Treatment Advances in Pediatric Anxiety Disorders

Moira A. Rynn
Soon to be Dukie
## Disclosure

<table>
<thead>
<tr>
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Disclosure

- Most of the medications discussed in this presentation do not have FDA approval in the pediatric population.
- This will be highlighted throughout the presentation.
Drawing of a heart with the words "me mom" and "At School."
In Her Own Words...

“Mom, I need you to be there for me. I am getting pressure in the classroom. The work is making me nervous. Even with the easy pluses - 1 + 1 = what? I say, “I can’t do this.” I want to run out of the classroom. The work makes me nervous. My teacher has to slow down. She’s saying stuff too fast and I can’t catch up.”

- 8 year old girl
Outline

• Clinical Characteristics

• Acute and Long-term Treatment
  ➢ Triad Anxiety Disorders
  ➢ Obsessive Compulsive Disorder

• Treatment Development
Main Milestones of Childhood

• **Language**: speaking, communicating, understanding and reading non-verbal cues

• **Cognitive**: ability to reason, think, learn, problem-solve

• **Social**: develop and keep meaningful relationships; and respond to others’ feelings
Anxiety: Developmental Progression

Common Fears
- Preschool: Imaginary Objects/situations
- Grade School: Health/harm, Scrutiny/Competence
- Adolescence: Social adequacy, Performance

Anxiety Disorders
- Preschool: Phobic objects/situations, SAD
- Grade School: OCD, GAD
- Adolescence: Social anxiety, Panic Disorder
When Does Anxiety Become Problematic?

- Avoidance/Disruption
- Interferes with functioning (not facing developmental challenges)
- Distress
- Duration
Cumulative Lifetime Prevalence of Major Classes of DSM-IV Diagnoses

NCS-A, N=10,123

Merikangas et al., 2010
## Prevalence Estimates for Anxiety Disorders among US Adolescents

<table>
<thead>
<tr>
<th>DMS-IV Disorder</th>
<th>Lifetime Prevalence by Sex %</th>
<th>Lifetime Prevalence by Age %</th>
<th>Lifetime Prevalence Total %</th>
<th>Lifetime Prevalence-Severe Impairment %</th>
<th>12-Month Prevalence %</th>
<th>1-Month Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>13-14 y</td>
<td>15-16 y</td>
<td>17-18 y</td>
<td></td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>3.4</td>
<td>1.4</td>
<td>2.5</td>
<td>2.5</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>3.0</td>
<td>1.5</td>
<td>1.0</td>
<td>2.8</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>11.2</td>
<td>7.0</td>
<td>7.7</td>
<td>9.7</td>
<td>10.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>22.1</td>
<td>16.7</td>
<td>21.6</td>
<td>18.3</td>
<td>17.7</td>
<td>19.3</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>2.6</td>
<td>2.0</td>
<td>1.8</td>
<td>2.3</td>
<td>3.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Posttraumatic Stress Disorder</td>
<td>8.0</td>
<td>2.3</td>
<td>3.7</td>
<td>5.1</td>
<td>7.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Separation Anxiety Disorder</td>
<td>9.0</td>
<td>6.3</td>
<td>7.8</td>
<td>8.0</td>
<td>6.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>38.0</td>
<td>26.1</td>
<td>31.4</td>
<td>32.1</td>
<td>32.3</td>
<td>31.9</td>
</tr>
</tbody>
</table>

*Beedso-Baum & Knappe, 2012; Merikangas et al., 2011; Kessler et al., 2012*
Childhood Anxiety Disorders

Greater risk for:

- Adult depression and anxiety
- Substance abuse/dependence
- Suicidal behaviors

1 Pine et al., 1998
2 Compton et al., 2007
3 Woodward et al., 2001
Genetics of Anxiety Disorders

- Moderate level of familial aggregation (OR=4-6)
- Proportion of the phenotypic variability explained by genetic factors ranged from 30 to 50%
- Similar to depression but less than disruptive behaviors & bipolar disorder

Hettema et al., 2001
Environment

- Parenting style (i.e. overprotective/over controlling style)
- Stressful life events both acute and chronic
- Modeling observed behaviors
- May be partially mediated by genetic influences
Pediatric Anxiety Disorders

• **Generalized Anxiety Disorder (GAD):** excessive anxiety and worry about multiple areas school, social activities, health

• **Separation Anxiety Disorder (SAD):** developmentally inappropriate and excessive anxiety concerning separation from primary care givers

• **Social Anxiety Disorder (SoP):** persistent fear of social performance situations or to scrutiny by others

• **Obsessive Compulsive Disorder (OCD):** repetitive behavior or thoughts that neutralize anxiety
Clinical Characteristics of Anxious Youth

### Table 3
Anxiety disorders diagnostic summary.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current diagnosis, n (%)</th>
<th>ADIS CSR rating, M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD</td>
<td>16 (3.29)</td>
<td>SAD 5.47 (1.41)</td>
</tr>
<tr>
<td>SP</td>
<td>56 (11.50)</td>
<td>SP 5.42 (0.92)</td>
</tr>
<tr>
<td>GAD</td>
<td>33 (6.78)</td>
<td>GAD 5.30 (0.77)</td>
</tr>
<tr>
<td>SAD &amp; SP</td>
<td>33 (6.78)</td>
<td>SAD 5.27 (1.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 5.15 (1.00)</td>
</tr>
<tr>
<td>SAD &amp; GAD</td>
<td>39 (8.01)</td>
<td>SAD 5.18 (0.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD 5.56 (0.91)</td>
</tr>
<tr>
<td>SP &amp; GAD</td>
<td>135 (27.72)</td>
<td>SP 5.57 (1.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD 5.50 (0.91)</td>
</tr>
<tr>
<td>SAD &amp; SP &amp; GAD</td>
<td>175 (35.93)</td>
<td>SAD 5.35 (0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP 5.29 (1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD 5.43 (0.98)</td>
</tr>
</tbody>
</table>

*Note: SP, social phobia; GAD, generalized anxiety disorder; SAD, separation anxiety disorder; ADIS CSR, Anxiety Disorders Interview Schedule Clinician Severity Rating.*
## School Refusal, Over Anxious, and Separation Anxiety Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis (Age Range)</th>
<th>Duration</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gittelman-Klein &amp; Klein (1971)</td>
<td>School Phobia (6-14 yrs)</td>
<td>6 wks</td>
<td>Imipramine</td>
<td>35</td>
<td>100-200</td>
<td>Imipramine &gt; PBO</td>
</tr>
<tr>
<td>Berney et al., 1981</td>
<td>School refusal (9-14 yrs)</td>
<td>12 wks</td>
<td>Clomipramine</td>
<td>51</td>
<td>40-75</td>
<td>Clomipramine = PBO</td>
</tr>
<tr>
<td>Klein et al., 1992</td>
<td>SAD (6-15 yrs)</td>
<td>6 wks</td>
<td>Imipramine</td>
<td>21</td>
<td>75-275</td>
<td>Imipramine = PBO</td>
</tr>
<tr>
<td>Bernstein, et al., 1990</td>
<td>School refusal (7-18 yrs)</td>
<td>8 wks</td>
<td>Alprazolam</td>
<td>24</td>
<td>0.75-275</td>
<td>Alprazolam = Imipramine</td>
</tr>
<tr>
<td>Simeon et al., 1992</td>
<td>Overanxious or avoidant (8-17 yrs)</td>
<td>4 wks</td>
<td>Alprazolam</td>
<td>30</td>
<td>0.5-3.5</td>
<td>Alprazolam = PBO</td>
</tr>
<tr>
<td>Graae et al., 1994</td>
<td>SAD (7-13 yrs)</td>
<td>8 wks</td>
<td>Clonazepam</td>
<td>15</td>
<td>0.5-2.0</td>
<td>Clonazepam = PBO</td>
</tr>
</tbody>
</table>
# Triad Anxiety Disorders & Social Phobia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis (Age Range)</th>
<th>Duration</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUPP Anxiety Study Group: Walkup, et al., 2001</td>
<td>GAD; SoP; SAD (6-17 yrs)</td>
<td>8 wks</td>
<td>Fluvoxamine</td>
<td>128</td>
<td>50-300</td>
<td>Fluvoxamine &gt; PBO</td>
</tr>
<tr>
<td>Birmaher et al., 2003</td>
<td>GAD; SoP; SAD (7-17 yrs)</td>
<td>12 wks</td>
<td>Fluoxetine</td>
<td>74</td>
<td>20</td>
<td>Fluoxetine &gt; PBO</td>
</tr>
<tr>
<td>Wagner et al., 2004</td>
<td>SoP (8-17 yrs)</td>
<td>16 wks</td>
<td>Paroxetine</td>
<td>322</td>
<td>10-50</td>
<td>Paroxetine &gt; PBO</td>
</tr>
<tr>
<td>March et al., 2007</td>
<td>SoP (8-17 yrs)</td>
<td>16 wks</td>
<td>Venlafaxine ER</td>
<td>293</td>
<td>37.5-225</td>
<td>Venlafaxine ER &gt; PBO</td>
</tr>
</tbody>
</table>

**Outcome**

- CGI/I <4: 76%
- CGI/I ≤2: 61%
- CGI/I = 1: 47.8% or ≥70% reduction on SAS: 47.2%
- CGI/1 = 1/2: 56%
## Generalized Anxiety Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis (Age Range)</th>
<th>Duration</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
<th>% Meeting Remission or Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rynn et al., 2001</td>
<td>GAD (5-17 yrs)</td>
<td>9 wks</td>
<td>Sertraline</td>
<td>21</td>
<td>50</td>
<td>Sertraline &gt; PBO</td>
<td>CGI/I = 1: 18%</td>
</tr>
<tr>
<td>Rynn, et al. (in prep)</td>
<td>GAD (5-17 yrs)</td>
<td>16 wks</td>
<td>Sertraline</td>
<td>51</td>
<td>50 -200</td>
<td>Sertraline &gt; PBO</td>
<td>HAMA≤7: 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months later: 64%</td>
</tr>
<tr>
<td>Rynn et al., 2007</td>
<td>GAD (6-17 yrs)</td>
<td>8 wks</td>
<td>Venlafaxine ER</td>
<td>313</td>
<td>37.5 -225</td>
<td>Venlafaxine ER &gt; PBO</td>
<td>CGI/I &lt;3: 69% and 48%</td>
</tr>
</tbody>
</table>
# Obsessive Compulsive Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration Weeks (Age Range)</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
<th>% Remission or Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeVeaugh-Geiss et al., 1992</td>
<td>8 (10-17 yrs)</td>
<td>Clomipramine</td>
<td>126</td>
<td>75-200</td>
<td>Clomipramine &gt; PBO</td>
<td>CGI-I &lt; 2: 60%</td>
</tr>
<tr>
<td>March et al., 1998</td>
<td>12 (6-17 yrs)</td>
<td>Sertraline</td>
<td>187</td>
<td>25-200</td>
<td>Sertraline &gt; PBO</td>
<td>25% &gt; in CY-BOCS: 53%</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>or CGI-I score of &lt; 2 : 42%</td>
</tr>
<tr>
<td>Riddle et al., 2001</td>
<td>10 (8-17 yrs)</td>
<td>Fluvoxamine</td>
<td>120</td>
<td>50-200</td>
<td>Fluvoxamine &gt; PBO</td>
<td>25% &gt; CYBOCS : 42.1%</td>
</tr>
<tr>
<td>Geller et al., 2001</td>
<td>13 (7-17 yrs)</td>
<td>Fluoxetine</td>
<td>103</td>
<td>20-60</td>
<td>Fluoxetine &gt; PBO</td>
<td>40% &gt; CYBOCS: 49%</td>
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</table>
Pooled Analysis CBT Modality for Childhood Anxiety

<table>
<thead>
<tr>
<th>CBT Modality</th>
<th>% Remission Dx</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual-CBT</td>
<td></td>
<td>170</td>
</tr>
<tr>
<td>Group-CBT</td>
<td></td>
<td>162</td>
</tr>
<tr>
<td>Family-CBT</td>
<td></td>
<td>121</td>
</tr>
</tbody>
</table>
Child Anxiety Multimodal Study CAMS: N=488, 7-17 Years Old for 12 Weeks

COMB > CBT = Sertraline > PBO

CGI-I 1 and 2 (ITT, LOCF)

Walkup et al., 2008
## CAMS Remission

### Response and Remission Rates of CAMS Study Subjects at Week 12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No AD remission</th>
<th>CGI-I remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMB (n = 140)</td>
<td>68.3 [58.7, 76.5]</td>
<td>45.6 [36.2, 55.3]</td>
</tr>
<tr>
<td>SRT (n = 133)</td>
<td>45.9 &lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.9 [25.9, 42.9]</td>
</tr>
<tr>
<td>CBT (n = 139)</td>
<td>46.2 [37.9, 54.8]</td>
<td>20.4 [14.4, 28.0]</td>
</tr>
<tr>
<td>PBO (n = 76)</td>
<td>23.7 [15.5, 34.6]</td>
<td>15.0 [3.4, 46.4]</td>
</tr>
</tbody>
</table>

<sup>b</sup> No variability in this estimate across imputations, thus confidence interval not applicable.
CAMS Remission

Remission Rates and Social Phobia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% no AD</th>
<th>CGI-I remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No SOP</td>
<td>SOP</td>
</tr>
<tr>
<td>COMB</td>
<td>88.0</td>
<td>64.0</td>
</tr>
<tr>
<td>SRT</td>
<td>52.0</td>
<td>44.4</td>
</tr>
<tr>
<td>CBT</td>
<td>72.0</td>
<td>40.6</td>
</tr>
<tr>
<td>PBO</td>
<td>46.1</td>
<td>19.1</td>
</tr>
</tbody>
</table>
Predictors for Best Response

Baseline Variables that Predict Remission (p<0.05):

• Lower baseline anxiety severity*
• Absence of social phobia*
• Nonminority race/ethnicity*
• Younger age
• Absence of a comorbid internalized disorder (e.g. depression, anxiety)

*Denotes variables that, when combined into a single model, still significantly predicted remission based on ADIS-C/P
Pediatric OCD Study (POTS)

COMB > CBT = Sertraline > PBO

Excellent Responder (YBOCS ≤ 10)

COMB = CBT > Sertraline = PBO

Percent Response

PBO SER CBT COMB

3 21 39 54
Long-term Treatment
Triad Anxiety Follow-up Studies

Fluoxetine 1 Year Follow-up

- 56 of 74 subjects completed the 1 year F/U
- 42 received medications and 10 did not
- FLX/FLX continued significant improvement (CGI-S, p=0.047, CGI-I, p=.01)
- PBO/FLX =greatest improvement
- PBO/no medication = least improvement

Fluvoxamine 6 Month Follow-up

- 94% (33 of 35) subjects who initially responded and continued on fluvoxamine remained well
- 71% (10 of 14) of fluvoxamine non-responders responded to fluoxetine
- 56% (27 of 48) of placebo non-responders responded to fluvoxamine

Clark et al., 2005
Walkup, J. et al. (2002)
CAMS Response: 12 to 36 weeks
CAM Extended Long-term Study (CAMELS)

Ginsburg et al., 2014
CAMELS Naturalistic Follow-up

- N = 288; 11-26 years; M = 16.8
- Responders vs non-responders.
- Remission = absence of all study anxiety disorders
- 46.5% were in remission 6 years after randomization. Acute treatment responders were more likely to be in remission
- The following predicted remission:
  - Male, family functioning and Higher SES
Adverse Events
Safety Concerns

- Antidepressant treatment leads to more frequent adverse events as compared to placebo
- Physical development and growth
- Activation and psychiatry symptoms greater in children
- Medication withdrawal symptoms
- Monitoring of suicidal ideation and behaviors
First Line Treatments

- Monotherapy:
  - CBT
  - SRI & SNRI
- Combination Treatment
- Family/Environment
- Maximize Treatment

But approximately 30 to 50% do not achieve this response:
Antipsychotic Use for Sedative Properties

Percent of Anxiety Disorder Visits

96-'97 98-'99 00-'01 02-'03 04-'05 06-07

Antipsychotic Prescribing Rate

Comer et al., 2011
EX/RP arm had significantly greater reduction in Y-BOCS scores at wk 8 versus Risperidone or PBO arms.

Simpson et al., 2013
The Pediatric OCD Treatment Study II

Treatment Arms N=124; 7-17 years

- Medication Management (MM)
- MM + CBT
- MM + Instructions on CBT

Franklin et al., 2011
Response Status:
MM + CBT = 68.6%
MM + instruction = 34.0%
MM only = 30.0%
Anxiety Disorders Treatment Development

- Children diagnosed with GAD and fMRI results studies
  - Greater pretreatment amygdala activation associated with better response to both CBT and pharmacological treatments.\(^1\)
  - Increased right VLPFC activation relative to controls in the medication \((t(15) = 3.01, p < 0.01)\) and CBT \((t(15) = 3.22, p < 0.01)\) groups following treatment. \(^2\)

\(^1\)McClure et al., 2007
\(^2\)Maslowsky et al., 2010
Anxiety Disorders Treatment Development

- Children and adolescents with GAD underwent fMRI scanning before and after treatment with either an SRI medication (Fluoxetine) or CBT.

- Found negative association between activation in the left amygdala in an afraid–fear vs afraid–happy contrast task and post-treatment CGI-I score ($\rho=-0.65$, $p<0.02$).

- Suggests that SRIs and CBT treatment are most effective for the youth with amplified amygdala reactivity.

McClure et al., 2007
- Associations between OCD and genes related to the glutamate system

- Disrupting glutamatergic transmission in corticostriatal circuits (i.e. deletion of the synaptic protein Sapap3 or the transmembrane protein Slitrk5) leads to OCD-like behaviors in mice.

- Medications that modulate glutamatergic transmission (e.g., riluzole in adults) show preliminary data effect of in some patients.

Pittenger et al., 2011
• Human MRS studies have linked striatal glutamatergic abnormalities to OCD symptoms.

• Rosenberg et al (2000) examined the caudate nucleus in 11 psychotropic drug-naïve youth with OCD.

• Compared to matched controls, patients had increased glutamatergic compounds that decreased with successful paroxetine treatment.

• Decrease correlated with a decrease in OCD severity measured by the CYBOCS (r=0.80, p=.006).
Riluzole (RIL)

Riluzole is a potent antiglutamatergic agent.

- FDA approved for amyotrophic lateral sclerosis
- Increased extra-synaptic glutamate reuptake glial cells
- Stimulation of growth factor synthesis, BDNF
- Promotion of neurogenesis

Side effects: nausea and sedation
Rare: hepatotoxicity and in children reports of pancreatitis

Mathew et al., 2008; Coric et al., 2005
Placebo-Controlled Trial of Add-on RIL for the Treatment of OCD

• RIL vs PBO for 12 weeks
• N= 60 treatment-resistant children & adolescents with OCD (17 subjects also had concomitant ASD)
• Aged 7-17 years; M=14.5; Mean CY-BOCS at baseline 28.2
• Outcome measures: CY-BOCS, CGI-S and CGAS
• Dose range of 10 mg to the maximum of 100 mg/day
There was no effect of study group on change in the CY-BOCS total scores between baseline and week 12; average improvement in the RIL group (21± 18%, 5.52± 4.40 points) very similar to that observed in PBO (19± 15%; 5.83± 4.86 points; F. 0.04, p. 0.84).

Grant et al., 2014
Enhancement of Psychotherapy with D-cycloserine (DCS)

- N-methyl-D-aspartate (NMDA) is a glutamate receptor complex involved with synaptic plasticity and memory
- DCS is a partial agonist of the glycine site of the NMDAR
- Enhancement of NMDA receptor activity may enhance extinction of previously conditioned fear

Kessler & Mayberg, 2007
D-Cycloserine – Pediatric OCD

- CBT+ D-Cycloserine (25-45kg=25 mg/day and 46-90 kg=50 mg/day) = CBT+PBO; (N=30) for 8 wks

  - Primary comparison was not statistically significantly different.
  - Treatment group showed small to moderate treatment effects (d = .31-.47) on primary outcome measures (C-YBOS & CGI measures).

Storch et al., 2010
Minocycline: “Repurposing Approach”

- 2nd generation tetracycline; high CNS penetration; & FDA approved for children 8 & older
- Modulates glutamate, anti-oxidant & anti-inflammatory properties
- Human clinical trials of neurological diseases minocycline may have neuroprotective effects.
- Animal studies suggest minocycline inhibits glutamate-induced cell death, increases glial glutamate transport & inhibits microglial proliferation.
Open Pilot Data

Pediatric Study

- N = 6 (ages 12 - 19) diagnosed with OCD with CYBOCS score ≥16 (mean=24) & 12 weeks of adequate SSRI dose.
- Stayed on SSRI with the addition of minocycline (dosing from 75 mg to 100 mg bid).
- 4 out of 6 met response defined as a CYBOCS reduction of at least 30%.
  *(unpublished data)*

Adult Study

- N= 9 treatment-resistant adults with OCD & adequate SSRI trial
- Continued SSRI with minocycline 200 mg a day for 12 weeks.
- 2 of 9 responded ≥ 40% YBOCS reduction & had OCD onset in childhood

*Rodriguez CI et al, 2011*
Medication Strategies Targeting Brain Mechanisms in Pediatric OCD

- Hypothesis 1: When added to SSRI medication, minocycline will be superior to PBO in reducing OCD symptoms.

- Hypothesis 2: Adding minocycline (versus placebo) to an SSRI will reduce glutamate levels in the head of caudate.

- Hypothesis 3: Reduction in glutamate levels will be associated with reduction in OCD severity.

PIs: Moira Rynn, M.D., Helen Blair Simpson, M.D., Ph.D., Larry Kegeles, M.D., Dikoma Shungu, Ph.D. (Weill Cornell Medical Center) NIMH #1R34MH095502-01
Screening
- Recruiting 45 youth ages 8-20 diagnosed with OCD
- Demonstrate partial response to SRI treatment; stable dose for 12 weeks

Pre-treatment
- Eligible participants will receive a pre-treatment MRS scan to measure striatal glutamate levels prior to randomization

Treatment Phase
- Participants randomized to receive minocycline or placebo for 12 weeks
- Randomization 2:1 and stratified by age

Post-treatment
- Participants will compete a post-treatment MRS scan upon study completion or at time of discontinuation

Follow-up
- Three months of no-cost follow-up care will be offered
- Follow-up assessment administered at end of 3 months
Abnormal Functioning of Control and Reward Circuits in Unmedicated Adults with OCD

Hyperactivation of a right hemisphere frontostriatal circuit during the engagement of control on a conflict task.

Marsh et al, Biological Psychiatry, April 2013

Abnormal recruitment of mesolimbic and ventral striatal circuitry during reward-based learning.

Untreated OCD Diagnosed with OCD:
How does these overlapping circuits function earlier in development?

• **Aim 1**: To use multimodal imaging to assess the function, connectivity, and organization of control and reward circuits in untreated youth with OCD.

• **Aim 2**: To determine how these circuits change following significant reduction in symptoms.

• Unmedicated pediatric OCD (6-17 years) and matched healthy control (HC) participants are scanned and assessed at baseline.

• OCD participants are scanned again following 16-20 weeks of CBT.

• Healthy participants are re-scanned within the same time frame.

• Circuit-based changes in the OCD group are compared to non-specific changes in HC group.

R21MH101441 (Marsh & Rynn)
Conclusions

- There are effective first line treatments & limited data to inform second line approaches.
- There is still a significant number of children and adolescents that do not respond.
- Treatment response differences most likely are due to differences in underlying anxiety pathophysiology & will require developmentally informed investigation.
- Longitudinal studies of pediatric anxiety samples with multilevel of analysis will be important to understand brain-behavior anxiety interface.
Thank you!

CU Pediatric Anxiety & Mood Research Clinic

Our Team/ Collaborators

- Blair Simpson, M.D., Ph.D
  Professor of Clinical Psychiatry, CUMC
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- Anthony Puliafico, Ph.D.
  Co-director of Psychology Pediatric Anxiety and Mood Research Clinic
- Dikoma Shungu, Ph.D.
  Professor of Physics in Radiology, Radiology, Weill Cornell Medical College
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  Associate Professor of Clinical Psychology (in Radiology), CUMC
- Rachel Marsh, Ph.D.
  Associate Professor of Clinical Psychology (in Psychiatry), CUMC
- Anne Marie Albano, Ph.D., ABPP
  Associate Professor of Clinical Psychology (in Psychiatry), CUMC
Obsessive-Compulsive Disorder

• OCD often begins in childhood and adolescence.

• Neuroimaging data suggest anatomical and functional disturbances in cortico-striato-thalamocortical (CSTC) circuits in OCD, but most studies include adult patients.

• Our previous fMRI findings from adults with OCD suggest functional deficits in the fronto-striatal circuits that support control and reward processes (Marsh et al, 2013; 2015).

• Unknown is how these circuits change following the remission of OCD symptoms, particularly in pediatric patients.
Cortico-Striato-Thalamocortical (CSTC) Circuits

Dorsal

Ventral

Prefrontal Cortex

SMA

Self-Regulatory Capacities

ACC

DLPFC

OFC

Reward Processing

Habit (S-R) Learning

Striatum

Caudate nucleus

Putamen

Globus pallidus

Subthalamic nucleus

Substantia nigra

NEW YORK STATE OF OPPORTUNITY.

New York State Psychiatric Institute

COLUMBIA UNIVERSITY
DEPARTMENT OF PSYCHIATRY
College of Physicians and Surgeons

Division of Child & Adolescent Psychiatry
The Simon Task
Prior Research on Pediatric OCD

- Some previous studies have assessed changes in the structure (Benazon, 2003; Rosenberg, 2000; Huyser, 2013) and function (Huyser, 2010; 2011) of regions within CSTC circuits following CBT in pediatric OCD.

- No significant changes in the structure of subcortical regions, but grey matter in OFC increases with changes in symptom severity (Huyser, 2013).

- Increased activation of ACC and dorsomedial PFC on a Flanker task following CBT (Huyser et al, 2011).
# Pediatric OCD Study

<table>
<thead>
<tr>
<th></th>
<th>OCD, Baseline (n = 23)</th>
<th>OCD, F/U (n = 18)</th>
<th>HC, Baseline (n = 12)</th>
<th>HC, F/U (n = 6)</th>
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<tr>
<td><strong>Age (years)</strong></td>
<td>12.39 (3.23)</td>
<td>11.94 (3.08)</td>
<td>9.25 (2.67)</td>
<td>10.43 (2.70)</td>
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<td><strong>Sex</strong></td>
<td>10 F, 13 M</td>
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<td>4 F, 8 M</td>
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<tr>
<td><strong>WASI Full-Scale IQ</strong></td>
<td>106.70 (16.84)</td>
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<td>110.58 (10.57)</td>
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<td><strong>CYBOCS</strong></td>
<td>24.00 (5.32)</td>
<td>15.44 (7.85)</td>
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<td><strong>CGI-S</strong></td>
<td>Severity: 4.65 (0.71)</td>
<td>Severity: 3.39 (1.42)</td>
<td>Global Improvement: 2.56 (0.92)</td>
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</table>
Pediatric OCD Study

- **Diagnostic Assessments:**
  - Anxiety Disorders Interview Schedule for Children for DSM-IV (ADIS-C/P Revised)
  - Family History Screen (FHS)
  - The Tanner Scale
  - Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS)
  - Hamilton Depression Scale (HAM-D, 17-item)
  - Columbia Suicide-Severity Rating Scale (C-SSRS):

- **Self-Report Questionnaires:**
  - OCD onset Form
  - Child Obsessive-Compulsive Impact Scale-Revised (COIS-R)
  - Family Accommodation Scale (FAS)
  - Isolated Tics/Tic Disorder Assessment
  - Sensitivity to Punishment and Sensitivity to Reward Questionnaire-Children (SPSRQ-C)
  - Intolerance of Uncertainty Scale for Children (IUSC)
  - Barratt Impulsivity Scale (BIS) Brief
  - The Short Grit Scale

- **Neuropsychological Testing:**
  - Wechsler Abbreviated Scale of Intelligence (WASI-II)
  - The PhenX Toolkit Hand Dominance Measure
  - Continuous Performance Task
  - Reinforcement Learning Go/no-go task
  - Decision-Making Tasks
  - The Weather Prediction Task
Image Acquisition

- MRI scans acquired on a GE Signa 3 Tesla whole-body scanner with a Nova 32-channel head coil.

- BRAVO SAG3D images: TI=450ms, TR=7.86ms, TE=3.1ms, nex=0.75, matrix=300 x 300, FOV=24.0, flip=12°, 220 slices (0.8mm), voxel resolution=0.4688 x 0.4688 x 0.8 mm.

- T2CUBE SAG3D images (for segmentation): TR=2500ms, TE=95.202ms, nex=1.0, matrix=320 x 320, FOV=25.6, flip=90°, 220 slices (0.8mm), voxel res.= 0.8 x 0.8 x 0.8 mm).

- High Order Shimming (to improve image quality and homogeneity): TR=1558.0ms, TE=7.0ms, nex=1.0, matrix=64 x A/P, FOV=24.0, flip=60°, 32 slices (5.8mm), voxel res.= 5.8 x 5.8 x 5.8 mm.

- B0 field maps (distortion correction) and TOPUPs.

- Whole-brain EPI (task and resting state) acquired with a multi-band acceleration factor 6: TR =850 ms, TE =25.0ms, flip angle =60°, BW =5208.33 Hz/Px, matrix =96 x 96, FOV =19.2, 11 slices (2.0 mm isotropic voxels).
Preliminary Findings – Simon Task at Baseline

- At baseline, activation of left MFG in response to incongruent vs. congruent stimuli was greater in HC compared to OCD participants ($p=0.005; k=70$).

- OCD participants did not activate CSTC circuits during the resolution of cognitive conflict.
At follow-up, after CBT, increased activation was detected in bilateral fronto-parietal regions:

- left superior and bilateral inferior frontal and precentral gyri
- bilateral parietal cortices

OCD participants began to engage these circuits with the reduction of symptoms.
Preliminary Findings – CPT II

Baseline

• OCD participants made more commission errors than HCs: $M_{\text{OCD}}=55.3; M_{\text{HC}}=47.7; t_{39}=2.98, p < .01$

• OCD participants had more difficulty discerning target from non-targets (detectability): $M_{\text{OCD}}=54.7; M_{\text{HC}}=49.8; t_{39}=2.06, p < .05$

• Hyper-vigilance, performance monitoring?

After CBT

• No significant group differences (Commissions: $t_{19}=0.91, p=.38$; Detectability: $t_{19}=1.39, p=.18$)

Commission errors and detectability positively associated with CGI and CYBOCS scores at baseline but not after CBT, further reflecting changes in attentional processes.
Summary

• Our baseline findings of reduced activation of frontal cortices contrasts with our previous findings from unmedicated adults with OCD (Marsh et al, 2013), perhaps due to developmental processes.

• Following CBT, activation of frontal regions increased in children and adolescents with OCD, consistent with findings from a previous pediatric OCD study using a Flanker task (Huyser, 2013).

• Increased activation of fronto-parietal cortices is consistent with their better performance on the CPT following treatment.

• Fronto-parietal control and attentional circuits might be a target for treatment response in pediatric OCD.
Summary

• Future fMRI analyses will test the significance of diagnosis x time interactions on conflict-related activations (once we recruit and scan more healthy children at baseline and F/U).

• Future analyses will also focus on ventral reward and ‘habit learning’ circuits, using the VR task, and changes in the structural and functional connectivity of both dorsal and ventral CSTC circuits in pediatric OCD.

• The resolution of abnormalities in either of these circuits (dorsal or ventral) with symptoms would support using the circuits (and our brain measures) as targets for the development of novel treatments and prevention techniques.
Thank you

The Cognitive Development and Neuroimaging Laboratory

- Mihaela Stefan
- Marilyn Cyr
- Xiaofu He
- Katie Davis
- Mirjana Domakonda
- Emily Steinberg
- Martine Fontaine
- Amy Margolis
- Sophie Gindea Schiff

The Pediatric Anxiety and Mood Disorders Clinic at the NYSPI and CUMC

- Moira Rynn
- Paula Yanes-Lukin
- Tony Puliafico
- Pablo Goldberg
- Dylan Braun
- Psychology interns

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** All the families who participate in our research studies

The MRI Unit at the NYSPI
## Disclosures – Moira Rynn

<table>
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<th>Research Funding</th>
<th>Advisor/Consultant</th>
<th>Employee</th>
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