Medications and Psychotherapy to Target Neural Networks in Youth at High-Risk for Bipolar Disorder

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Impact of Pediatric Bipolar Disorder

- Bipolar onset begins in childhood or adolescence 50-67% of the time\(^1\)
- 420,000 – 2,072,000 U.S. children could suffer from bipolar I or II disorder\(^2\)
- Community diagnosis has increased 40x in past 10 years\(^3\)
- Children with BD have poor psychosocial outcomes: higher rate of substance use, suicide attempts, school failure\(^4,5\)

\(^1\) Perlis 2004; Leverich 2007; \(^2\) Post & Kowatch, 2006
\(^3\) Moreno, Archives, 2007
\(^4\) Carter 2003; \(^5\) Leverich 2007
Bipolar Spectrum in Children

SMD  ADHD+FH  DEP+FH  BP NOS  BP II  BP I

Possible Prodromal States

Severe Mood Dysregulation

“Full” Bipolar Disorder
Bipolar Spectrum in Children

Possible Prodromal States

Severe Mood Dysregulation

“Full” Bipolar Disorder

SMD  ADHD+FH  DEP+FH  BP NOS  BP II  BP I
Corticofugal Control in Bipolar Disorder

ACC=anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; Hypoth=hypothalamus; Inf=inferiors; pCing=posterior cingulate cortex.

Chang K et al. Arch Gen Psychiatry. 2004;61:781-792.
Figure 1. Functional connectivity in youth at risk for BD

A. During emotion task:

- DLPFC (9/46)
- sgACC (25)
- Striatum
- Hipp.
- Cerebellar Vermis
- Amygdala

B. During rest:

- dACC
- Precuneus/PCC
- Thalamus
- VMPFC (10/11)
- Amygdala

DLPFC = dorsolateral prefrontal cortex; sgACC = subgenual anterior cingulate cortex, Hipp. = hippocampus; VLPFC = ventrolateral prefrontal cortex; VMPFC = ventromedial prefrontal cortex; dACC = dorsal ACC; PCC = posterior cingulate cortex
Amygdala Volumes in BD by Age

Pfeifer et al., *JAACAP*, 2008
HR>HC Fear-Calm

Right Amygdala

Left DLPFC (BA 9)

Left VLPFC (BA 47)

L Subgenual Cingulate (BA 25)

R Medial Frontal Gyrus (BA 10/11)

Cerebellar Vermis

y=11

y=4

z=0

z=20

z=25

z=-48
HR > HC Fear - Calm

Bilateral Caudate/VS

Right Parahippocampal Gyrus

z = 12

z = -28
Treatment/Early Intervention
## Early Interventions in Children at High Risk for BD

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Reduction of Manic Sx</th>
<th>Reduction of Depressive Sx</th>
<th>Beat Placebo?</th>
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</thead>
<tbody>
<tr>
<td>Lithium vs Pbo(^1)</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>No</td>
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<tr>
<td>Divalproex,(^2) Open-label</td>
<td>24</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
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<tr>
<td>Divalproex vs Pbo(^3)</td>
<td>53</td>
<td>+ (prevented relapse)</td>
<td>+ (prevented relapse)</td>
<td>No (only with ++ Fam Hx)</td>
</tr>
<tr>
<td>Quetiapine,(^4) Single-blind, prospective</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
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Family-Focused Treatment (FFT) for High Risk Youth

- Time-limited: 12 outpatient sessions over 4 months
- Begins with assessment of family
- Three component modules:
  - **Psychoeducation** about mood disorders (*symptoms, early recognition, etiology, treatment, self-management*)
  - **Communication skills training** (*behavioral rehearsal of effective speaking and listening strategies*)
  - **Problem solving skills training**

Our pilot study demonstrated that neural changes accompany symptom change.

Right Amygdala Activation at Baseline Predicts Response to FFT-HR, But Not EC
Conclusions

• Bipolar disorder is common in children and adolescents (1%)
• Children, adolescents, and adults usually have a prodromal phase before the first manic episode
• Targeted pharmacologic and psychotherapeutic interventions at the right time may help restore healthy neuronal connectivity/function
• Long term follow up to determine prevention is necessary.
## Acknowledgements

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<tr>
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<td>Lucas Center for Neuroimaging</td>
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