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 at 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

50% OR 50%
Win         Zero

50% OR 50%
Loss        Zero

50% OR 50%
Win         Loss
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)


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 vlPFC activity during reward expectancy.

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

Chase et al., Translational Psychiatry 2017

voxelwise: $p<0.001$, peak level FWE $p<0.05$
Replication of impulsive sensation seeking results

Replication Sample  \(N=127\)  Combined Sample  \(N=227\)

Adjusted UPPS-P Negative Urgency Score

\[ \beta = 0.28, t=2.44, p=0.0169 \]  \[ \beta = 0.27, t=2.41, p=0.0184 \]

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

*Kale Edmiston, Jay Fournier*
Impulsivity – Negative urgency
Links between left vlPFC activity to RE and future BD risk

UPPS-P Negative Urgency

L vlPFC Reward Expectancy-related Activity

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
Electroencephalography (EEG) study of left vIPFC activity during reward expectancy

EEG measures neural activity with *high temporal resolution*.

*High sensitivity to vIPFC activity*: relatively thin intervening tissue

Prefrontal cortical activity (oscillatory power) in the *beta/gamma band* associated with uncertain reward

Reflects *dopaminergic activity* in brain reward circuitry

Positively correlated with *sensation seeking*
Reward expectancy-related beta power is positively associated with sensation seeking.

Coffman et al., 2021. J. Affective Disorders
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?

Relative value of delayed (larger) vs. immediate (smaller) reward option
Discounted value of delayed option

More likely to choose immediate smaller than delayed larger rewards

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

Less impulsive - Discount delayed larger rewards more slowly

More impulsive - Discount delayed larger rewards earlier

Time delay (months) of larger reward

0           1             2              3               4              5             6

0           0.5            1
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 vlPFC beta power before choosing immediate, smaller rewards.

**Preliminary data**

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

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

7 adults with BD (3 female; BDI; euthymic, 28.72±8.87 yrs): \( \text{mean } k=1.012±0.51 \)
6 healthy control adults (3 female; 31.85±8.95 yrs): \( \text{mean } k=0.49±0.14; \ T=2.19 \)
\( p=0.05 \)

**Adults with BD have greater left vlPFC 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

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

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

Identify white matter *predictors of worsening subthreshold hypomaniac 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

*Lima Santos et al., in review*
Specific clusters in three white matter tracts predicted future increases in mania in young adults not yet diagnosed with Bipolar Disorder.

Lima Santos et al., in review

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

$n=81$

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

Lima Santos et al., in review

$n=75$ 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.

Bertocci et al., 2019. Molecular Psychiatry
Theta burst Stimulation (TBS)

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

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

4 healthy control adults (HC) (33.91 ± 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)

Figure 1. Higher β power in BD adults vs. HC on the delay discounting task is downregulated by left vIPFC cTBS
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!

Collaborators:

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