Task Control Networks in Pediatric Anxiety and Obsessive-Compulsive Disorders

Targets for Neuroscience-Guided Intervention?

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Anxiety: normal to disorder

Typical → Atypical

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

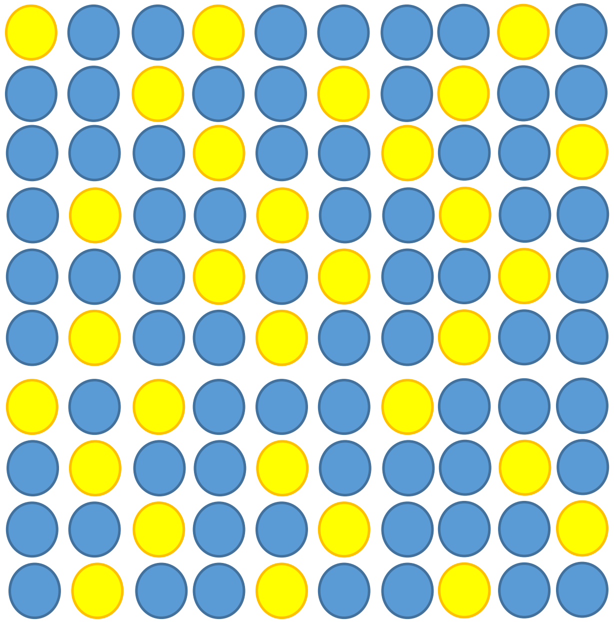
Anxiety Disorders Start EARLY

Disorder	Age 3 Assessment N	%	95% CI	Age 6 Assessment 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 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

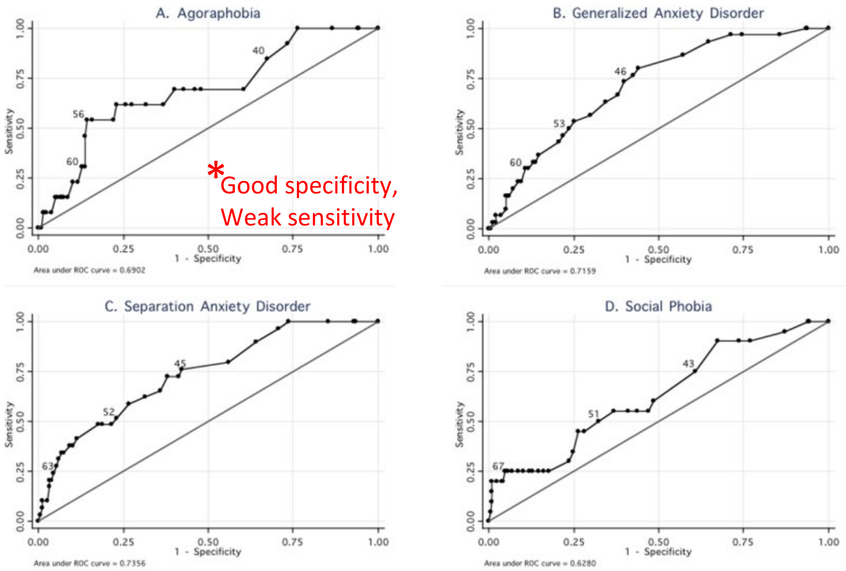
Baseline Internalizing and Externalizing CBCL scales predicting subsequent psychiatric disorders.

	Externalizing T-Score		Internalizing T-Score	
Psychiatric Disorder	Coefficient[95% Confidence Interval]	p-value	Coefficient[95% Confidence Interval]	p-value
*Agoraphobia	−0.06 [−0.15,0.03]	0.21	0.09 [0.05,0.14]	< 0.001
*Generalized Anxiety Disorder	−0.04 [−0.09,0.01]	0.11	0.09 [0.04,0.13]	< 0.001
*Separation Anxiety Disorder	0.00 [−0.06,0.05]	0.88	0.08 [0.04,0.13]	< 0.001
Specific Phobia	0.03 [−0.02,0.08]	0.17	0.04 [−0.01,0.10]	0.12
*Social Phobia	−0.03 [−0.08,0.02]	0.23	0.07 [0.02,0.11]	0.005
Panic Disorder	−0.06 [−0.15,0.03]	0.19	0.03 [−0.05,0.10]	0.46
Disruptive Behavior Disorders	0.10 [0.03,0.16]	0.004	0.01 [−0.04,0.06]	0.72
Major Depressive Disorder	0.10 [0.01,0.18]	0.03	−0.01 [−0.07,0.04]	0.57

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

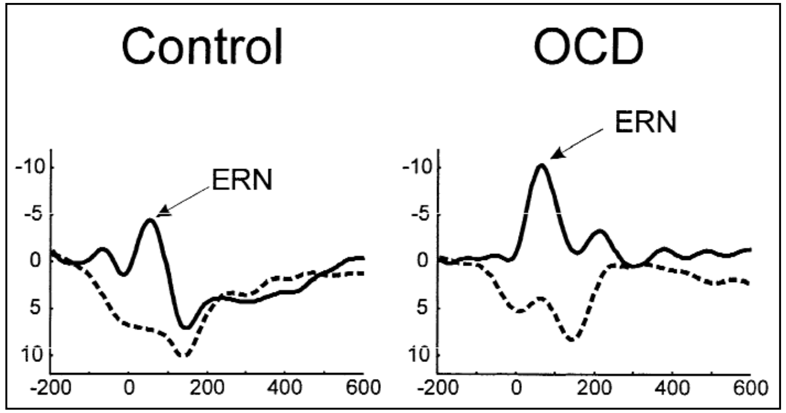
*CBCL Internalizing predicts later ADs, but weak predictor (low sensitivity)

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

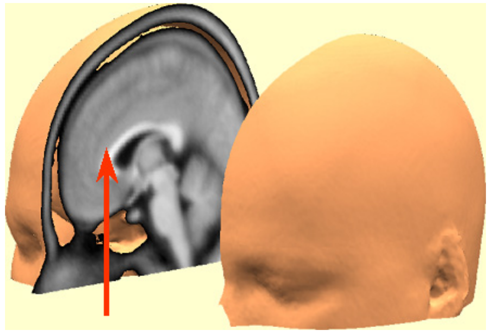


Petty et al, 2009

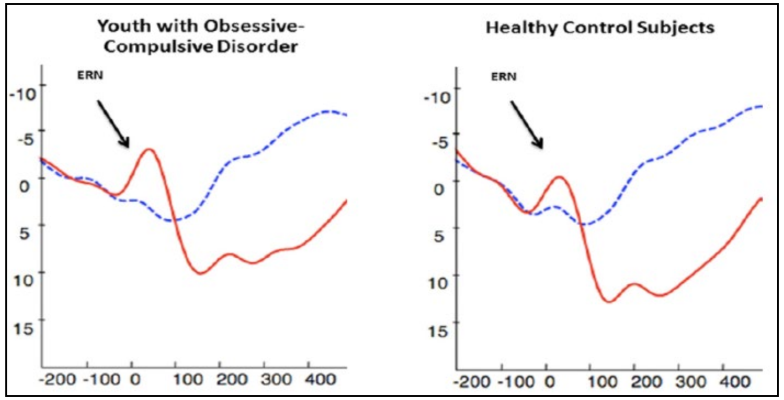
Electrophysiologic response to errors: Increased ERN in Anxiety/OCD



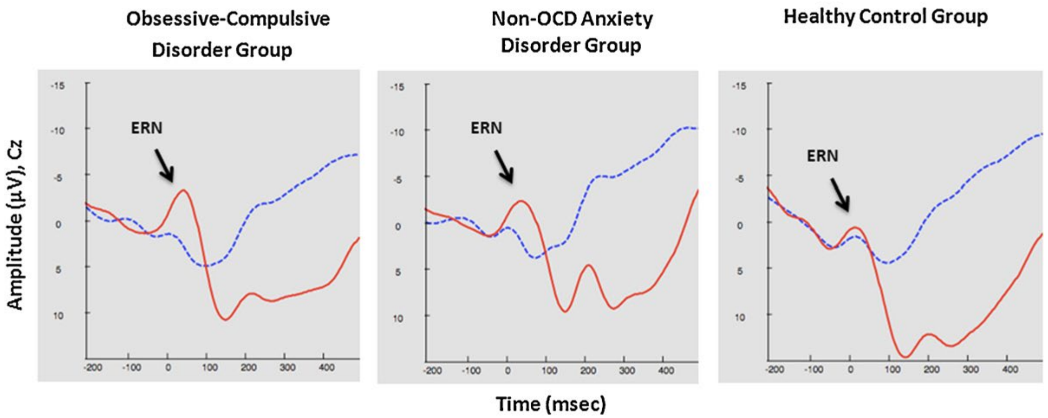
Gehring et al, 2000



Anterior Cingulate Cortex (ACC)



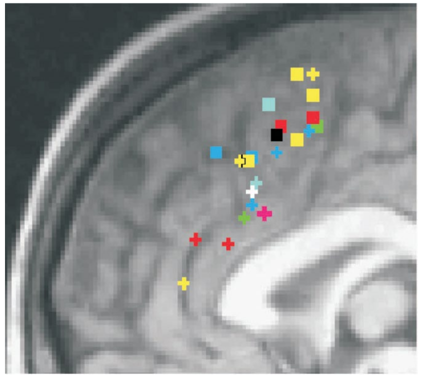
Hanna et al, 2011



Carrasco et al, 2013

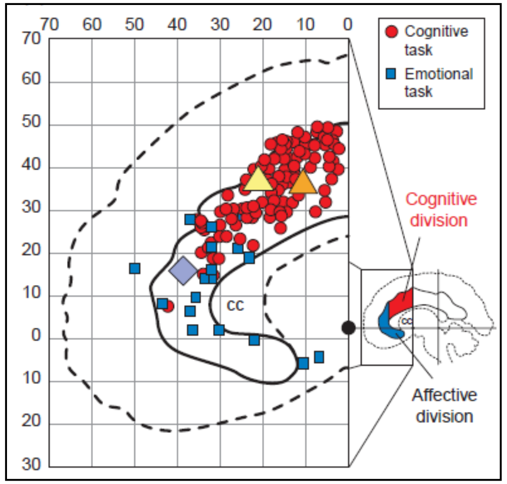
ERN in Anxiety/OCD: Functional Significance?

- <u>Affective response to errors</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>Errors/Interference</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")

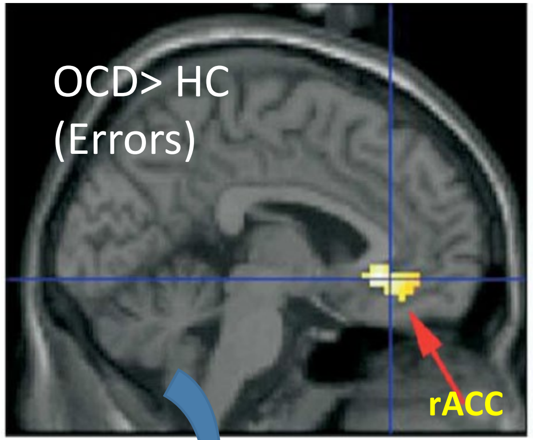


Hester et al, 2004

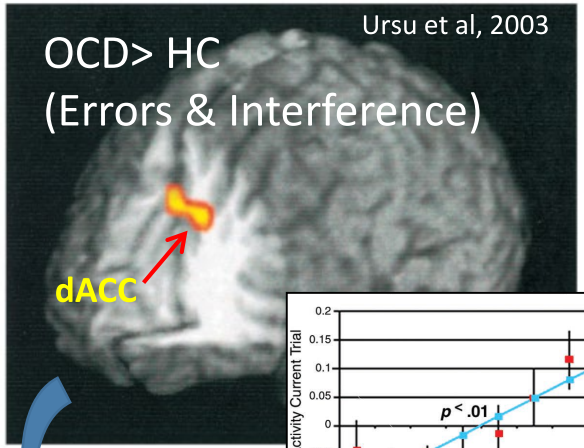
fMRI of Error Response in adult OCD
Does spatial localization clarify function?

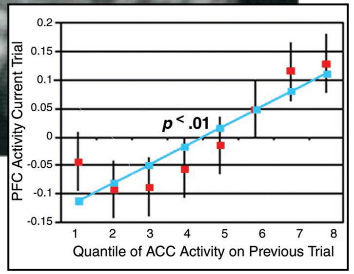


Bush et al, 2000



Fitzgerald et al, 2005



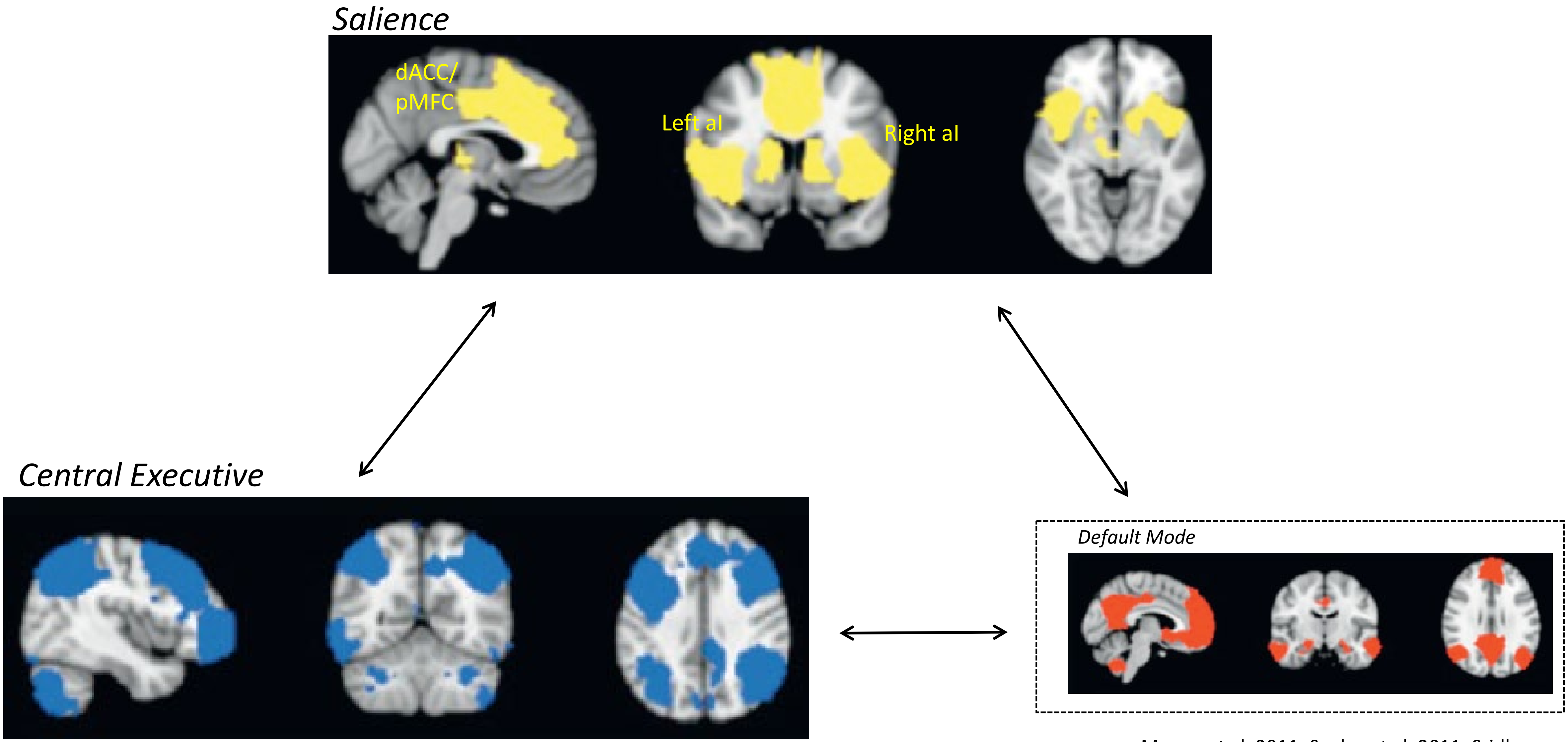


Kerns et al, 2004

Affective hypersensitivity? (etiologic)

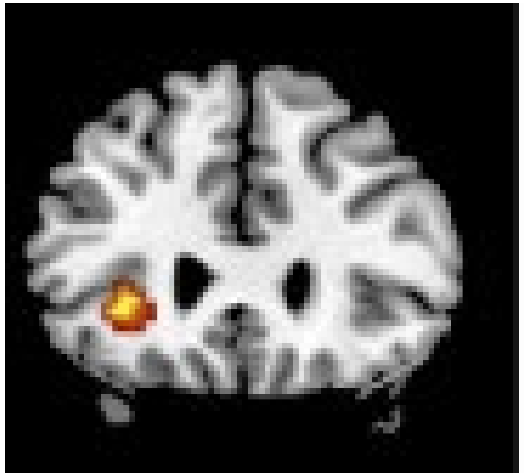
Behavioral adaptation? (compensatory)

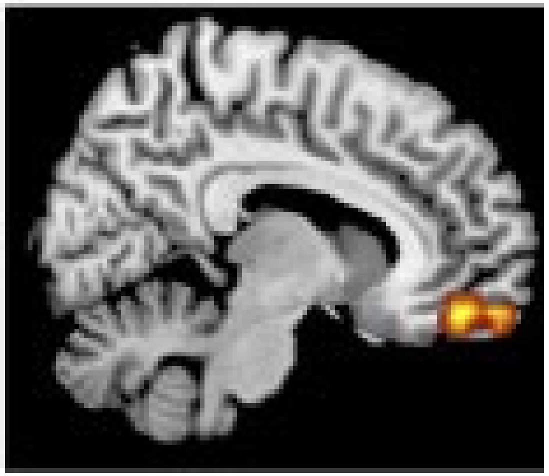
Task Control Networks



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

Salience Network in adult OCD: Hyperactivity of aI, vmPFC



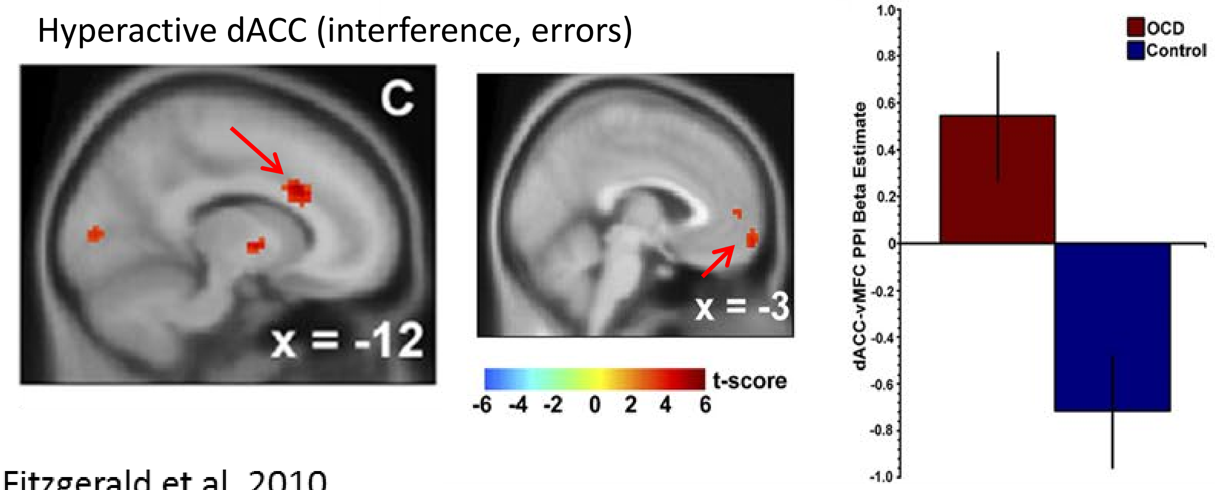


Stern et al, 2011

Task control networks in pediatric OC, anxiety disorders

Salience + Default Mode Networks

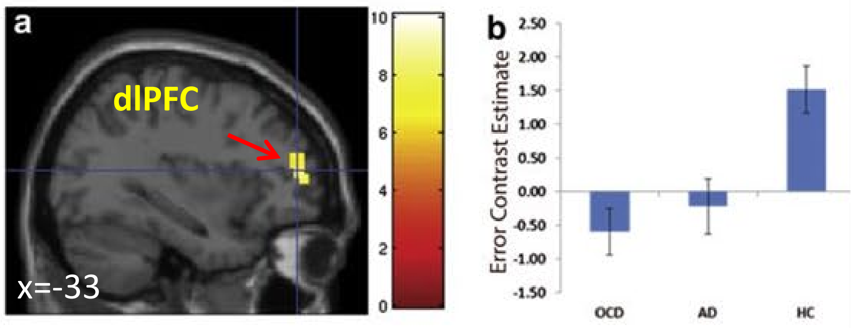
Hyperactive dACC (interference, errors)



Fitzgerald et al, 2010

Central Executive Network

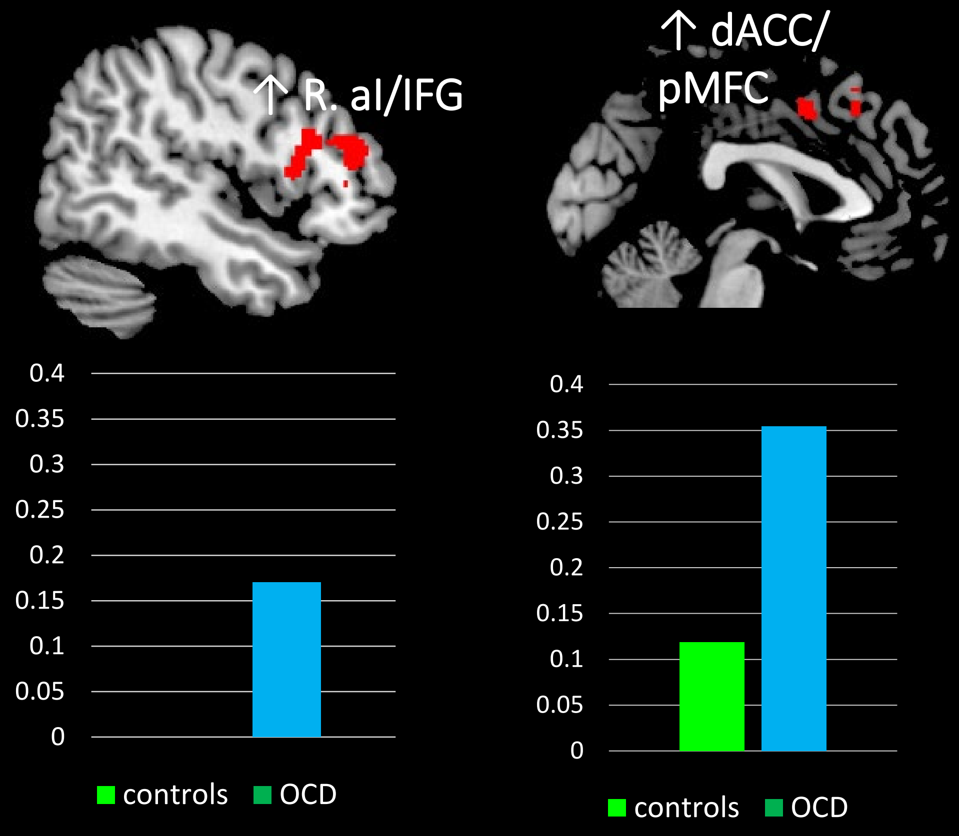
Hypoactive dlPFC (errors)



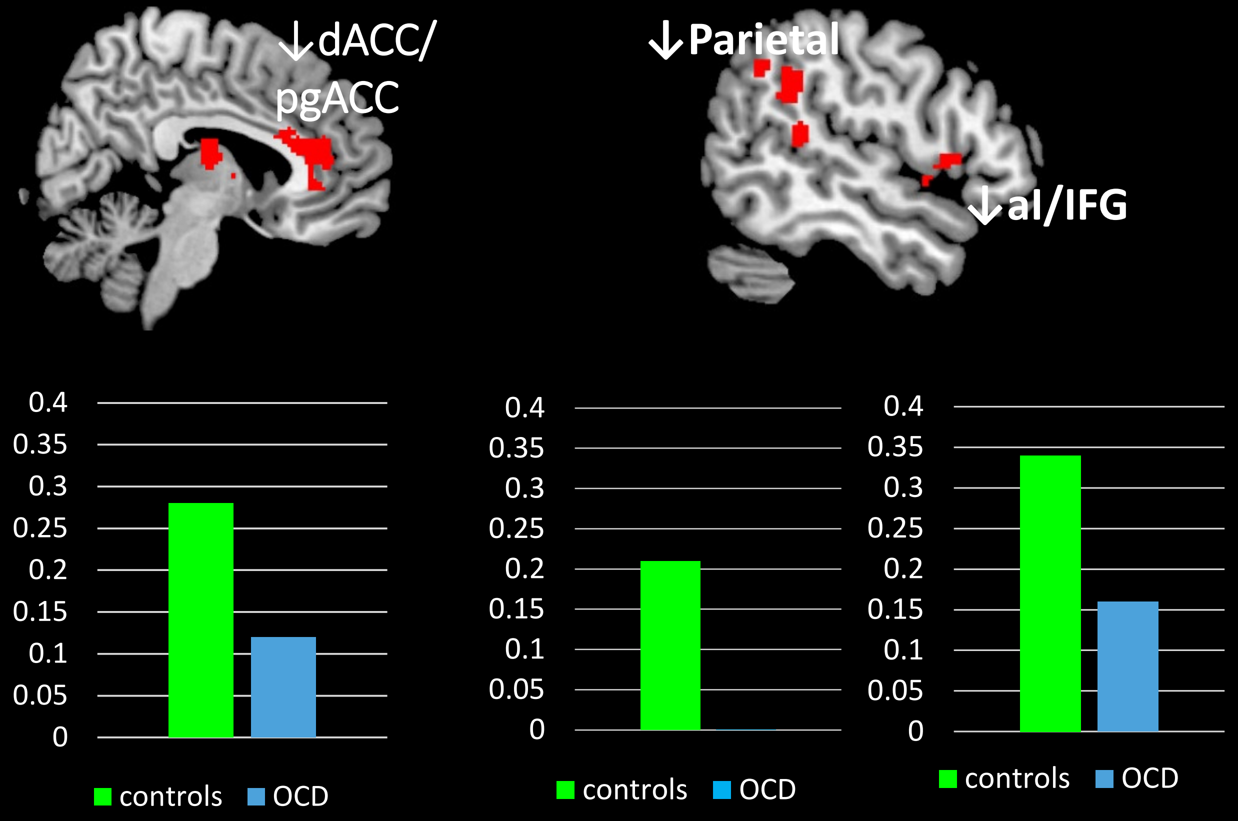
Fitzgerald et al, 2013

Meta-analysis: Task Control Networks in OCD

Errors: ↑ Salience Network

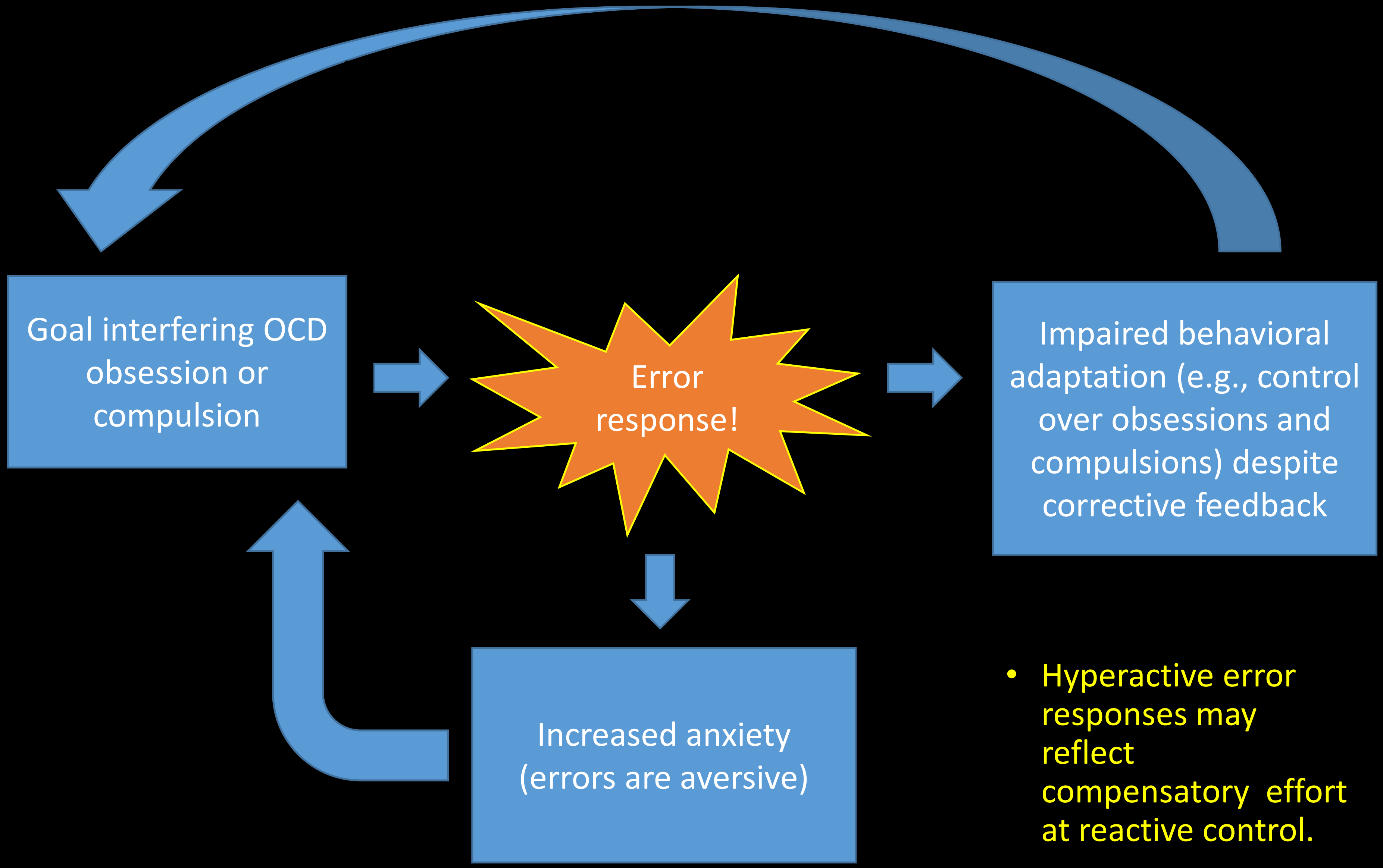


Inhibitory control * : ↓ Salience, Central Executive Networks



*impaired inhibitory control performance

Norman et al, under revision

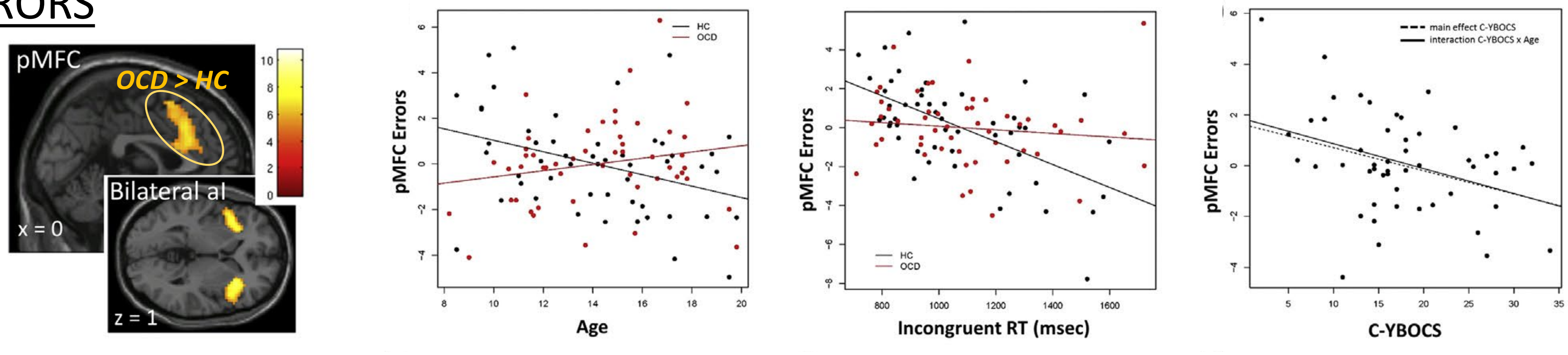


- Hyperactive error responses may reflect compensatory effort at reactive control.

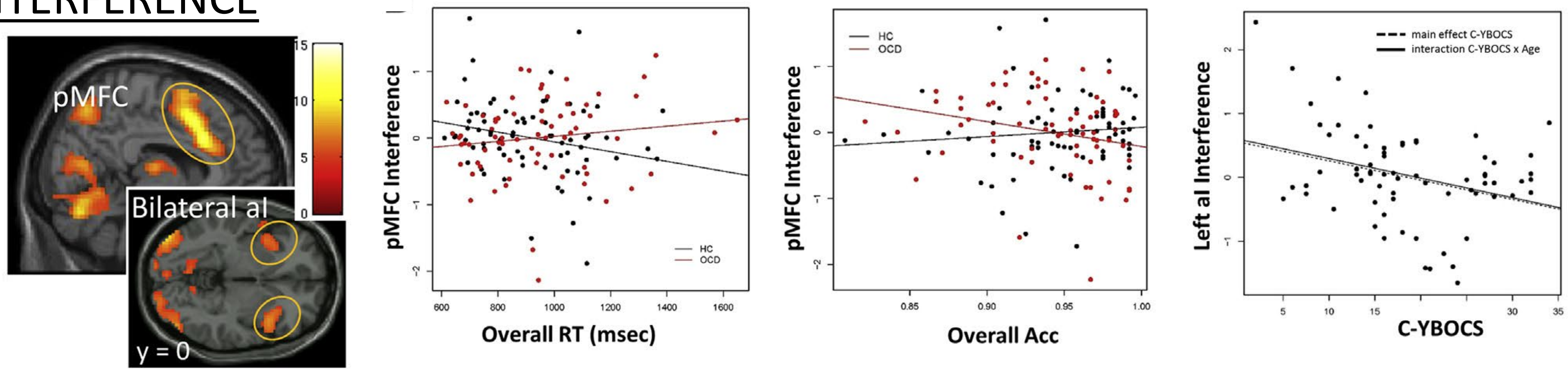
Norman et al, under revision

Hyperactive Salience Network : Compensatory?

ERRORS



INTERFERENCE



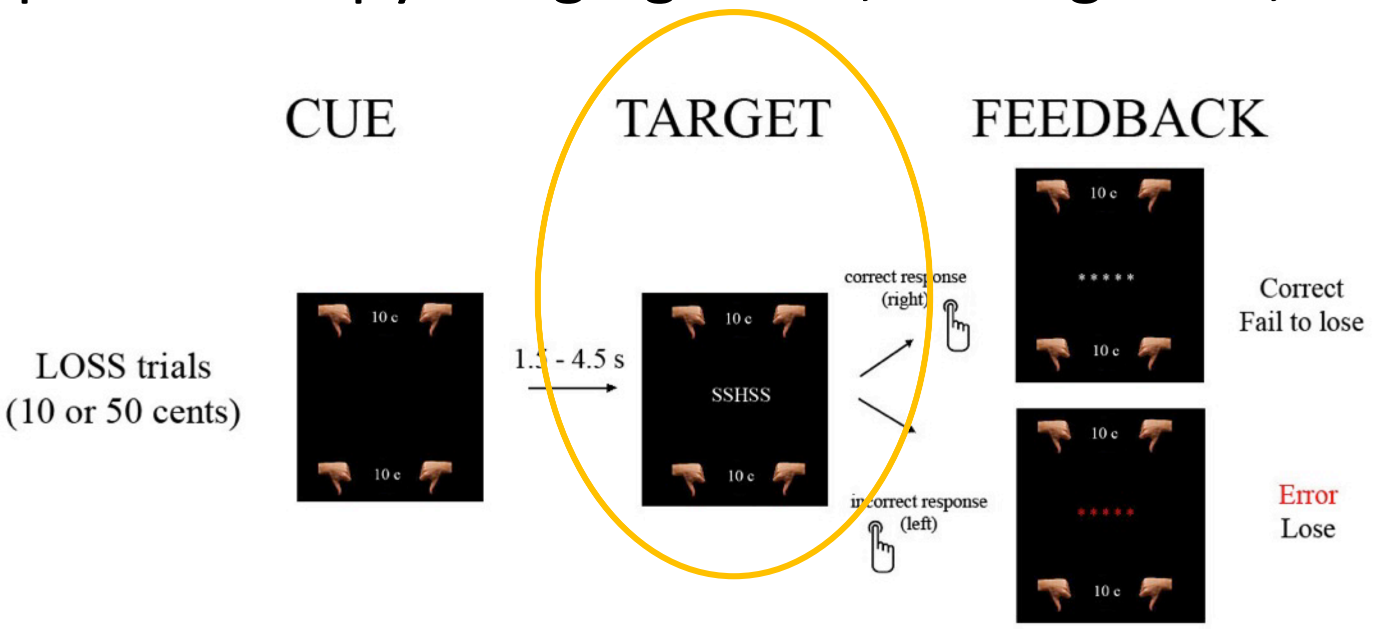
Manipulating Task Control Networks

CBT as Probe

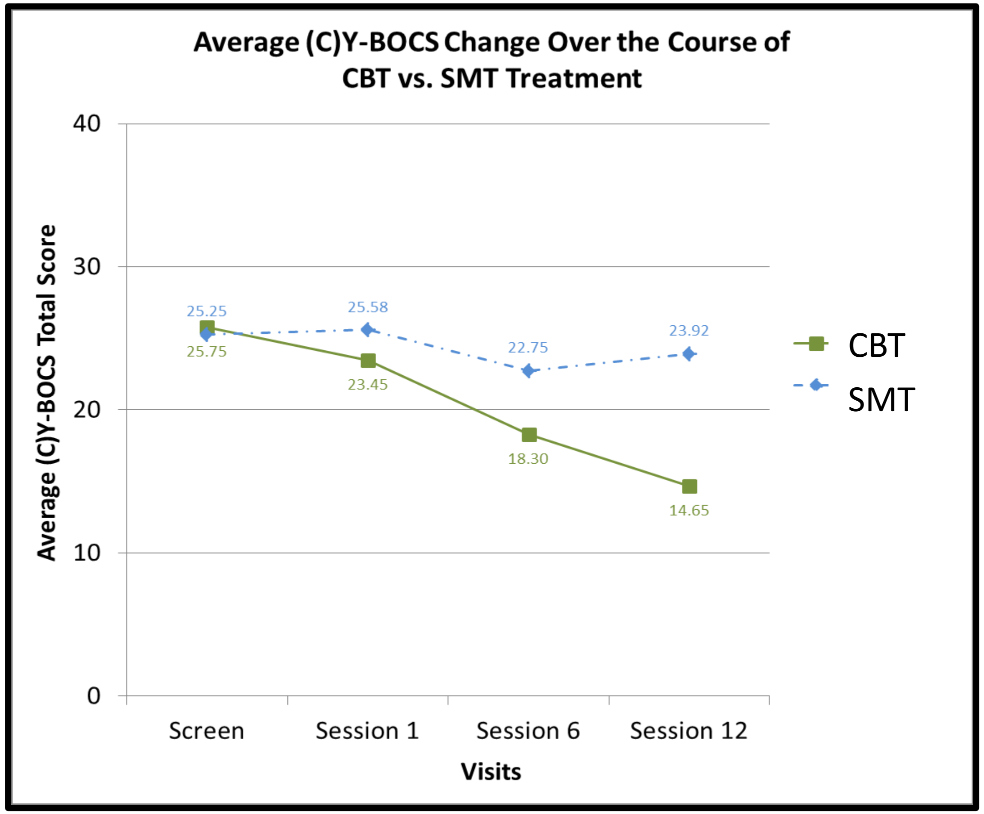
OCD: Task control network function & CBT outcome

- 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

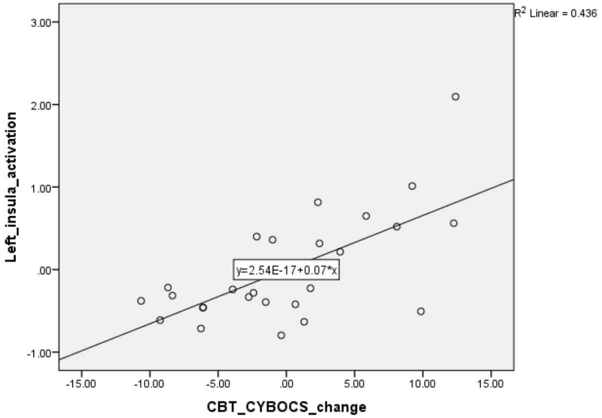


OCD: CBT Effect

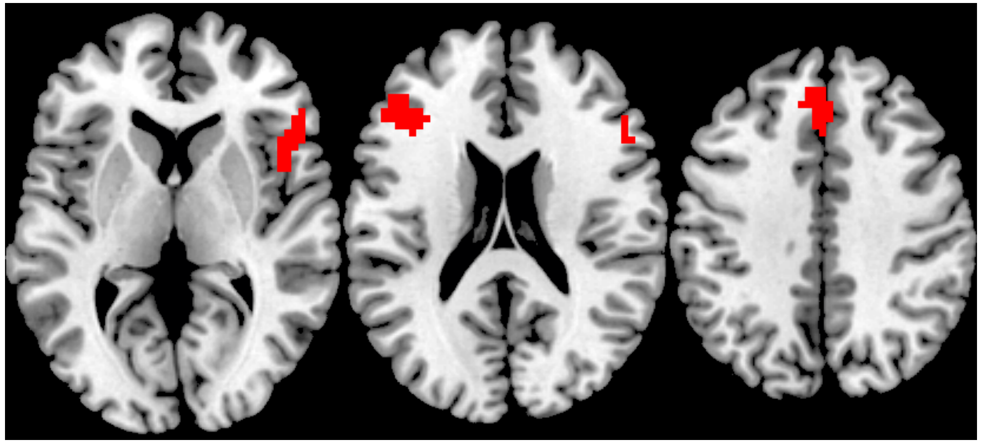


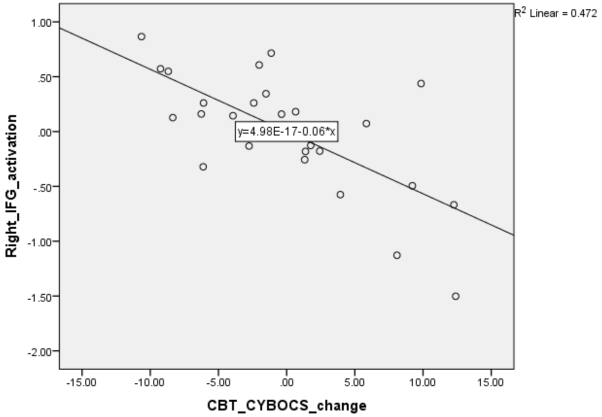
OCD: Better CBT outcome predicted by TCN function

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



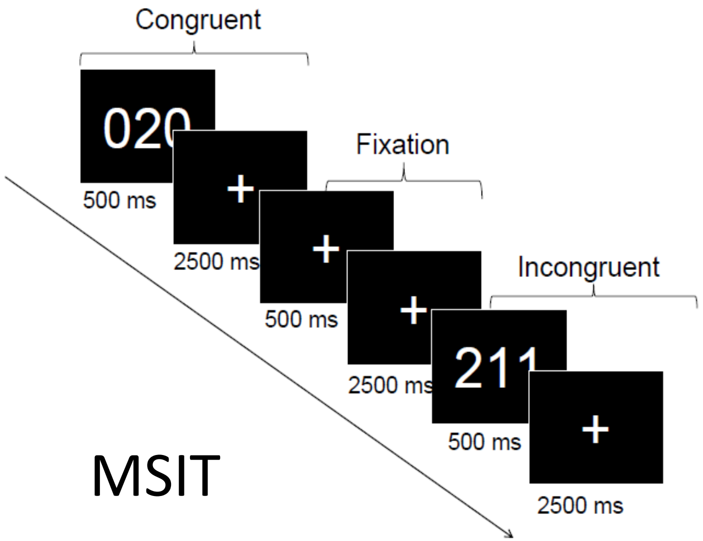
INTERFERENCE: ↑ Salience, Central executive network (right aI/IFG, left dlPFC, dACC); pre-CBT, n = 32





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

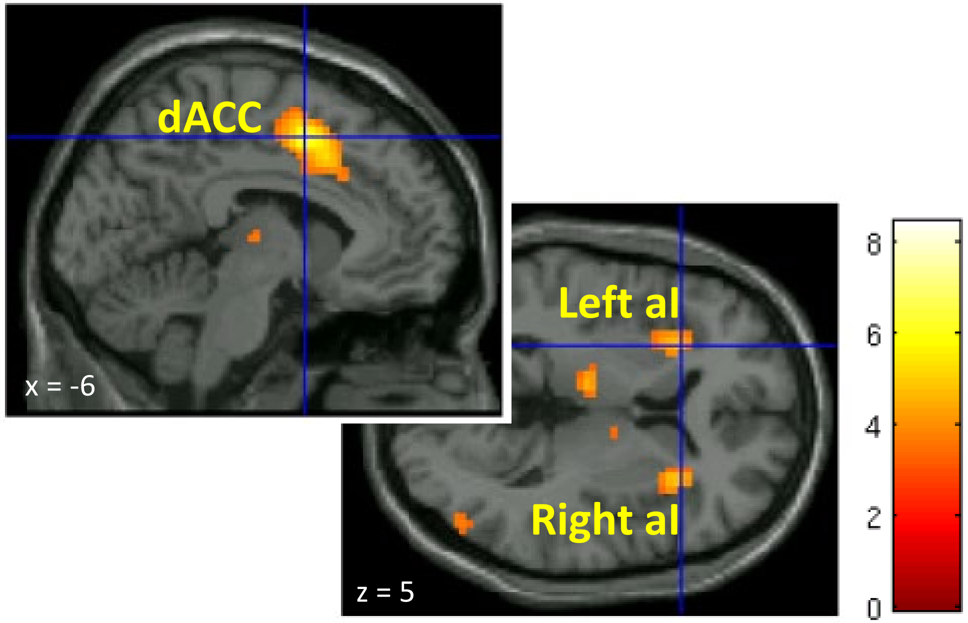


MSIT

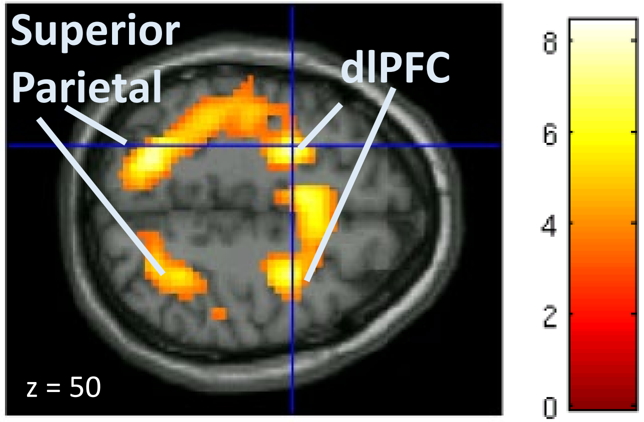
Anxiety: Task Control Network Activations to MSIT

Regions of interest: Interference-processing

<u>Salience Network</u>



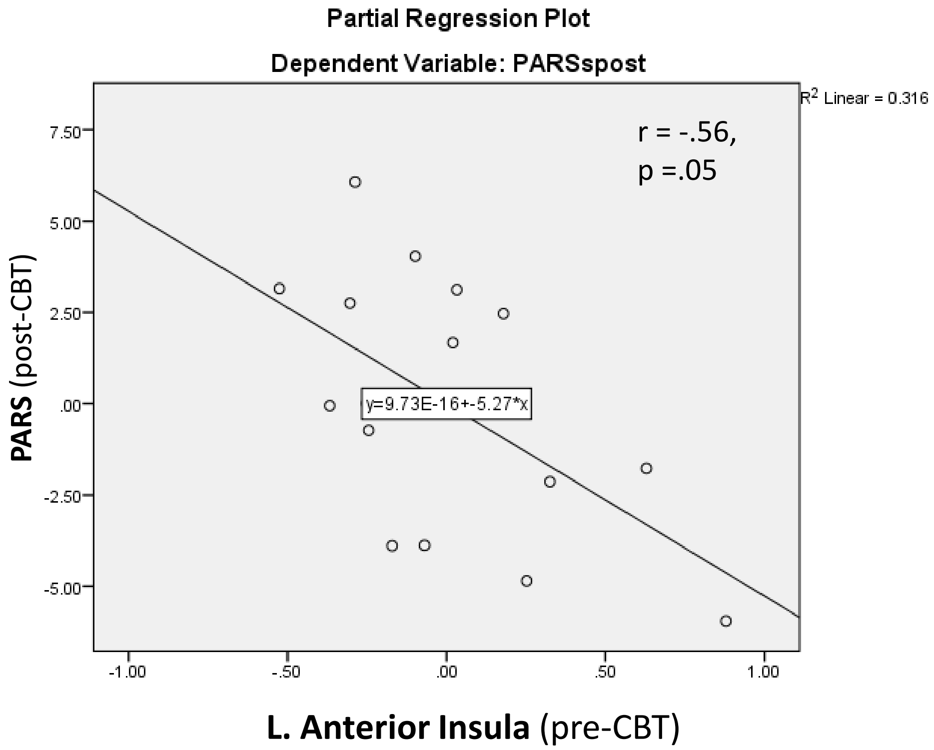
<u>Central Executive Network</u>

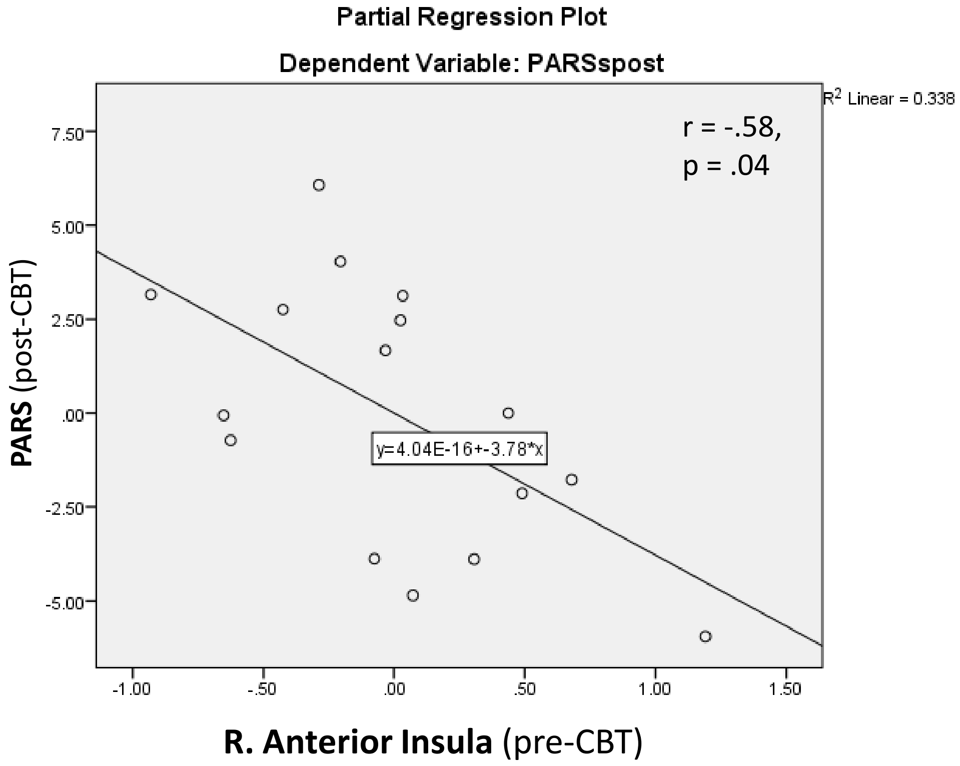


pfwe < .001 unc

Anxiety: TCN as Predictor of CBT response

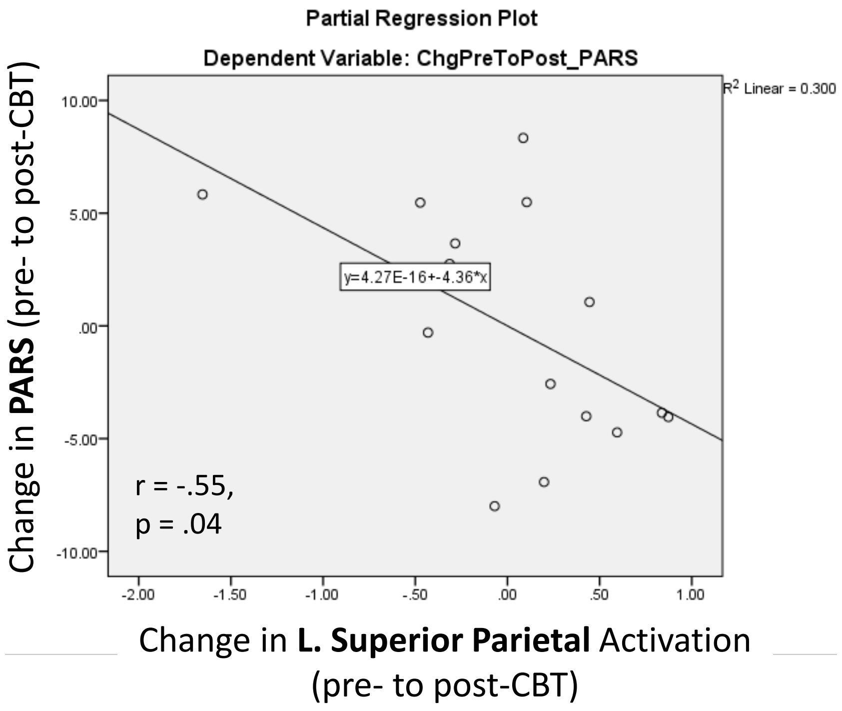
Interference: ↑ pre-CBT SN, better CBT response



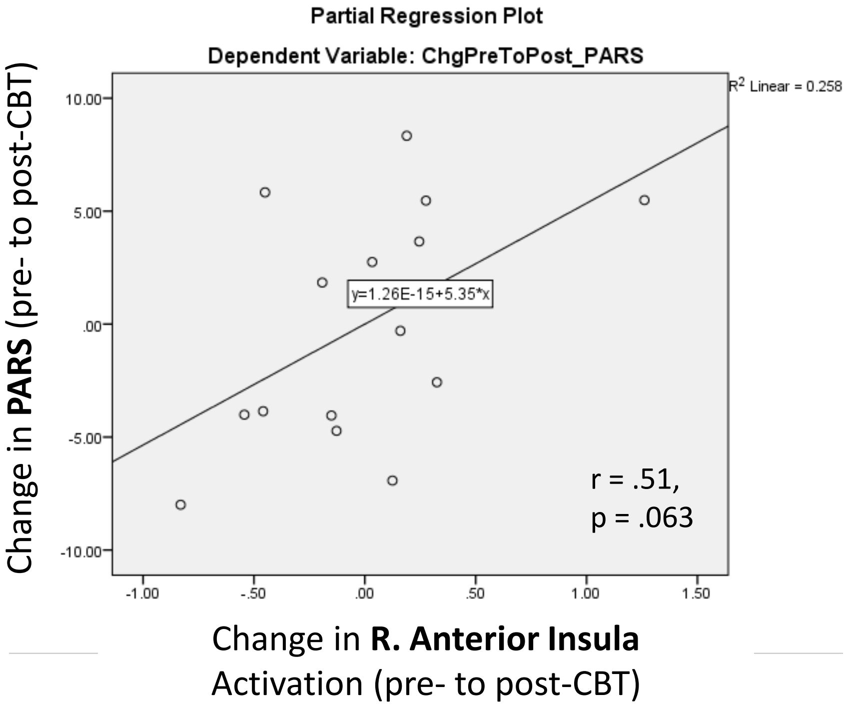


Anxiety: TCN as mechanism of change?

Interference: ↑ΔCentral executive network

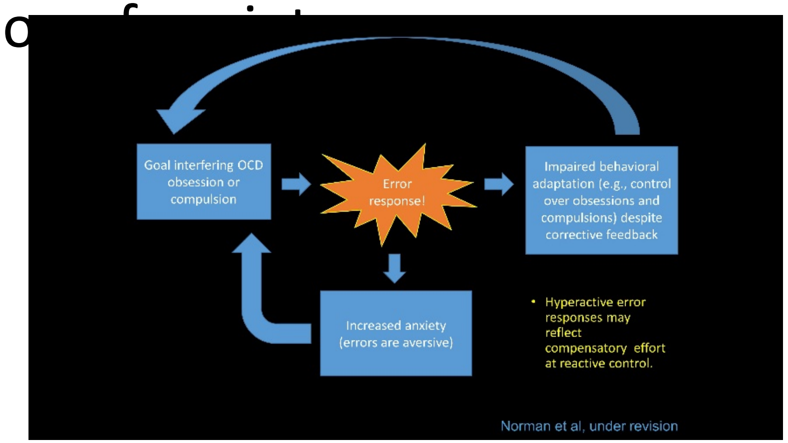


Interference: ↓ ΔSalience network



Summary: fMRI-CBT in OCD/Anxiety

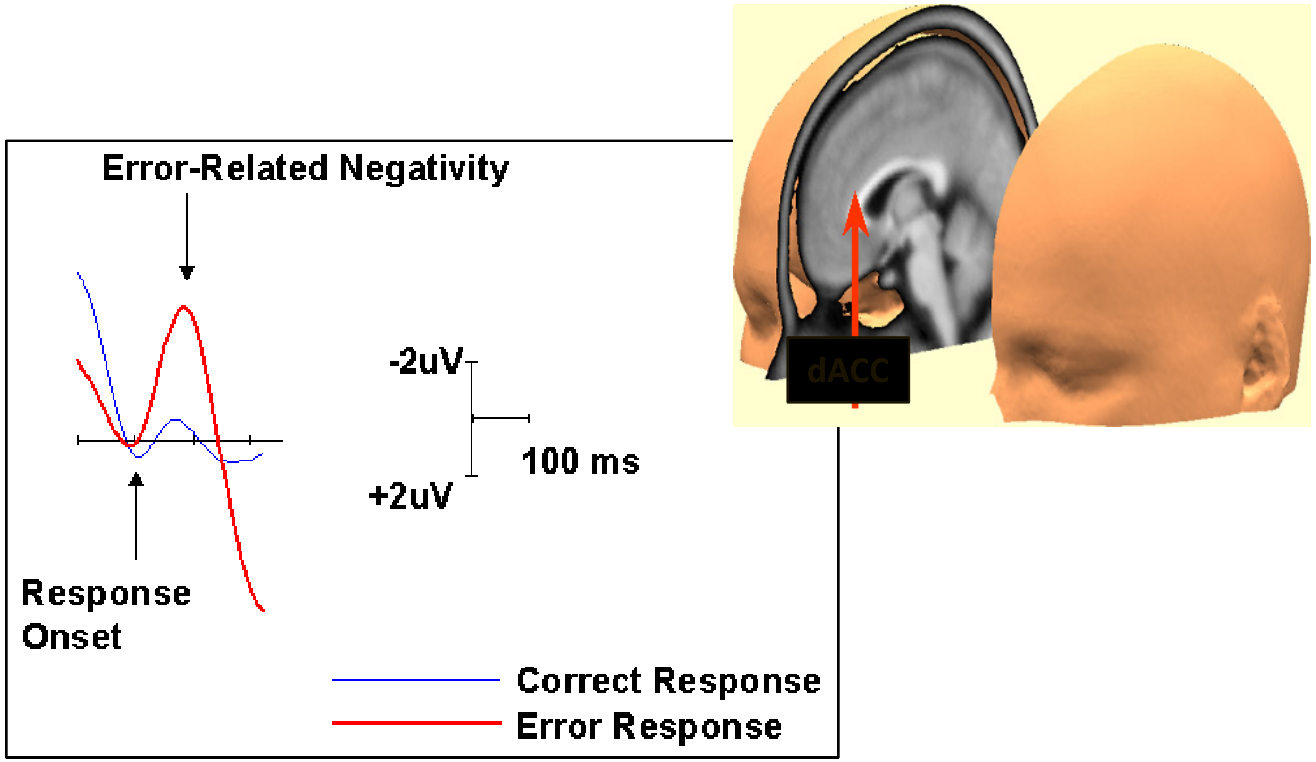
- Pre-CBT: greater SN predicts better response
- CEN *increase* → anxiety decrease
  - Increased engagement **left superior parietal cortex** associated with reduced anxiety after CBT
- SN (CO) network *decrease* → anxiety decrease
  - ~Decreased engagement **right anterior insula** associated with reduced anxiety after CBT
- Distinction between FP and cingulo-opercular (CO) networks?
  - Differential roles of FP and CO in generation and reductio
    symptoms



Manipulating Task Control Networks

Cognitive Training, the ERN and Early Childhood Anxiety

Error-related Negativity (ERN)

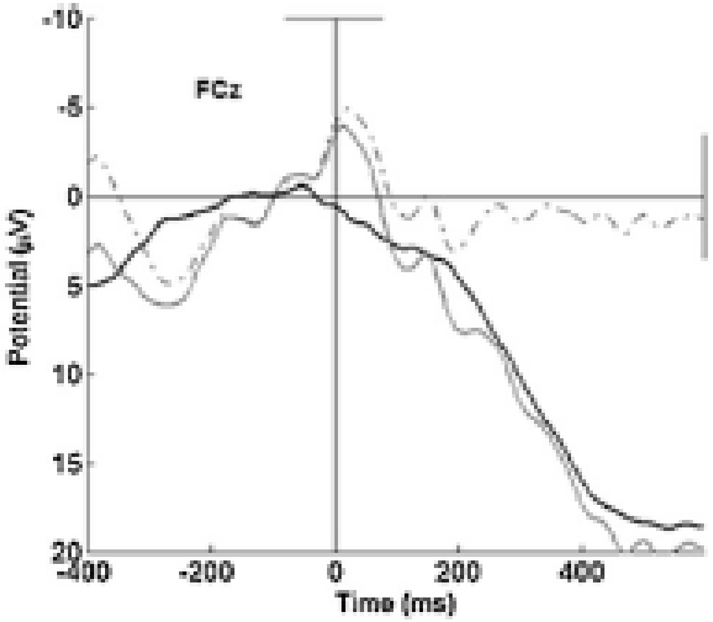


Gehring et al, 2000

ERN can be detected EARLY

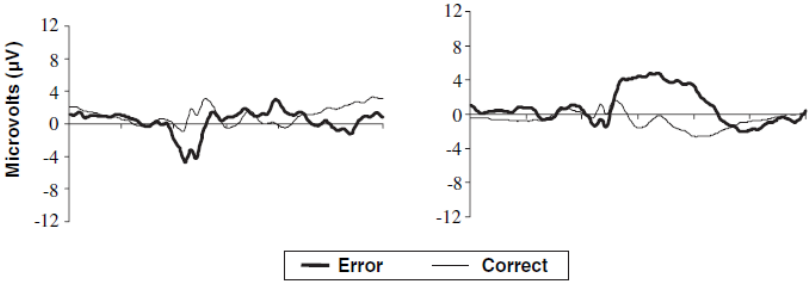
3 years

3 and 4 yr. olds



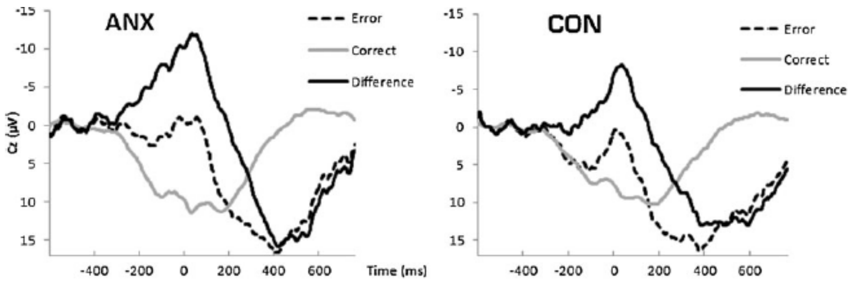
Grammer et al, 2014

8-14 yrs (n = 9, GAD, SAD, SoPho, SpPho)



Ladouceur et al, 2006

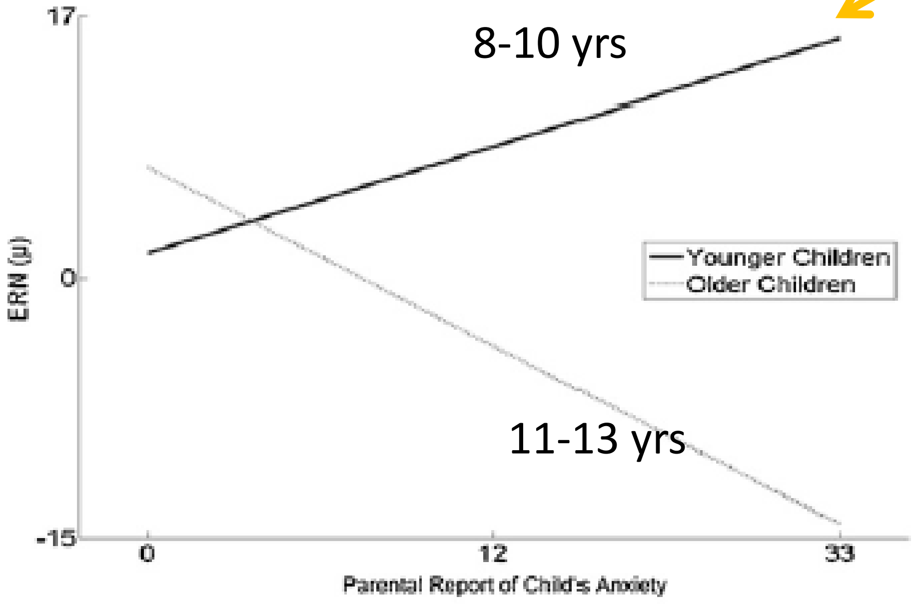
6 years (n = 48, SpPho,SAD,SoPho,GAD,OCD,agora)



Meyer et al, 2013

ERN & the Continuum of Anxiety

8-13 yrs (n = 55)



Meyer et al, 2012

Reversal ERN-internalizing in younger children?

Developmental shift in the relation of ERN – internalizing???

ERN α Internalizing: Gender Effect

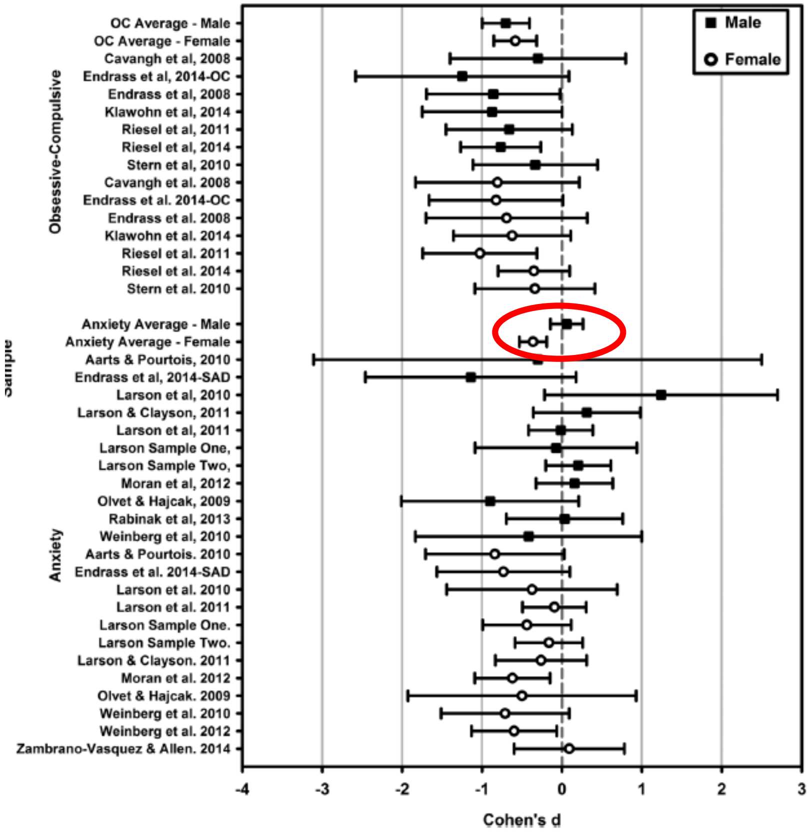
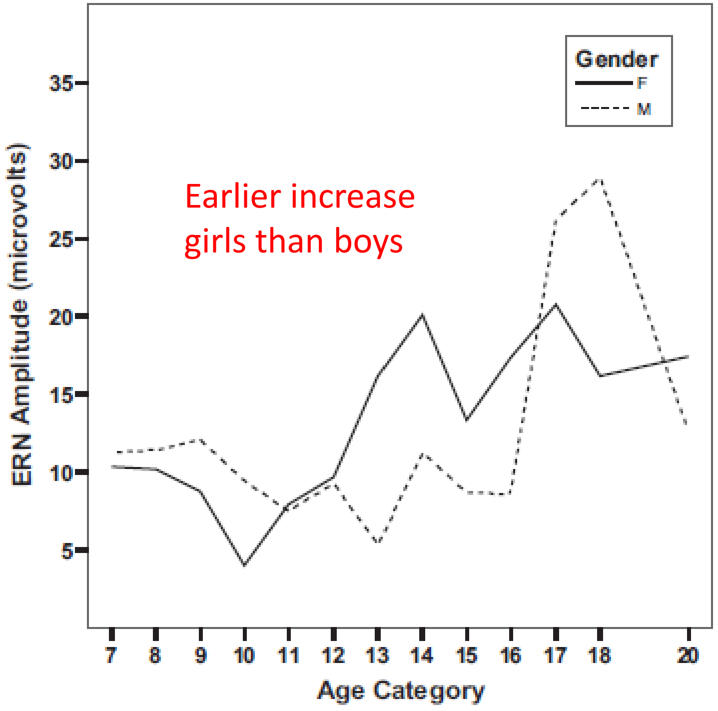


Table 2. *Results of the Meta-Analysis*

Sample	*d*	*k*	*N*	*p*	95% CI
All samples	−.361	37	1,460	< .001	−0.496; −0.225
OC symptoms[a]	−.637	14	455	< .001	−0.836; −0.439
Anxiety symptoms[a]	−.209	23	1,005	.005	−0.370; −0.049
OC–men[b]	−.703	7	202	< .001	−0.999; −0.406
OC–women[b]	−.584	7	253	< .001	−0.852; −0.316
Anxiety–men[c]	.060	11	411	.57	−0.144; 0.264
Anxiety–women[c]	−.362	12	594	< .001	−0.533; −0.190

Moser et al, 2016

ERN: Development Differs by Gender



Davies et al, 2004

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)

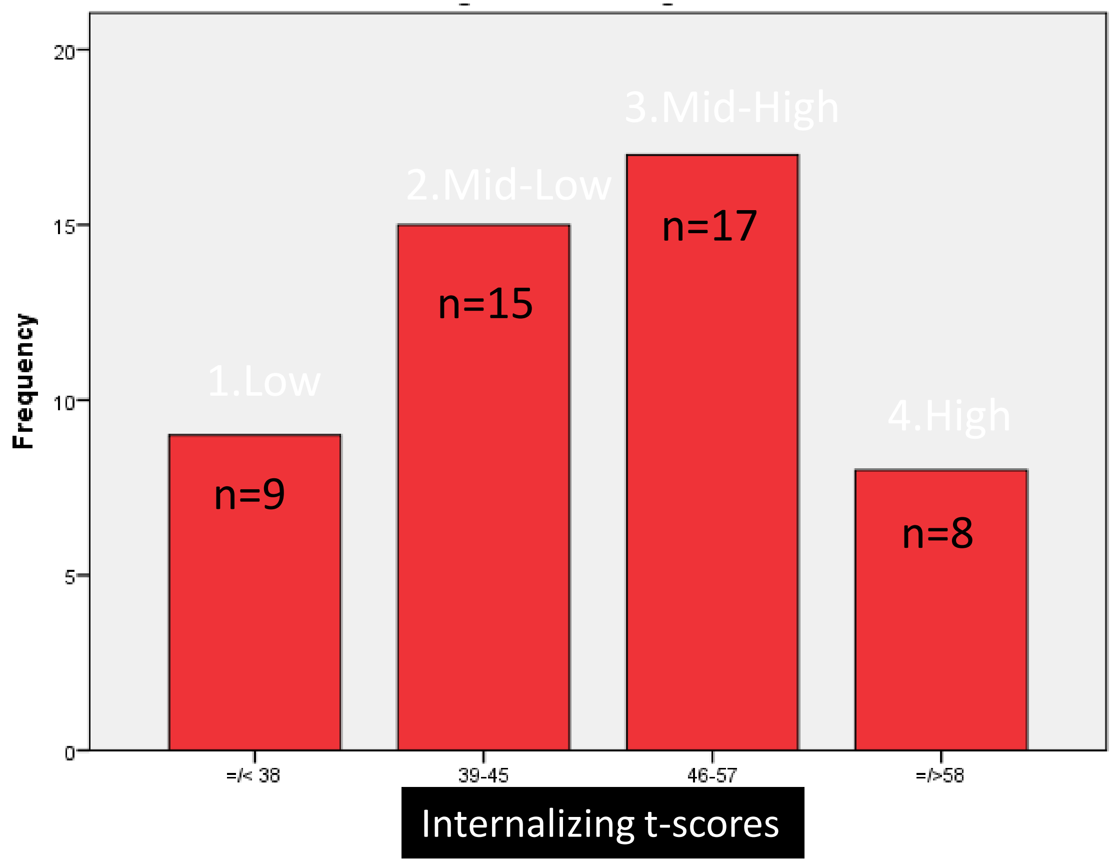
Achenbach & Rescorla, 2001

- 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



Internalizing by Age and Gender

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

*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

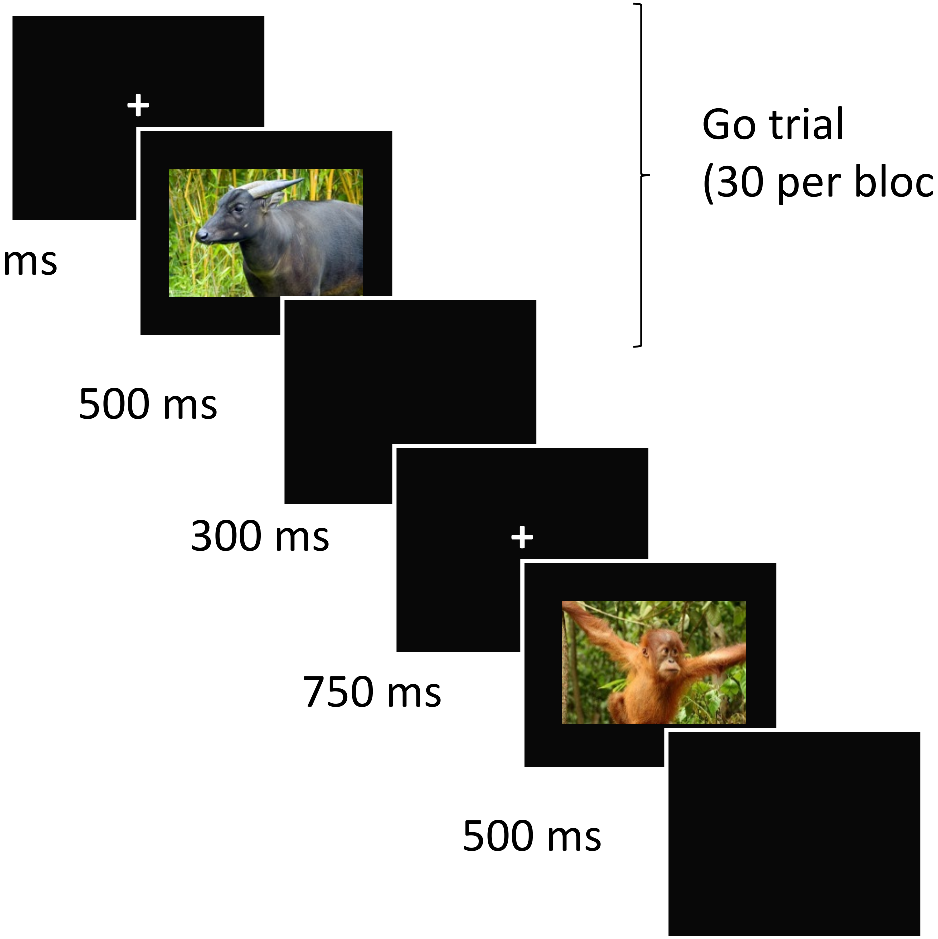
Zoo Game

Zookeeper Melissa

Orangutan helper

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

Zoo Game



300 ms

750 ms

500 ms

Go trial
(30 per block, 8 blocks)

300 ms

750 ms

500 ms

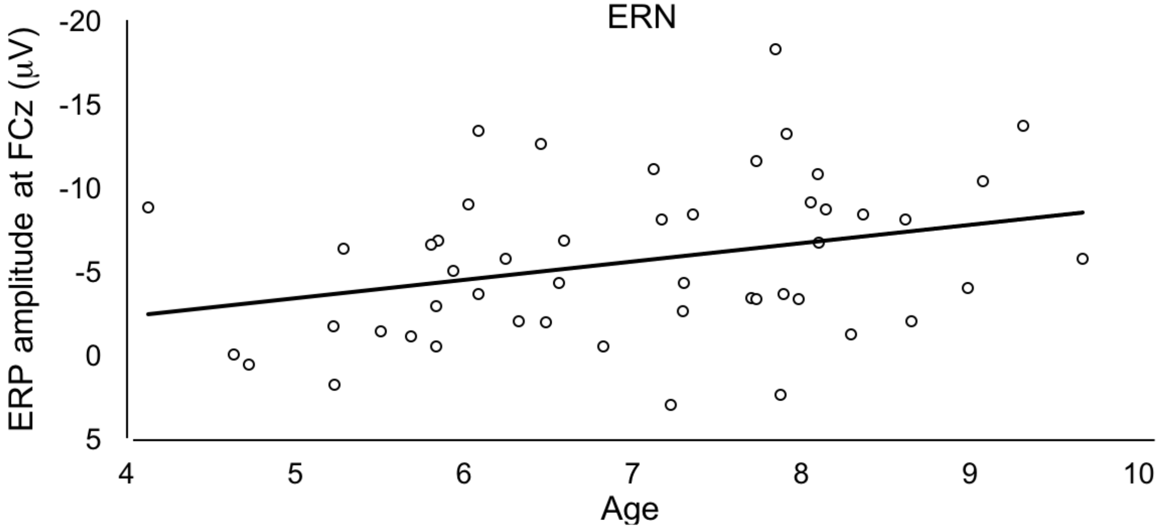
NoGo trial
(10 per block, 8 blocks)

Results: Behavioral

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

*More errors in younger than older (p=0.03), M than F (*p* =0.001)
**Slower RTs in younger than older (p = .02)

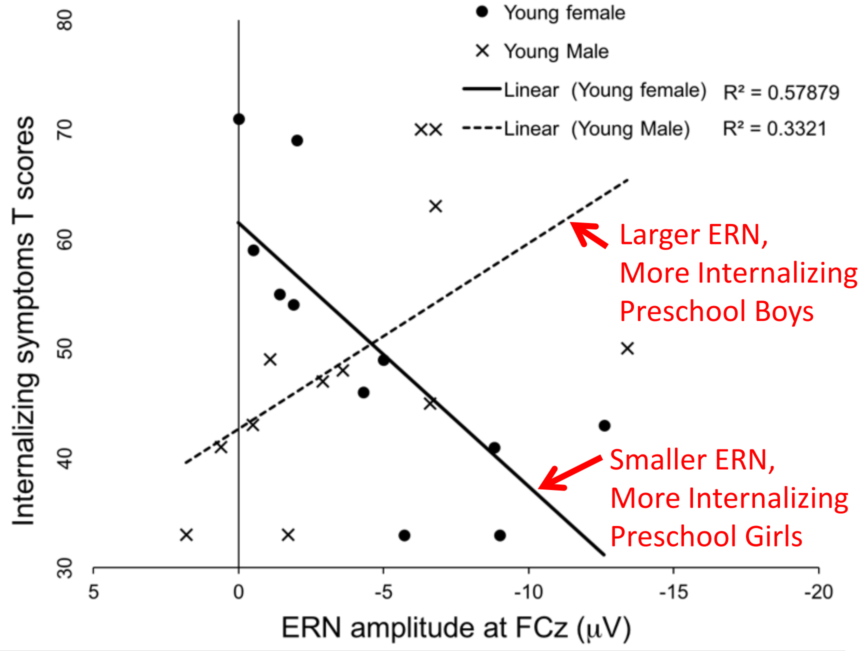
ERN increase with age

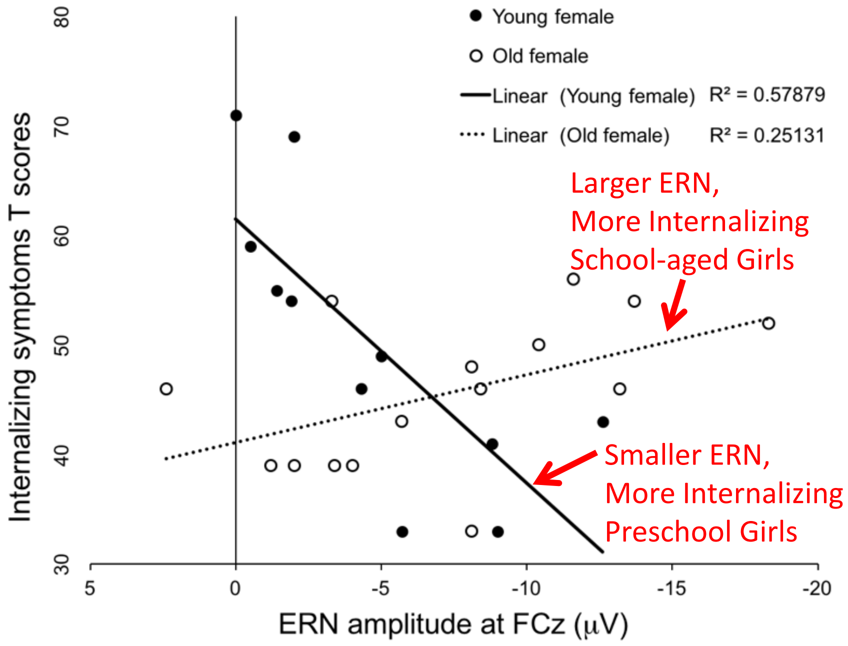


Age *B* = -.29, p = .055
(controlling gender, p = .89; NoGo errors, p = .25)

ERN Predicts Internalizing

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





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?

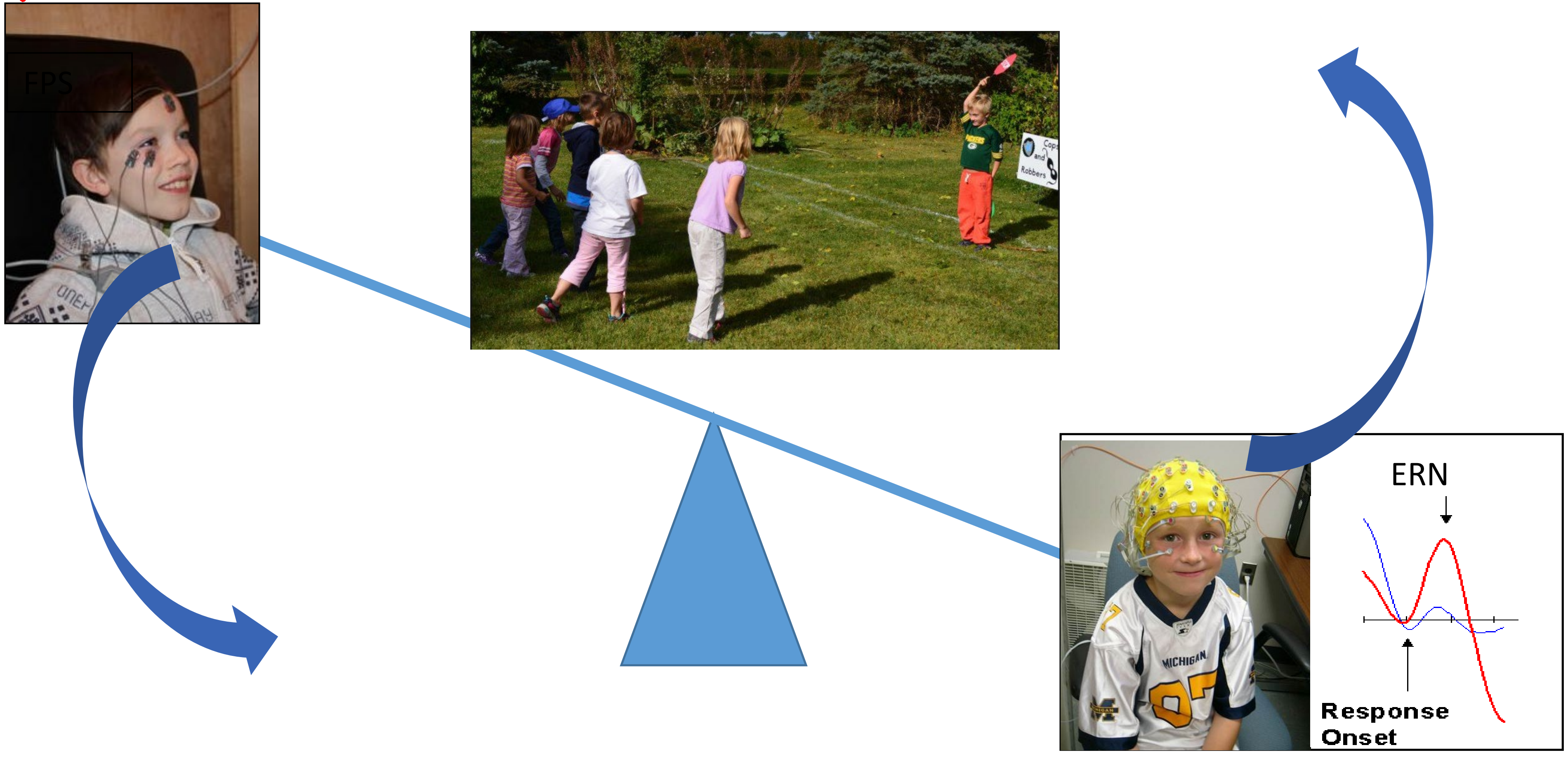
Next Steps

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.
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- Luan Phan, M.D.
- Tim Johnson, Ph.D.
- Maria Muzik, M.D., M.S.
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- R01 MH102242
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