

Resting-State Connectivity and Response to Psychotherapy Treatment in Adolescents and Adults With OCD: A Randomized Clinical Trial

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Objective: Cortical-subcortical hyperconnectivity related to affective-behavioral integration and cortical network hypoconnectivity related to cognitive control have been demonstrated in obsessive-compulsive disorder (OCD); the study objective was to examine whether these connectivity patterns predict treatment response.

Methods: Adolescents (ages 12–17) and adults (ages 24–45) were randomly assigned to 12 sessions of exposure and response prevention (ERP) or stress management therapy (SMT), an active control. Before treatment, resting-state connectivity of ventromedial prefrontal cortical (vmPFC), cingulo-opercular, frontoparietal, and subcortical regions was assessed with functional MRI. OCD severity was assessed with the Yale-Brown Obsessive Compulsive Scale before, during, and after treatment. Usable fMRI and longitudinal symptom data were obtained from 116 patients (68 female; 54 adolescents; 60 medicated).

Results: ERP produced greater decreases in symptom scores than SMT. ERP was selectively associated with less vmPFC-subcortical (caudate and thalamus) connectivity in both age

groups and primarily in unmedicated participants. Greater symptom improvement with both ERP and SMT was associated with greater cognitive-control (cingulo-opercular and frontoparietal) and subcortical (putamen) connectivity across age groups. Developmental specificity was observed across ERP and SMT treatments, such that greater improvements with ERP than SMT were associated with greater frontoparietal-subcortical (nucleus accumbens) connectivity in adolescents but greater connectivity between frontoparietal regions in adults. Comparison of response-predictive connections revealed no significant differences compared with a matched healthy control group.

Conclusions: The results suggest that less vmPFC-subcortical connectivity related to affect-influenced behavior may be important for ERP engagement, whereas greater cognitive-control and motor circuit connectivity may generally facilitate response to psychotherapy. Finally, neural predictors of treatment response may differ by age.

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Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental health condition characterized by intrusive thoughts and repetitive behaviors. Cognitive-behavioral therapy with exposure and response prevention (ERP) is a first-line treatment for OCD that involves patients learning to face symptom-provoking stimuli and resisting the urge to perform compulsive behaviors (1). Although ERP is associated with large effect sizes in relationship to symptom improvement (1), there is great variability in treatment response across patients (2). Why some individuals respond better to ERP than others remains poorly understood. The use of neuroimaging to define brain-based predictors has the potential to answer this question.

Recently, neuroimaging studies have demonstrated that brain activation and connectivity prior to treatment can be

used to predict the response to ERP across a variety of conditions, including OCD (3–5). Brain regions implicated in these studies are involved in two functional neuroanatomical models of behavior that are relevant for both OCD symptomatology and ERP mechanisms. One model is based on cortico-striato-thalamo-cortical (CSTC) connections, originally described in animal work (6), that are involved in habitual behavior, cognitive control, response inhibition, motivation, and fear extinction (7). The other model involves a tripartite network defined on the basis of resting-state intrinsic connectivity.

In OCD, excessive CSTC metabolic activity that increases with symptom provocation has been most consistently localized to CSTC loops encompassing the ventromedial prefrontal cortex (vmPFC), striatum, and thalamus (8–11). Given

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TABLE 1. Participant demographic and clinical characteristics stratified by treatment group and age^a

Characteristic	ERP Group				SMT Group			
	Adolescents (N=27)		Adults (N=31)		Adolescents (N=27)		Adults (N=31)	
	N	%	N	%	N	%	N	%
Female	18	67	16	52	18	67	16	52
Minority race	5	19	2	6	1	4	8	26
Hispanic	4	15	3	10	1	4	1	3
Serotonergic medications ^b	18	67	14	45	15	56	13	42
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	15.76	1.56	31.99	5.73	15.50	1.68	32.03	6.01
Age at onset (years)	10.59	3.49	10.65	3.27	9.70	3.99	14.10	5.07
Illness duration (years)	5.17	3.33	21.35	6.71	5.80	3.75	17.93	6.88
Y-BOCS score								
Baseline	26.19	5.34	23.76	5.15	27.61	5.04	26.90	4.68
Midtreatment	19.98	6.47	17.29	6.29	24.87	6.27	23.81	4.86
End of treatment	13.46	9.62	11.62	6.24	21.73	8.49	23.08	7.29
	B	SE	B	SE	B	SE	B	SE
Change over time	-1.06***	0.10	-0.98***	0.08	-0.44***	0.11	-0.30***	0.09

^a For full sample details, including patient withdrawal from study, comorbidity status, and additional clinical measures, see the online supplement. d=Cohen's d; ERP=exposure and response prevention; OCD=obsessive-compulsive disorder; SMT=stress management therapy; Y-BOCS=Yale-Brown Obsessive Compulsive Scale (child or standard version).

^b Selective serotonin reuptake inhibitors: citalopram (N=2), escitalopram (N=10), fluoxetine (N=14), fluvoxamine (N=5), paroxetine (N=3), sertraline (N=19); selective norepinephrine reuptake inhibitors: venlafaxine (N=1), milnacipran (N=1); norepinephrine-dopamine reuptake inhibitor: bupropion (N=1); tricyclic antidepressant: clomipramine (N=4); others: buspirone (N=4), trazodone (N=1).

†p<0.1. *p<0.05. **p<0.01. ***p<0.001.

the role of the vmPFC in emotionally driven evaluative functions (e.g., reward processing and internal mood states) (12), excessive activity within these loops has been hypothesized to drive OCD symptoms (7) and could make it difficult for patients to break the vicious cycle of anxiety-provoking thoughts and repetitive behavior that are targeted in treatment. Indeed, less vmPFC-limbic connectivity has been found to predict better ERP outcomes (13), in line with traditional learning theories that ERP may reduce fear by extinction (14, 15) or inhibitory learning (16), processes that rely on the frontolimbic circuitry of the vmPFC (7). On the other hand, greater activity in the striatum and in the thalamus have been identified as indicators that specifically predict a better treatment response in those with OCD than in those with anxiety disorders (17).

The other neuroanatomical model of behavior, the tripartite network model, focuses on resting-state intrinsic connectivity of the frontoparietal network (FPN) involved in executive function and cognitive control, the cingulo-opercular network (CON) involved in salience processing, and the default mode network (DMN) involved in self-referential processing and episodic memory retrieval (18). In OCD, aberrant connectivity of the vmPFC within the DMN has been theorized to partially underlie the intrusive off-task thoughts that characterize obsessive symptoms (19). Compared to those without OCD, patients with OCD show atypical connectivity of the DMN with CON and FPN regions and less task-related deactivation of the DMN (19–21). In this tripartite network framework, ERP may recruit top-down cognitive-control processes through CON and FPN circuitry as patients resist the urge to perform compulsive behaviors (7, 22). It is possible that patients with greater capacity to

successfully engage these control circuits may show greater symptom improvements from ERP than those with less capacity to engage these circuits (17). In line with the notion that ERP regulates compulsive behavior in response to obsessions, activation and connectivity of these networks can predict response to ERP (17, 23–26).

Critically, striato-thalamic regions interconnect distant parts of the cerebral cortex, including regions of the DMN, CON, and FPN, via CSTC loops (27, 28), which provide neurofunctional connections through which these cortical networks may interact. A recent meta-analysis (20) reported that functional connectivity between the tripartite networks and the CSTC loops differentiated OCD patients from healthy control participants, suggesting that examining connections from both of these models is important to furthering our understanding of OCD. However, previous studies have not fully tested the extent to which connectivity between subcortical nodes of the CSTC and cortical areas of the DMN, FPN, and CON predict treatment outcomes. Other limitations of the neuroimaging literature on treatment prediction in OCD include small sample sizes and the lack of an active control therapy group. Moreover, few studies have examined neuroimaging predictors of treatment response in adolescents with OCD (25), despite evidence for age-related differences in the efficacy of ERP (1, 29) and developmental changes in functional connectivity with age (30).

In this study, we addressed these limitations by examining how resting-state functional connectivity between the subcortical nodes of the CSTC loops and cortical areas related to affect modulation (e.g., the vmPFC) and cognitive control predict symptom improvement with ERP in a large sample of adolescents and adults with OCD. We included an active

Healthy Control Group				Group Comparisons					
Adolescents (N=32)		Adults (N=31)		ERP vs. SMT		OCD Adolescents vs. Adults		OCD vs. Healthy Control Group	
N	%	N	%	χ^2	df	χ^2	df	χ^2	df
20	63	20	65	0.00	1	0.24	1	0.41	1
12	38	17	55	0.29	1	0.61	1	22.55***	1
5	16	2	6	3.01 [†]	1	0.32	1	0.56	1
—	—	—	—	0.27	1	0.60	1	—	—
Mean	SD	Mean	SD	t	d	t	d	t	d
15.50	1.23	31.54	6.03	-0.06	-0.01	—	—	-0.69	-0.13
—	—	—	—	1.80 [†]	0.34	2.84**	0.53	—	—
—	—	—	—	-0.91	-0.17	—	—	—	—
—	—	—	—	2.48*	0.46	-1.63	-0.30	—	—
—	—	—	—	5.16***	0.96	-1.53	-0.29	—	—
—	—	—	—	6.73***	1.26	-0.04	-0.01	—	—
				B	SE	B	SE		
				0.65***	0.09	-0.12	0.10		

control psychotherapy condition, namely, stress management therapy (SMT), to specifically isolate the neural predictors of response to ERP. Based on the literature, we predicted that less connectivity within vmPFC-based CSTC loops, less connectivity between the DMN and cognitive-control regions of the CON and FPN, and greater connectivity between cortical areas related to cognitive control would predict better treatment outcomes (31). We further predicted that these connectivity patterns would be associated with better outcomes in response to ERP compared with SMT, given the proposed greater demands of ERP on cognitive-control processes (32). We also tested whether these associations differed between adolescents and adults. We expected that the associations between resting-state functional connectivity and symptom improvements over time would vary with age; however, given the absence of relevant previous work across these developmental stages, we did not form specific hypotheses regarding the directionality of the predicted effects. Comparisons with typically developing control subjects were performed to contextualize any significant associations.

METHODS

Participants

A total of 116 patients (68 female; 54 adolescents; 60 medicated) with OCD and usable resting-state functional MRI (fMRI) and OCD symptom assessment data and 63 healthy control volunteers (40 female; 32 adolescents) were included in the present analyses. Approximately 52% of the patients were taking a serotonergic medication. Other clinical and demographic details are provided in Table 1 and in Tables S1 and S2 in the online supplement. Participants were recruited from outpatient psychiatry programs and an online research registry at the University of Michigan Health System, social media and community advertisements, and referrals from

community clinicians. Patients in the adolescent subgroup were required to be 12–17 years old, and those in the adult subgroup were required to be 24–45 years old; these age ranges were selected to represent more plastic (adolescent) relative to more stable (adult) periods of brain development. Patients were required to have experienced symptom onset before age 16 and to be experiencing at least a moderate level of symptom severity at baseline (i.e., ≥ 16 on the child or standard version of the Yale-Brown Obsessive Compulsive Scale [Y-BOCS] [33, 34]). Healthy control subjects had no lifetime history of any psychiatric disorder except simple phobias and had no family history of OCD. Written informed consent or assent was obtained from all patients or legal guardians, in accordance with procedures reviewed and approved by the Institutional Review Board of the University of Michigan. Full details on exclusionary criteria and non-completers are provided in a CONSORT chart in the online supplement. We previously reported an analysis of task-based fMRI data in a subset of this sample (26). The present report is the first analysis of the resting-state fMRI data.

Study Design

Patients were randomized using an in-house block randomization procedure to receive either 12 weeks of individual ERP or 12 weeks of individual SMT that focused on coping skills. This assignment was stratified based on medication status, gender, and age group. Full details of the treatment protocols are provided in the online supplement. Assessments of OCD symptom severity were performed at baseline (mean=1 week of treatment, SD=2 days), midtreatment (mean=6 weeks of treatment, SD=5 days), and posttreatment (mean=12 weeks of treatment, SD=5 days) by an independent rater who was blind to treatment group assignment. Prior to randomization, patients underwent MRI scanning, on average within 12 days (SD=7 days) of beginning therapy.

Resting-State fMRI

In order to define regions of interest (ROIs) for the resting-state analysis, we used an incentive flanker task, which is a stimulus-response compatibility task, that robustly activates the FPN and CON and deactivates the DMN (26). Striato-thalamic regions were selected based on published coordinates (35, 36). The full details of data acquisition, processing, and ROI selection are provided in Table S3 in the online supplement. For each region, a sphere with a 4.35-mm radius was placed around central coordinates based on either activations during task-based fMRI in the same subjects (cognitive-control and DMN regions) or published studies (striato-thalamic regions). Mean blood-oxygen-level-dependent time series were then extracted for each ROI and correlated to create an ROI-ROI connectivity matrix for each subject. Diagonal and duplicate cells were removed, and Fisher's r -to- z transformation was applied to the Pearson correlation coefficients at each remaining cell of the resultant matrices. Repeated-measures linear mixed-effects models with restricted maximum likelihood were used to examine the effects of ROI connectivity on symptom improvement. All models were implemented in the nlme package for R (37), included a random intercept for participant, and controlled for motion (mean framewise displacement), gender, treatment adherence (see the online supplement), and medication status (on vs. off medication). Results for all analyses were the same when covarying for maximum framewise displacement and number of frames removed due to motion scrubbing. Corrections for multiple comparisons were performed using the Benjamini-Hochberg false discovery rate (FDR) based on the number of ROI-ROI connections ($N=190$).

In model 1, we examined whether the effect of baseline connectivity on Y-BOCS scores differed across psychotherapy groups. Here, a week-by-connectivity-by-psychotherapy group interaction term, controlling for age group, was the predictor of interest. In each model, week was entered as the exact therapy week when the assessment took place (e.g., week 1, 6, or 12), such that the resulting beta values can be interpreted as predicted change in the Y-BOCS score per week, although participants underwent only three assessments. In model 2, we examined whether baseline connectivity was associated with symptom improvement across psychotherapy groups; here, the predictor of interest was the interaction of treatment week and connectivity, controlling for psychotherapy group and age group. Effects of age group were explored in models 3 and 4. Model 3 examined whether the association between baseline connectivity and Y-BOCS scores changed as a function of age group, controlling for psychotherapy group. Model 4 examined the four-way interaction between week, baseline connectivity, psychotherapy group, and age group. Significant interactions were explored using simple slope analyses. Full model syntax and equations are provided in the online supplement. Finally, the ROI-ROI connections associated with significant symptom improvement (i.e., those showing a significant negative slope associated with Y-BOCS scores from week 1 to week 12) were

compared with the same connections in the healthy control group to examine connectivity differences as a function of OCD diagnosis (see the online supplement).

RESULTS

Clinical Outcomes

The primary clinical outcomes are presented in Table 1. Patients treated with ERP showed a significantly larger decrease in symptoms than those treated with SMT ($\eta_p^2=0.18$, 95% CI=0.11, 0.25). Both psychotherapy groups showed a significant decrease in symptoms over time, although the change was clinically significant (38, 39) only in the ERP group (ERP group: $\eta_p^2=0.69$, 95% CI=0.61, 0.74; SMT group: $\eta_p^2=0.21$, 95% CI=0.11, 0.31). There were no effects of age on symptom improvement in either group.

Resting-State fMRI

Model 1: differential predictors by psychotherapy group. Two connections, both including the ventromedial prefrontal cortex, selectively predicted greater decreases in symptom scores with ERP compared with SMT. Relatively less baseline connectivity between the vmPFC and left subcortical regions (caudate and thalamus) was associated with greater symptom improvement over time in the ERP group, whereas relatively greater baseline connectivity was associated with greater symptom improvement over time in the SMT group (Figure 1 and Table 2; see also Figure S2 in the online supplement); these effects were primarily driven by the unmedicated subgroup (see Figure S7 and Tables S8–S10 in the online supplement).

Model 2: predictors common across psychotherapy groups. Greater baseline connectivity between CON and FPN regions (i.e., the presupplementary motor area [pre-SMA] with the right dorsolateral prefrontal cortex [dlPFC] and left inferior parietal lobule [IPL]), within CON regions (i.e., the pre-SMA with the dorsal anterior cingulate cortex [dACC]; the dACC with the right anterior insula), and between cognitive-control regions and the putamen (i.e., the dACC and right insula with the right dorsal putamen; the left dlPFC with the right ventral putamen) predicted greater decreases in symptom scores with psychotherapy when collapsed across ERP and SMT groups (see Figure 2; see also Figure S3 and Table S4 in the online supplement).

Models 3 and 4: age effects. Greater connectivity between FPN regions (the right dlPFC and bilateral parietal lobes) and the nucleus accumbens (NAc) predicted larger decreases in symptom scores in adolescents and relatively smaller decreases in symptom scores in adults, across ERP and SMT conditions. Greater connectivity within the FPN (between the left and right postcentral gyrus; between the left IPL and dorsal putamen) also predicted greater decreases in symptom scores across conditions, but only in adults. Greater connectivity of the caudate (between the bilateral caudate and left insula; between the left and right caudate) was associated

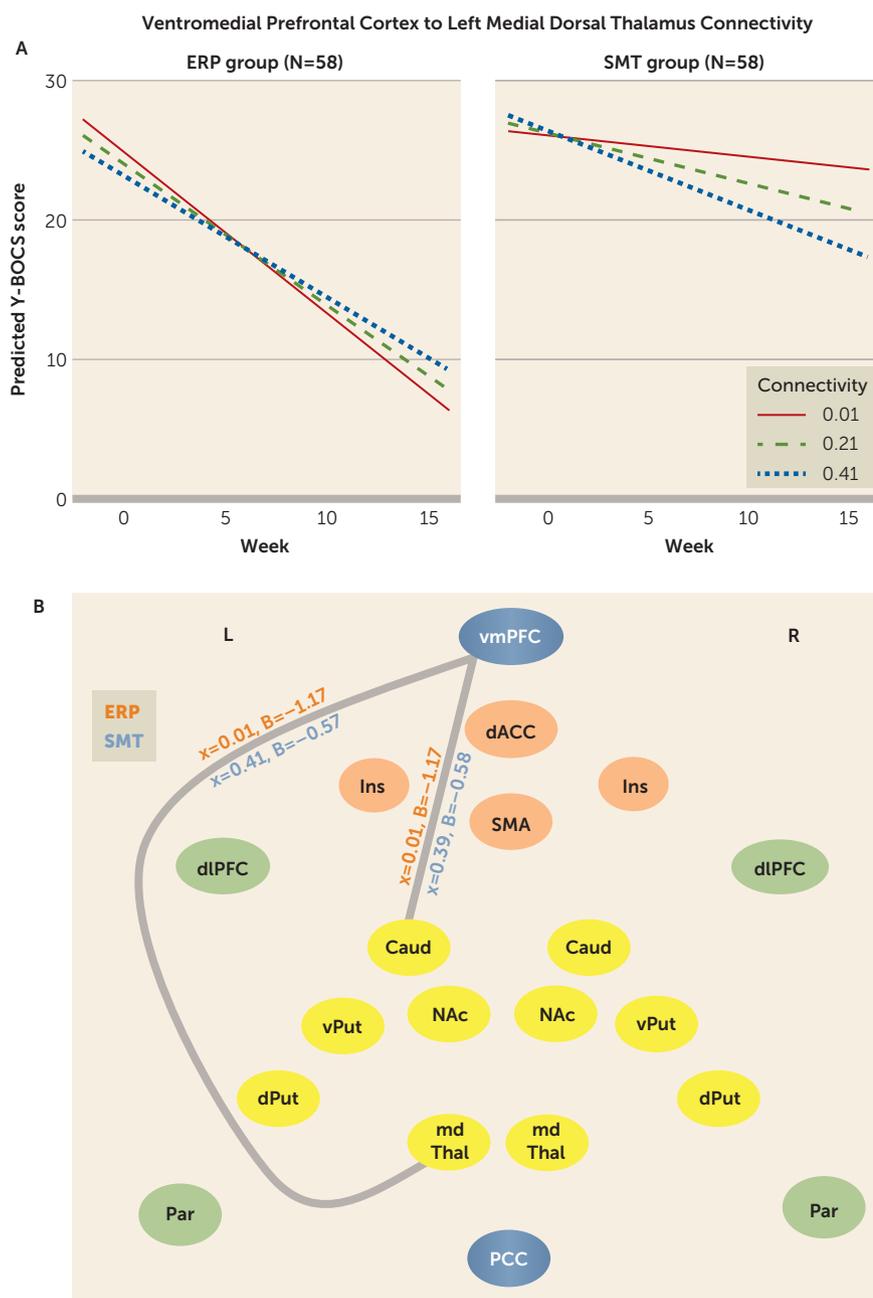
with greater decreases in symptom scores in adolescents and smaller decreases in symptom scores in adults (Figure 3; see also Figures S3–S5 and Table S5 in the online supplement). There were no age-specific patterns of connectivity that predicted differential responses to ERP and SMT.

Comparisons with a healthy control group. Among the connections identified in models 1, 2, and 3, there were no significant differences in baseline connectivity between the OCD and healthy control groups or any significant age-by-diagnostic group interactions. There was greater vmPFC-thalamic connectivity in the OCD group than in the healthy control group, although the difference fell short of statistical significance ($p_{FDR} < 0.1$) (see Tables S6 and S7 in the online supplement).

DISCUSSION

In this study, we examined baseline resting-state functional connectivity (rsFC) patterns as predictors of psychotherapy outcomes in individuals with OCD to identify connections that selectively predicted treatment response to ERP compared with psychotherapy more generally. We also examined age effects. ERP was associated with a greater reduction in OCD symptoms than SMT, and response to ERP (vs. SMT) was specifically predicted by baseline rsFC of the vmPFC with subcortical regions. Symptom improvement for both treatments were predicted by baseline rsFC of the cognitive-control and subcortical networks, collapsed across age groups. We found age-specific

FIGURE 1. Model 1: ROI-ROI connections associated with decreases in symptom scores as a function of time and treatment group^a



^a Panel A shows vmPFC to left medial thalamus connectivity associated with Y-BOCS scores in the two treatment groups. For each treatment group, the predicted decrease in symptom scores is shown at the mean (green dashed line), high (+1 SD; blue dotted line), and low (–1 SD; red solid line) levels of connectivity. In panel B, ROI-ROI connections shown in gray represent significant time-by-connectivity-by-treatment group interactions on Y-BOCS scores (FDR-adjusted $p < 0.05$). Relatively less baseline connectivity between the vmPFC and subcortical areas was associated with steeper reductions in symptoms in the ERP group (orange values above the line), while relatively greater connectivity was associated with steeper reductions in symptoms in the SMT group (blue values below the line). For each treatment group, beta values (B) indicate the simple slope (predicted amount of decrease in symptom score per treatment week) at x, which is the value of connectivity that was associated with greater decreases in symptom scores for each psychotherapy group (i.e., $+/-1$ SD from the mean in simple slopes based on post hoc analyses). Caud=head of the caudate; dACC=dorsal anterior cingulate cortex; dIPFC=dorsolateral prefrontal cortex; dPut=dorsal caudal putamen; ERP=exposure and response prevention; Ins=anterior insula; L=left; md Thal=medial dorsal thalamus; NAc=nucleus accumbens; Par=parietal cortex; PCC=posterior cingulate cortex; R=right; ROI=region of interest; SMA=supplementary motor area; SMT=stress management therapy; vmPFC=ventromedial prefrontal cortex; vPut=ventral rostral putamen; Y-BOCS=Yale-Brown Obsessive Compulsive Scale (child or standard version).

TABLE 2. Model 1. Linear mixed model examining two ROI-ROI connections associated with treatment response over time as a function of psychotherapy group^a

Model and Fixed Effects	B	SE	df	t	AIC
vmPFC-left caudate					
Main model					
Week	-1.17***	0.09	226	-12.74	
rsFC	-3.82	3.97	107	-0.96	
Treatment	0.83	1.60	107	0.52	
Medications	0.18	0.98	107	0.18	
Sex	1.59	1.04	107	1.52	
Motion	-1.67	5.39	107	-0.31	
Age group	1.25	1.01	107	1.24	
TARS	-0.51**	0.14	107	-3.53	
Week×rsFC	0.76	0.33	226	2.32	
Week×treatment	1.01	0.13	226	7.78	
rsFC×treatment	5.21***	5.84	107	0.89	2162.46
Week×rsFC×treatment	-1.86*	0.48	226	-3.88	2149.41
ERP group					
Week×rsFC	-6.13 ^b	5.06	107	-1.21	
1 SD above rsFC	-0.87 ^d	0.09	113	-9.76	
1 SD below rsFC	-1.17 ^d	0.09	113	-13.02	
SMT group					
Week×rsFC	-1.10 ^c	0.36	113	-3.09	
1 SD above rsFC	-0.58 ^d	0.09	113	-6.09	
1 SD below rsFC	-0.18 ^b	0.09	113	-2.04	
vmPFC-left medial thalamus					
Main model					
Week	-1.18***	0.09	226	-12.77	
rsFC	-0.28	3.88	107	-0.07	
Treatment	1.23	1.59	107	0.77	
Medications	0.11	0.99	107	0.11	
Sex	1.53	1.03	107	1.53	
Motion	-1.84	5.35	107	-0.34	
Age group	1.17	1.03	107	1.14	
TARS	-0.47**	0.14	107	-3.25	
Week×rsFC	0.77	0.32	226	2.41	
Week×treatment	1.03***	0.13	226	7.88	
rsFC×treatment	2.63	5.51	107	0.48	2166.35
Week×rsFC×treatment	-1.82*	0.45	226	-4.02	2147.62
ERP group					
Week×rsFC	0.78 ^b	0.32	113	2.46	
1 SD above rsFC	-0.86 ^d	0.09	113	-9.63	
1 SD below rsFC	-1.17 ^d	0.09	113	-13.09	
SMT group					
Week×rsFC	-1.05 ^c	0.32	113	-3.23	
1 SD above rsFC	-0.57 ^d	0.09	113	-6.28	
1 SD below rsFC	-0.15	0.09	113	-1.58	

^a Akaike information criterion values show the improvement in model fit by adding the interaction of interest to the model. For significant three-way interactions of week-by-baseline rsFC-by-treatment group (indicated by “ERP group” and “SMT group”), post hoc analyses (not corrected for multiple comparisons) are presented of the interaction of week-by-baseline rsFC in each psychotherapy group separately, as well as the simple slopes for +/-1SD from the mean of baseline rsFC values. AIC=Akaike information criterion; ERP=exposure and response prevention; ROI=region of interest; rsFC=resting-state functional connectivity at baseline; SMT=stress management therapy; TARS=Treatment Adherence Rating Scale; vmPFC=ventromedial prefrontal cortex. Asterisks indicate FDR-corrected p values for comparison of 190 ROI-ROI connections.

^b p<0.05 uncorrected for multiple comparisons.

^c p<0.01 uncorrected for multiple comparisons.

^d p<0.001 uncorrected for multiple comparisons.

*p<0.05. **p<0.01. ***p<0.001.

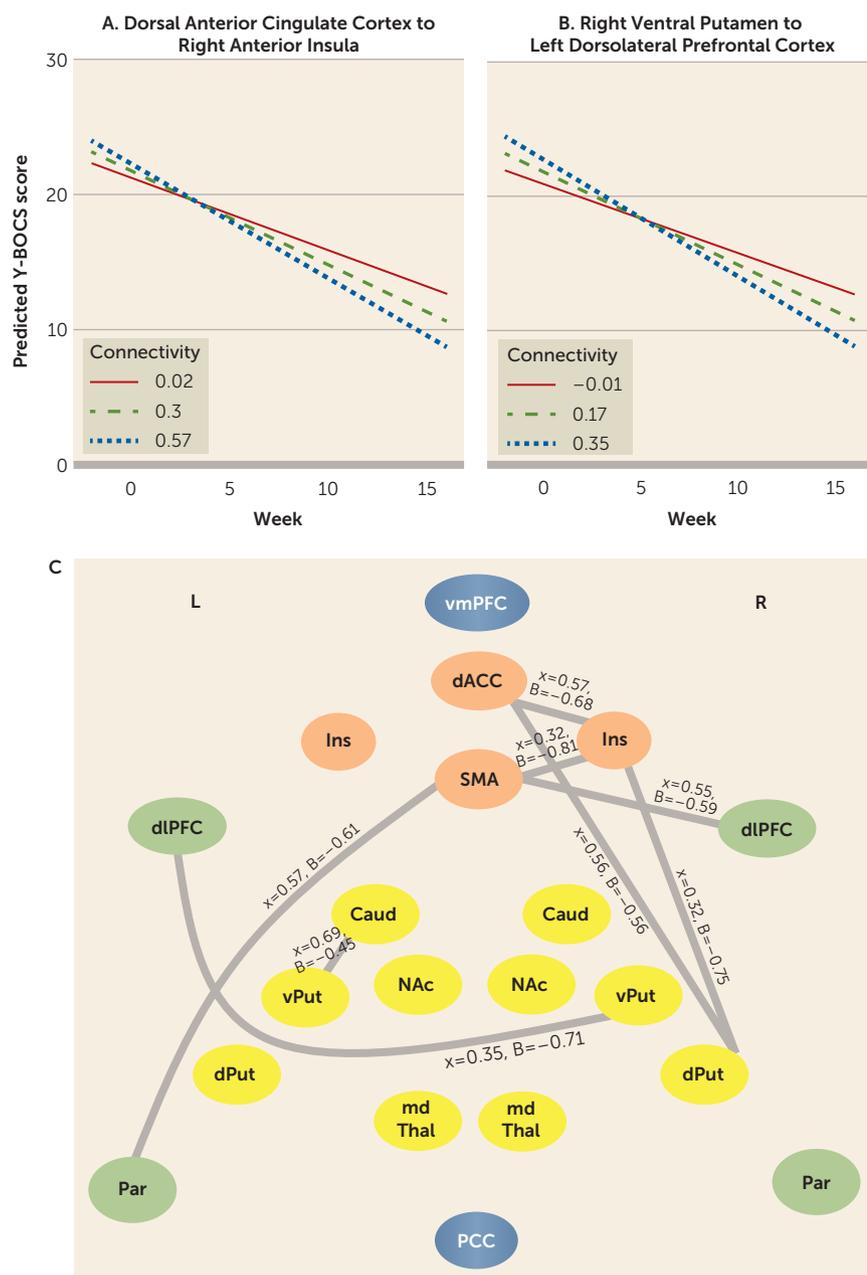
associations of ventral striatal and cognitive-control connections with symptom improvement. This is the first study, to our knowledge, to examine rsFC predictors of

response to ERP compared with an active control psychotherapy, and the first study to directly compare neural predictors of treatment response in adolescents and adults.

Specific and Nonspecific Predictors of Psychotherapy Response

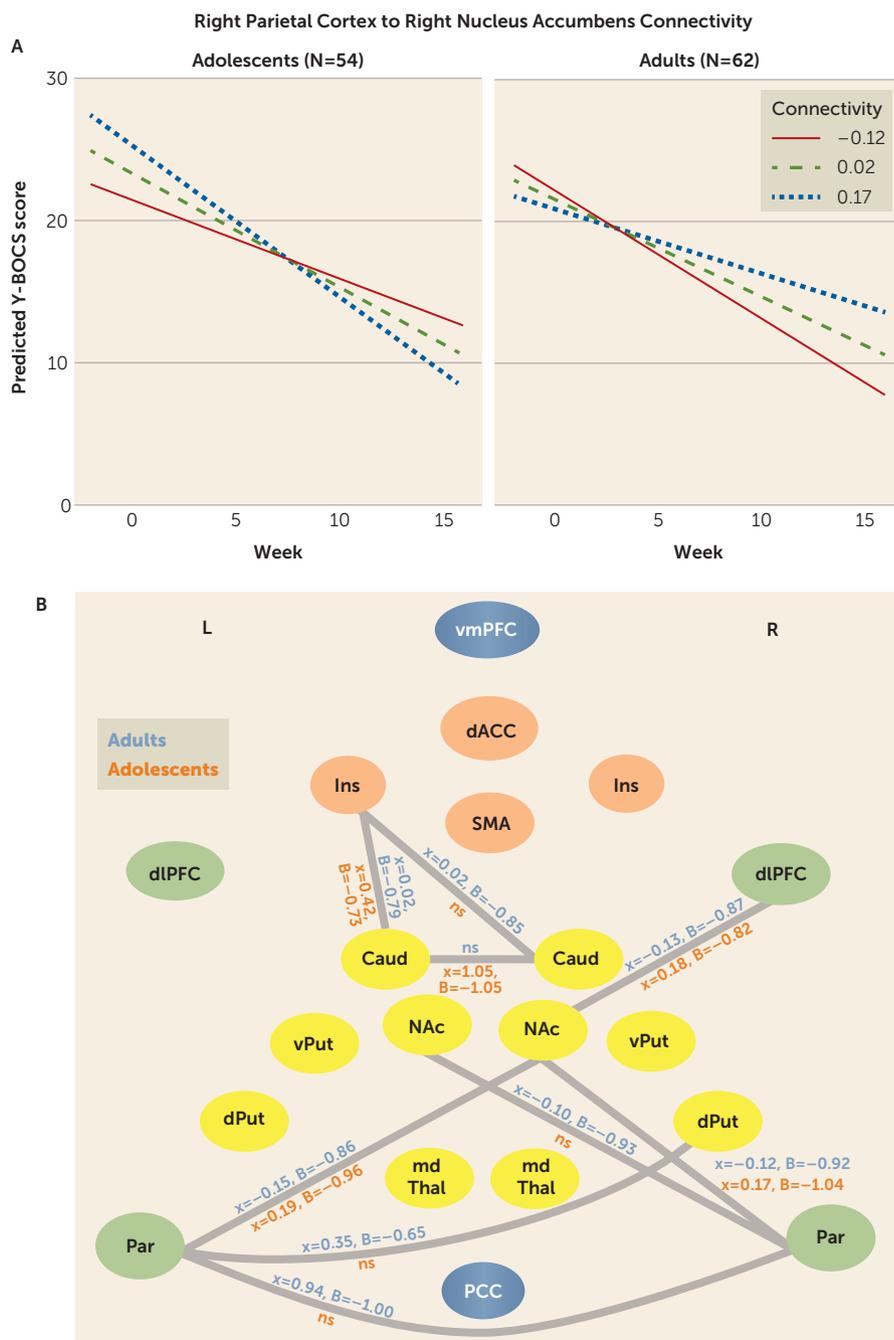
Knowing, prior to treatment initiation, what factors are associated with a greater symptom improvement could enhance the development of treatments and therapeutic outcomes (e.g., through priming interventions that are delivered before ERP to maximize the likelihood of treatment response). Previous fMRI studies have been unable to identify treatment-specific predictors because of the lack of an active control treatment. In our study, ERP was associated with greater symptom improvement in patients with weak connectivity rather than strong positive connectivity of the vmPFC to the thalamus and caudate, whereas SMT was associated with a greater symptom improvement if the patients showed the reverse pattern—strong positive connectivity rather than weak connectivity. We had expected that aberrant network connections would be important for predicting treatment response, but the absence of differences in the connectivity of our selected network nodes between the treatment and healthy control groups provides potentially important information. While it is difficult to draw firm conclusions from negative results, our findings suggest that network connections involved in treatment response may not be the same network connections related to the psychopathology. One implication may be that enhancing target network function, for example, through brain stimulation or neurofeedback training, might not

FIGURE 2. Model 2: ROI-ROI connections associated with decreases in symptom scores as a function of time collapsed across age and treatment groups^a



^a Panel A shows dACC to right insula connectivity, an example of connectivity between cognitive control regions, and the association with Y-BOCS scores over time. Panel B shows right ventral putamen to left dIPFC connectivity, an example of connectivity between cognitive control regions and the putamen, and the association with Y-BOCS scores over time. For each connection, the predicted decrease in symptom scores is shown at the mean (green dashed line), high (+1 SD; blue dotted line), and low (-1 SD; red solid line) levels of connectivity. In panel C, for all ROI-ROI connections shown in gray, greater baseline connectivity is associated with steeper reductions in symptoms (FDR-adjusted $p < 0.05$). Beta values (B) indicate the simple slope (predicted amount of decrease in symptom score per treatment week) at x, which is the value of connectivity that was associated with greater decreases in symptom scores for all participants (i.e., +/−1 SD from the mean in simple slopes based on post hoc analyses). Caud=head of the caudate; dACC=dorsal anterior cingulate cortex; dIPFC=dorsolateral prefrontal cortex; dPut=dorsal caudal putamen; Ins=anterior insula; L=left; md Thal=medial dorsal thalamus; NAc=nucleus accumbens; Par=parietal cortex; PCC=posterior cingulate cortex; R=right; ROI=region of interest; SMA=supplementary motor area; vmPFC=ventromedial prefrontal cortex; vPut=ventral rostral putamen; Y-BOCS=Yale-Brown Obsessive Compulsive Scale (child or standard version).

FIGURE 3. Model 3: ROI-ROI connections associated with decreases in symptom scores as a function of time and age group^a



^a Panel A shows right parietal cortex to right NAc connectivity, an example of connectivity with the NAc, that was associated with a steeper decrease in symptom scores in the adolescent group. For each age group, the predicted decrease in symptom scores is shown at the mean (green dashed line), high (+1 SD; blue dotted line), and low (-1 SD; red solid line) levels of connectivity. In panel B, ROI-ROI connections shown in gray represent significant time-by-connectivity-by-age group interactions on Y-BOCS scores (FDR-adjusted $p < 0.05$). Connections associated with greater decreases in symptom scores for adults are displayed as blue values above the line, and those for adolescents are displayed as orange values below the line. For each age group, x indicates the value of connectivity that was associated with greater decreases in symptom scores, and beta values (B) indicate the simple slope (predicted amount of decrease in symptom score per treatment week) at that x value. All simple slopes are significant at $p < 0.001$. Caud=head of the caudate; dACC=dorsal anterior cingulate cortex; dIPFC=dorsolateral prefrontal cortex; dPut=dorsal caudal putamen; Ins=anterior insula; L=left; md Thal=medial dorsal thalamus; NAc=nucleus accumbens; Par=parietal cortex; PCC=posterior cingulate cortex; R=right; ROI=region of interest; SMA=supplementary motor area; vmPFC=ventromedial prefrontal cortex; vPut=ventral rostral putamen; Y-BOCS=Yale-Brown Obsessive Compulsive Scale (child or standard version).

focus on the regions that exhibit differences from the normative signal. Instead, it may be more advantageous to boost activity in “healthy circuits” to optimize treatment response.

Our findings suggest that ERP and SMT may rely on differences in the organization of vmPFC-subcortical connectivity, which might suggest two different approaches to treatment. SMT seeks to lower anxiety levels in general, whereas in ERP, a therapist guides a patient to tolerate progressively greater levels of anxiety-inducing situations. This vmPFC-striato-thalamic circuit is thought to be involved in affectively coding certain behavioral programs, and if circuit strength reflects the “attachment” to compulsive behaviors, patients with relatively lower vmPFC-subcortical connectivity may have better chances of engaging with the extinction-generating exercises of ERP. On the other hand, those with stronger affective attachment to their compulsive behaviors may respond well to simple relaxation strategies. While speculative and in need of replication, the findings point to potentially different mechanisms underlying the two types of treatment.

Contrary to our hypotheses, connections of cingulo-opercular and frontoparietal regions were associated with symptom improvement with *both* ERP and SMT. Greater connectivity between cognitive-control regions and between these regions and the putamen predicted a steeper reduction in OCD symptoms irrespective of treatment modality. Regions of

the CON, such as the medial SMA and right anterior insula, are proposed to orchestrate recruitment of FPN regions in a flexible manner in line with ongoing task demands (40). Previous task-based fMRI studies suggest that inefficiency of CON-based signaling to recruit FPN regions during cognitive tasks in patients with OCD may lead to the impaired cognitive control observed in those with the disorder (31). Greater connectivity of CON and FPN regions could therefore represent greater functioning in these networks, which in turn may support self-regulatory abilities in patients who respond well to psychotherapy. Given the involvement of the putamen in motor control, action selection, and habit formation (41, 42), greater connectivity of cognitive-control regions with the putamen could indicate better functioning of networks involved in top-down control over habitual patterns, which would facilitate the ability to resist compulsions during treatment and engage in goal-directed behavior (43); in the absence of relevant task data, this interpretation is speculative.

Developmental Sensitivity

Importantly, we report additional predictors of symptom improvement that were developmentally sensitive and not treatment specific. These predictors predominantly involved connectivity between FPN regions (e.g., the dlPFC and parietal lobes) and the nucleus accumbens, which were more positively associated with symptom improvement in adolescents than in adults across both types of therapy. The NAc is widely recognized as a key node of the reward system (44). Additionally, ventral striatal connectivity with the prefrontal cortex is associated with better cognitive control and decision making in healthy adolescents (45, 46). This connectivity also plays a regulatory role during cognitive reappraisal in healthy young adults (47). Thus, while speculative, enhanced FPN-NAc communication may promote motivation and cognitive control functions that are necessary to make positive behavioral changes in adolescents with OCD. In contrast, in adults, responses to both ERP and SMT were predicted by greater connectivity within the FPN and between FPN regions and the dorsal putamen. Connectivity within the FPN increases during healthy adolescence to support improved cognitive control function (48), while a greater influence of FPN regions, particularly the dlPFC, over putamen-instantiated motor output has been theorized as protective in OCD (49). Together, these findings support the notion that NAc connectivity is particularly important for adaptive functioning during adolescence compared with other age ranges, while the neural substrates underlying cognitive control and motor output may be more closely tied to adaptive outcomes in adulthood (45, 48).

Limitations

Several limitations should be kept in mind. The network nodes that were selected for the connectivity analyses were defined by a task that engages cognitive control and by published studies, which were used to identify nodes thought

to be important for OCD based on the tripartite and CSTC models. As we examined only connectivity, not task-evoked activation, the functional significance of the connections might be different in the context of activated, engaged networks. Indeed, in an interim analysis of a partial data set drawn from that presented here, we found additional task-evoked predictors of treatment response (26). Furthermore, the absence of baseline differences from our normative sample does not preclude the existence of other connections that may differ between the groups outside of the selected ROIs. Another limitation of our study is the absence of a waiting list condition to demonstrate that the findings common to both ERP and SMT are due to an intervention and not just time. Future studies could investigate differences between other OCD treatments (e.g., medications) to determine whether our findings are specific to psychotherapy. Future studies could also examine baseline symptom severity as a treatment moderator, which could not be examined in the context of the present mixed model with three time points.

With regard to our developmental findings, those in the adolescent group showed more movement during the resting-state scan than those in the adult group. However, we controlled for motion in all analyses, and motion was unrelated to treatment outcomes. To compare across groups, it was necessary to use the same brain template for normalization. While total brain volume remains relatively stable from adolescence to young adulthood, the use of an adult brain template could have contributed to age-related findings. Additionally, as all participants were required to have a childhood onset of symptoms, based on research demonstrating potential phenomenological differences between childhood- and adult-onset OCD, longer illness duration in the adult group could have partially contributed to our findings. Furthermore, we did not explore pubertal status in the adolescent group, which may be a more sensitive measure than chronological age, and future work could examine the period of emerging adulthood. Additionally, our sample was predominantly Caucasian, and future studies would benefit from examining racial minorities. Antidepressant medications may affect connectivity within CSTC loops; however, medication status was controlled for in all analyses, and post hoc analyses (see Tables S8–S11 in the online supplement) demonstrated no significant brain-by-medication status interactions or any relationship between medication status and baseline rsFC. Lastly, preregistration is an important tool for improving reproducibility in the neuroimaging sciences; the analyses reported here were not preregistered, and follow-up work with preregistered analyses is required to confirm the present results.

Conclusions

We examined rsFC predictors of symptom improvement in response to ERP for OCD in adolescents and adults. Our design included an active control therapy, namely, SMT, which allowed us to examine the specificity of neural

predictors of response to ERP. Across age groups, we found that vmPFC-striato-thalamic circuitry was uniquely associated with symptom improvement with ERP, while connectivity of cognitive control regions was associated with symptom improvement irrespective of treatment type. Additionally, ventral striatal connectivity distinguished treatment response in adolescents compared with adults. Our findings help delineate the neural circuitry that supports response to psychotherapy based on treatment modality and suggest that developmental differences are an important factor to consider when examining the neural mechanisms of psychotherapy.

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Examination Questions for Resting-State Connectivity and Response to Psychotherapy Treatment in Adolescents and Adults With OCD: A Randomized Clinical Trial

1. **Pre-treatment resting-state connectivity of the ventromedial prefrontal cortex with subcortical regions**
 - A. Predicted OCD symptom decline to exposure and response prevention, specifically
 - B. Was not significantly related to treatment outcomes
 - C. Predicted OCD symptom decline in adults only
 - D. Was significantly greater in the healthy control group than the OCD group
2. **Connections of the cingulo-opercular and frontoparietal networks:**
 - A. Were related to OCD symptom decline in both psychotherapy groups
 - B. Were related to OCD symptom decline in both adolescents and adults
 - C. Are thought to orchestrate cognitive control
 - D. All of the above
3. **Based on the findings of the present article, in what way could fMRI research be used in the future to enhance treatment outcomes?**
 - A. By providing more accurate diagnosis based on brain profiles
 - B. By measuring serotonin levels in the prefrontal cortex for those on SSRIs
 - C. By targeting neural networks implicated in treatment response through priming interventions prior to treatment initiation
 - D. By replacing standard psychotherapy with brain stimulation