Developing New Treatments for Childhood Anxiety and OCD:
Can Cognitive Control Help Kids Grow Out of Illness?

Kate D. Fitzgerald, MD
Ruane Professor of Child and Adolescent Psychiatry
Columbia University/New York State Psychiatric Institute

COLUMBIA

NEW YORK STATE | New York State Psychiatric Institute

Anxiety Serves a Purpose

Anxiety/OCD: Normal to Disorder

Typical → *Atypical*

Age	Normative Development	Anxiety Disorder
Pre-school	imaginary, objects/situations	specific phobias, separation anxiety
Grade School	health/harm, competence	generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD)
Adolescence	social adequacy and performance	GAD, social phobia, panic

Intense
Frequent
Distressing
Difficult to control
Gets in the way

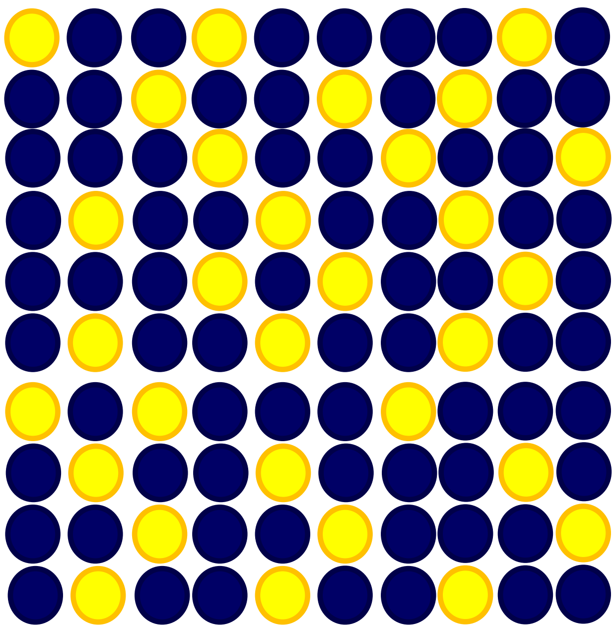
Anxiety Problems Start EARLY

	Age 3 Assessment			Age 6 Assessment		
Disorder	N	%	95% CI	N	%	95% CI
Any diagnosis[a]	127	27.5	23.5–31.9	123	26.6	22.8–30.8
Any emotional disorder	91	19.7	16.2–23.7	87	18.8	15.5–22.7
Any depression[b]	6	1.3	0.6–2.8	25	5.4	3.7–7.9
Major depression or dysthymia	2	0.4	0.1–1.6	15	3.2	2.0–5.3
Depression not otherwise specified	4	0.9	0.3–2.2	10	2.2	1.2–3.9
Any anxiety disorder	89	19.3	15.9–23.1	72	15.6	12.6–19.2
Specific phobia	44	9.5	7.2–12.5	38	8.2	6.1–11.1
Separation anxiety	26	5.6	3.9–8.1	22	4.8	3.2–7.1
Social phobia	17	3.7	2.3–5.8	10	2.2	1.2–3.9
Generalized anxiety disorder[b]	18	3.9	2.5–6.1	7	1.5	0.7–3.1
Agoraphobia	15	3.2	2.0–5.3	8	1.7	0.9–3.4
Selective mutism	7	1.5	0.7–3.1	3	0.6	0.2–1.9
Any behavioral disorder	51	11.0	8.4–14.3	57	12.3	9.7–15.7
ADHD[b]	11	2.4	1.3–4.2	25	5.4	3.7–7.9
Oppositional defiant disorder	47	10.2	7.7–13.3	41	8.9	6.6–11.8
Two or more diagnoses	42	9.1	6.8–12.1	41	8.9	6.6–11.8

Buffered et al, 2012

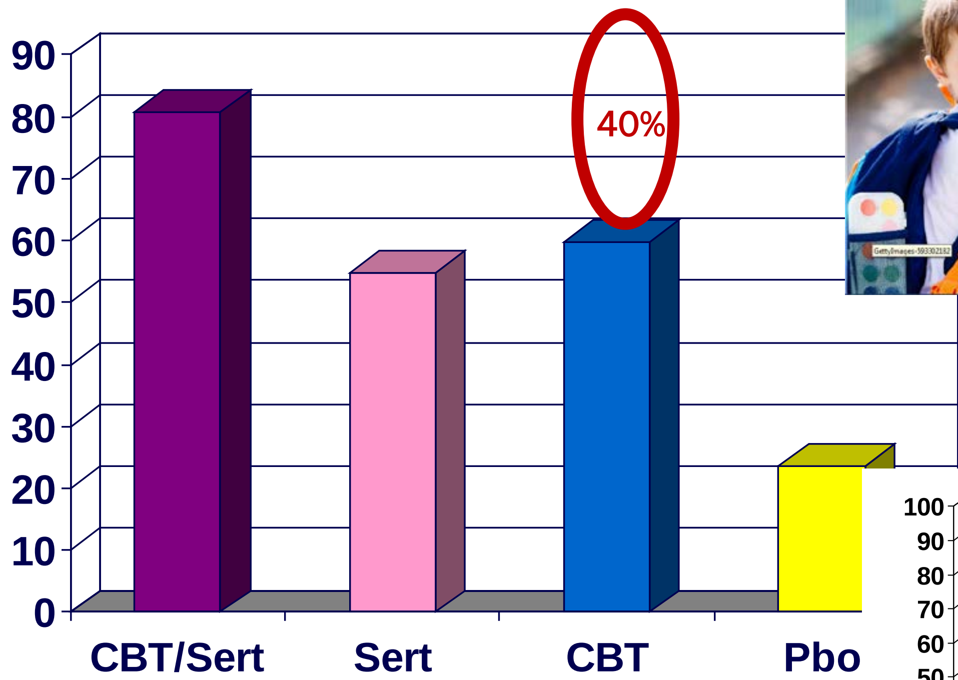
Who Do Clinically Anxious Children Grow Up to Be?

1 in 3 with anxiety disorder by adolescence!

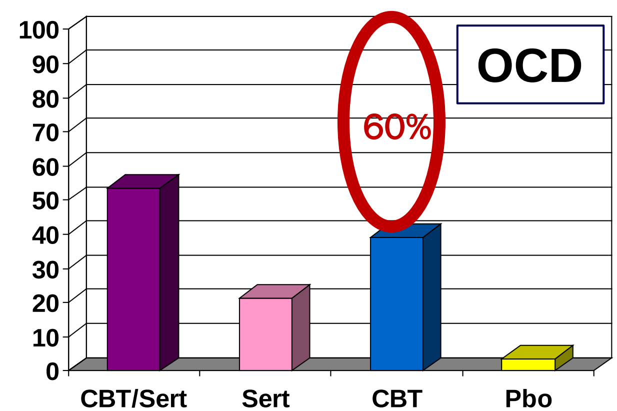


Merikangas et al, 2010

How Can We Help?



Walkup et al, 2008

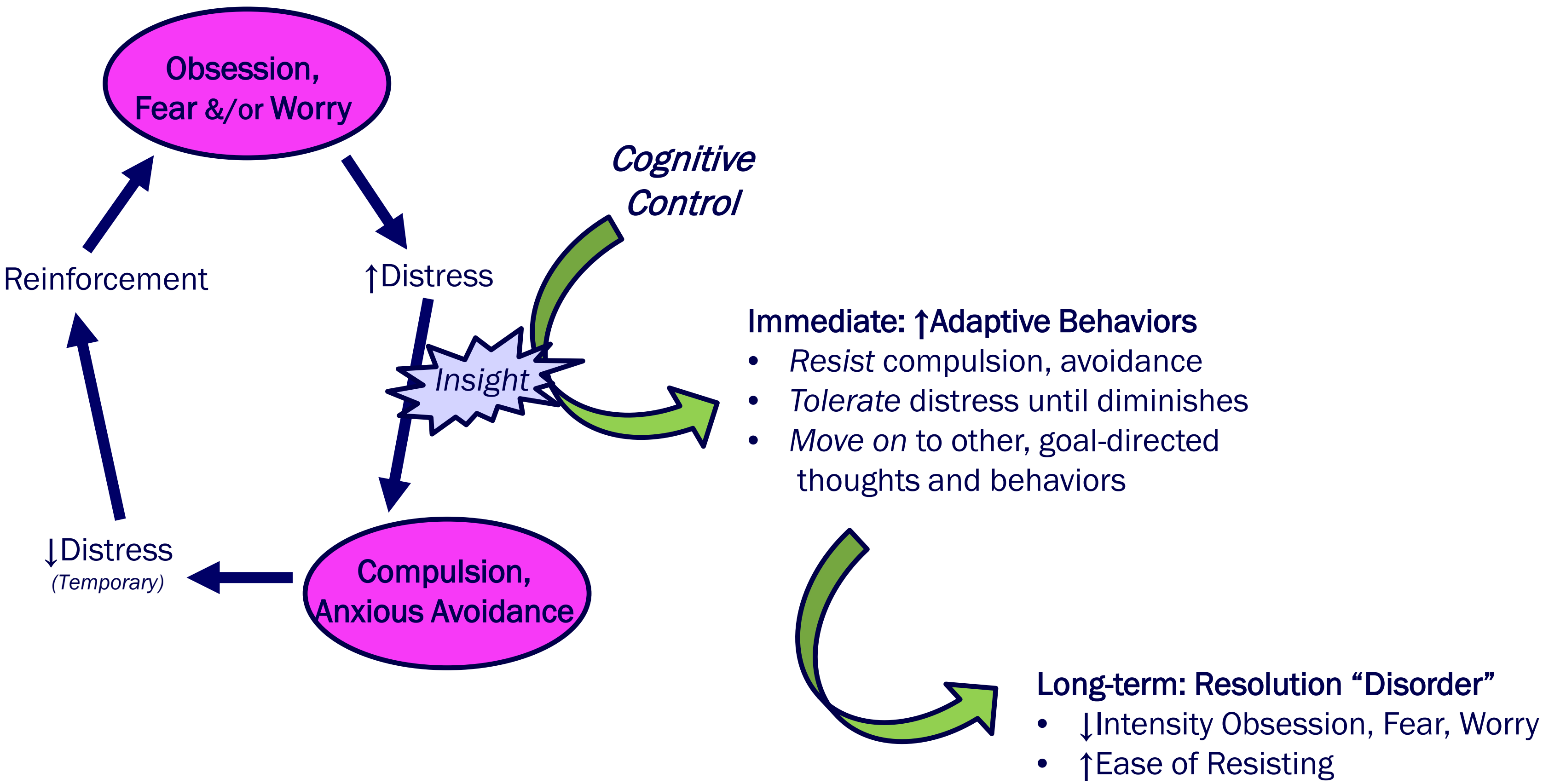


POTS, 2004

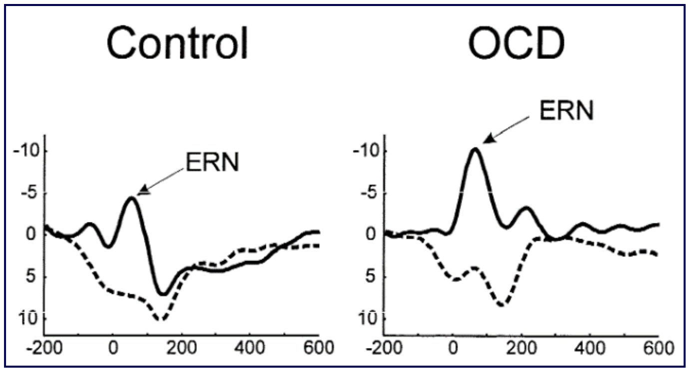
SERT=sertraline

How does CBT work?

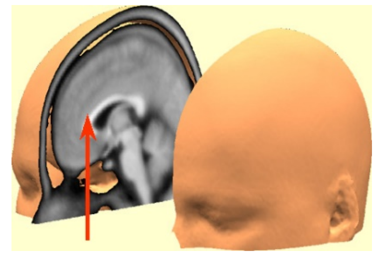
Cognitive Control: Breaking the Vicious Cycle



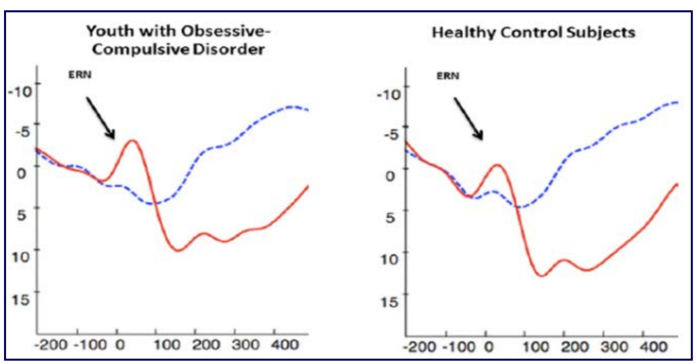
Error-related Negativity (ERN) in OCD/Anxiety



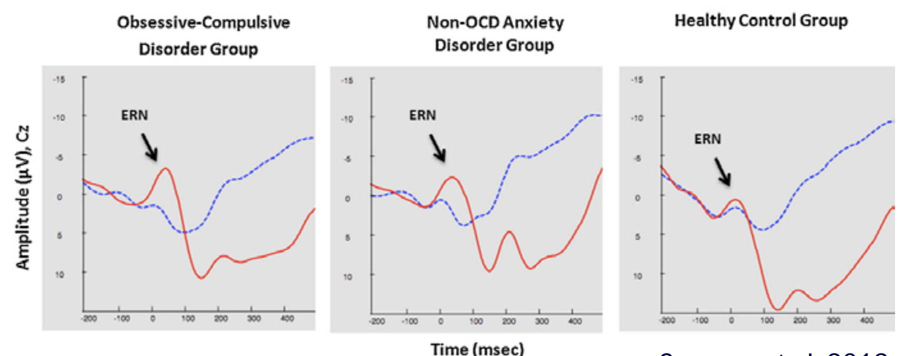
Gehring et al, 2000



Anterior Cingulate Cortex (ACC)



Hanna et al, 2012



Carrasco et al, 2013

ERN in Anxiety/OCD: Functional Significance?

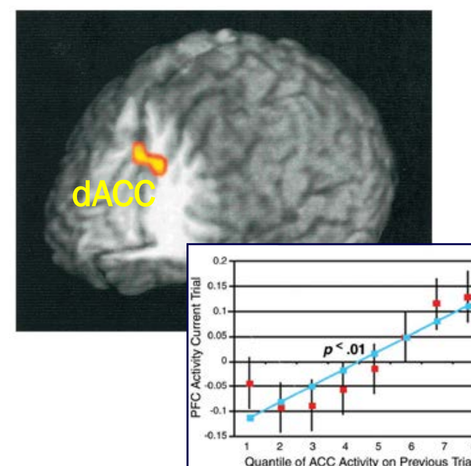
<u>Affective response?</u>

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

<u>Adaptive response?</u>

- 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")

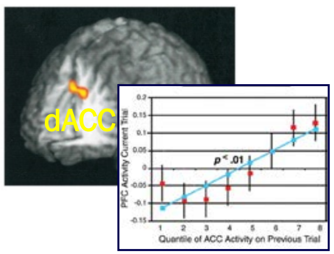


Where does Cognitive Control come from?

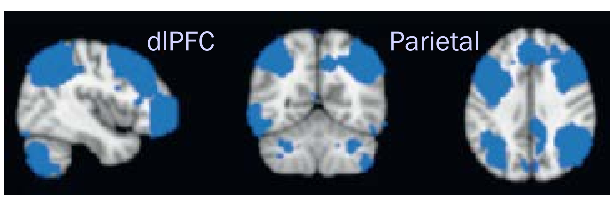
Task Positive or “Control” Networks

Cingulo-Opercular Network (CON)

Salient events (e.g., errors)

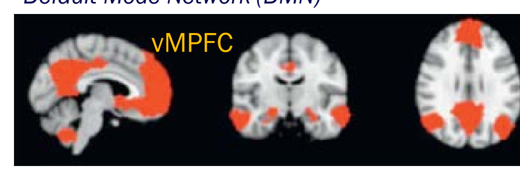


Frontal Parietal Network (FPN)



Adaptive control

Default Mode Network (DMN)

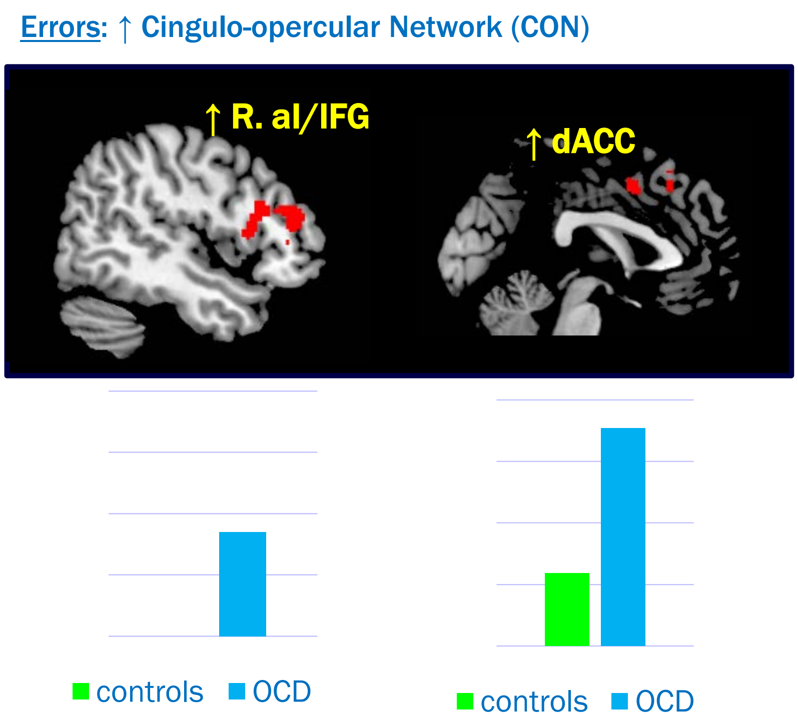


Default Mode/Task Negative

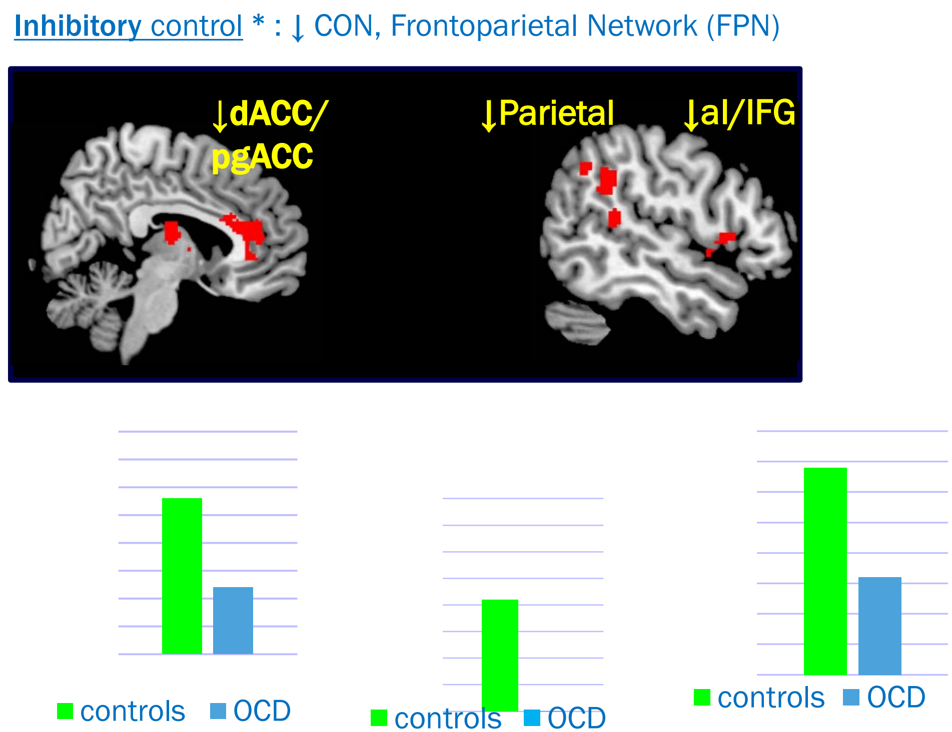
Menon et al, 2011; Seeley et al, 2011; Sridharan et al, 2008

Neural Networks for Cognitive Control

Another example from OCD



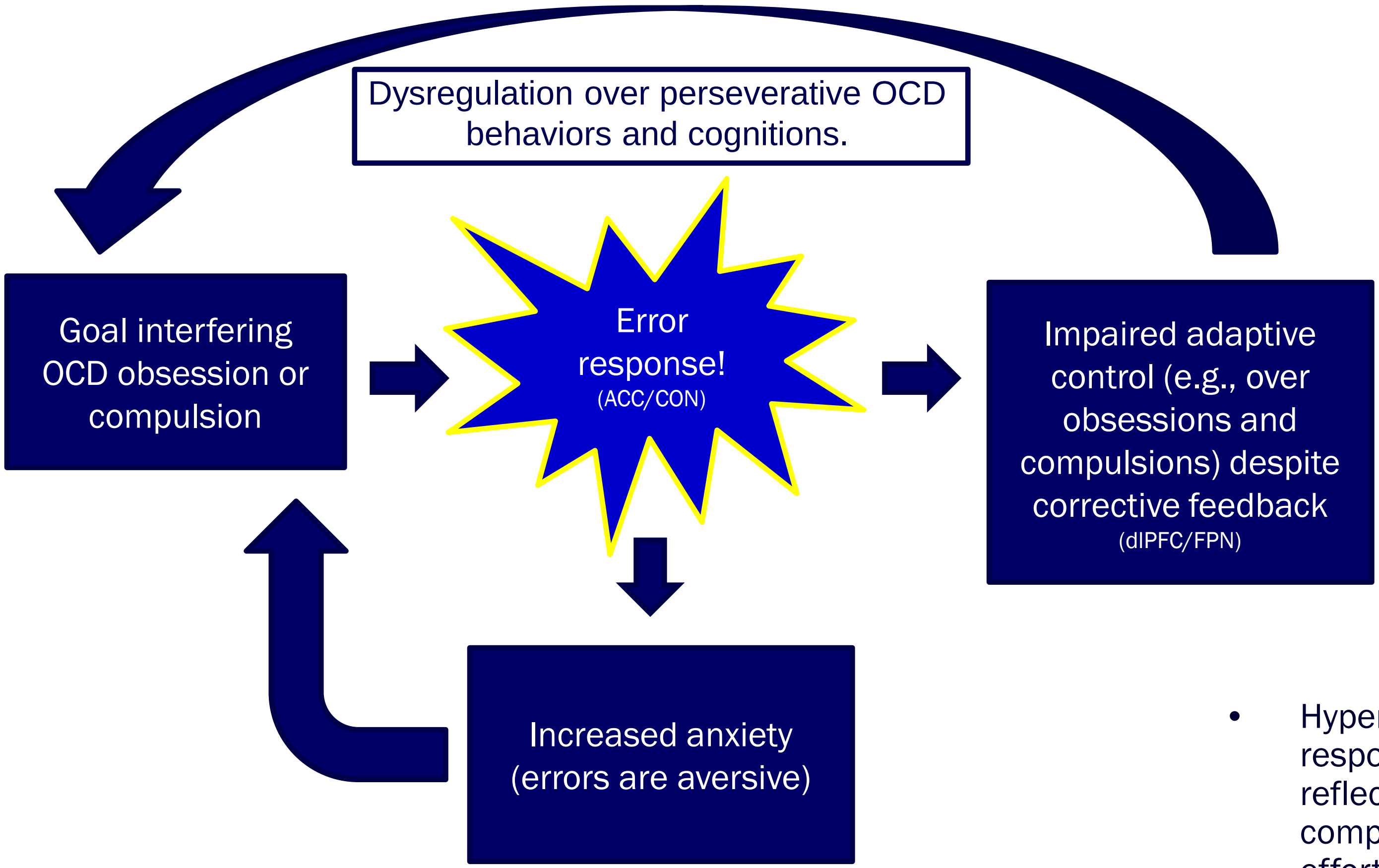
N = 239 OCD, 231 HC



N = 245 OCD, 239 HC

Norman et al, 2019

Errors and Inhibitory Control in OCD



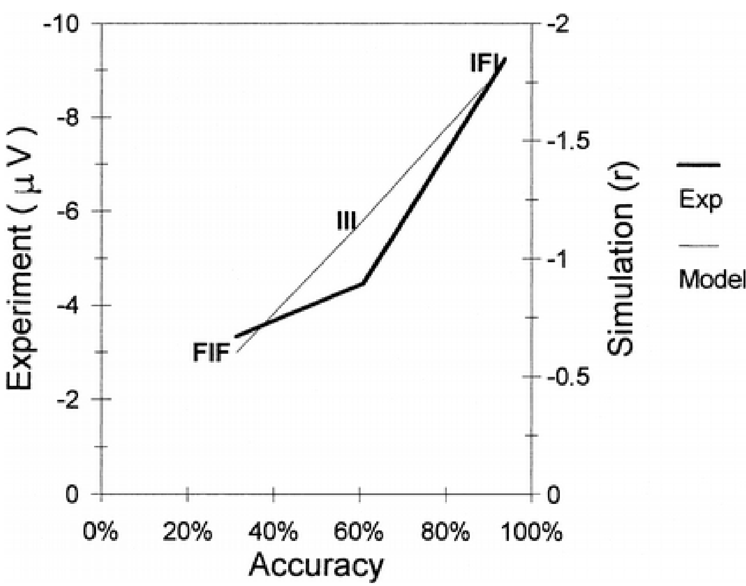
- Hyperactive error responses may reflect compensatory effort at reactive control.

Norman et al, 2019

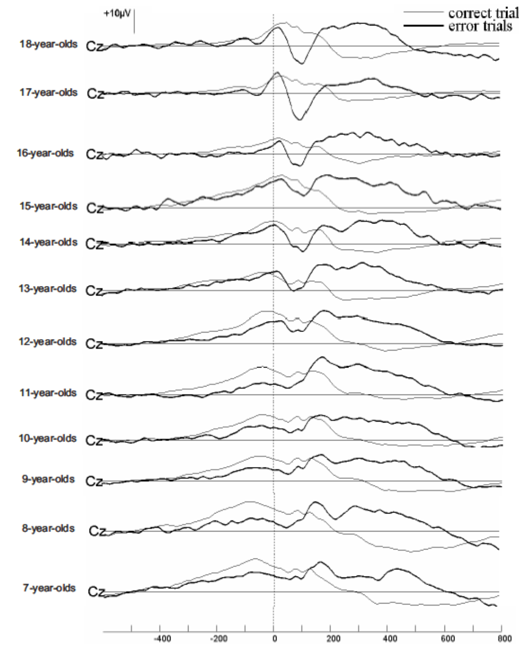
ACC-based Response to Errors

Helpful, hurtful, and/or different with age?

Larger ERN, Better Performance, Older Age



Holroyd and Coles, 2012 (n = 15, adults)



Davies et al, 2004

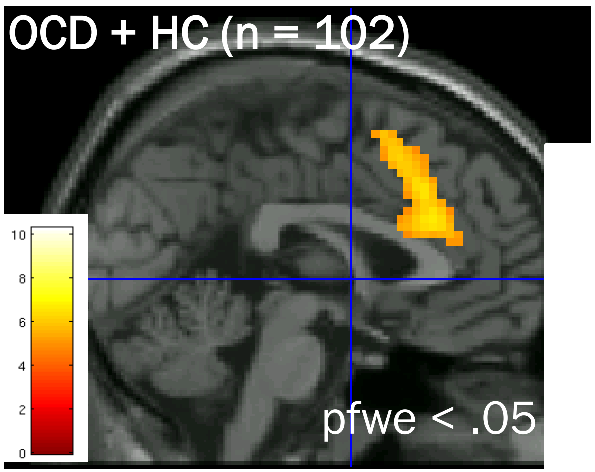
Table 2. Bivariate Correlations Between ERN and P_e Amplitude (μV) in Error Trials and Amplitude (μV) of Correct Trials at Midline Sites and Behavioral Measures With Outliers Removed

	ΔERN at C_z	ERN at F_z	CRN at F_z	P_e at P_z
Total Correct Responses on Go Trials	−.07 (N = 308)	.01 (N = 308)	.10 (N = 311)	**.15*** (N = 307)**
Reaction Time on Correct Responses on Go Trials	.14* (N = 312)	.02 (N = 312)	−.16* (N = 316)	−.20** (N = 311)
Total Correct No-Go Trials	**−.20** (N = 314)**	−.13 (N = 314)	.02 (N = 317)	**.22*** (N = 313)**
Total Errors of Commission	**.15** (N = 308)**	.10 (N = 308)	−.05 (N = 311)	**−.25*** (N = 307)**
Reaction Time on Errors of Commission	**.12* (N = 313)**	.01 (N = 313)	−.13 (N = 316)	**−.21*** (N = 312)**
Total Errors of Omission	**.20** (N = 304)**	.07 (N = 304)	−.09 (N = 307)	**−.27*** (N = 303)**
Total Correct Go Trials Following Errors of Commission	**.13* (N = 311)**	.08 (N = 311)	−.02 (N = 314)	**−.18*** (N = 310)**
Reaction Time on Correct Go Trials Following Errors of Commission	.11 (N = 313)	.06 (N = 313)	−.07 (N = 317)	**−.13* (N = 312)**
Total Accuracy	**−.23** (N = 308)**	−.14 (N = 307)	.06 (N = 310)	**.27*** (N = 306)**

Torpey et al, 2012 (N = 328, 5 to 7 year-olds)

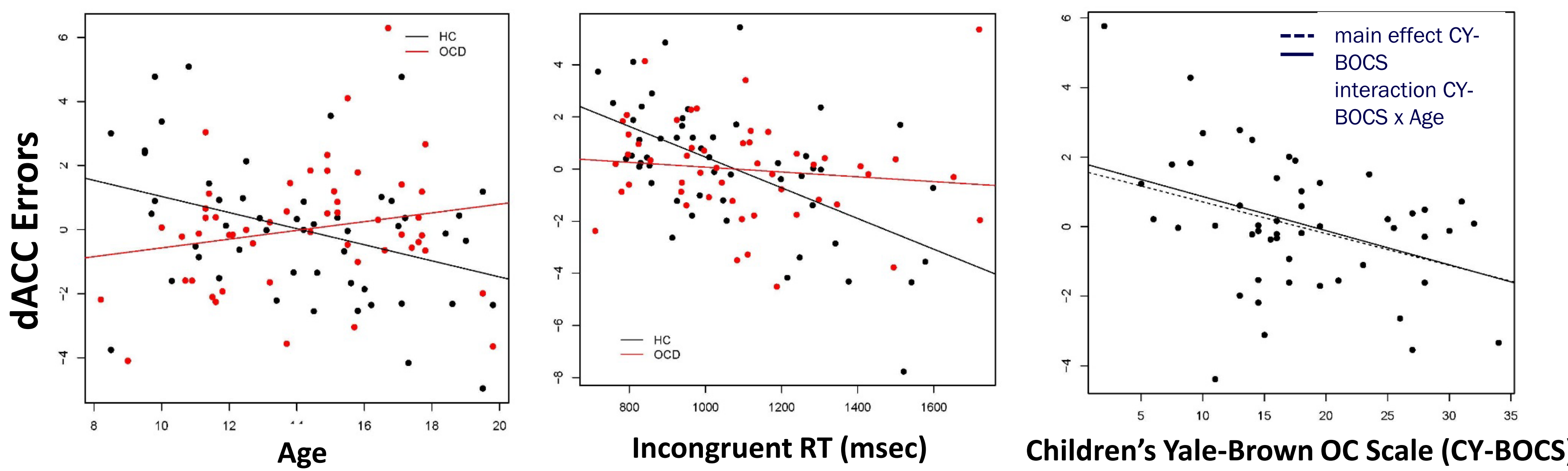
Greater Error Response in Child OCD:

Medicated, older age, less OCD, better performance



Hyperactive error response
A good thing?

Fitzgerald et al, 2018

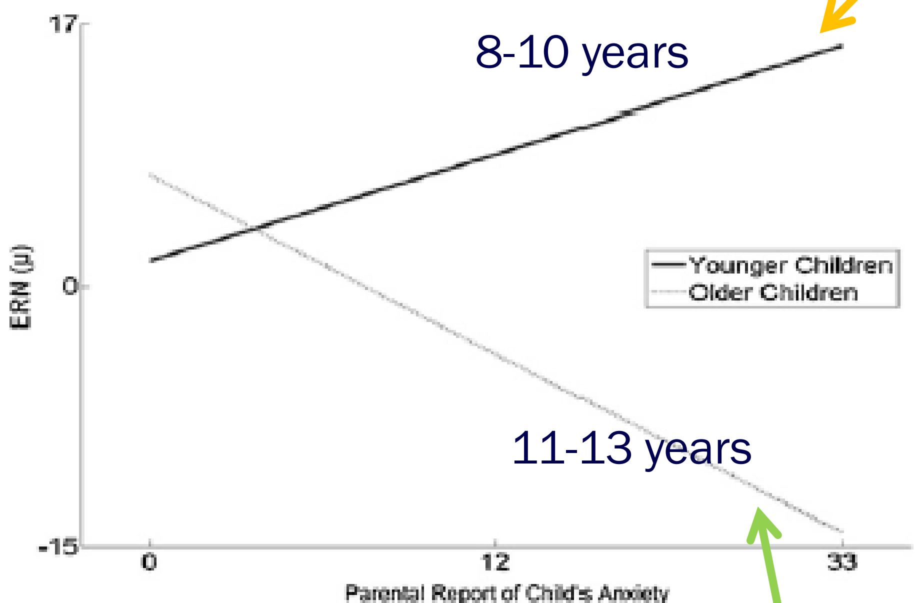


ERN, Anxiety & *Children*

Community Sample

Smaller (less negative) ERN,
More anxiety in
younger children

8-13 years (n = 55)

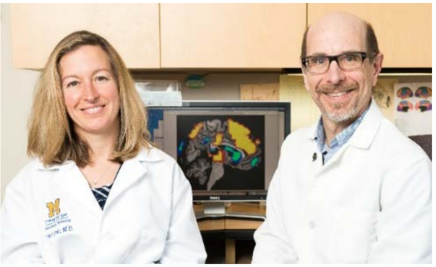


Meyer et al, 2012

Developmental shift in ERN–anxiety relationship

- Young: Small ERN, low cognitive control, and early anxiety emergence?
- Older: Larger ERN-anxiety, compensatory with age?

Larger (more negative) ERN,
More anxiety in older children



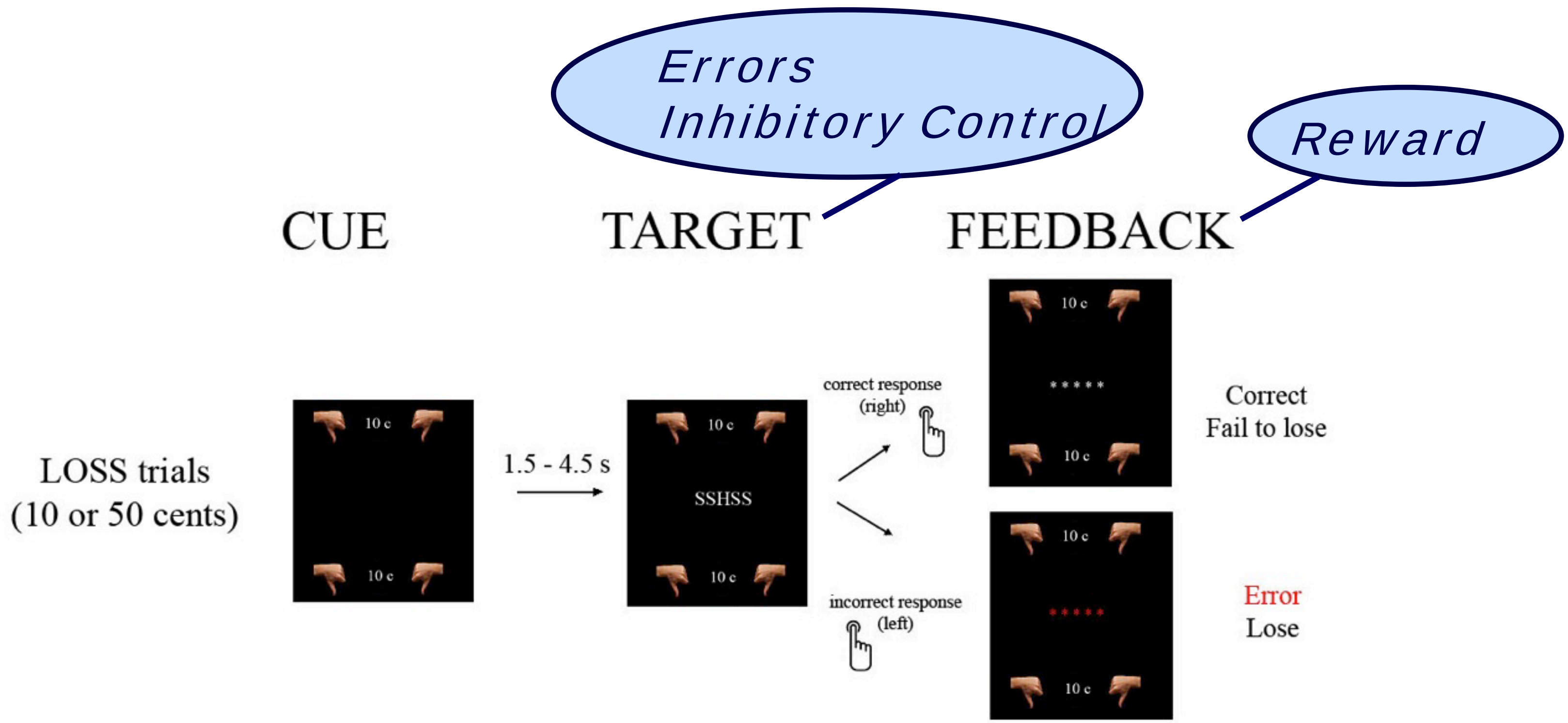
TCN & Symptom Change in OCD

Can Task Control Network (TCN) Function Predict Symptom Change?

Norman et al, 2020

OCD-CBT: Study Design

- Randomized trial: CBT vs. stress management training (SMT)
- 42 CBT, 45 SMT patients with OCD
  - Teens (13-17) & adults (25-45)
  - Onset age 15 years, (C)Y-BOCS ≥ 16, half medicated
  - Pre- to post-therapy: fMRI, Incentive Flanker Task



OCD-CBT: Hypotheses

<u>Central Hypothesis</u>: More Cognitive Control in Brain→Better CBT Response in Adolescent/Adult OCD

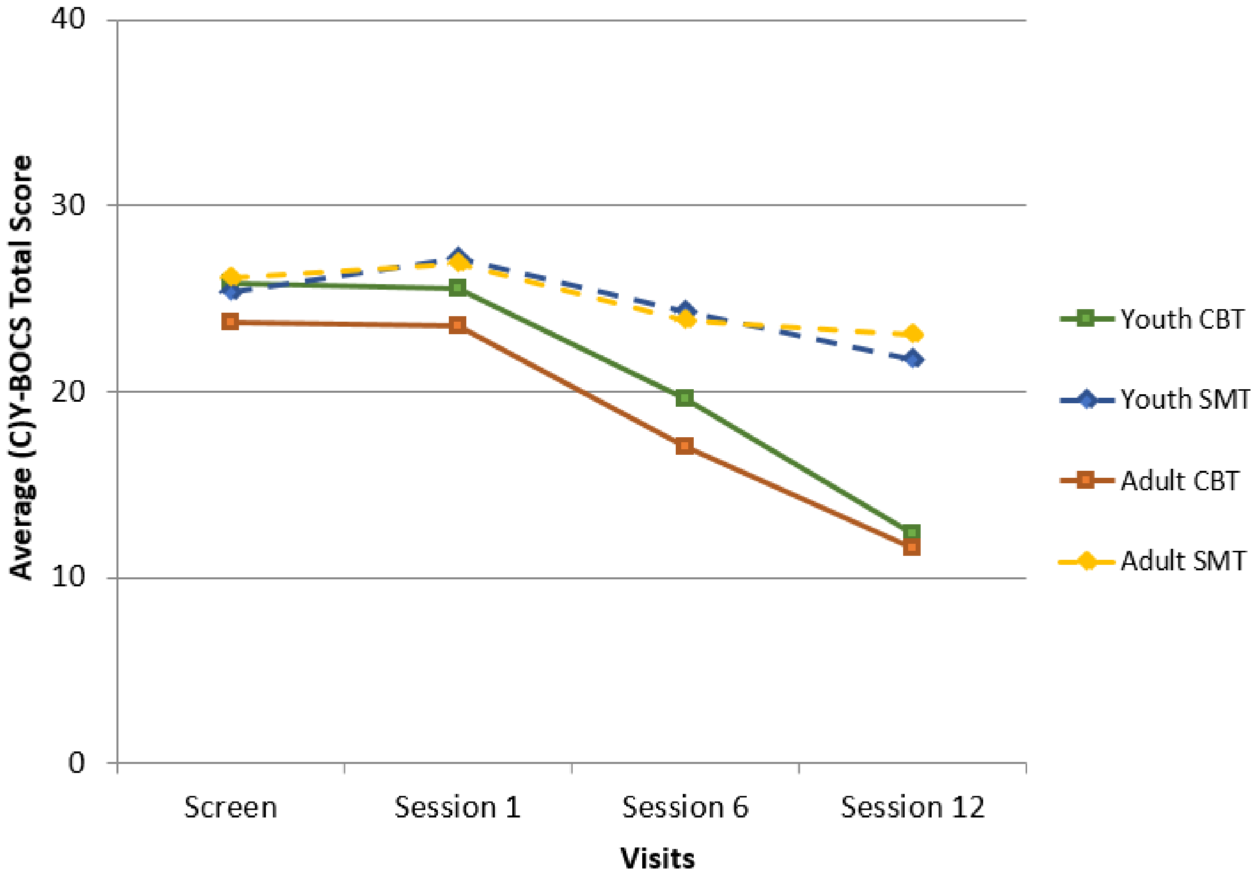
More "normal" baseline TCN function → Better CBT outcomes?

1. <u>Errors</u>: ↓ CON (More efficient? Less need to compensate?)
2. <u>Inhibitory control</u>: ↑ CON, ↑ FPN (More inhibitory control)
3. <u>Reward</u>: ↑ orbito-frontal cortex (OFC, Motivation)

Patient Characteristics

	CBT		SMT	
	Adolescents (n = 19)	Adults (n = 23)	Adolescents (n = 20)	**Adults (n = 25)**
Age (years)	15.5 ± 1.6	31.4 ± 5.8	15.4 ± 1.8	**31.8 ± 5.6**
YBOCS (Baseline)	**26.7 ± 5.6**	**23.7 ± 5.0**	**28.1 ± 5.2**	**26.9± 4.0**

Treatment Response: CBT vs SMT



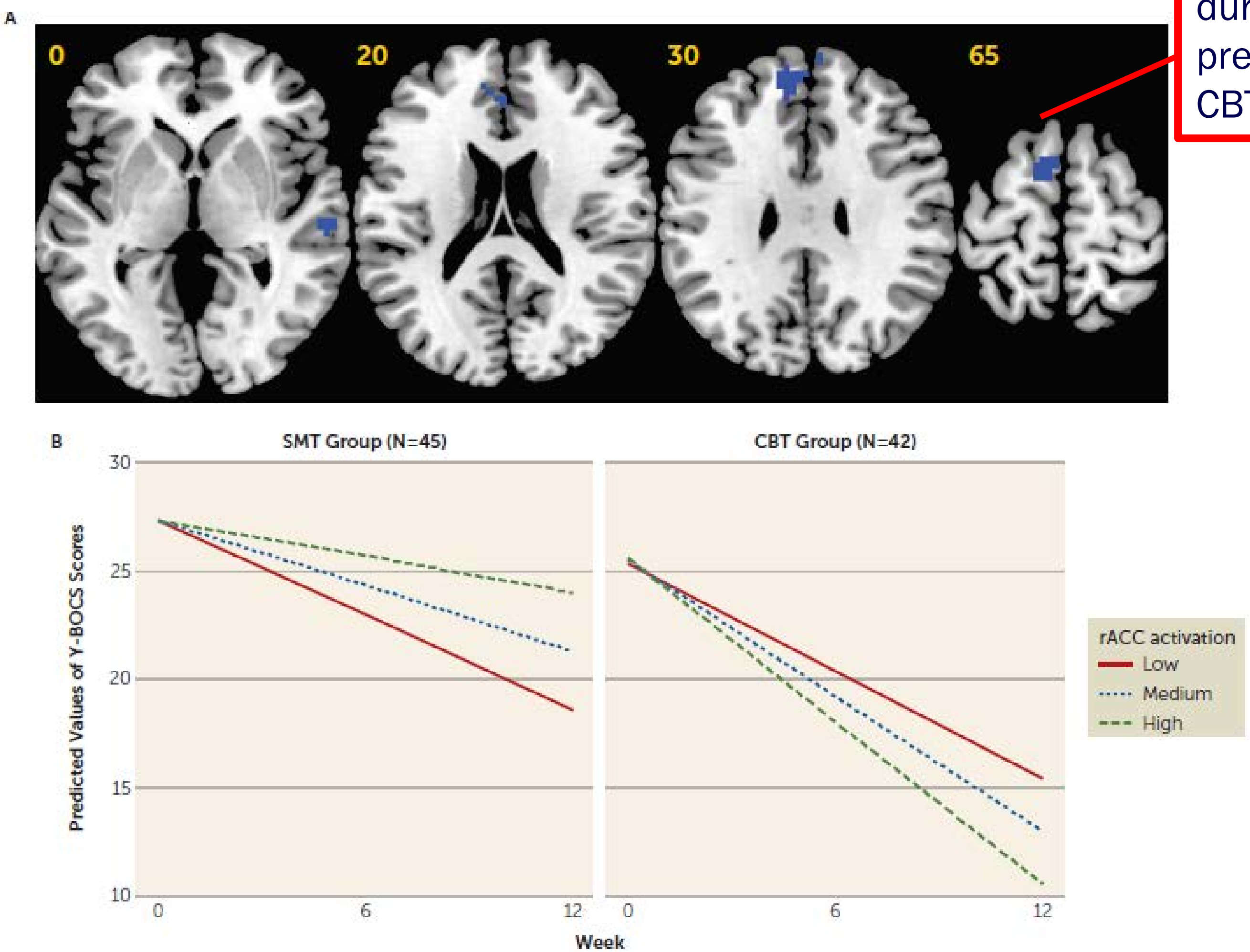
OCD severity reduced after CBT & SMT, but CBT significantly more effective.

And, brain predictors……

Neural Predictors: CBT-Specific (CBT x SMT interaction)

Inhibitory Control (cognitive interference)

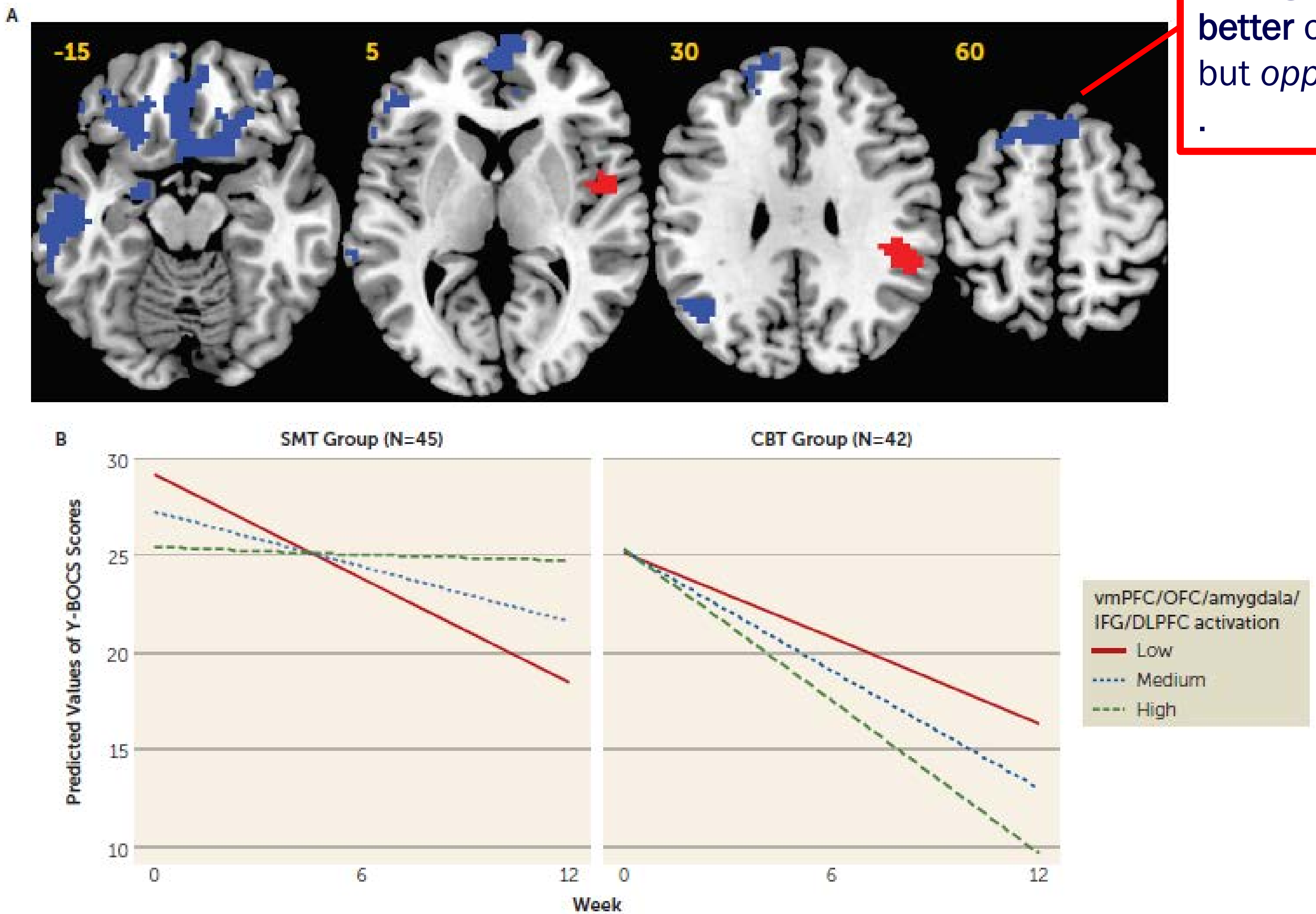
Greater ACC response during inhibitory control predicts **better** outcomes in CBT, but *opposite* for SMT.



Norman et al, 2020

Neural Predictors: CBT-Specific (CBT x SMT interaction)

Reward Processing

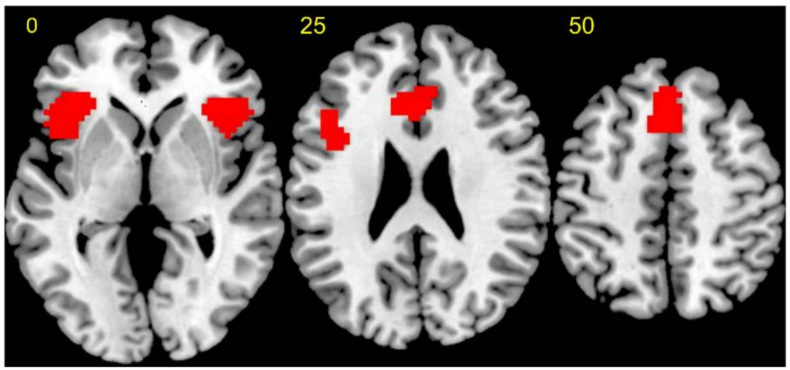


Greater OFC response during reward predicts **better** outcomes in CBT, but *opposite* for SMT.
.

Norman et al, 2020

Neural Predictors

Errors



Baseline activation

not significant

Baseline activation as predictor

- ACC engaged by errors....but not predictive to CBT response
- Caveat: lower power due to smaller number of trials

Norman et al, 2020

Conclusions: OCD-CBT Incentive Flanker Task

- Greater baseline inhibitory control (ACC) and reward (OFC) function enables patients to benefit from CBT
  - ACC-based inhibitory control: Dismiss obsessions, resist compulsions and engage in CBT
  - OFC-based Reward: Motivation to implement adaptive control required by CBT
- Specific to CBT
- *Can further boosting ACC-indexed cognitive control function help resolve symptoms?*

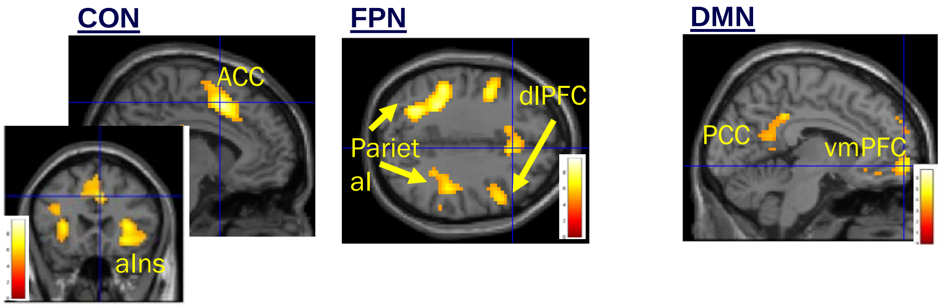
Regions that fire together wire together (Neural networks)

Can *resting state connectivity* in cortical-subcortical networks for cognitive control predict CBT outcomes?

Different predictors at different ages?

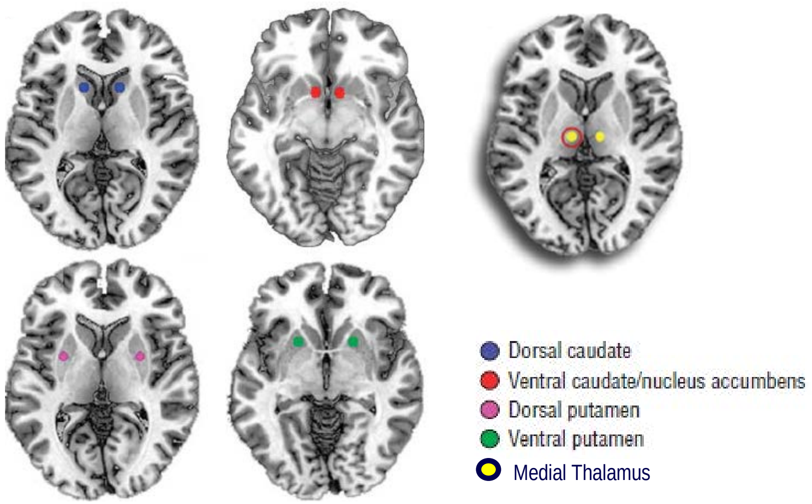
Resting State Connectivity Analysis

Task Control Networks



(from IFT in same subjects)

Subcortical

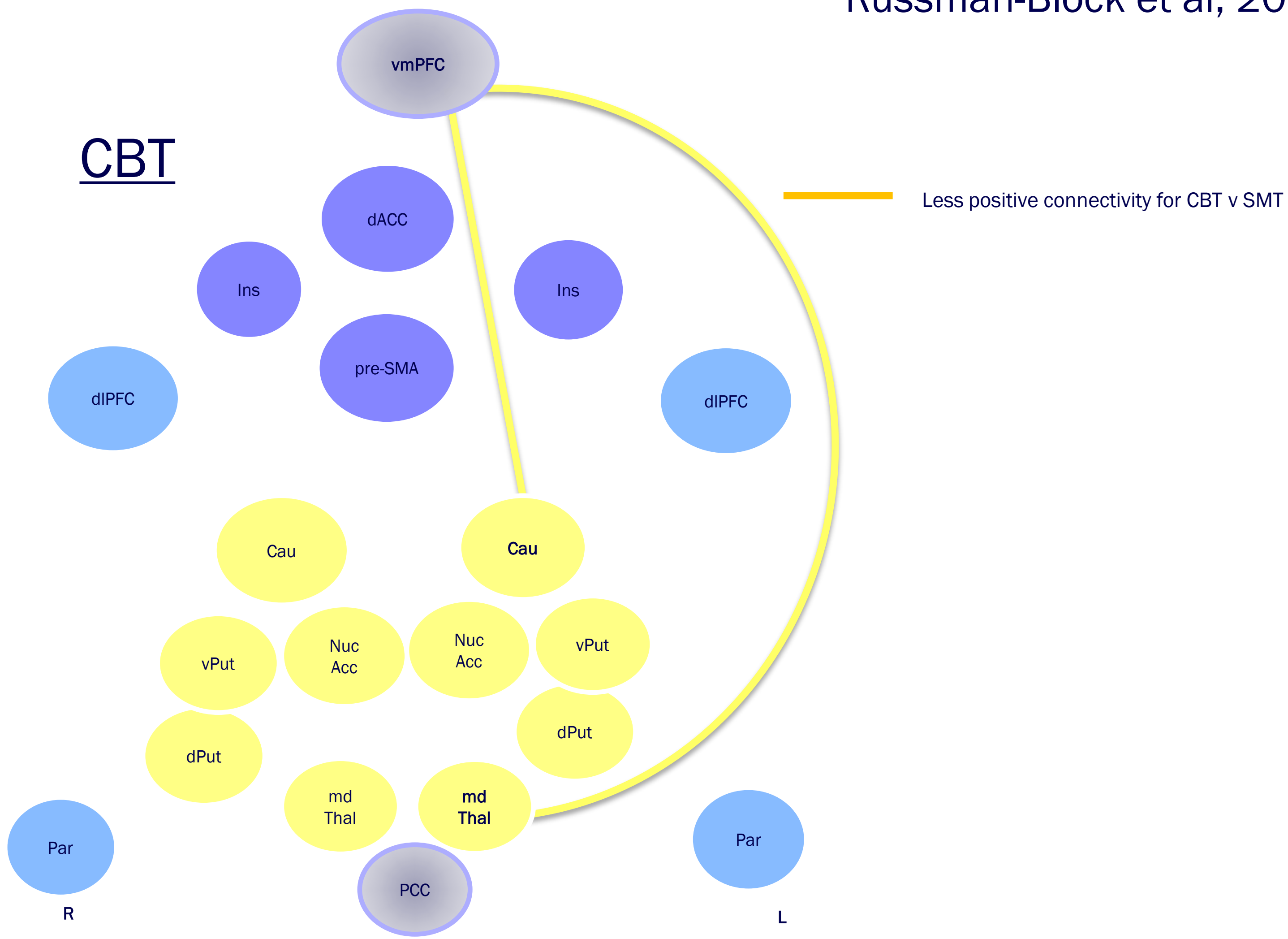


*Dimartino et al, 2008
*Harrison et al, 2009
*Fitzgerald eta l, 2011

20 Regions → 190 Connections. Which ones predict CBT response?

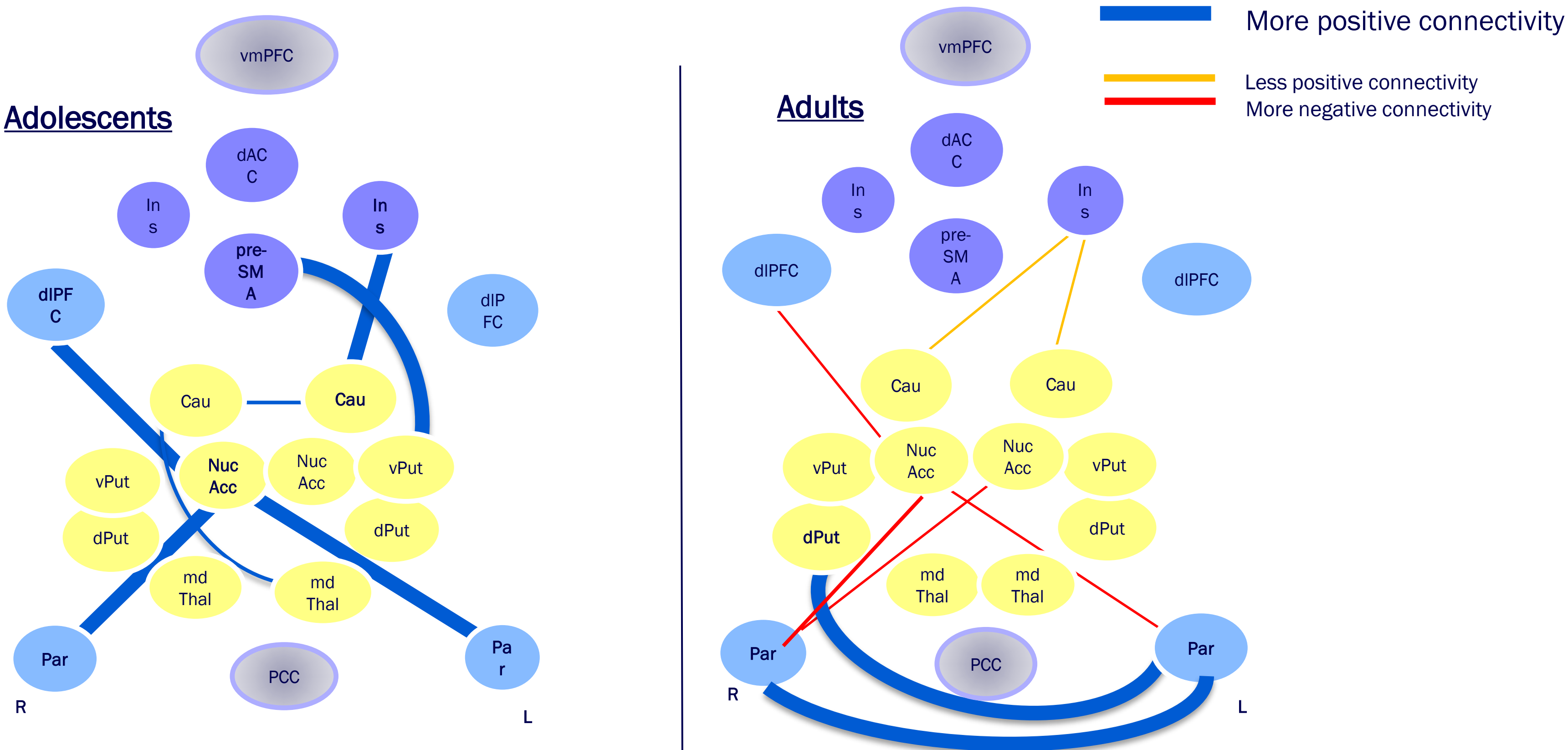
CBT-selective predictors (across Adolescents and Adult)

Russman-Block et al, 2022



↓ DMN (vmPFC) - Subcortical: Less positive connectivity, better CBT response

Developmentally sensitive predictors



↑ FPN, CON regions – Ventral Striatal

↑ *within* Task Control Network (FPN), *between* FPN – Putamen

Russman-Block et al, 2022

Conclusions: rsfcMRI predictors

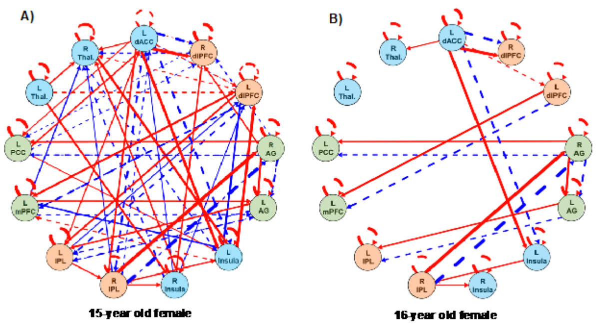
- CBT-specific:
  - ↓vmPFC – Subcortical connectivity
    - Less affective influence over action selection?
- Developmentally sensitive predictors:
  - *Adolescents:* ↑FPN, CON - subcortical reward circuitry (nuc accumbens)
    - Dismiss OC urges in favor of goal-directed behaviors, across psychotherapies?
  - *Adults:* ↑FPN - subcortical motor circuity (dPut)
    - Resist compulsive urges, across psychotherapies?
  - Developmental sensitive predictors = non-specific (i.e., predictive across CBT, SMT)

OCD-CBT GIMME: Searching for CBT Mechanism

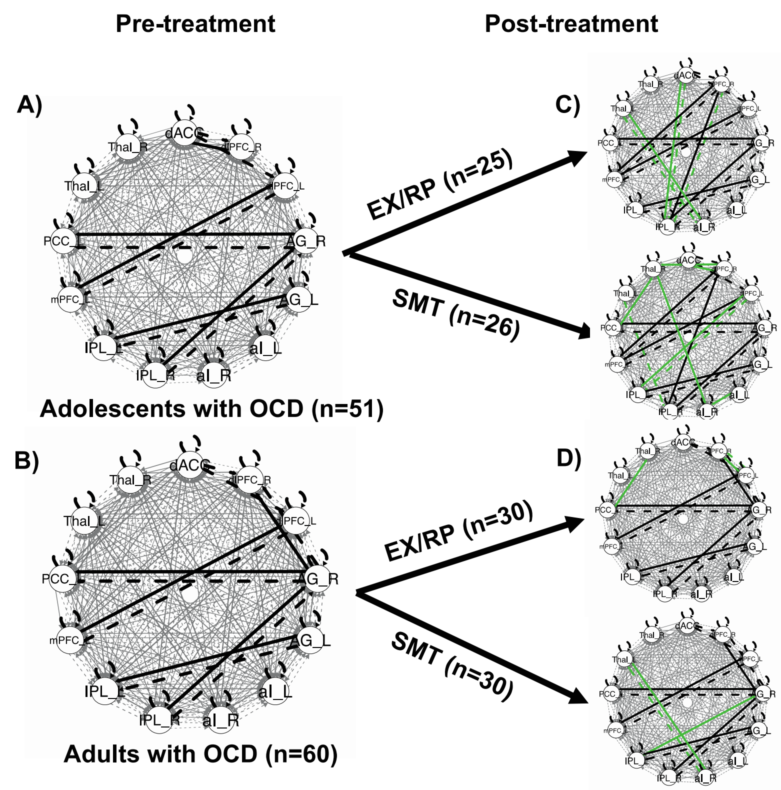
- Why predictor findings only?
  - Group Averaging Methods → Null Results (NCT02437773)
    - Are we throwing out the baby (i.e, individual differences) with the bathwater (change signal)?
- Group Iterative Multi-level Modelling (GIMME)
  - Individual Heterogeneity
  - Person-specific *and* group-level information
  - Task-based functional network connectivity
    - FPN, CON, DMN (13 nodes, Seitzman atlas)
    - # of connections within and between networks
  - Contemporaneous and lagged connections across task (IFT)
  - Models: Treatment Condition (CBT, SMT), Time, Age Group effects

OCD-CBT GIMME

Individual Differences

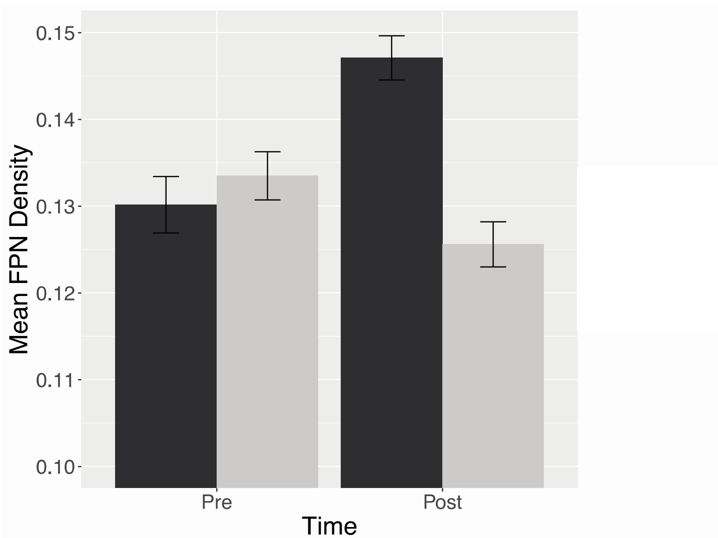


Group-level models



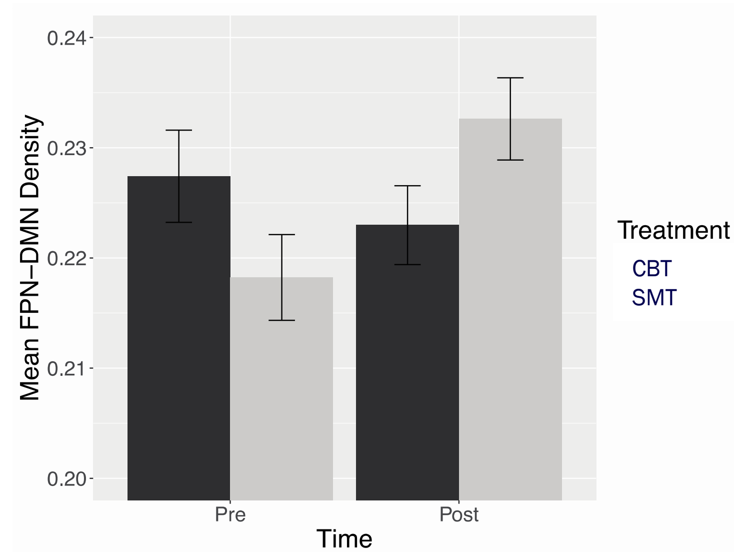
CBT-specific tripartite network change

A)



↑ FPN Connectivity
(*within* network)

B)



↓ FPN – DMN Connectivity
(*between* networks)

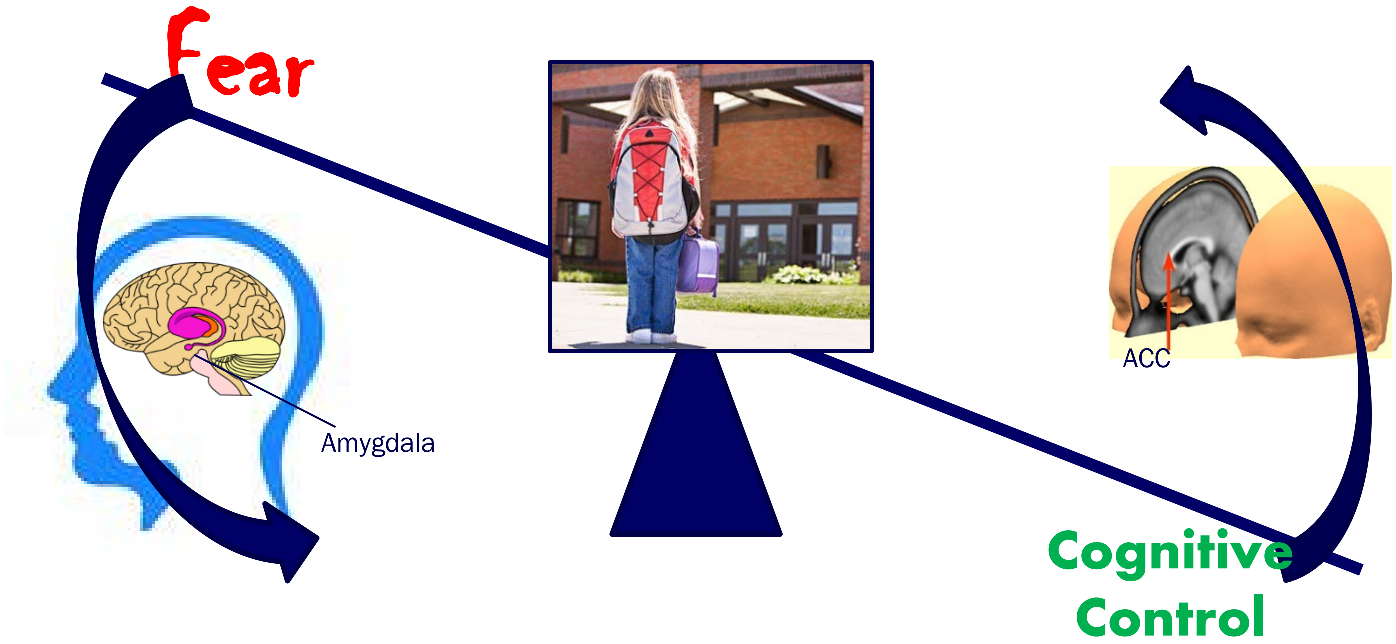
Conclusions: OCD-CBT GIMME

- CBT-specific changes
  - ↑FPN, ↓ FPN-DMN
- Stable across adolescent and adult patients
  - Shift functional tripartite network connections towards maturity across the age span?

Anxiety in Early Childhood

Can cognitive control be trained to reduce anxiety symptoms?

Kidpower: Training the brain in anxious preschoolers



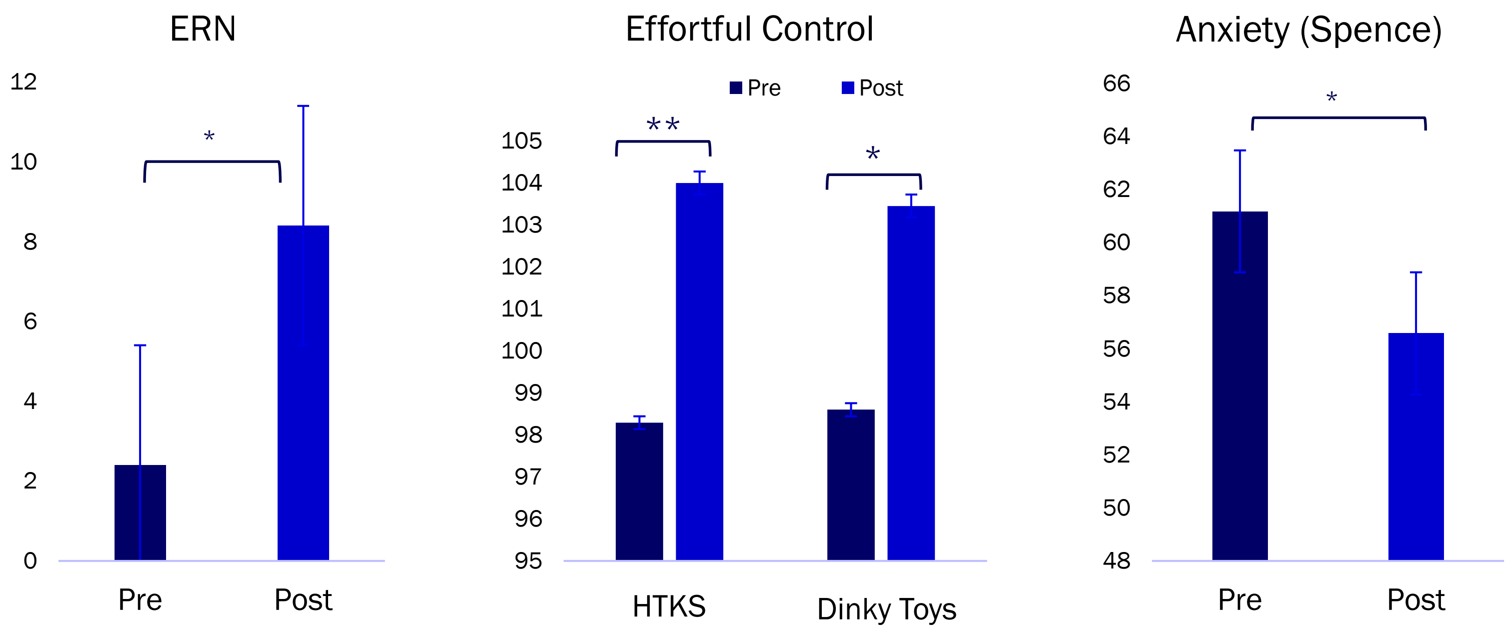
Kidpower: Training the Brain

Kidpower Kids

Measures	Completers (n=32)	Non-completers (n = 12)	Test statistics
Age (years)	5.66 ± .7 (4.25-6.99)	5.08 ± 1.0 (4.00-6.75)	$t(15.44) = 1.81$ $p = .09$
Gender	18F (56%)	7F (58%)	$X^2 = 0.015$, df = 1, p = 1.00
Spence PAS (t-scores)	62.7 ± 10.9 (41.00-87.00)	63.64 ± 15.7 (44.00-85.00)	$t(13.47) = 0.19$ $p = .86$
CBCL, ADHD	55.56 ± 5.66 (50.00-73.00)	56.00 ± 6.72 (50.00-71.00)	$t(41) = 0.21$ $p = .83$

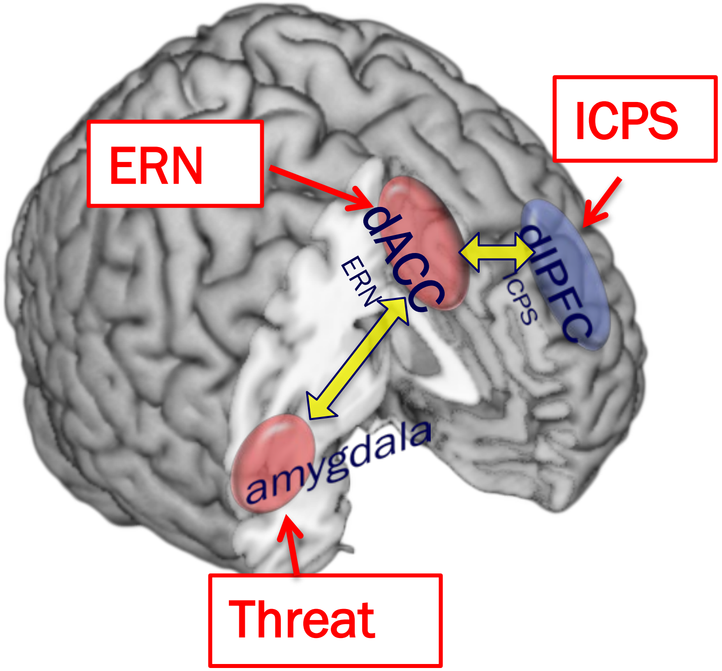
N = 44 enrolled, t-score ≥ 60 on CBCL DSM-Anxiety subscale
N = 32 completers (pre/post assessments, ≥ 3 days of 4-day camp)

Kidpower: Effects of Intervention



Kidpower: Next steps

- Randomized trial of Kidpower vs. Playgroup control
- Continue collecting ERN as index of ACC-based cingulo-opercular network for salience detection
- Add Interchannel Phase Synchrony (ICPS) to index dlPFC-based frontal parietal network (FPN) for adaptive control
- Add behavioral assessment of fear



Can brain be modulated to stop anxiety and OCD early?

- TPN networks relevant to expression of OCD and anxiety
- Relevance of development?
  - Yes! Age-specific involvement of ERN in expression of OCD and anxiety symptoms
  - But…some functional relations may be conserved at some ages (e.g., OCD-CBT)
- Experimental strategies: Kidpower +/- CBT +/- Reward contingencies
  - Kidpower vs. exposure-based CBT vs combination?
    - Treatment Selection, guided by brain
  - Other neuromodulatory techniaues
    - Cognitive training apps (e.g., Aklili)
    - Transcranial magnetic stimulation
- How do neural systems for Cognitive Control/Fear/Reward interact?
- Long-term goal: Brain-based personalization
  - Different modulation, different child-specific “profiles” (Cognitive control, Fear, Reward)

Thank You!

- Jim Abelson, MD, PhD
- Angela Ayoub, LMSW
- **Emily Bilek, PhD**
- Katie Check, LMSW
- C. Emily Durbin, PhD
- Liz Duval, PhD
- Greg Hanna, MD
- Amanda Hicks, LLP
- **Joe Himle, PhD**
- Faith Horbatch, BA
- Jessica Hruschak, BA
- Ka Ip, MS
- Tim Johnson, PhD
- Eunice Kim, BA
- Jamie Lawler, PhD
- **Yanni Liu, PhD**
- Sharon Lo, MS
- Riley Lowe, BA
- Kristin Manella, BA
- Brody Mantha, LLMSW
- **Chris Monk, PhD**
- Frederick Morrison, PhD
- **Jason Moser, PhD**
- Maria Muzik, MD
- Jennifer Nidetz, LMSW
- **Luke Norman, PhD**
- Lisa O'Donnell, PhD
- **Luan Phan, MD**
- Scott Peltier, PhD
- Julie Premo, PhD
- Aileen Prout, LMSW
- Andrea Roberts, MS
- **Kate Rosenblum, PhD**
- Meryl Rueppel
- Katherine Raguckas
- Laura Stchur, LMSW
- Cameron Strong, BA
- Ashley Synger, MA
- **Steve Taylor, MD**
- Lauren Warsinske, LLMSW
- Robert Welsh, PhD
- Huan Yang, MD

STUDY FAMILIES!!!

NIH National Institute of Mental Health

AIM FOR MENTAL HEALTH