Using Neuroscience to Evaluate and Guide Treatment for Pediatric Mood Disorders

Brain and Behavior Research Foundation Webinar
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## Disclosure of Potential Conflicts

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Objectives

• How mood symptoms commonly present in youth
• Historical perspectives and current state of the science
• How neuroscience can guide us toward better evaluation
• How neuroscience can guide us toward better treatment
• Limitations of current levels of evidence
• Design considerations for future studies
Evaluation: Disability Associated With Pediatric Mood Disorders

• Mood disorders are the 1\textsuperscript{st} and 4\textsuperscript{th} leading causes of disability among young people worldwide\textsuperscript{1}
  1. Unipolar depressive disorders
  2. Road traffic accidents
  3. Schizophrenia
  4. Bipolar disorder
  5. Violence

• Depressive symptoms in youth can be disabling\textsuperscript{2}
  – Anhedonia and psychomotor retardation may limit socializing with friends, participating in extracurricular activities, or attending school\textsuperscript{2}

**Evaluation: Understanding the lifelong impact of mood disorders**

- **START EARLY:** For most adults with mood disorders, onset occurred during childhood.
- **CHRONIC:** Early-onset mood disorders are associated with poorer long-term prognosis and increased risk for suicide compared with adult-onset bipolar disorder.
- **FREQUENT:** Mood disorder diagnoses in children and adolescents have been increasing.
- **COMPLEX:** Comorbid conditions often complicate diagnosis and treatment.
A case of a child with mood symptoms

Graphic Illustrations courtesy of CMEology
I DUNNO.

IT'S JUST THAT LATELY I CAN'T,
Y'KNOW, CONCENTRATE. I DUNNO WHY. FOR
THE LAST COUPLE OF MONTHS I HAVEN'T BEEN
SLEEPING. MY MOM COMPLAIN I NEVER EAT
ENOUGH AND I'M TIRED ALL
THE TIME.

I USED
TO LOVE SCHOOL, BUT
NOW I DON'T ENJOY MUCH OF
ANYTHING. I FEEL LIKE I'M
ALWAYS CRANKY.
DO YOU THINK YOUR FAMILY UNDERSTANDS WHAT YOU'RE GOING THROUGH?

NOT REALLY. A YEAR AGO THEY STUCK ME IN A HOSPITAL, AND NOW I THINK THEY WANT TO DO IT AGAIN.

TELL ME ABOUT THE HOSPITAL. HOW'D YOU WIND UP THERE?
IT WAS ABOUT A YEAR AGO. I WAS ONLY SLEEPING A FEW HOURS A NIGHT. I COULDN'T GET ALONG WITH ANYBODY. MY PARENTS SAID I WAS TALKING TOO FAST, THAT I WAS ALWAYS ARGUING, WHICH I WASN'T. THEY WERE STARTING THE ARGUMENTS.

I COULDN'T HELP IT...THOUGHTS WERE RACING AROUND IN MY HEAD. IT WAS LIKE A MONTH. MY MOM FOUND SOMETHING I WROTE IN MY JOURNAL ABOUT DYING AND THEY PUT ME IN THE HOSPITAL.

TO BE CONTINUED...
Treatment Approach in Pediatric Mood Disorders: Current Guidelines

• Treatment of specific disorders and associated behaviors
• Balance between behavioral/cognitive/ psychosocial and psychopharmacological interventions
• Identify and monitor/track target symptoms
• Comorbidity is the rule
• One medication at a time
• Assess for side effects
• Re-challenge
• Limited response rate related to increased vulnerability to side effects
Physiologic Factors That Influence Drug Disposition in Children over Development


Kids are not mini-adults!
The placebo response is real, especially for pediatric major depressive disorder

Bridge et al., JAMA, 2007
Treatment Goals in Pediatric Mood Disorders

• Ultimate goal is REMISSION
• Accurately formulate the target symptoms
• Manage the “side effects”
• Manage comorbid disorders
• Treat the Parents/Family/System
• Manage the impact of negative/stressful life events, school issues, family conflict

Singh, MK, *Clinical Handbook on the Diagnosis and Treatment of Pediatric Mood Disorders*, APA Press, 2019
Historical Perspectives and Contemporary Challenges in Youth

- Strong placebo effect
- Modest added treatment effect
- Most do not achieve full remission even after prolonged treatment
- Adding CBT benefits depressed suicidal teens and may prevent episodes
- Depression is clinically heterogeneous
- Longer-term effects of mood symptoms and treatment unknown
- Mixed states are common but understudied

Treatment: Youth with Bipolar I Depression have similar efficacy/safety profiles with or without subsyndromal hypomania

Findings: Complex symptoms can be systematically evaluated in youth and be shown to respond to a pharmacological intervention compared to placebo.

Future Directions: Better understand the longer-term effects of treatment on complex symptoms, especially if they drive prognosis.

Singh et al., *JCAP*, In Press
The importance of an accurate diagnosis and appropriate treatment

Why not a magic bullet?

Figure 1: Adapted from Bernstein (2010). The inverse Moore’s Law for pharmaceuticals. The number of small molecule and biological USFDA approvals per inflation-adjusted $ billion in research investment, 1950-2010. The apparent log-linear ‘decline in research productivity’ represents the failure of complex physiological phenomena to respond to simple interventions. Western medicine, as defined in the latter half of the 20th Century, has hit a brick wall, a catastrophic regime of exponential cost increase.

We Need **Three** Key BREAKTHROUGHS to Prevent Mood Disorders from Lasting a Lifetime:

1. Biomarkers for early detection.
2. Pre-emptive interventions for those at risk or in pre-symptomatic stages.
3. Better treatments for people living with depression that PREDICT and TRACK outcomes.

Insel, A bridge to somewhere, *Translational Psychiatry*, 2011
Call to Action

1. Measure individual and family factors of risk and resilience
2. Leverage neuroscience to understand how mood disorders emerge
3. Test the safety and effectiveness of developmentally informed interventions
4. Harness cutting edge computational innovations to predict outcomes
5. Translate science to meet clinical unmet needs

Mukherjee S, *What the Coronavirus Crisis Reveals About American Medicine*, The New Yorker, April, 2020

Singh MK, *Cultivating Hope*, JAMA, May 12, 2020
1. Resilience is an intriguing solution

Defined as:
• a complex and dynamic process
• the ability to adapt successfully to adversity, stressful life events, significant threat, or trauma.
• being on a continuum and can be cultivated with the potential for change across the life span
1. Evaluation: Who will be resilient? Who will develop a mood disorder?

Family history of depression is our model system.

Singh et al., *Bipolar Disorders*, 2014
1. Evaluation: the brain can provide clues about stages of depression

Risk Marker

Disorder Marker

Singh et al., Limbic Intrinsic Connectivity in Depressed and High-Risk Youth, JAACAP, 2018

n.s. = not significant; * p<0.05, ** p<0.01, *** p<0.001
1. Stronger brain connectivity predicts resilient outcomes after 3 years and tracks with more prosocial behaviors

Nimarko et al., *Development and Psychopathology*, 2018
1. Treatment: Can we cultivate prosocial behaviors to change the brain and change the outcome?
1. How do we cultivate prosocial behaviors?

Traditional

- Educate about symptoms

Add Prosocial Behavior Training

- Communication Skills
- Problem Solving Skills

Enhanced Care (EC)

Family Focused Therapy (FFT)
1. Family Focused Therapy (FFT) Delays New Mood Episodes by 20 more weeks than Enhanced Care (EC)

Finding: Family prosocial skills-training for youths at high risk for bipolar disorder is associated with longer intervals between depressive episodes.

Future Direction: Clarify the relation between changes in family function and changes in the course of high-risk syndromes.

Miklowitz, D. et al., JAMA Psychiatry, 2020
1. Differences in Brain Connectivity in High Risk (HR) versus Healthy Comparison (HC) Youth

Independent Components Analysis

Singh et al., In Review
1. FFT is associated with increased connectivity which tracks with improved depression outcome

Singh et al., In Review
1. Putative Mechanisms of Action of Psychotherapy in Pediatric Mood Disorders

**Finding:** We found that family-focused therapy is associated with improved functional connectivity between networks in the brain important for emotion processing and regulation.

**Future Directions:** Clarifying treatment-related changes in these neural pathways may lead to earlier identification of bipolar disorder, personalized interventions, and potentially, more adaptive long-term outcomes.

- Improves emotion regulation
- Targets parent expressed emotion (treats the system)
- Improves quality of family relationships and physical well-being
- Improves prosocial behavior
- Interactive effect of medication plus psychotherapy (adherence)
- Neuroplasticity?

Singh et al., In Review.
Yatham et al., *Bipolar Disorders*, 2018; 20; 97-120
2. Leveraging Neuroscience to Understand Mechanisms Underlying Symptoms and How to Treat Them

Comorbidity is the rule rather than the exception in youth.

Early life stress contributes early and significantly to neurodevelopment.

Antidepressant treatment response in youth modestly separates from placebo.

Combination psychotherapy + medication yields the best short-term results, but when and how long to treat youth is unknown.

ACC = Anterior Cingulate Cortex; Nacc = Nucleus accumbens.

**Diagram Description:**
- **ACC** (↑activity): Anterior Cingulate Cortex activity.
- **Nacc** (↑activity): Nucleus accumbens activity.
- **Insula** (↑activity): Insula activity.
- **Amygdala** (↑volume): Amygdala volume.
- **Impaired insulin sensitivity in youth with depression.**
- **Predictor variable (Baseline).**
- **Aberrant Approach Motivation Neural Circuits and Behaviors.**
- **Worsening depressive symptoms.**
- **Outcome variable (at 24 months).**
- **Neurobehavioral Mediators (from Baseline to 6 months).**

**Text:**

**Comorbidity is the rule rather than the exception in youth.**

**Early life stress contributes early and significantly to neurodevelopment.**

**Antidepressant treatment response in youth modestly separates from placebo.**

**Combination psychotherapy + medication yields the best short-term results, but when and how long to treat youth is unknown.**
2. Evaluation with MOMENTUM: Measuring Obesity and Mood Effects on Neurobehaviors Througgh Maturation

Longitudinal Study Design

- 120 overweight (BMI > 85th percentile) girls and boys (ages 9-17 years) treatment seeking for depressive symptoms.
- Assessed at baseline, 6 months, and 24 months
- Scanned with multimodal MRI (structure, resting state, fMRI with food and monetary rewards) at baseline and at 6 months -> early mediators of clinical outcome
2. Evaluation: Neural and endocrine response to oral glucose challenge

• Higher vs lower insulin resistance:
  – BEHAVIOR
  – STRUCTURE
  – CONNECTIVITY
• Clinical correlates to depression

Singh et al., *Hormones and Behavior*, 2018
2. Evaluation: Dysfunctional Intrinsic ACC and Hippocampal connectivity to fronto-limbic reward network

Bidirectional fronto-limbic reward network: hippocampus, amygdala, temporal pole, brainstem, subcallosal cortex, orbitofrontal cortex, and nucleus accumbens; middle frontal and lingual gyrus

Singh et al., *Hormones and Behavior*, 2018
2. Evaluation: Low versus High Levels of Abuse moderates reward network connectivity

Sun et al., *Frontiers in Psychiatry*, 2018
2. Evaluation: Abuse level moderates the relation between neural connectivity and insulin and glucose response

**FINDINGS:**
- **HIGH abuse group:** insulin and glucose response negatively correlated with NAcc-prefrontal cortex, NAcc-paracingulate and amygdala-precuneus connectivity (Panels A, B, D)
- **LOW abuse group:** area under the insulin curve negatively correlated with insula-precuneus connectivity (Panel C)

**FUTURE DIRECTIONS:** Examine the longitudinal trajectories of depressive symptoms and insulin resistance in subgroups exposed and unexposed to abuse.

Sun et al., *Frontiers in Psychiatry*, 2018
2. Treatment: Neural correlates of liraglutide effects in individuals at risk for Alzheimer’s disease

**FINDINGS:** Liraglutide improves intrinsic connectivity within hippocampal default mode network; baseline fasting glucose associated with greater connectivity; no cognitive differences found between treatment groups

**FUTURE DIRECTIONS:** Integrate knowledge from adult studies and design trials that target reward dysfunction across multiple domains to address related comorbid conditions in a more unified fashion.

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Fig. 1. Brain regions showing an inverse association between fasting plasma glucose and connectivity with bilateral hippocampus at Time Point 1. Statistical maps are thresholded using a cluster Z threshold > 2.0 and p < 0.05 (corrected).

Fig. 2. Brain regions showing increased connectivity with the bilateral hippocampus in the treatment group relative to the placebo group at Time Point 2. Statistical maps are thresholded using a cluster Z threshold > 2.0 and p < 0.05 (corrected).

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2. Evaluation: Distinct Functional Networks Subserve Suicidal Ideation and NSSI in Depressed Adolescents

SI+ < SI-: $\beta = 0.35 \pm 0.26$, $t(63)=2.240$, $p=0.028^*$
SI+ < CTL: $\beta = 0.65 \pm 0.49$, $t(63)=3.711$, $p=0.0004^*$

*NSSI+ < NSSI-: $\beta = 0.72 \pm 0.38$, $t(63)=3.267$, $p=0.002^*$
NSSI+ < CTL: $\beta = 0.86 \pm 0.46$, $t(63)=3.506$, $p=0.0008^*$

* covarying for age, sex, motion, medication

Ho et al., in prep
2. Evaluation: Depressed Adolescents with Suicidal Ideation Exhibit Elevated Glutamate in Anterior Cingulate Cortex

\[ \beta = 0.33 \pm 0.04 \]
\[ t(33) = 2.15, \, p = 0.039^* \]

* covarying for age, sex, BMI

Ho et al., in prep
2. Treatment: Adapted Dialectical Behavior Therapy for Adolescents (DBT-A) with a High Risk of Suicide in a Community Clinic

**FINDINGS:**
- DBT-A was more effective than Treatment As Usual + Group Support at reducing NSSI, use of antipsychotics, and improving C-GAS
- No suicide attempts were reported in either group at the end of the treatment
- DBT-A is an effective and feasible treatment in adolescents with a high risk of suicide.

**FUTURE DIRECTIONS:** Research in larger samples and combined with neuroscience tools could aid in the development of novel interventions to promote adaptive emotional regulation.

(Santamarina-Perez et al., *Suicide and Life-Threatening Behavior*, 2020)
FINDINGS: Adolescents with NSSI have aberrant baseline amygdala-mPFC connectivity compared with healthy controls. Stronger negative amygdala-prefrontal connectivity was associated with greater posttreatment improvement in NSSI.

FUTURE DIRECTIONS: Given the potential for neuroplasticity during adolescence, larger sample sizes of youth randomized to different treatments could permit examination of treatment-specific effects.
3. Testing The Safety and Effectiveness of Developmentally Informed Interventions

- Medications
- Educational Interventions
- Psychotherapy
3. Treatment Challenge: Few FDA Approved Agents

### Acute Depression

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<td>2002</td>
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<td>Escitalopram (12-19 years)</td>
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### Longer-Term

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Unmet Need

Lee et al. *Pharmacoepidemiol Drug Saf*, 2011
## 3. More FDA-Approved Agents for Pediatric Bipolar Disorders

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<tr>
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<td>2013</td>
<td>OFC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1974</td>
<td>Lithium&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2018</td>
<td>Lurasidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2008</td>
<td>Aripiprazole&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>2009</td>
<td>Quetiapine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2009</td>
<td>Olanzapine&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>2015</td>
<td>Asenapine&lt;sup&gt;b&lt;/sup&gt;</td>
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Unmet Need

OFC=Olanzapine/Fluoxetine Combination

<sup>a</sup>Age 12-17 years; <sup>b</sup>Age 10-17 years; <sup>c</sup>Age 13-17 years.

3. Treatment: Neurofunctional Responses to Seroquel (Quetiapine) while viewing negative and neutral pictures

**FINDINGS:** Lower baseline activation in the left dorsolateral prefrontal cortex and higher baseline activation in the left ventrolateral prefrontal cortex predicted greater improvement in CDRS-R scores from baseline to follow-up in youth randomized to Seroquel vs Placebo.

**FUTURE DIRECTIONS:** Larger studies of these youth would help to clarify the effects of Seroquel on brain activation. Utilize best practices for evidence for prediction.

Chang et al., JCAP, 2018; ;28(6):379-386; Poldrack et al., JAMA Psychiatry, 2019
3. Treatment Challenge: How Should We Treat Depressed Youth Who Are at High-Risk For BD?

Well...definitely therapy first if possible...then...

- SSRI?
- Buproprion?
- Lamotrigine?
- Lithium?
- Quetiapine?

Angal et al., *Bipolar Disorders*, 2019; 21(4):383-386
3. Evaluation: Mania in SSRI Trials in Youth

- At least 29 published case reports with treatment emergent mania or hypomania when youth exposed to SSRIs
- Symptoms appear any time between two weeks to one year after initial SSRI exposure.
- In 21% of studies, family history of BD.
- **Age effect**: in youth with family history of BD, antidepressant-related adverse events leading to discontinuation higher in younger versus older youth

Goldsmith et al. (2011) *Pediatric Drugs.*

3. Evaluation: Aberrant Amygdala Structure and Function in Pilot Study of High Risk Youth Exposed to Antidepressants

Reduced amygdala volume in high risk youth with antidepressant-related mania-like symptoms ($t= 2.9 \ p=.01$)

Amygdala hyperactivity during emotion processing in high risk youth with with antidepressant-related mania-like symptoms ($p=0.05$, FWE-corrected)

Strawn JR et al. Bipolar Disord. 2014;16(5):523-530
3. (Deeper) Evaluation: Aberrant amygdala surface, prefrontal-limbic connectivity, and physiological arousal

Morphology: Deformed Amygdala

Network Over-connectivity

Physiology: Abnormal Vital Signs

Figure 1. High-risk youth exposed to antidepressants have reduced left amygdala radial distances than high-risk youth naive to antidepressants.

Figure 2. Increased VLPFC-amygdalar connectivity in high-risk youth versus controls.

Figure 3

Figure 5

Kelley et al., *Bipolar Disorders*, 2013
3. Evaluation/Treatment: Risk Factors for developing Arousal Induced by Medication (AIM)

**Drug Factors**
(dose, time/pace of dosing, bioavailability, metabolism, drug-drug interactions)

**Neural Factors**
amygdala volume, prefrontal-limbic connectivity, physiology

**Premorbid Psychiatric Symptoms**
e.g. mania, ADHD, anxiety

**Demographic Factors**
(Age, Sex)

**Genetics**
(CYP P450 polymorphisms)

**FINDINGS:** Aberrant neural structure and function in youth exposed to antidepressants.

**FUTURE DIRECTION:** RCT (antidepressant vs placebo) to examine risk factors and biological mechanisms underlying adverse reactions to antidepressants and better understand the placebo effect.

3. Treatment: Behavioral Treatments Can Reduce Need for Medications

**FINDINGS:** Children admitted to an inpatient psychiatry unit for aggression had high rates of externalizing disorders and high rates of as needed (PRN) and seclusions/restraints/holds (S/R/H). Rates of PRN and S/R/H were significantly lower when there was a behavior modification program in place vs not.

**FUTURE DIRECTIONS:** build a range of treatment outcomes into judging effectiveness including PRN use, and measures of frequency and severity of aggression as well as S/R/H use.
**FINDINGS:** Higher brain sex differentiation scores in 8-21 year old youth in the Philadelphia Neurodevelopmental Cohort correlated with higher levels of externalizing symptoms in males, which also reached GWAS significance.

**FUTURE DIRECTIONS:** Latent variables/classes might be more predictive than single variables; interpretability of data-derived features depends on clear translation of research findings to clinically relevant outcomes.

Phillips et al. *JAACAP*, 2018; Hagan et al., In Preparation
5. Novel Therapeutic Discoveries to Translate Science to Meet Clinical Unmet Needs

**Pilot Study for Spark Digital CBT App for Adolescents with Depression**

**FINDINGS:** Digital app delivering CBT to 30 adolescents over 5 weeks was feasible, well-liked, reduced depressive symptoms, negative affect, and anxiety, and increased positive affect. It was effective both as a stand-alone or adjunct to treatment as usual.

**FUTURE DIRECTIONS:** Real-world and sham-controlled randomized trials in larger cohorts. Nurture strategic partnerships to leverage technology to meet clinical unmet needs.

Lake and Limbix Team, In Preparation
5. Novel Therapeutic Discoveries to Translate Science to Meet Clinical Unmet Needs

Open Label Intermittent Theta Burst Stimulation in Treatment Refractory Adolescent Depression

**FINDINGS:** 10 open sessions of TBS over 2 weeks was feasible, well-tolerated, and had clinical effects in 16-24 year old youth with depression.

**FUTURE DIRECTIONS:** Sham-controlled randomized trials in larger cohort; Nurture strategic partnerships to leverage technology to meet clinical unmet needs.

Dhami et al., *J Affective Disorders*, 2019
Contemporary Drug Development Challenges and Strategies For Youth

CHALLENGES

• Progress in novel therapeutics has been slow in youth.
• Pediatric drug trials include participants from a wide age range and heterogeneous symptoms
• Subjective outcome measures and the placebo effect also contribute to the failure of psychopharmacologic trials

PIPELINE STRATEGIES

• understand safety
• Investigate complementary treatments
• investigate and leverage the placebo response
• repurpose existing treatments for other uses
• collaborative research participation (trial networks)
• trials that study or integrate mechanisms of change during psychotherapy

Grabb and Gobburu, Progress in Neurobiology, 2017; Singh and Cho, In Press
Learning from the past...

• Large placebo effect in pediatric depression trials
  – how do we leverage it?

• Risk benefit ratio is complicated for treatment of bipolar disorders
  – can pragmatic (PCori) and effectiveness trials help us do better treatment matching?

• We don’t have anything good for anything bad
  – Can we develop strategic partnerships to accelerate access and discovery?
  – How do we stimulate the next generation of clinician scientists make the advancements needed?

• We don’t know if we can prevent mood disorders from lasting a lifetime
  – Can well designed mechanistic and longitudinal studies determine whether early neurobehavioral mediators predict progressive and distal mood symptom change and treatment response?
…to create a roadmap for the future

1. Biomarkers for early detection.

2. Pre-emptive interventions for those detected to be at risk or those in pre-symptomatic stages of a mental illness.

3. Better treatments for people living with symptoms that PREDICT and TRACK outcomes.

Insel, A bridge to somewhere, *Translational Psychiatry*, 2011
Key Take-Aways

• Children are not mini-adults
• Youth with or at risk for mood disorders may show early signs of neurobiological dysfunction even before symptom onset.
• Effective and safe preventive, pharmacological, and psychotherapeutic interventions exist.
• More combination, comparative effectiveness, and maintenance trials designed to examine longer-term outcomes are needed.
Acknowledging our Village

Thanks to all patients, research participants, and families who inspire our work!

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