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Increased Amygdala Activation During Symptom Provocation Predicts Response to Combined Repetitive Transcranial Magnetic Stimulation and Exposure Therapy in Obsessive-Compulsive Disorder in a Randomized Controlled Trial

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ABSTRACT

BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) combined with exposure and response prevention is a promising treatment modality for treatment-refractory obsessive-compulsive disorder (OCD). However, not all patients respond sufficiently to this treatment. We investigated whether brain activation during a symptom provocation task could predict treatment response.

METHODS: Sixty-one adults with OCD (39 female/22 male) underwent symptom provocation with OCD- and fear-related visual stimuli during functional magnetic resonance imaging prior to an 8-week combined rTMS and exposure and response prevention treatment regimen. Participants received one of the following 3 rTMS treatments as part of a randomized controlled trial: 1) 10-Hz rTMS (110% resting motor threshold) to the left dorsolateral prefrontal cortex, 2) 10-Hz rTMS (110% resting motor threshold) to the left presupplementary motor area, or 3) 10-Hz control rTMS (60% resting motor threshold) to the vertex. Multiple regression and correlation were used to examine the predictive value of task-related brain activation for treatment response in the following regions of interest: the dorsomedial prefrontal cortex, amygdala, dorsolateral prefrontal cortex, and left presupplementary motor area.

RESULTS: The different treatment groups responded equally to treatment. Higher pretreatment task-related activation of the right amygdala to OCD-related stimuli showed a positive association with treatment response in all groups. Exploratory whole-brain analyses showed positive associations between activation in multiple task-relevant regions and treatment response. Only dorsal anterior cingulate cortex activation to fear-related stimuli showed a negative association with treatment outcome.

CONCLUSIONS: Higher pretreatment right amygdala activation during symptom provocation predicts better treatment response to combined rTMS and exposure and response prevention in OCD.

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Obsessive-compulsive disorder (OCD) is a common and debilitating psychiatric disorder characterized by obsessions and compulsions (1). Conventional treatment consists mostly of cognitive behavioral therapy (CBT), usually exposure and response prevention (ERP) psychotherapy (2), and selective serotonin reuptake inhibitors (3). Although progress has been made in the treatment of OCD by optimizing psychotherapeutic and psychopharmacological methods (4), 40% to 60% of patients continue to experience symptoms despite initial adequate treatment (3), and about 10% remain severely affected with treatment-refractory OCD (5).

Novel treatments that modulate brain circuits, such as repetitive transcranial magnetic stimulation (rTMS), have been proposed for the treatment of OCD (6). rTMS is a noninvasive brain stimulation technique that focally stimulates particular brain regions using trains of magnetic pulses (7). The rationale behind using rTMS to treat OCD is based on the association between OCD symptoms and functional alterations in cortico-striato-thalamo-cortical brain circuits (8,9). Different rTMS treatment protocols, such as low-frequency rTMS to the right dorsolateral prefrontal cortex (DLPFC), high-frequency rTMS to the bilateral DLPFC, and low-frequency rTMS to the pre-supplementary motor area (preSMA), have been shown to reduce OCD symptoms (6). Nevertheless, an rTMS response rate of only 35% has been reported previously (10), indicating the need for predictors of treatment response to rTMS. If predictors of clinical response are reliable and replicable, they can facilitate the selection of patients with OCD for rTMS

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treatment, thereby bringing the goal of patient-tailored psychiatric treatment of OCD one step closer.

Previous studies have investigated possible predictors of treatment response to treatment modalities such as CBT in patients with OCD. Using functional magnetic resonance imaging (fMRI) during a symptom provocation task (SPT), Olatunji *et al.* (11) found that stronger activation in brain regions involved in emotional processing, such as the amygdala and anterior temporal lobe, was associated with better treatment response to CBT. In contrast, they found that stronger activation in areas involved in emotion regulation, such as the DLPFC, was associated with worse treatment response. A recent meta-analysis on task-based fMRI-derived predictors of treatment response to CBT in anxiety-related disorders found that higher pretreatment neural activity in frontal (e.g., left dorsomedial prefrontal cortex [DMPFC]), striatal (e.g., left and right caudate) and sensorimotor (specifically the right SMA) brain regions, among others, was associated with better treatment response (12).

In the current study, we aimed to investigate whether brain activation in a priori–defined brain regions of interest (ROIs) relevant for emotional processing and regulation, measured with fMRI during an SPT, could predict response to combined rTMS and ERP in adults with OCD. Data from a double-blind, 3-arm randomized controlled trial has been used to answer this research question (13). The following ROIs were used in the analyses: the DMPFC due to its role in the dorsal cognitive circuit (8), although it was not an rTMS stimulation location in this trial; the amygdala due to its role in the frontolimbic circuit relevant for extinction learning (8,14); and the DLPFC and preSMA as rTMS targets in this trial. To the best of our knowledge, no studies have investigated the predictive value of brain activation during symptom provocation in the context of clinical response to combined rTMS and ERP. Based on previous studies that investigated predictors of response to other treatment modalities (mostly CBT) and based on symptom provocation studies in OCD (11,12), we hypothesized that higher pretreatment task-related activation of the DMPFC and the amygdala would be associated with better treatment response. We also hypothesized that lower pretreatment activation of the rTMS stimulation locations (the DLPFC and preSMA) during symptom provocation would be associated with better treatment response because the excitatory rTMS was meant to increase the compensatory roles that these areas may play in OCD (15).

METHODS AND MATERIALS

The double-blind, 3-arm randomized controlled trial was registered at clinicaltrials.gov under the registry name "TMS Induced Plasticity Improving Cognitive Control in OCD" (https://clinicaltrials.gov/ct2/show/NCT03667807). For details on the main findings of the trial, see Fitzsimmons *et al.* (13).

Participants

Patient inclusion criteria were 1) age between 18 and 65 years; 2) a primary DSM-5 diagnosis of OCD; 3) a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), indicating moderate to severe OCD; 4) unmedicated or consistent medication for at least 12 weeks before randomization; 5) at least 1 previous attempt at CBT; 6) at least 1 previous attempt with serotonergic medication or strong preference for nonpharmacological treatment; and 7) capacity to provide informed consent. Patient exclusion criteria were 1) MRI and/or rTMS could not be performed safely (e.g., pregnancy, claustrophobia, epilepsy); 2) comorbid Tourette syndrome, schizophrenia, or bipolar disorder; 3) active suicidal ideation; 4) use of antipsychotics within the past 12 weeks; or 5) previous rTMS treatment.

Sixty-six adults with OCD met the criteria and were randomly allocated to one of the 3 treatment groups (DLPFC, preSMA, or vertex rTMS) in a 1:1:1 ratio using the Castor Electronic Data Capture system (https://www.castoredc.com/) (Figure S1). A member of the research team who was not involved in the assessments performed the randomization procedure.

All procedures that contributed to the current study were approved by the medical ethical board of Vrije Universiteit Medical Center and complied with guidelines as described in the Declaration of Helsinki. All participants provided written informed consent.

Treatment Procedures

Participants underwent an 8-week treatment regimen that included 16 sessions (2 sessions per week) of rTMS in one of the 3 conditions directly followed by ERP, as well as 3 therapy sessions without rTMS (2 at the beginning and 1 at the end of treatment, during which ERP was introduced and relapse prevention was discussed). Patients were allowed to continue prescribed selective serotonin reuptake inhibitors or clomipramine as long as medication usage remained stable during study participation. Benzodiazepines, antipsychotics, and other psychotropic drugs were tapered off at least 12 weeks before the start of treatment. The patients, ERP therapists, and assessors who performed the clinical/cognitive assessments were blinded to treatment allocation. rTMS administrators were not blinded but were also not involved in the assessments.

The resting motor threshold (RMT) was determined during the baseline measurement. Participants received one of the 3 following rTMS treatments, depending on group allocation: 1) 10-Hz rTMS to the left DLPFC (3000 pulses at 110% RMT, 30 10-second trains, 30-second intertrial interval, 20 minutes total); 2) 10-Hz rTMS to the left preSMA (3000 pulses at 110% RMT); or 3) 10-Hz control rTMS to the vertex (3000 pulses at 60% RMT). The control rTMS was administered at a lower intensity over the vertex because this maximizes auditory and procedural placebo effects while minimizing neural stimulation. The Tower of London task identified the DLPFC stimulation site, and the stop signal task identified the preSMA site. For each participant, DLPFC coordinates were based on the maximum activation during the Tower of London task and preSMA coordinates on the maximum activation during the stop signal task. Immediately following each rTMS session, participants received ERP for 60 minutes.

Data Acquisition and Task Paradigm

Symptom Provocation During fMRI. Participants underwent fMRI scanning on a GE Signa HDxT 3T MRI scanner (General Electric) equipped with a 32-channel phased-array head coil. Scanning parameters are listed in the Supplement.

During fMRI, participants performed an SPT in which they viewed 3 different types of visual stimuli: OCD-related images (pertinent to washing, checking, and symmetry symptom dimensions), fear-inducing images, and emotionally neutral images (i.e., scrambled images). The complete task design is described in the Supplement.

Directly after the fMRI session, participants rated each OCD-related and fear-inducing image that they were shown, based on how much distress they experienced while looking at the image, using a visual analog scale ranging from 1 (no distress, no tension) to 9 (extremely distressing, high levels of tension). For each individual participant, based on these scores, the images were divided into high distress images (25% most distressing) and low distress images (75% least distressing).

Clinical and Demographic Measures. The main clinical outcome measure was the Y-BOCS, a 10-item questionnaire used to assess the severity and variety of symptoms experienced by patients with OCD (16). Assessments were carried out by trained, blinded therapists as part of usual care. In addition, various demographic and clinical measurements were performed at baseline. Demographic factors included age, sex, education level divided in 10 categories based on the Dutch education system (Verhage score), and the PhenX handedness assessment (17). Clinical measurements included the age of onset of OCD symptoms, Beck Depression Inventory (BDI) (18), Beck Anxiety Inventory (BAI) (19), Emotion Regulation Questionnaire (20), Structured Clinical Interview for DSM-5, and medication use.

Data Processing

fMRI data were preprocessed using fMRIprep version 21.0.1 (https://fmriprep.org/en/stable/), an open source preprocessing application that contains processing of the following steps: slice timing correction, susceptibility-derived distortion correction (which corrects for distortions in the phase encoding direction's magnetic field), and realignment and normalization to Montreal Neurological Institute space. The fMRIprep boilerplate is provided in the Supplement. Data derived from the processing script were checked for qualitative data problems, such as susceptibility artifacts, motion artifacts, and missing data. SPM version 12, an fMRI analysis software package that runs in MATLAB (version R2022b; The MathWorks, Inc.), was used for further preprocessing, including 8-mm full width at half maximum smoothing, high-pass filtering (128 seconds), and motion regression (see the Supplement for details).

Task-induced change in brain activation, as seen in the blood oxygenation level–dependent (BOLD) signal, was calculated for the following 4 contrasts: 1) OCD > scrambled, 2) fear > scrambled, 3) OCD+fear > scrambled, and 4) activation during images rated high on the distress scale contrasted with activation during images rated low on the distress scale (henceforth referred to as the $\text{distress}_{\text{high}} > \text{distress}_{\text{low}}$ contrast).

Activation in the following brain ROIs was used in the statistical analyses: the DMPFC, amygdala, DLPFC, and preSMA. Analyses using activation of the rTMS stimulation locations (DLPFC and preSMA) were performed separately from analyses using the DMPFC and amygdala ROIs. The ROI locations for the left and right DMPFC were defined as 10-mm spheres around coordinates found in a previous meta-analysis that investigated neural predictors of CBT response in anxiety-related disorders (12). AAL atlas ROIs were used for region localization of the left and right amygdala. The ROI locations for the DLPFC and preSMA were based on the individual rTMS stimulation coordinates. Details about ROI creation and the process of determining these stimulation coordinates are provided in the Supplemental Methods.

Statistical Analyses

The analysis plan was preregistered in Open Science Framework at https://osf.io/6rax8 prior to data analysis.

Clinical Data Analysis. Descriptive statistics and statistical analyses of the clinical outcome were performed using SPSS. The effects of the treatments on the Y-BOCS scores in the different treatment groups were analyzed with a 3×2 mixed analysis of variance with treatment condition as a between-subjects factor (3 levels: DLPFC, preSMA, and vertex) and time as a within-subjects factor (2 levels: pretreatment and posttreatment). All statistical analyses of clinical data were performed as 2-tailed tests, with $p < .05$ as the threshold for statistical significance.

ROI Analyses. To analyze whether activation in the left and right DMPFC and the left and right amygdala during the SPT at baseline could predict treatment response, a multiple regression analysis was performed. For this analysis, all treatment groups were taken together as 1 cohort. Contrast estimates were extracted using MarsBaR (version 0.44). The BOLD signal in the 4 brain ROIs mentioned were used as predictors, and the change in Y-BOCS scores (defined as the difference between the Y-BOCS scores pre- and posttreatment) was used as the dependent variable. Baseline Y-BOCS scores and medication status (i.e., medicated or not medicated) were added as covariates to the models. All 4 task contrasts were used in separate models. Multicollinearity was tested with variance inflation factor values, which revealed no significant issues with multicollinearity.

Separate correlation analyses were performed between treatment response and activation in brain ROIs defined around the individual rTMS target regions. These analyses are described in the Supplement.

Whole-Brain Analyses. To ascertain whether pretreatment brain activation was associated with treatment response in brain areas other than those mentioned above, second-level exploratory whole-brain analyses were performed in SPM12 using a general linear model (extent threshold of $k = 10$ and $p < .001$, uncorrected, 2 tailed) with baseline Y-BOCS scores and medication status as covariates.

Responder Analyses. Logistic regression analyses with a dichotomous outcome, i.e., responder versus nonresponder, were performed to assess the sensitivity, specificity, and positive and negative predictive value of predictors for treatment response. A responder was defined as a participant with a ≥35% reduction in Y-BOCS score from pre- to posttreatment (21). Different models were generated, each with distinct

predictors comprising of the BOLD response in the left DMPFC, right DMPFC, left amygdala, and right amygdala ROIs, as well as baseline scores on the Y-BOCS and the BDI. Receiver operating characteristic (ROC) curves were also established. In addition, differences between responders and nonresponders in clinical and demographic characteristics measured pretreatment were assessed with an independent *t* test, a Mann-Whitney *U* test, or a χ^2 test, as appropriate.

RESULTS

Demographics and Clinical Results

Of the 66 initial participants, 61 completed the treatment protocols and were clinically assessed posttreatment (Figure S1). Demographic and clinical characteristics of patients included in the analyses are provided in Table 1. Despite randomization, participants in the 3 treatment conditions showed significant differences in age, BDI scores, BAI scores, and comorbid depression. Of the 61 participants, 35 (57.4%) were classified as responders.

Statistical analyses of clinical results showed that there was a significant main effect of time on the Y-BOCS scores ($F_{1,58}$ = 163.834, $p < .001$, η_p^2 = 0.739), indicating a reduction in symptoms posttreatment across all treatment groups (Figure 1A). There was no significant main effect of treatment condition on the Y-BOCS scores ($F_{2,58}$ = 2.104, p = .131, η_p^2 = 0.068), and there was no significant interaction between treatment condition and time ($F_{2,58}$ = 0.200, p = .819, η_p^2 = 0.007), indicating no significant difference between intervention protocols in reducing OCD symptoms. Clinical results are provided more elaborately in Fitzsimmons *et al.* (13).

Table 1. Demographic and Clinical Characteristics of Study Participants

	All Participants, N = 61	DLPFC Group, n = 19	preSMA Group, n = 23	Vertex Group, n = 19	Statistical Analyses of the 3 Groups	
					Statistic	p Value
Demographic Data						
Age, Years	36.97 (12.93)	40.26 (12.37)	31.52 (13.30)	40.26 (11.26)	$F_{2,58}$ = 3.555	.035
Sex					χ^2_2 = 0.880	.644
Female	39 (63.9%)	13 (68.4%)	13 (56.5%)	13 (68.4%)		
Male	22 (36.1%)	6 (31.6%)	10 (43.5%)	6 (31.6%)		
Handedness					χ^2_2 = 1.516	.469
Right	53 (86.9%)	16 (84.2%)	19 (82.6%)	18 (94.7%)		
Left	8 (13.1%)	3 (15.8%)	4 (17.4%)	1 (5.3%)		
Education Level[a]	9 [2]	9 [2]	9 [3]	9 [2]	H_2 = 1.472	.479
Clinical Data						
Age of Onset, Years	15.41 (7.74)	15.79 (8.43)	15.52 (7.31)	14.89 (7.89)	$F_{2,56}$ = 0.065	.937
Baseline Y-BOCS	28.18 (4.58)	28.79 (5.68)	29.30 (3.35)	26.21 (4.24)	$F_{2,58}$ = 2.767	.071
Baseline ERQ Reappraisal	3.63 (1.18)	3.40 (1.23)	3.66 (1.14)	3.82 (1.22)	$F_{2,58}$ = 0.604	.550
Baseline ERQ Suppression	3.17 (1.10)	3.20 (1.05)	3.30 (1.08)	2.99 (1.19)	$F_{2,58}$ = 0.434	.650
Baseline BDI	18.48 (10.75)	22.00 (11.35)	21.57 (10.25)	11.21 (6.86)	$F_{2,58}$ = 7.725	.001
Baseline BAI	20.79 (10.30)	20.58 (10.40)	24.39 (10.29)	16.63 (9.01)	$F_{2,58}$ = 3.173	.049
Medication Use	37 (60.7%)	14 (73.7%)	14 (60.9%)	9 (47.4%)	χ^2_2 = 2.757	.252
Current Comorbidity						
Depressive disorder	12 (19.7%)	4 (21.1%)	8 (34.8%)	–	χ^2_2 = 7.999	.018
ADHD	7 (11.5%)	2 (10.5%)	2 (8.7%)	3 (15.8%)	χ^2_2 = 0.540	.763
General anxiety disorder	6 (9.8%)	3 (15.8%)	2 (8.7%)	1 (5.3%)	χ^2_2 = 1.241	.538
Panic disorder	2 (3.3%)	1 (5.3%)	–	1 (5.3%)	χ^2_2 = 1.252	.535
Specific phobia	2 (3.3%)	2 (10.5%)	–	–	χ^2_2 = 4.571	.102
Alcohol use disorder	2 (3%)	1 (5.3%)	1 (4.3%)	–	χ^2_2 = 0.963	.618
Insomnia	2 (3.3%)	1 (5.3%)	1 (4.3%)	–	χ^2_2 = 0.963	.618
Hypersomnia	1 (1.6%)	–	–	1 (5.3%)	χ^2_2 = 2.247	.325
Dysthymia	1 (1.6%)	–	1 (4.3%)	–	χ^2_2 = 1.680	.432
Social anxiety disorder	1 (1.6%)	1 (5.3%)	–	–	χ^2_2 = 2.247	.325
Body dysmorphic disorder	1 (1.6%)	–	–	1 (5.3%)	χ^2_2 = 2.247	.325
Anorexia nervosa	1 (1.6%)	1 (5.3%)	–	–	χ^2_2 = 2.247	.325
PTSD	1 (1.6%)	–	1 (4.3%)	–	χ^2_2 = 1.680	.432

Values are presented as mean (SD), *n* (%), or median [IQR]. For statistical analyses, either a 1-way analysis of variance (in case the outcome variables were continuous and normally distributed), a χ^2 (N = 61) (in case the outcome variables were dichotomous), or a Kruskal-Wallis H test (in case the outcome variables were not continuous or were not normally distributed) was performed.

ADHD, attention-deficit/hyperactivity disorder; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DLPFC, dorsolateral prefrontal cortex; ERQ, Emotion Regulation Questionnaire; preSMA, presupplementary motor area; PTSD, posttraumatic stress disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]Level of education is expressed on a 10-point scale, with 1 = no level of school or university completed and 10 = completed university degree.

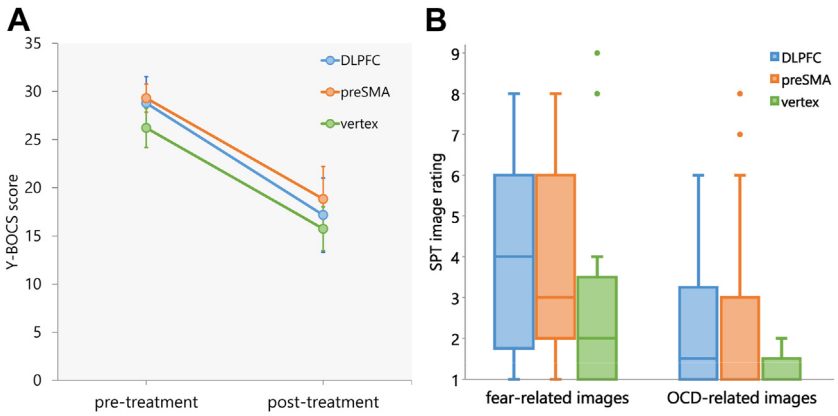

Figure 1. **(A)** Pretreatment and posttreatment Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores for the different treatment groups. Dots depict the mean and whiskers depict the 95% CI. **(B)** Distress ratings for fear-related and obsessive-compulsive disorder (OCD)–related images for the different treatment groups. Central lines within the boxes depict the median; the ends of the boxes depict the interquartile range; whiskers depict the biggest and smallest data point values found (not including outliers); and dots depict outliers. Outliers are defined as data points that are more than 1.5 times the interquartile range above the third quartile. DLPFC, dorsolateral prefrontal cortex; preSMA, presupplementary motor area; SPT, symptom provocation task.

Distress Ratings During Symptom Provocation

Results of the SPT distress ratings are provided in Figure 1B. Two participants rated every image with a 1 on the distress scale, and 1 participant did not complete the distress ratings questionnaire. Thus, those 3 participants were excluded from all analyses using the distress ratings. Distress ratings for fear-related images (median = 3.0, IQR = 5.0) were significantly higher than those for OCD-related images (median = 1.0, IQR = 1.0) ($z = -4.761$, $p < .001$). Distress ratings for neither the fear-related images ($H_2 = 2.414$, $p = .299$) nor the OCD-related images ($H_2 = 4.700$, $p = .095$) were significantly different between the treatment groups.

ROI Analyses

Results of the regression analyses with the DMPFC and amygdala ROIs for the 4 task contrasts are provided in Table 2. Mean activation of the different ROIs in the various contrasts are provided in Table S1. Activation of the right amygdala in the OCD > scrambled contrast was significantly associated with a better treatment response. As post hoc analyses, similar regression analyses were performed, with baseline BDI scores as a covariate instead of medication status, because medication status did not have much impact on the regression models, and comorbid depression has previously been associated with lesser likelihood of response to rTMS treatment for OCD (22). The results of these analyses are provided in Table 3. In the regression models that included the BDI, the baseline BDI had a significant negative correlation and baseline Y-BOCS scores had a significant positive correlation with treatment response. Notably, activation of the right amygdala was also significantly correlated with treatment response in the fear > scrambled and OCD+fear > scrambled contrasts in these models.

Results of the correlation analyses with personalized ROIs in rTMS target regions are provided in Supplemental Results and Tables S2 and S3. These analyses showed that only pretreatment task-related activation of the preSMA (using the $\text{distress}_{\text{high}} > \text{distress}_{\text{low}}$ contrast) had a significant positive correlation with the change in Y-BOCS scores in the preSMA treatment group ($p = .47$; 95% bias-corrected and accelerated CI, 0.19–0.66; $p = .022$).

Whole-Brain Analyses

The results of the whole-brain analyses are provided in Tables S4 to S11 and Figures S2 to S5. These summarize the brain regions that showed a positive or negative correlation between BOLD response and change in Y-BOCS scores after treatment. There were clusters of brain activation spread widely across the brain that were positively associated with change in Y-BOCS scores after treatment. In the OCD > scrambled contrast, these included areas such as the basal ganglia (i.e., putamen and caudate), thalamus, SMA, and DLPFC. The only negative correlation found was that between the BOLD response in the dorsal anterior cingulate cortex (fear > scrambled contrast) and the change in Y-BOCS scores.

Responders Versus Nonresponders

Of all 61 participants, 35 (57.4%) were classified as responders (Table S12). Responders had significantly lower BDI and BAI scores than nonresponders at baseline.

The results of the logistic regression analyses are provided in Table S13. The regression analyses were performed with 3 different models. Each model included a different set of predictors. Model 1 included pretreatment activation of the left DMPFC, right DMPFC, left amygdala, and right amygdala as predictors. Model 2 included activation of the left DMPFC, right DMPFC, left amygdala, and right amygdala, as well as the baseline Y-BOCS scores and the baseline BDI as predictors. Model 3 only included the baseline Y-BOCS and the baseline BDI as predictors. For the 4 task contrasts, model 1 was never statistically significant, but models 2 and 3 were statistically significant for all contrasts. Overall model summaries are provided in Table S14. The results of the ROC curve analyses for each of these models (including the area under the curve [AUC], accuracy, sensitivity, specificity, positive predictive value, and negative predictive value) are provided in Table 4. The ROC curves themselves are provided in Figures S6 and S7.

As shown in Table S13, based on the 95% CIs of the odds ratios, the only variable that consistently predicted response to treatment was the baseline BDI score; each point increase in BDI score made the chance of response 0.87 times more likely. No other variable that was used in these logistic regression

Table 2. Regression Models With Activation in ROIs as Predictors, Baseline Y-BOCS Scores and Baseline Medication Status as Covariates, and Change in Y-BOCS Scores After Treatment As the Outcome Variable

Variables	B	SE	β	*t*	*p*	VIF Value
Contrast: OCD > Scrambled						
(Constant)	1.013	5.250		0.193	.848	
Left DMPFC	20.537	14.807	0.366	1.387	.171	4.545
Right DMPFC	−10.734	11.783	−0.228	−0.911	.366	4.102
Left Amygdala	−8.592	7.998	−0.192	−1.074	.287	2.088
Right Amygdala	17.110	8.140	0.338	2.102	.040	1.687
Baseline Y-BOCS	0.301	0.185	0.212	1.626	.110	1.110
Medication	0.617	1.666	0.047	0.370	.713	1.036
Contrast: Fear > Scrambled						
(Constant)	0.007	5.574		0.001	.999	
Left DMPFC	−4.587	18.936	−0.069	−0.242	.810	4.869
Right DMPFC	−5.758	12.970	−0.122	−0.444	.659	4.606
Left Amygdala	−2.683	8.528	−0.054	−0.315	.754	1.803
Right Amygdala	17.130	10.930	0.266	1.567	.123	1.744
Baseline Y-BOCS	0.306	0.191	0.215	1.597	.116	1.104
Medication	0.454	1.712	0.034	0.265	.792	1.019
Contrast: OCD+Fear > Scrambled						
(Constant)	0.471	5.304		0.089	.930	
Left DMPFC	1.778	5.363	0.052	0.332	.742	1.557
Right DMPFC	−4.396	3.511	−0.165	−1.252	.216	1.104
Left Amygdala	−2.997	4.592	−0.114	−0.653	.517	1.937
Right Amygdala	9.687	5.019	0.306	1.930	.059	1.595
Baseline Y-BOCS	0.308	0.185	0.217	1.660	.103	1.079
Medication	0.174	1.689	0.013	0.103	.918	1.035
Contrast: $Distress_{high}$ > $Distress_{low}$						
(Constant)	1.701	5.485		0.310	.758	
Left DMPFC	15.863	12.158	0.333	1.305	.198	3.833
Right DMPFC	−2.056	8.833	−0.061	−0.233	.817	4.019
Left Amygdala	−6.355	8.508	−0.155	−0.747	.459	2.511
Right Amygdala	11.125	10.119	0.215	1.099	.277	2.241
Baseline Y-BOCS	0.265	0.184	0.189	1.437	.157	1.020
Medication	1.745	1.782	0.134	0.979	.332	1.098

VIF values indicate the extent of multicollinearity in the model, giving an index that measures how much the variance of an estimated regression coefficient is increased due to collinearity.

DMPFC, dorsomedial prefrontal cortex; OCD, obsessive-compulsive disorder; ROI, region of interest; VIF, variance inflation factor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 3. Regression Models With Activation in ROIs as Predictors, Baseline Y-BOCS Scores and Baseline BDI Scores as Covariates, and Change in Y-BOCS Scores After Treatment as the Outcome Variable

Variables	B	SE	β	*t*	*p*	VIF Value
Contrast: OCD > Scrambled						
(Constant)	−2.670	4.561		−0.585	.561	
Left DMPFC	4.040	13.514	0.072	0.299	.766	4.927
Right DMPFC	1.472	10.687	0.031	0.138	.891	4.392
Left Amygdala	−11.109	6.977	−0.249	−1.592	.117	2.068
Right Amygdala	18.664	7.116	0.369	2.623	.011	1.677
Baseline Y-BOCS	0.671	0.186	0.472	3.598	.001	1.463
Baseline BDI	−0.321	0.079	−0.529	−4.057	<.001	1.445
Contrast: Fear > Scrambled						
(Constant)	−5.056	4.792		−1.055	.296	
Left DMPFC	−20.344	16.709	−0.304	−1.218	.229	5.096
Right DMPFC	10.183	11.778	0.216	0.865	.391	5.106
Left Amygdala	−9.078	7.496	−0.183	−1.211	.231	1.872
Right Amygdala	19.645	9.418	0.305	2.086	.042	1.741
Baseline Y-BOCS	0.765	0.196	0.538	3.895	<.001	1.560
Baseline BDI	−0.353	0.082	−0.584	−4.323	<.001	1.487
Contrast: OCD+Fear > Scrambled						
(Constant)	−3.323	4.545		−0.731	.468	
Left DMPFC	0.891	4.660	0.026	0.191	.849	1.556
Right DMPFC	−2.325	3.073	−0.087	−0.757	.453	1.120
Left Amygdala	−5.695	4.028	−0.217	−1.414	.163	1.973
Right Amygdala	11.082	4.356	0.350	2.544	.014	1.591
Baseline Y-BOCS	0.674	0.183	0.475	3.682	.001	1.395
Baseline BDI	−0.323	0.077	−0.534	−4.184	<.001	1.366
Contrast: $Distress_{high}$ > $Distress_{low}$						
(Constant)	−0.884	4942		−0.179	.859	
Left DMPFC	11.435	11.110	0.240	1.029	.308	3.885
Right DMPFC	−3.991	8.003	−0.118	−0.499	.620	4.005
Left Amygdala	−0.616	7.912	−0.015	−0.078	.938	2.636
Right Amygdala	2.986	9.310	0.058	0.321	.750	2.303
Baseline Y-BOCS	0.592	0.193	0.424	3.076	.003	1.355
Baseline BDI	−0.287	0.083	−0.491	−3.474	<.001	1.423

VIF values indicate the extent of multicollinearity in the model, giving an index that measures how much the variance of an estimated regression coefficient is increased due to collinearity.

BDI, Beck Depression Inventory; DMPFC, dorsomedial prefrontal cortex; OCD, obsessive-compulsive disorder; ROI, region of interest; VIF, variance inflation factor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

analyses was significant. However, as shown in Table 4, models that include both brain activation in the ROIs and clinical measures (i.e., model 2) in the ROC curve analyses seem to outperform models that only include clinical measures (i.e., model 3). The AUC and accuracy for model 2 is higher than the AUC and accuracy for model 3 in the OCD > scrambled, fear > scrambled, and OCD+fear > scrambled contrasts.

DISCUSSION

In this study, we aimed to investigate whether brain activation of a priori–defined ROIs relevant for emotional processing and regulation, measured with fMRI during an SPT, could predict treatment response to combined rTMS with ERP in adults with OCD. Examination of neural predictors of treatment outcome revealed that pretreatment task-related right amygdala activation during an SPT was positively associated with treatment response. The direction of this association is consistent with our hypothesis and previous research (11). Because all treatment groups received some form of rTMS, we cannot conclude that the pretreatment amygdala activation predicts treatment response to ERP alone rather than to combined rTMS and ERP.

Table 4. Results of the ROC Curve Analyses

Variables	Model 1	Model 2	Model 3
Contrast: OCD > Scrambled			
AUC	0.692	0.833	0.783
SE	0.068	0.052	0.059
p Value	.011	<.001	<.001
Accuracy	65.6%	77.0%	73.8%
Sensitivity	80.0%	82.9%	82.9%
Specificity	46.2%	69.2%	61.5%
Positive Predictive Value	66.7%	78.4%	74.4%
Negative Predictive Value	46.2%	75.0%	72.7%
Contrast: Fear > Scrambled			
AUC	0.680	0.831	0.783
SE	0.069	0.053	0.059
p Value	.017	<.001	<.001
Accuracy	57.4%	77.0%	73.8%
Sensitivity	71.4%	80.0%	82.9%
Specificity	38.5%	73.1%	61.5%
Positive Predictive Value	61.0%	80.0%	74.4%
Negative Predictive Value	50.0%	73.1%	72.7%
Contrast: OCD+Fear > Scrambled			
AUC	0.687	0.825	0.783
SE	0.068	0.054	0.059
p Value	.013	<.001	<.001
Accuracy	67.2%	77.0%	73.8%
Sensitivity	80.0%	80.0%	82.9%
Specificity	50.0%	73.1%	61.5%
Positive Predictive Value	68.3%	80.0%	74.4%
Negative Predictive Value	65.0%	73.1%	72.7%
Contrast: $Distress_{high}$ > $Distress_{low}$			
AUC	0.657	0.775	0.783
SE	0.073	0.064	0.059
p Value	.042	<.001	<.001
Accuracy	57.4%	68.9%	73.8%
Sensitivity	75.8%	81.8%	82.9%
Specificity	40.0%	60.0%	61.5%
Positive Predictive Value	62.5%	73.0%	74.4%
Negative Predictive Value	55.6%	71.4%	72.7%

ROC curve analyses include AUC, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. Different models with varying predictors were used, with responder vs. nonresponder as the dichotomous outcome variable. Model 1 includes the left DMPFC, right DMPFC, left amygdala, and right amygdala as predictors. Model 2 includes the left DMPFC, right DMPFC, left amygdala, right amygdala, the baseline Y-BOCS, and the baseline BDI as predictors. Model 3 only includes the baseline Y-BOCS and the baseline BDI as predictors.

AUC, area under the curve; BDI, Beck Depression Inventory; DMPFC, dorsomedial prefrontal cortex; OCD, obsessive-compulsive disorder; ROC, receiver operating characteristic; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Dysregulated fear responses mediated by frontolimbic circuitry, including brain regions involved in generating a fast emotional response (amygdala) and subsequently (re) appraising emotional relevance (prefrontal cortex), may drive the development and persistence of OCD symptoms (23). Previous work showed that compared with control individuals, individuals with OCD who were exposed to OCD-related stimuli exhibited increased amplitude and altered timing of BOLD response in the right amygdala (24). ERP seems to be particularly advantageous for patients with dysregulated fear by targeting the hyperactive frontolimbic circuitry involved in the experience of OCD symptoms by training the top-down control processes during exposure therapy. Clinically, patients who experience little fear or distress during ERP appear to benefit less from treatment (2).

Activation of the amygdala has been implicated in emotional encoding and processing (25,26), so these findings may also suggest that heightened encoding and processing during symptom provocation contributes to greater treatment effects. The amygdala plays a central role in processing emotional stimuli (27,28), as well as in the acquisition and extinction of conditioned fear (29) and by extension in extinction learning (14).

In the logistic regression models, only the baseline BDI was a significant predictor of treatment response. However, as shown in Table 4, the ROC curve analyses showed that models that incorporated both task-related activation of the amygdala and DMPFC and clinical measures (model 2) showed superior performance compared with models that contained only clinical measures (model 3). In the OCD > scrambled, fear > scrambled, and OCD+fear > scrambled contrasts, model 2 demonstrated a higher AUC and higher accuracy than model 3. Therefore, the fMRI measures may have clinical value when used in models that also include clinical measures, because they appear to enhance the predictive ability of such models.

The exploratory whole-brain analyses revealed that activation in numerous brain regions spread widely across the brain was (mostly positively) associated with treatment response (Tables S4–S11). For the OCD > scrambled contrast (Table S4), we found positive associations between improvement in OCD symptoms and activation in areas involved in the dorsal cognitive circuit (putamen, caudate, thalamus, SMA, and DLPFC). The dorsal cognitive circuit is related to executive functions such as control of emotional, motivational, and sensorimotor processes (23). A hypoactivated dorsal circuit, causing cognitive control deficits and an inability to modulate emotions and behaviors, may contribute to maintenance of OCD symptoms (8). Furthermore, a recent study found that pretreatment activation within the dorsal circuit during planning was associated with clinical response to specific rTMS conditions in OCD (30). More activation in the dorsal cognitive circuit, and thus possibly improved emotional processing and cognitive control, may make it more likely that patients will derive more benefit from ERP treatment. This is consistent with the emotional processing theory, which proposes that physiological activation plays an essential role in extinction learning during exposure-based interventions for anxiety-related disorders (31,32). This is also consistent with the finding that activation in various parts of the visual association cortex was correlated with treatment response. Previous research has demonstrated that psychological arousal modulates visual cortex activity (33). Olatunji *et al.* (11) also found positive associations between heightened activation in visual areas during an SPT and better treatment outcomes following CBT for OCD.

The current study has several limitations that need to be acknowledged. The lack of differences in treatment outcome between the different treatment groups may be explained by

the fact that even rTMS to the vertex at lower stimulation intensities could have had a therapeutic effect (34,35). The vertex treatment group also had significantly lower baseline BDI and BAI scores and fewer comorbid depressive disorders than the other treatment groups. The combination of the negative association between baseline BDI scores and treatment response and the lower BDI scores in the vertex group may explain why the vertex group, despite receiving lower intensity rTMS, responded similarly to the DLPFC and preSMA rTMS groups. Additionally, this study was not powered to detect clinical differences between the 3 treatment groups, and a larger sample size would be needed to conduct a thorough subgroup analysis. A limitation of the SPT is that a general set of OCD-related images was used. Personalized images tailored to each individual patient's specific OCD-related symptoms would be preferable to evoke more targeted responses. A limitation of the ROI analyses is the constrained number of ROIs that we could include in the models due to the limited number of predictors permissible in regression analyses to avoid the risk of overfitting. In addition, while we preregistered our ROI analyses to be completely upfront about our hypothesis-driven approach, the lack of a formal multiple testing correction can be seen as a limitation. However, strict corrections such as Bonferroni would be overly conservative given the interdependence between ROIs.

Conclusions

Higher pretreatment right amygdala activation during symptom provocation predicted better treatment response to rTMS with ERP in patients with OCD. Exploratory whole-brain analyses showed that increased pretreatment activation in the dorsal cognitive circuit was related to greater treatment response as well, possibly due to enhanced emotional processing and cognitive control during exposure. The data suggest that these patterns of brain activity are predictive of treatment response in general rather than being predictive of response to a specific type of rTMS treatment.

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