Neural and Behavioral Characteristics of Risk and Resilience in Youth Offspring of Parents with Mood Disorders

Global Consortium for Depression Prevention
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## Disclosures of Potential Conflicts

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Overview

- Mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), commonly begin in childhood or adolescence.

- Early signs of problems with mood may reflect a change in brain structure or function.

- Treatment may prevent, reverse, or worsen the natural course of mood problems before reaching adulthood.
Why this is important:

- Pediatric mood disorders are common and can have serious developmental consequences.

- We need to distinguish problem behaviors from behaviors typical of children to enhance our understanding of what needs treatment.

- Mood disorders can run in families.

- Diagnosing mood problems is challenging as there are no lab tests.

- Knowing risk factors and warning signs aids early identification and treatment.

Bitsko RH et al., *MMWR Worb Mortal Wkly Rep.* 2016; 65[9]:221-226
Case Review: Life of a “Moody” Child

Childhood
- Some stable premorbid factors influencing brain development:
  - Genetics
  - Temperament
  - Parenting
  - Attachment

Vulnerabilities
- In brain regions involved in emotion and motivation

Stress/Challenge

Adolescence
- Intact Emotional Function
- Prevention Strategy?
- Dysregulated emotion and motivation

Transition to Adulthood
- Resilience: Intact adaptive functions

Risk:
- Mood/psychiatric other adverse outcomes (diabetes, heart disease)
### Warning Signs

| Risk-taking behaviors with false beliefs of achievement, or low self-esteem |
| Getting only a few hours of sleep but not feeling sleepy during the day (Children need 8-10 hours of sleep; Adolescents 10-12 hours) |
| Sneaking out of the house, running away, sexual activity, using drugs |
| “I hear voices telling me to hurt myself” |
| “Energizer bunny” or having low energy – sluggish |
| “My brain is going 100 miles/hour”; Jumping from topic to topic |
| Grades getting worse from incomplete or unattempted school work |
| Less interest in activities that were previously pleasurable; spending more time alone; Feeling hopeless or helpless about the future; preoccupied with death |
| Poor or excessive appetite; physical ailments |
| Pacing about or appearing slow, not caring about appearance |
Mechanisms of Mood Disorders
Prefrontal cortex:
- Develops more in adolescence
- Executive function
- Regulates emotion

Limbic system:
- Primitive
- Amygdala
- Controls moods
- Fight or flight
Why are children not just mini versions of adults?

- Differences may be attributed to a child’s physical, emotional, cognitive, and social developmental stages
  - Mood lability, irritability, low frustration tolerance, temper tantrums, somatic complaints, and/or social withdrawal instead of verbalizing feelings of depression
  - Fewer melancholic symptoms and delusions
  - More suicide attempts in adolescents than depressed adults
  - Brain patterns are different

Diagnostic Challenge: Who has a mood disorder? Who will develop a mood disorder?

Family history is among the clearest risk factors.
Some Children at High-risk for Mood Problems Show Brain Patterns of Resilience

Increased connections between the Ventrolateral Prefrontal Cortex (VLPFC) and the brain network that controls executive functions.

Singh et al., *Bipolar Disorders*, 2014;16(7):678-689.
Davidovich et al., *J Affective Disorders*, 2016; 199:54-64.
Phillips et al., Is a Highly Dimorphic Brain Vulnerable to Psychopathology? Insights from Brain Imaging, Genetics, and Psychiatry, In Preparation
Some Children at High-risk for Mood Problems Show Brain Patterns of Vulnerability

Family Chaos is Associated with Disconnectivity in the Brain

Singh et al., *Bipolar Disorders*, 2014;16(7):678-689.

Connection between prefrontal cortex and limbic system

- **Low-risk**: $r=0.079$, $p=0.788$
- **High-risk**: $r=-0.707$, $p=0.005$
Higher Levels of Diurnal Stress Cortisol Relates to Higher Levels of Parental Psychopathology

Pearson’s r = 0.305, p=0.02
Family-Focused Treatment (FFT)

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

Family intervention speeds up recovery from mood episodes in youth at risk for Bipolar Disorder.

High Expressed Emotion Families, HR = 4.59, p = .014
Low Expressed Emotion Families, HR = 1.46; p = .11

EC=Educational control
FFT=family-focused therapy

P = .047;
Hazard ratio, 2.69

Family Therapy Improves Mood and Prefrontal Cortex Function

Mindfulness-based Cognitive Therapy for Anxiety in Bipolar Offspring

MBCT was also associated with:

- **INCREASED** activation in the bilateral insula, lentiform nucleus, thalamus, left anterior cingulate while viewing emotional stimuli during an emotional arousal task

- **DECREASES** in anxiety were correlated with change in activation in the bilateral anterior insula and anterior cingulate during the viewing of emotional stimuli

(Anterior Insula: self-awareness)
(Anterior Cingulate: conflict monitoring)

## Treatment Challenge: Few Approved Agents for Acute and Long-Term Treatment of Pediatric Depression

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<tr>
<th>Year</th>
<th>Drug</th>
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<tr>
<td>2002</td>
<td>Fluoxetine (7-17 years)</td>
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<tr>
<td>2009</td>
<td>Escitalopram (12-19 years)</td>
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### Unmet Need

Treatment Challenge: Few Approved Agents for Acute and Long-Term Treatment of Pediatric Bipolar Disorder

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Acute Mania</th>
<th>Acute Depression</th>
<th>Longer-Term</th>
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<tr>
<td>1970</td>
<td>Lithium(^a)</td>
<td>2007 Risperidone(^b)</td>
<td>2014 OlanzapineFluoxetine(^b)</td>
<td>1974 Lithium(^a)</td>
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<tr>
<td>2007</td>
<td>Risperidone(^b)</td>
<td>2008 Aripiprazole(^b),(^{(*-&gt;e)})</td>
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<td>Aripiprazole(^b),(^{(*-&gt;e)})</td>
<td>2009 Quetiapine(^b)</td>
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<tr>
<td>2009</td>
<td>Quetiapine(^b)</td>
<td>2009 Olanzapine(^c)</td>
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\(^{(*) Adjunctive (and monotherapy); \(^{a} Age \geq 12-17; \(^{b} Age 10-17; \(^{c} Age 13-17; \(^{(*) \rightarrow e} Extrapolated indication}

Treatment Challenge: How Should We Treat Depressed Youth Who Have a Family Member with Bipolar Disorder?

Well… therapy first if possible…then…what?

- Selective Serotonin Reuptake Inhibitor (SSRI)?
- Bupropion?
- Lamotrigine?
- Lithium?
- Quetiapine?


Schneck et al., A Pharmacologic Algorithm for Youth Who Are At High Risk for Bipolar Disorder, In Review.
Applying Current Research toward a global plan for preventing mood disorders

- Identify those at highest risk and early – Family history
- Develop large scale preventive interventions
- Use technology to scale up interventions
- Promote diversity
- Combine psychological, genetic and other biological elements – Clues from Neuroscience
- Reduce the impact on suicide, substance abuse, and unemployment.
Conclusions

• Be aware of warning signs of mood disorders in children.

• Evaluating children early in development and over time will increase our understanding of the causes and long-term effects of mood disorders.

• Effective therapies are currently available.

• New therapies and the safety of medications are being studied.
Thank you!

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