Task Control Networks in Pediatric Anxiety and Obsessive-Compulsive Disorders

Targets for Neuroscience-Guided Intervention?

Kate D. Fitzgerald, M.D., M.S.
Associate Professor
Child and Adolescent Psychiatry
University of Michigan Medical School
Anxiety: normal to disorder

**Typical ➔ Atypical**

<table>
<thead>
<tr>
<th>Age</th>
<th>Normative Development</th>
<th>Anxiety Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-school</td>
<td>imaginary, objects/situations</td>
<td>specific phobias, separation anxiety</td>
</tr>
<tr>
<td>Grade School</td>
<td>health/harm, competence</td>
<td>GAD, OCD</td>
</tr>
<tr>
<td>Adolescence</td>
<td>social adequacy and performance</td>
<td>GAD, Social Phobia, Panic</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age 3 Assessment</th>
<th>Age 6 Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Any diagnosis(^a)</td>
<td>127</td>
<td>27.5</td>
</tr>
<tr>
<td>Any emotional disorder</td>
<td>91</td>
<td>19.7</td>
</tr>
<tr>
<td>Any depression(^b)</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>Major depression or dysthymia</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Depression not otherwise specified</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>89</td>
<td>19.3</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>44</td>
<td>9.5</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>26</td>
<td>5.6</td>
</tr>
<tr>
<td>Social phobia</td>
<td>17</td>
<td>3.7</td>
</tr>
<tr>
<td>Generalized anxiety disorder(^b)</td>
<td>18</td>
<td>3.9</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>15</td>
<td>3.2</td>
</tr>
<tr>
<td>Selective mutism</td>
<td>7</td>
<td>1.5</td>
</tr>
<tr>
<td>Any behavioral disorder</td>
<td>51</td>
<td>11.0</td>
</tr>
<tr>
<td>ADHD(^b)</td>
<td>11</td>
<td>2.4</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>47</td>
<td>10.2</td>
</tr>
<tr>
<td>Two or more diagnoses</td>
<td>42</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Buffered et al, 2012
Who do these children grow up to be?

1 in 3 AD by adolescence!

Merikangas et al, 2010
Early internalizing occur along a continuum that predicts risk for later internalizing

N = 248 child at familial risk
Baseline: 5.0 ± 2.7 years
Follow up: 10.6 ± 3.1

*CBCL Internalizing predicts later ADs, but weak predictor (low sensitivity)

*Identify better, mechanistically based predictor that might also serve as target?

Petty et al, 2009
Electrophysiologic response to errors: Increased ERN in Anxiety/OCD

Gehring et al, 2000

Anterior Cingulate Cortex (ACC)

Hanna et al, 2011

Carrasco et al, 2013
ERN in Anxiety/OCD: Functional Significance?

- **Affective response to errors**
  - Worse than expected outcome
  - Large ERN = affective hypersensitivity to errors?
  - A bad thing? (drive OCD)
    - Intrusive sense that “something is wrong” characterizes OCD symptoms

- **Errors/Interference**
  - Mismatch between actual and intended response
  - Large ERN = make up for inefficiency elsewhere in error-processing network?
  - A good thing? (compensate for OCD)
    - Does ERN overcome deficient capacity to adjust behavior? (move on from anxious thoughts appropriately identified as “thinking errors”)
fMRI of Error Response in adult OCD
Does spatial localization clarify function?

- OCD > HC (Errors) (Fitzgerald et al, 2005)
- OCD > HC (Errors & Interference) (Ursu et al, 2003)
- Affective hypersensitivity? (etiologic)
- Behavioral adaptation? (compensatory)

Bush et al, 2000
Fitzgerald et al, 2005
Kerns et al, 2004
Task Control Networks

Salience

dACC/ pMFC

Central Executive

Default Mode

Salience Network in adult OCD: Hyperactivity of aI, vmPFC

Stern et al, 2011
Task control networks in pediatric OC, anxiety disorders

**Salience + Default Mode Networks**

Hyperactive dACC (interference, errors)

Fitzgerald et al, 2010

**Central Executive Network**

Hypoactive dIPFC (errors)

Fitzgerald et al, 2013
Meta-analysis: Task Control Networks in OCD

**Errors:** ↑ Salience Network

**Inhibitory control:** *↓* Salience, Central Executive Networks

*impaired inhibitory control performance

Norman et al, under revision
Goal interfering OCD obsession or compulsion

Increased anxiety (errors are aversive)

Error response!

Impaired behavioral adaptation (e.g., control over obsessions and compulsions) despite corrective feedback

- Hyperactive error responses may reflect compensatory effort at reactive control.

Norman et al., under revision
Hyperactive Salience Network: Compensatory?

ERRORS

INTERFERENCE
Manipulating Task Control Networks

CBT as Probe
OCD: Task control network function & CBT outcome

- Randomized clinical trial: CBT vs. Stress Management Training (SMT)
- 60 adolescent (13-17 yrs), 60 adult (25 –40 yrs) OCD
  - Half medicated, half unmedicated
- 30 adolescent, 30 adult HC
- Pre- to post- therapy imaging: fMRI, resting state, DTI
OCD: CBT Effect

Average (C)Y-BOCS Change Over the Course of CBT vs. SMT Treatment

Visits

Screen Session 1 Session 6 Session 12

Average (C)Y-BOCS Total Score

CBT
SMT
OCD: Better CBT outcome predicted by TCN function

ERRORS: ↓ Salience network (left aI); pre-CBT, n = 32

INTERFERENCE: ↑ Salience, Central executive network (right aI/IFG, left dIPFC, dACC); pre-CBT, n = 32
Anxiety: Task control network function & CBT outcome

- Randomized clinical trial: CBT vs. Relaxation Mentorship Training (RMT)
- 280 youth (7-18 years)
  - 210 Anxious (SAD, SoPho, GAD, etc): 2/3 CBT, 1/3 RMT
  - 70 HC
- Pre- to post- therapy imaging: fMRI, resting state, DTI

![Diagram of MSIT experiment](image-url)
Anxiety: Task Control Network Activations to MSIT

Regions of interest: Interference-processing

Salience Network

dACC

Central Executive Network

Superior Parietal
dlPFC

pfwe < .001 unc
Anxiety: TCN as Predictor of CBT response

Interference: ↑ pre-CBT SN, better CBT response

- L. Anterior Insula (pre-CBT) with PARS (post-CBT)
  - $r = -.56$, $p = .05$

- R. Anterior Insula (pre-CBT) with PARS (post-CBT)
  - $r = -.58$, $p = .04$
Anxiety: TCN as mechanism of change?

Interference: $\uparrow \Delta$Central executive network

Interference: $\downarrow \Delta$Salience network

Change in R. Anterior Insula Activation (pre- to post-CBT)

Change in L. Superior Parietal Activation (pre- to post-CBT)

$\text{Partial Regression Plot}$
Dependent Variable: ChgPreToPost_PARS

$\text{Change in PARS (pre- to post-CBT)}$

$r = .55, \quad p = .04$

$r = .51, \quad p = .063$
Summary: fMRI-CBT in OCD/Anxiety

• Pre-CBT: greater SN predicts better response

• CEN increase $\rightarrow$ anxiety decrease
  • Increased engagement left superior parietal cortex associated with reduced anxiety after CBT

• SN (CO) network decrease $\rightarrow$ anxiety decrease
  • Decreased engagement right anterior insula associated with reduced anxiety after CBT

• Distinction between FP and cingulo-opercular (CO) networks?
  • Differential roles of FP and CO in generation and reduction of anxiety symptoms
Manipulating Task Control Networks

Cognitive Training, the ERN and Early Childhood Anxiety
Error-related Negativity (ERN)

Gehring et al., 2000
ERN can be detected EARLY

3 years

Grammer et al, 2014
8-14 yrs (n = 9, GAD, SAD, SoPho, SpPho)

6 years (n = 48, SpPho, SAD, SoPho, GAD, OCD, agora)

Ladouceur et al, 2006

Meyer et al, 2013
ERN & the Continuum of Anxiety

8-13 yrs (n = 55)

Reversal ERN-internalizing in younger children?

Developmental shift in the relation of ERN – internalizing???
ERN $\alpha$ Internalizing: Gender Effect

Table 2. Results of the Meta-Analysis

<table>
<thead>
<tr>
<th>Sample</th>
<th>$d$</th>
<th>$k$</th>
<th>$N$</th>
<th>$p$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td>-.361</td>
<td>37</td>
<td>1,460</td>
<td>&lt;.001</td>
<td>-.496; -.225</td>
</tr>
<tr>
<td>OC symptoms$^a$</td>
<td>-.637</td>
<td>14</td>
<td>455</td>
<td>&lt;.001</td>
<td>-.836; -.439</td>
</tr>
<tr>
<td>Anxiety symptoms$^b$</td>
<td>-.209</td>
<td>23</td>
<td>1,005</td>
<td>.005</td>
<td>-.370; -.049</td>
</tr>
<tr>
<td>OC-men$^c$</td>
<td>-.703</td>
<td>7</td>
<td>202</td>
<td>&lt;.001</td>
<td>-.999; -.406</td>
</tr>
<tr>
<td>OC-women$^b$</td>
<td>-.584</td>
<td>7</td>
<td>253</td>
<td>&lt;.001</td>
<td>-.852; -.316</td>
</tr>
<tr>
<td>Anxiety-men$^c$</td>
<td>.060</td>
<td>11</td>
<td>411</td>
<td>.57</td>
<td>-.144; .264</td>
</tr>
<tr>
<td>Anxiety-women$^c$</td>
<td>-.362</td>
<td>12</td>
<td>594</td>
<td>&lt;.001</td>
<td>-.533; -.190</td>
</tr>
</tbody>
</table>

Moser et al, 2016
ERN: Development Differs by Gender

Davies et al, 2004

Earlier increase girls than boys
Study Questions

• Does ERN predict internalizing sxs in early childhood (4 – 9 years)?
• How do age and/or gender moderate the ERN-internalizing relationship in young children?
Sample Characteristics

• N = 56 children
• Ages 4 – 9 years
• Male and Female
• Recruitment sources
  • Longitudinal sample of children at familial risk for internalizing (78%)
  • UM Child Psychiatry Clinics (12%)
  • UM General Pediatrics (10%)
Study Overview

• Parent report on CBCL Internalizing Subscale
  • Broad band scale comprised of social withdrawal, somatic complaints and anxiety/depressive narrow band syndromes
  • 27 questions (e.g. Fearful, Too Neat, Little Affect)
    Achenbach & Rescorla, 2001

• Error-eliciting Go No Go Task for young children
  Grammer et al, 2013

• ERN: 32 electrode cap, Biosemi machine

• Linear Regression:
  • ERN, Age, Gender and interactions as predictors of CBCL Internalizing
RDoC Distribution of Internalizing

- 1.Low: n=9
- 2.Mid-Low: n=15
- 3.Mid-High: n=17
- 4.High: n=8
# Internalizing by Age and Gender

<table>
<thead>
<tr>
<th>Age Group*</th>
<th>Gender</th>
<th>N</th>
<th>CBCL t-score**</th>
</tr>
</thead>
<tbody>
<tr>
<td>YOUNG 4 – 6 years (n = 23)</td>
<td>F</td>
<td>11</td>
<td>50.3±12.8</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>12</td>
<td>49.3±12.5</td>
</tr>
<tr>
<td>OLD 7-9 years (n = 26)</td>
<td>F</td>
<td>15</td>
<td>45.6±6.8</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>11</td>
<td>44.5±12.0</td>
</tr>
</tbody>
</table>

*Data loss: <6 errors for 6 children (5.44 +/- .76 yrs, F); 1 ERN outlier (9.42 M); 1 CBCL missing (7.30 M).

**p's < .29
Zoo Game

Zookeeper Melissa

Orangutan helper

(Grammer et al, 2014; McDermott et al, 2014)
Zoo Game

Go trial
(30 per block, 8 blocks)

NoGo trial
(10 per block, 8 blocks)
## Results: Behavioral

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Gender</th>
<th>Error Trials*</th>
<th>Correct Go Trial RTs**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>YOUNG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 – 6 years</td>
<td>F</td>
<td>19.5±5.2</td>
<td>581±55</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>33.3±14.0</td>
<td>607±135</td>
</tr>
<tr>
<td>(n = 23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OLD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-9 years</td>
<td>F</td>
<td>18.0±6.7</td>
<td>517±62</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>25.0±11.9</td>
<td>525±72</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*More errors in younger than older (p=0.03), M than F (p =0.001)

**Slower RTs in younger than older (p = .02)
ERN increase with age

Age $B = -.29, p = .055$

(controlling gender, $p = .89$; NoGo errors, $p = .25$)
ERN Predicts Internalizing

...BUT, predicts *differently* in preschool-aged girls than preschool-aged boys or school-aged girls

![Graph showing relationship between ERN amplitude and internalizing symptoms for different age and gender groups.](image)

Age Group (Young, Old) x Gender x ERN: $B = -.23$, $p = .001$
Implications for Translation?

• Could ERN/TCN modulation reduce anxiety and/or risk for internalizing in early childhood?
• Does ERN/TCN need to be targeted differently in different children, depending on age and gender?
Next Steps

Stopping Anxiety Early
Can we help kids to “grow out” of anxiety?
Kidpower: Brain training to reduce anxiety

Fear

Effortful Control
Thank you!!!

- Steve Taylor, M.D.
- Yanni Liu, Ph.D.
- Luke Norman, Ph.D.
- Christopher Monk, Ph.D.
- Luan Phan, M.D.
- Tim Johnson, Ph.D.
- Maria Muzik, M.D., M.S.
- Kate Rosenblum, Ph.D.

- R01 MH102242
- R01 MH107419
- One Mind Institute