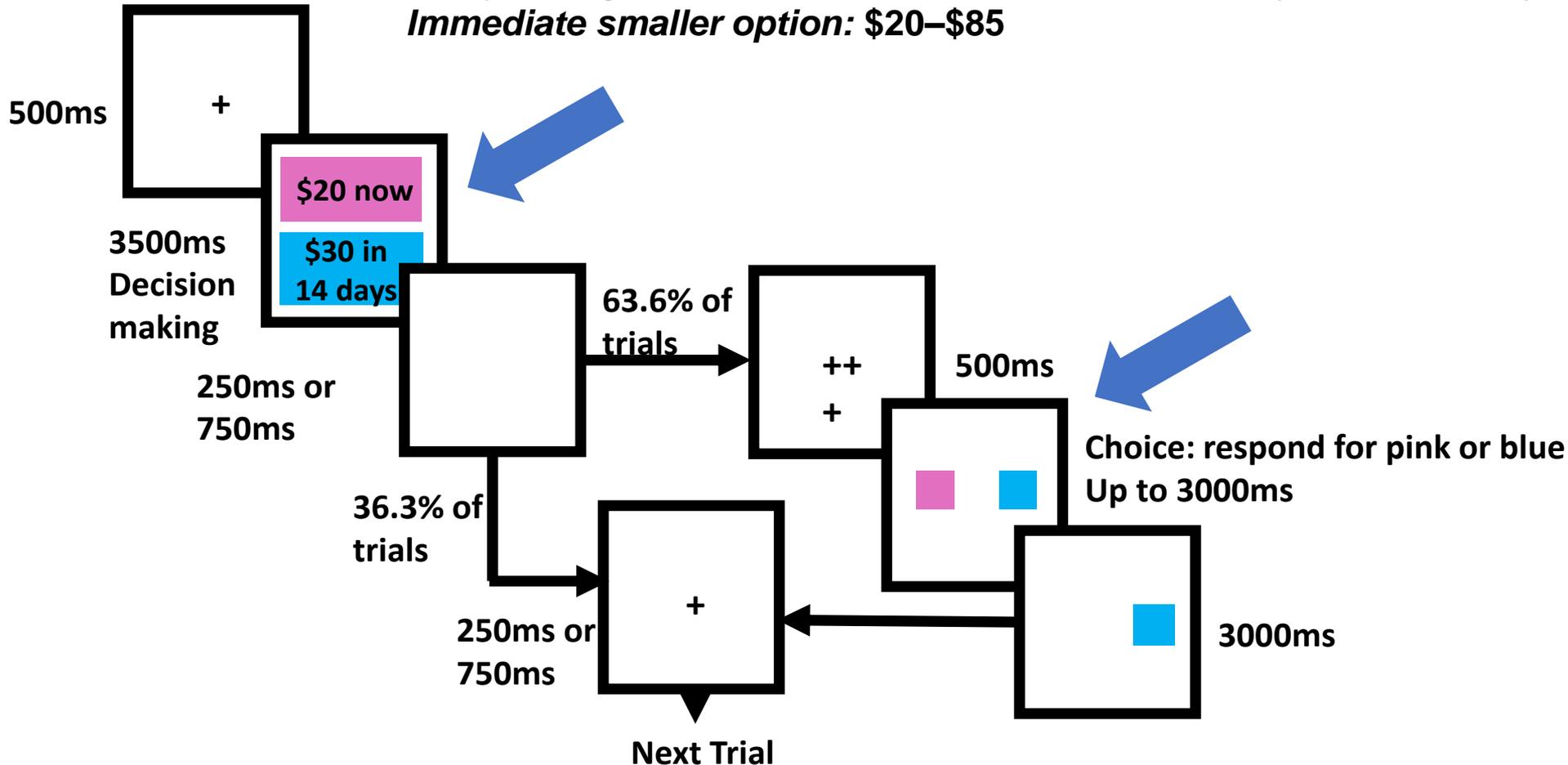
*K value= measure of delayed reward discounting:  
Larger k=more impulsive*



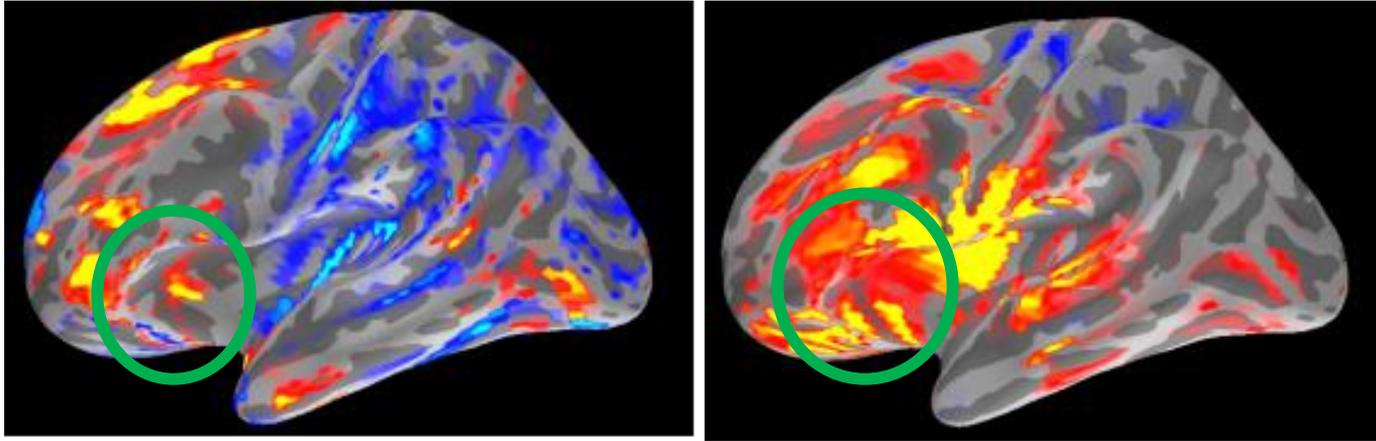
# Delay discounting task

Two (hypothetical) options: smaller immediate (pink) and larger delayed (blue) reward

*Delayed larger option: min \$21-max \$864; min 7 days-max 168 days*  
*Immediate smaller option: \$20-\$85*



# Adults with Bipolar Disorder show greater left vIPFC beta power before choosing immediate, smaller rewards



## *Preliminary data*

4 BD (4 female;  
2 hypomanic, type II,  
2 depressed, type I;  
25.5  $\pm$  11.1 yrs)  
5 HC (5 female;  
24.6  $\pm$  4.8 yrs)

BD (right): greater left vIPFC- localized beta power than healthy adults during intertemporal decision making prior to choice of immediate, smaller reward options

## *Adults with Bipolar Disorder more likely to choose immediate smaller rewards*

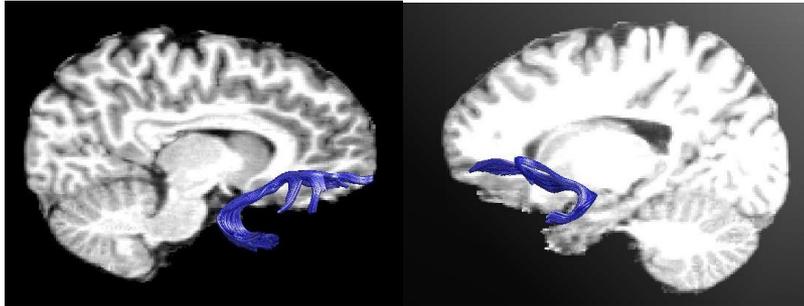
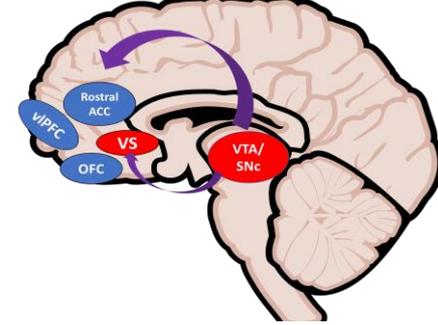
7 adults with BD (3 female; BDI; euthymic, 28.72  $\pm$  8.87 yrs): **mean  $k=1.012 \pm 0.51$**

6 healthy control adults (3 female; 31.85  $\pm$  8.95 yrs): **mean  $k=0.49 \pm 0.14$ ;  $T=2.19$**

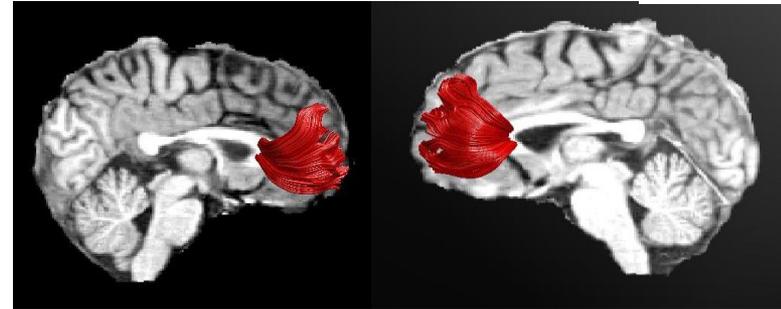
$p=0.05$

***Adults with BD have greater left vIPFC activity when deciding between reward options: predisposes to choosing immediate smaller rewards***

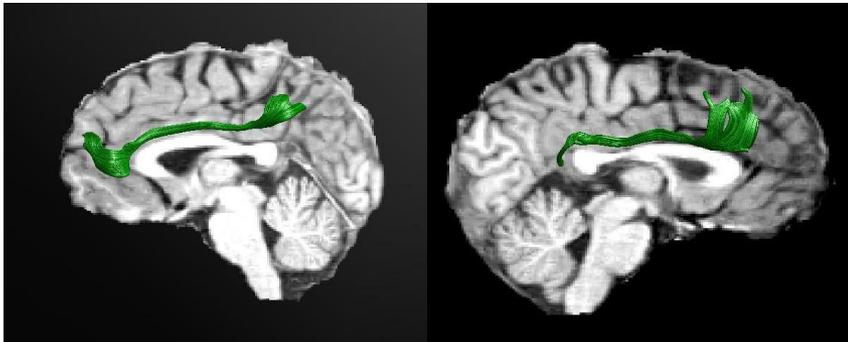
# White matter tracts in reward circuitry



Uncinate fasciculus



Forceps minor of the corpus callosum



Cingulum bundle

***Corpus callosum and cingulum bundle:  
Connect different prefrontal cortical (dACC, OFC, vIPFC) regions***

# Reward and emotional regulation white matter predictors of future Bipolar Disorder risk

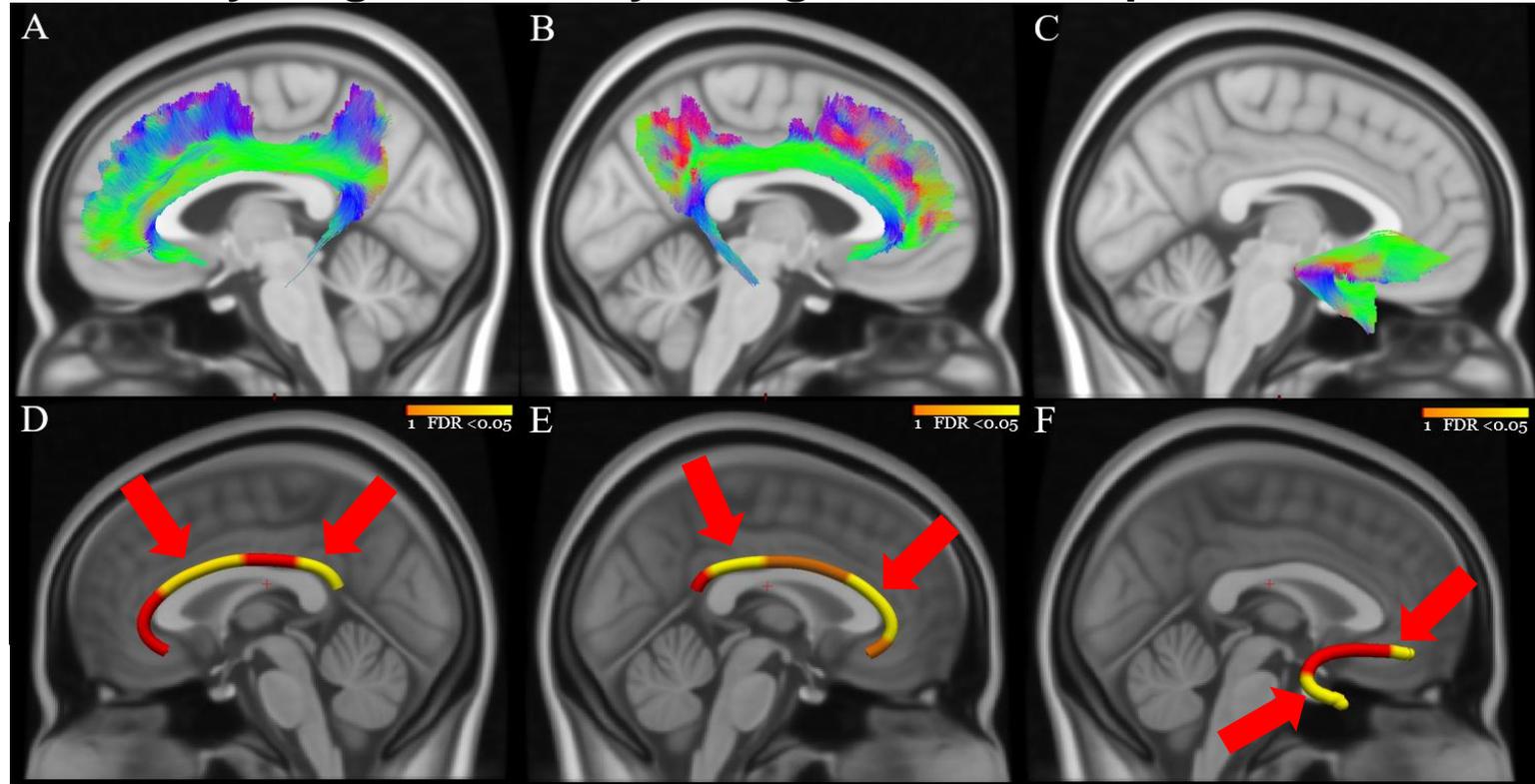
Identify white matter *predictors of worsening subthreshold hypomanic symptoms* in non-BD young adults

Evaluate whether these white matter markers *differentiate BD from healthy individuals*

Global probabilistic tractography and a tract-profile approach

*Fractional anisotropy (FA)*: a measure of the structural integrity (fiber collinearity) of white matter in tracts supporting reward and emotional regulation

# Specific clusters in three white matter tracts predicted future increases in mania in young adults not yet diagnosed with Bipolar Disorder



**n=81**  
**Lower FA Predicted greater future mania 6 months later**

**Left cingulum bundle middle and posterior**

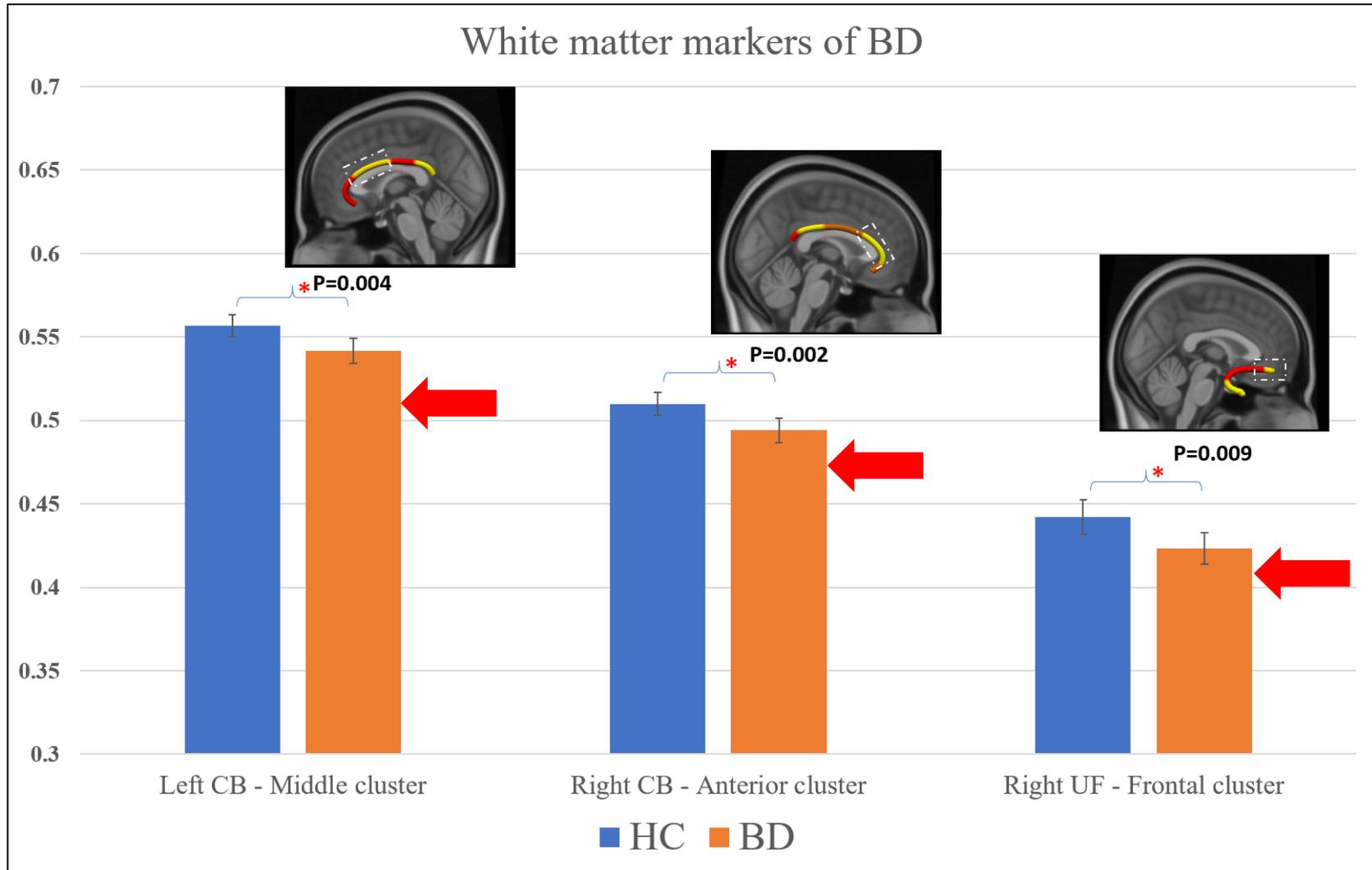
**Right cingulum bundle anterior and posterior**

**Right uncinate fasciculus frontal and temporal**

Cluster	$\beta$	SE	IRR	95% CI	$p^b$	FDR $p^{b,c}$
Left CB - Middle Cluster (size=30%)	-0.22	0.09	0.80	0.67 - 0.97	0.022	0.022
Left CB - Posterior cluster (size=20%)	-0.32	0.09	0.73	0.61 - 0.86	<0.001	0.001
Right CB - Anterior Cluster (size=30%)	-0.30	0.10	0.74	0.61 - 0.91	0.003	0.004
Right CB - Posterior cluster (size=20%)	-0.27	0.10	0.76	0.62 - 0.93	0.005	0.007
Right UF - Frontal cluster (size=10%)	-0.29	0.10	0.75	0.56 - 0.90	0.002	0.004
Right UF - Temporal cluster (size=30%)	-0.40	0.10	0.67	0.55 - 0.81	<0.001	<0.001

**Lima Santos et al., in review**

# Similar patterns of lower FA in these clusters in adults with Bipolar Disorder versus adults without Bipolar Disorder



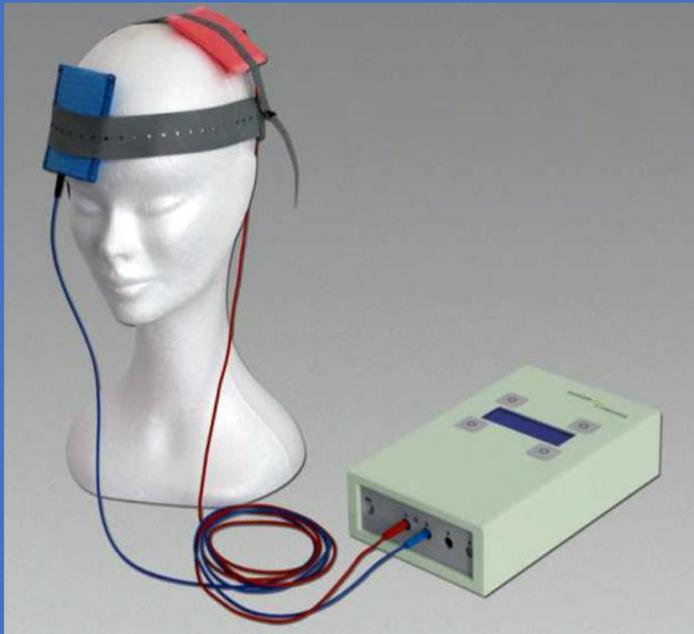
***n=75 adults with BD***  
***n=58 healthy control adults***

***All comparisons***  
***met FDR threshold***

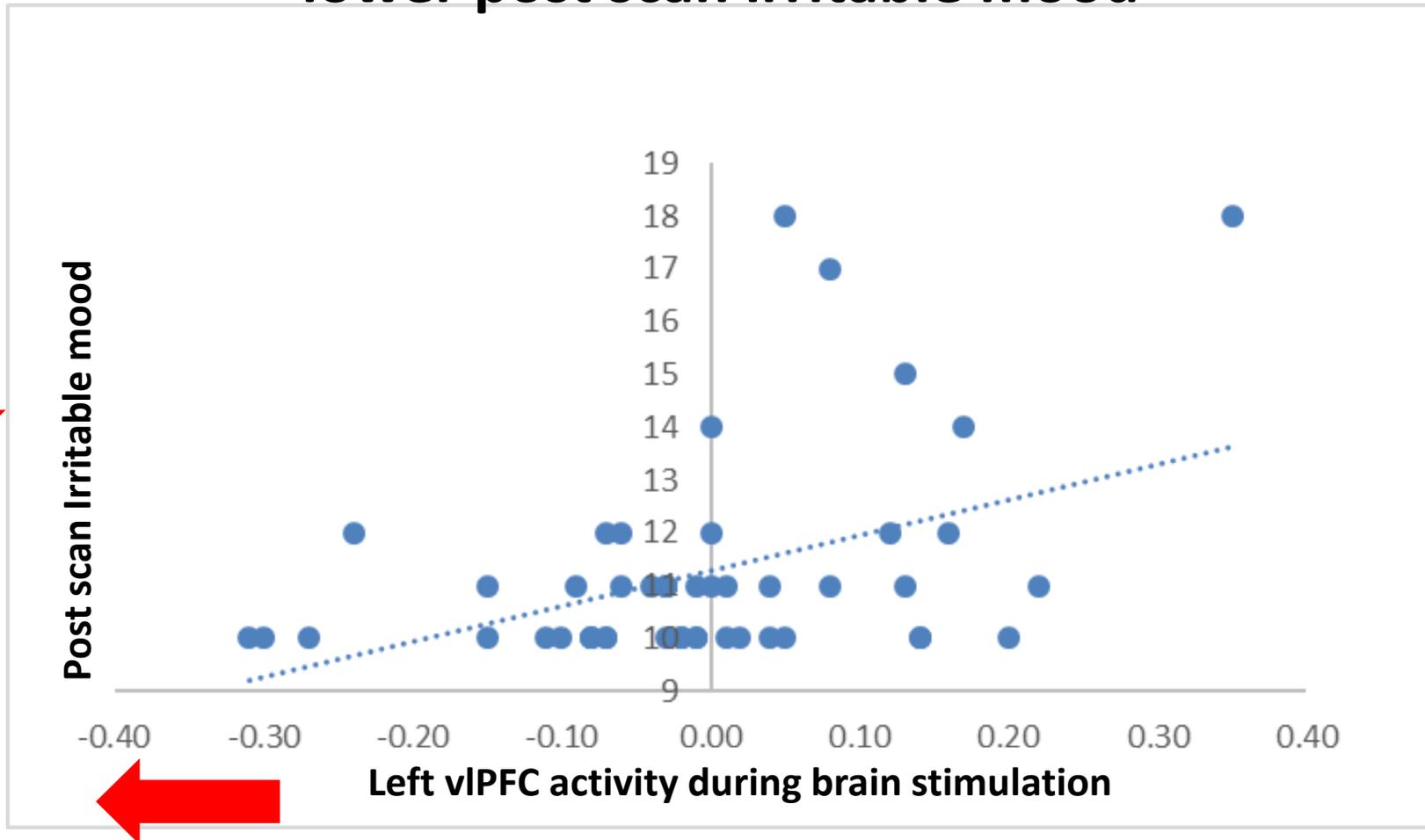
***Lima Santos***  
***et al., in review***

# How neural biomarkers can lead to novel treatments

# *Neural targets for treatments: Neuromodulation: Transcranial Direct Current Stimulation (tDCS)*



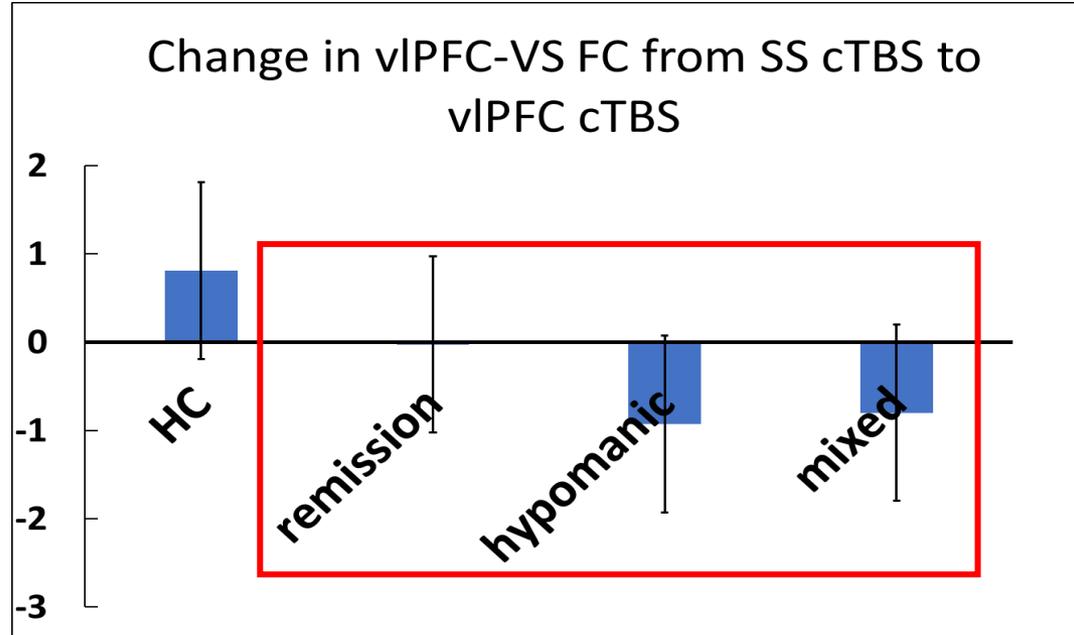
# Lower left vIPFC activity during inhibition of left prefrontal cortex is associated with lower post scan irritable mood



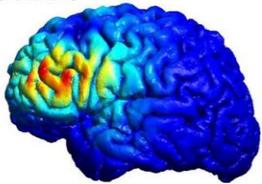
# Theta burst Stimulation (TBS)



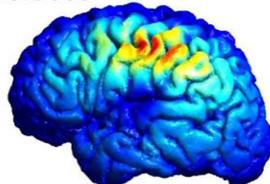
FC parameter estimate changes



A: Left vIPFC



B: Left SSS



V/m

0.03 17 34 0.015 12 24

A. E-field at left vIPFC with left vIPFC TBS coil placement.

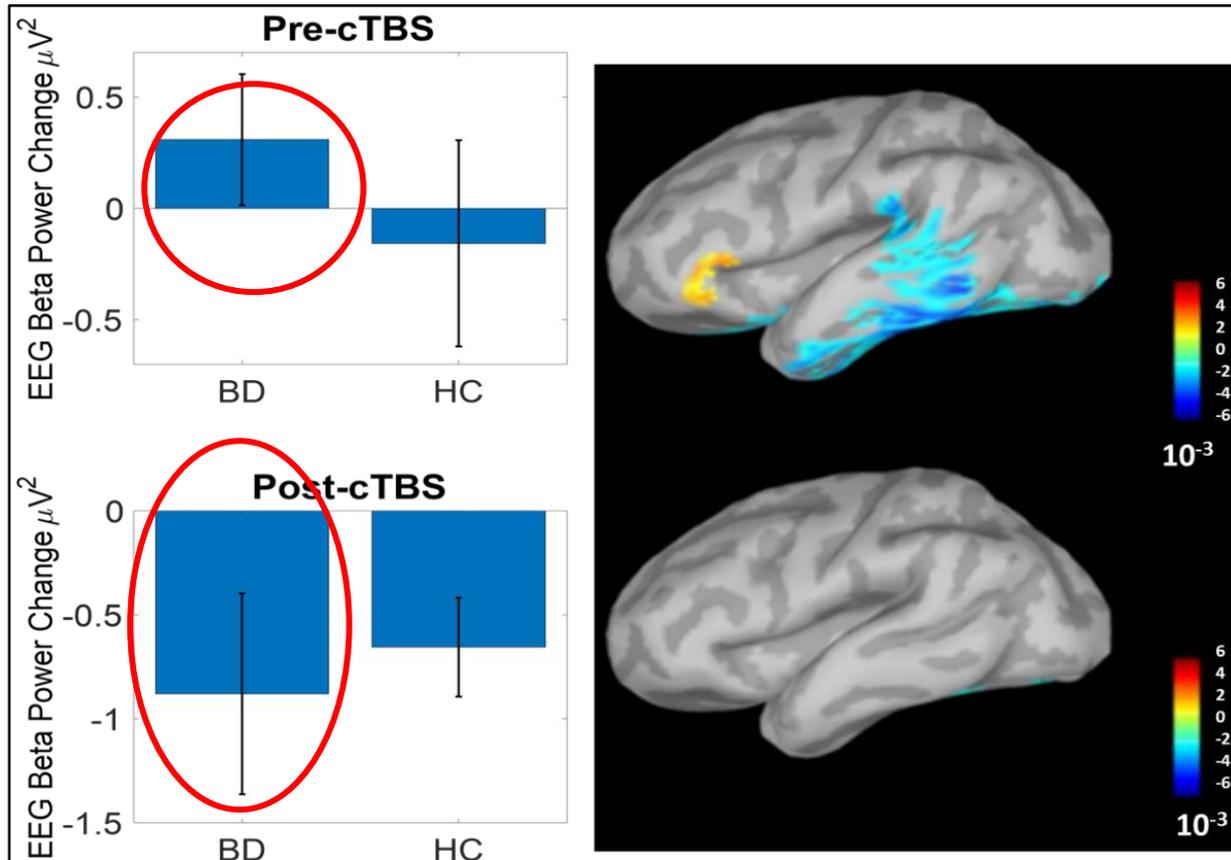
B. at left SS, with left SS coil placement

*Preliminary data*

**Greater reduction in left vIPFC-left VS connectivity to reward expectancy after left vIPFC cTBS vs. left SS cTBS in 6 BD vs. 6 healthy control adults**

*PIs: Phillips, Ferrarelli*

# EEG: Higher beta power in adults with Bipolar Disorder versus non-Bipolar Disorder healthy adults before choosing immediate smaller rewards is downregulated by left vIPFC cTBS



**Figure 1. Higher  $\beta$  power in BD adults vs. HC on the delay discounting task is downregulated by left vIPFC cTBS**

4 Bipolar Disorder (BD) adults ( $35.02 \pm 8.65$  years; 2 female; BD type I, in remission)

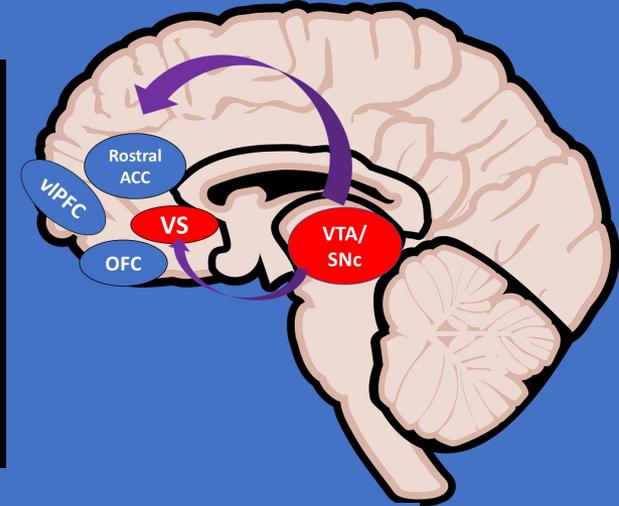
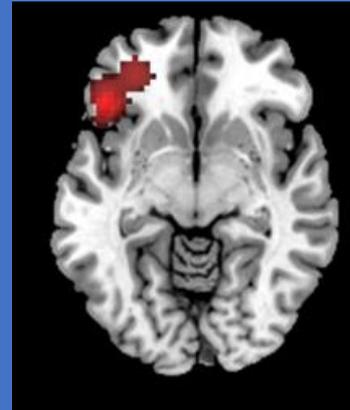
4 healthy control adults (HC) ( $33.91 \pm 8.13$  years; 2 female)

EEG cortical source maps: in a representative BD adult before (top) and after (bottom) left vIPFC cTBS

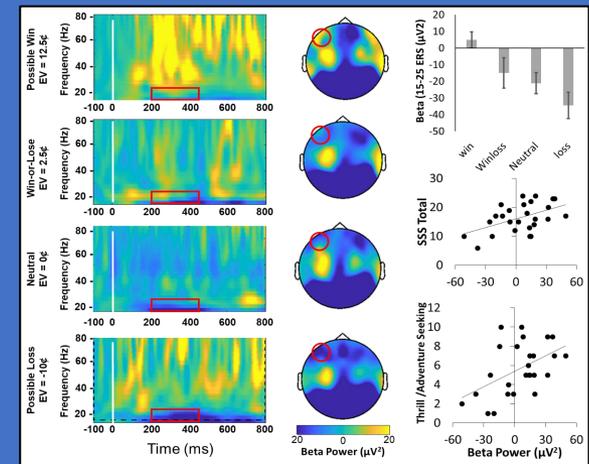
(color bars: current source density distribution normalization)

# Summary

## Multimodal neuroimaging



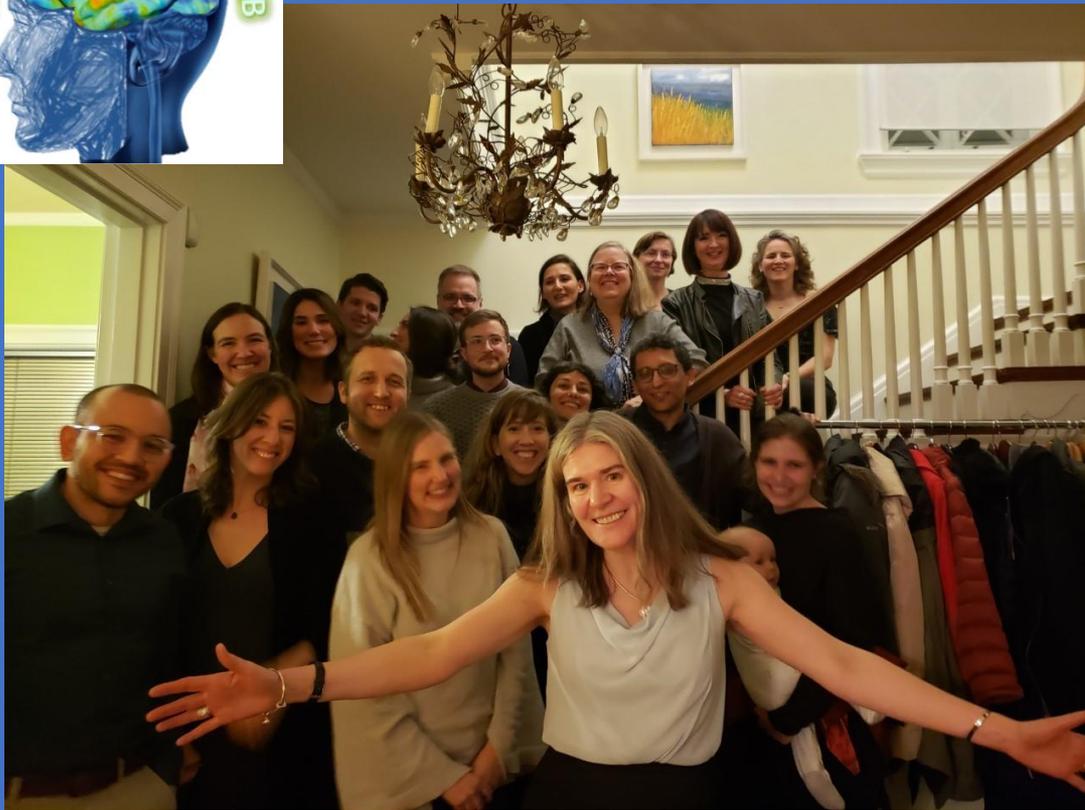
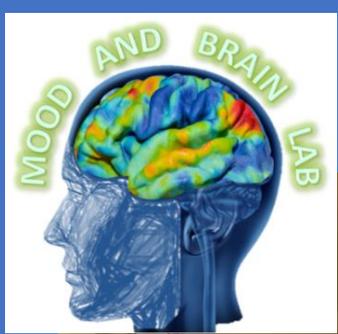
Elevated **left vIPFC** activity to reward expectancy associated with Bipolar Disorder and future mania/hypomania risk



Left vIPFC: a promising **neural target** for novel neuromodulation interventions



# Thank you!



R37MH100041 P50 MH106435  
R01 MH060952 R01 MH122990  
R01 MH059929 R01MH115466



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MRRC Bellefield's Clinic Staff · Children's Hospital · OAC · All patients and families*