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Journal

Proceedings of the National Academy of Sciences of the United States of America, 115(9)

ISSN

0027-8424

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Publication Date

2018-02-27

DOI

10.1073/pnas.1716686115

Peer reviewed

Multivariate resting-state functional connectivity predicts response to cognitive behavioral therapy in obsessive–compulsive disorder

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Edited by Cameron Carter, University of California, Davis, CA, and accepted by Editorial Board Member Marlene Behrmann January 10, 2018 (received for review September 21, 2017)

Cognitive behavioral therapy (CBT) is an effective treatment for many with obsessive–compulsive disorder (OCD). However, response varies considerably among individuals. Attaining a means to predict an individual's potential response would permit clinicians to more prudently allocate resources for this often stressful and time-consuming treatment. We collected resting-state functional magnetic resonance imaging from adults with OCD before and after 4 weeks of intensive daily CBT. We leveraged machine learning with cross-validation to assess the power of functional connectivity (FC) patterns to predict individual posttreatment OCD symptom severity. Pretreatment FC patterns within the default mode network and visual network significantly predicted post-treatment OCD severity, explaining up to 67% of the variance. These networks were stronger predictors than pretreatment clinical scores. Results have clinical implications for developing personalized medicine approaches to identifying individual OCD patients who will maximally benefit from intensive CBT.

OCD | CBT | resting state | functional connectivity | machine learning

Obsessive–compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and/or repetitive behaviors (compulsions) (1). OCD has a lifetime prevalence of ~1–2% worldwide (2) and is associated with poor quality of life, functional impairment, and increased use of health care services (3).

Cognitive behavioral therapy (CBT), including intensive CBT, shows moderate-to-high effectiveness for OCD (4, 5). However, response varies significantly among individuals (6). In addition, specialized CBT is expensive, stressful, and time-consuming and often has limited availability (7). This underscores the importance of developing reliable predictors of response to treatment to aid clinical decision-making.

Many studies have identified psychometric and demographic features that correlate with treatment response (8) but, unfortunately, do not consistently predict outcome (9). Neuroimaging biomarkers have recently shown promise at predicting response to treatment (10). However, only one small study using symptom provocation functional magnetic resonance imaging (fMRI) (11) and one study of brain connectivity using resting-state fMRI (12) have drawn correlations between baseline neural measures and subsequent response to CBT. Feusner et al. (13) previously found that pretreatment brain network small-worldness, a graph theory measure derived from resting-state fMRI, was associated with the trajectory of OCD symptoms up to 12 mo after intensive CBT and that small-worldness increased pre- to post-CBT.

Another OCD study (14)—this time of serotonin reuptake inhibitor (SRI) treatment—found significant pretreatment to posttreatment changes in network connectivity in the frontoparietal, cinguloopercular, somatosensory–motor, and visual networks. Although this study also did not focus on predicting response to treatment, the observation that connectivity changed

with treatment in these networks provides a rationale for examining their predictive ability in relationship to clinical outcomes.

No studies to date have applied multivariate approaches to investigate changes in brain connectivity pretreatment to post-treatment, to predict treatment outcome, or to predict symptom trajectory after treatment. Multivariate analyses of brain connectivity offer advantages of simultaneously capturing patterns involving multiple connections, likely better reflecting the complexity of brain networks than standard univariate approaches. Multivariate pattern recognition analyses have proven to be more sensitive than conventional univariate analyses in assessing the link between neuroimaging and behavioral variables to predict the presence or absence of other brain disorders (15, 16).

Here we utilized a multivariate approach to explore pretreatment network connectivity patterns that might presage posttreatment symptom severity. Multivariate analysis was applied to whole-brain resting-state fMRI acquired before and after 4 wk of intensive CBT and before and after a waitlist control condition. Our search were data-driven but restricted to networks where connectivity patterns had previously been found to change with treatment (14) because networks that reorganize during treatment might also be predictive of treatment

Significance

The ability to predict an individual's potential response to treatment would permit clinicians to more prudently allocate resources that support cognitive behavioral therapy for obsessive–compulsive disorder (OCD), an often stressful and time-consuming treatment. The current study lays important groundwork for an exciting advance toward personalized medicine in psychiatry that up to this point has eluded the field. This study marks a success in using multivariate pattern recognition to identify neurobiological predictors of treatment response. In addition, it advances knowledge of the neurophysiology of OCD and of mechanistic processes involved in the therapeutic response, which could be used to refine existing treatments or to develop novel treatments based on identified potential brain targets.

Author contributions: N.R., T.D.M., C.S., J.O., and J.D.F. designed research; N.R., T.D.M., F.M., C.S., and J.D.F. performed research; N.R., T.D.M., J.R., and J.D.F. contributed new reagents/analytic tools; N.R., T.D.M., and F.M. analyzed data; and N.R., T.D.M., F.M., J.R., J.O., and J.D.F. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. C.C. is a guest editor invited by the Editorial Board.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1716686115/-DCSupplemental.

Published online February 12, 2018.

outcome. These included the above-mentioned frontoparietal, cinguloopercular, somatosensory-motor, and visual networks. To these we added the default mode network (DMN) (17–20) and the dorsal and ventral attention networks (21), where previous studies found abnormal connectivity in OCD. We additionally included the subcortical network given the well-known cortico-striato-thalamo-cortical hyperactivity in OCD, including (but not limited to) caudate and putamen, which might be affected by CBT (22, 23). All network-defined regions of interest (ROIs) were derived from Power et al. (24), who parcellated the brain into functional networks based on resting-state connectivity data and metaanalysis of task fMRI studies (24).

Finally, the amygdala, compared with many other brain regions, has shown particular value in predicting response to CBT for OCD (11, 12) and has frequently exhibited abnormalities in OCD involving blood oxygenation level-dependent (BOLD) activation (25–29) and/or functional connectivity (21, 30–32). Therefore, we performed additional analyses in which we added bilateral amygdala ROIs from the Harvard Oxford Atlas to the list of ROIs within each network.

Methods and Materials

Recruitment and Assessment. We recruited participants from University of California, Los Angeles (UCLA), clinics and through flyers and Internet advertisements. All experimental procedures were approved by the UCLA Institutional Review Board, and all participants provided written informed consent before participation. OCD diagnosis was established through interviews by one author (J.D.F.), who has clinical experience with this population. Primary OCD and comorbid diagnoses were determined using the *Anxiety Disorders Interview Schedule for DSM-IV-Mini (ADIS-IV-Mini)* (33). OCD participants were eligible if they scored at least a 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) (34). Participants could be unmedicated or taking SRIs if there were no changes in medication within 12 wk of enrollment. For detailed inclusion/exclusion criteria, please see [Supporting Information](#).

Psychometric Evaluations. Primary outcome was the YBOCS. Secondary measures pretreatment to posttreatment included the Hamilton Anxiety Scale (HAMA) (35) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (36). General functionality and social/occupational performance was rated with the Global Assessment Scale (GAS) (37). An independent evaluator, not involved in treatment or assessments, administered psychometric instruments.

Treatment. All 42 OCD participants underwent manualized (38) exposure and response prevention (ERP)-based intensive CBT. Individual treatment plans consisted of 90-min sessions, 5 d per week, for 4 wk, as previously described (13). Approximately half ($n = 21$) were randomized to a 4-wk minimal-contact waitlist-first condition followed by treatment.

fMRI Acquisition and Processing. Whole-brain BOLD fMRI was collected using a 7-min echo-planar imaging sequence [3T Siemens Trio; 12-channel head coil; repetition time/echo time (TR/TE) = 2,000/25 ms; flip 78°; voxels 3 mm³; 1-mm gap; 35 axial slices; field of view 195 mm anterior to posterior, 195 mm right-left, 139 mm foot to head] within 1 wk before treatment and within 1 wk after treatment. Those randomized to the waitlist-first condition were also scanned within 1 wk before they started the 4-wk waitlist, as well as before and after treatment. Participants were instructed to rest with eyes closed and not to sleep. T1-weighted structural MRI [axial magnetization-prepared rapid gradient-Echo (MPRAGE), TR/TE = 1,900/3.26 ms, voxels 1 mm³] was coacquired for registration.

Functional data were preprocessed without spatial smoothing using the FMRI Software Library 5.0.4 (<https://fsl.fmrib.ox.ac.uk/fslwiki>). Data were motion-corrected using FMRIB's Linear Image Registration Tool for Motion Correction (MCFLIRT) and band-pass filtered (0.009–0.08 Hz). Seven and 12 degrees-of-freedom transforms were used to register functional images to MPRAGE and to Montreal Neurological Institute space, respectively, and images were resampled to 2 mm³. Nuisance covariates included global signal and cerebrospinal fluid signal (along with their first derivatives) as well as 6 head motion parameters, for a total of 10 parameters; these were removed by linear regression. Motion was assessed using DVARS (root-mean-squared change in volume-to-volume BOLD signal) (39) and framewise displacement (FD) (39, 40) to compare pre- vs. post-CBT and to exclude those with DVARS > 2 SD above the mean and those with FD > 0.3 in either session. Two

participants' data were excluded due to excessive head motion (FD > 0.3 for one and DVARS > 2 SD in another), resulting in a total of 42 participants for our functional analyses. There were no significant differences in motion as measured by DVARS pre-CBT (29.1 ± 4.4) vs. post-CBT (28.5 ± 4.7) ($P = 0.44$, paired t test). Nor were there significant differences in motion as measured by FD pre-CBT (0.13 ± 0.06) vs. post-CBT (0.13 ± 0.05) ($P = 0.59$, paired t test). Before functional connectivity-based analyses, each voxel's time course was z-scored.

Functional Connectivity Matrix Construction. Mean BOLD time courses were extracted from the average activity across voxels in 196 spherical ROIs with 5-mm radius (24). These belonged to the aforementioned cinguloopercular ($n = 14$ ROIs), frontoparietal ($n = 25$), ventral attention ($n = 9$), dorsal attention ($n = 11$), visual ($n = 31$), somatosensory-motor ($n = 35$), default mode ($n = 58$), and subcortical ($n = 13$) networks of interest (14, 17–19, 22, 23, 41–45). Matrices of correlation coefficients were created for each participant by computing pairwise correlations of each ROI's mean BOLD time course with that of all other ROIs (Fig. 1A). For additional analyses, bilateral amygdala ROIs from the Harvard Oxford Cortical and Subcortical Structural Atlas (<https://fsl.fmrib.ox.ac.uk/fsl/wiki/Atlases>) were thresholded at 50% population probability and included in the list of ROIs within each network.

Feature Selection. For each participant, features included the functional connectivity (FC) values between the ROIs within each network, pretreatment YBOCS score, and a binary medication variable indicating whether or not psychotropics were being taken at time of scan. We included YBOCS and medication as features because they represent potentially informative, and readily obtained, a priori clinical information that might add predictive value. Thus, each participant's feature set consisted of $n(n-1)/2 + 2$ features, n being the number of ROIs in the network of interest (Fig. 1B).

Machine Learning Multivariate Regression Analyses. To control for variations in age, sex, illness duration, and IQ [Wechsler Abbreviated Scales of Intelligence (WASI) scores] across participants, each feature was iteratively submitted to multiple linear regression with the aforementioned variables as predictors. The residuals were used as the new features.

We built a least absolute shrinkage and selection operator [LASSO (46)] regression model whose regularization parameter was optimized using the least angle regression (LARS) algorithm (47) on an $N - 1$ cross-validation that maximized the Pearson correlation between actual and predicted post-treatment YBOCS scores. To minimize overfitting, we used these optimized model parameters in an $N - 10$ cross-validation, where a random subset of 10 participants (~25%) were left out and the model was trained on the remaining participants. For our 42 participants, this yielded four folds, plus an additional fold of the cross-validation that left out two participants. Using the model's intercept term and outcome beta values as coefficients for each feature value, we used the weighted sum of each left-out participant's features to obtain predicted behavioral measures of interest ($\hat{Y}$). After the five folds, whereby each participant was left out exactly once, we correlated the array of predicted values ($\hat{Y}$) with the actual values (Y), yielding Pearson's R and R^2 —a measure of our model's feature-dependent ability to capture the behavioral variance across participants. We repeated this five-fold cross-validation 10 times and averaged the R values to converge on a true estimate of our test statistic independent of which participants were randomly included in each fold. We also report the RMSE [$\sqrt{\frac{1}{N} \sum_{i=1}^N (\hat{Y}_i - Y_i)^2}$] values averaged across the 10 iterations.

Machine Learning Classification Analyses. For a series of follow-up analyses, we used the same feature sets to train a linear nu-support vector classifier (nu-SVC, $c = 1$; ref. 48). For each analysis of interest, we used a leave-10-participants-out cross-validation approach that balanced training class examples by randomly removing examples from the overrepresented class. We ran this cross-validation 10 times and report the average accuracy values.

Significance Testing. We first report the significance of the correlation coefficients by comparing the R -value to a Student's t distribution (p_t). To account for multiple comparisons across our different networks of interest, we used a Bonferroni-corrected significance level of $p \leq .006$ (0.05/8 networks). To confirm that our classification scheme was not subject to bias and was immune to parametric assumption violations, we also compared significant R values ($p_t \leq .006$) to an empirical null distribution created with a bootstrap procedure (p_{bs}). See [SI Methods](#).

For all SVM analyses, significance was determined by the binomial inverse of the cumulative distribution function to identify the smallest number of

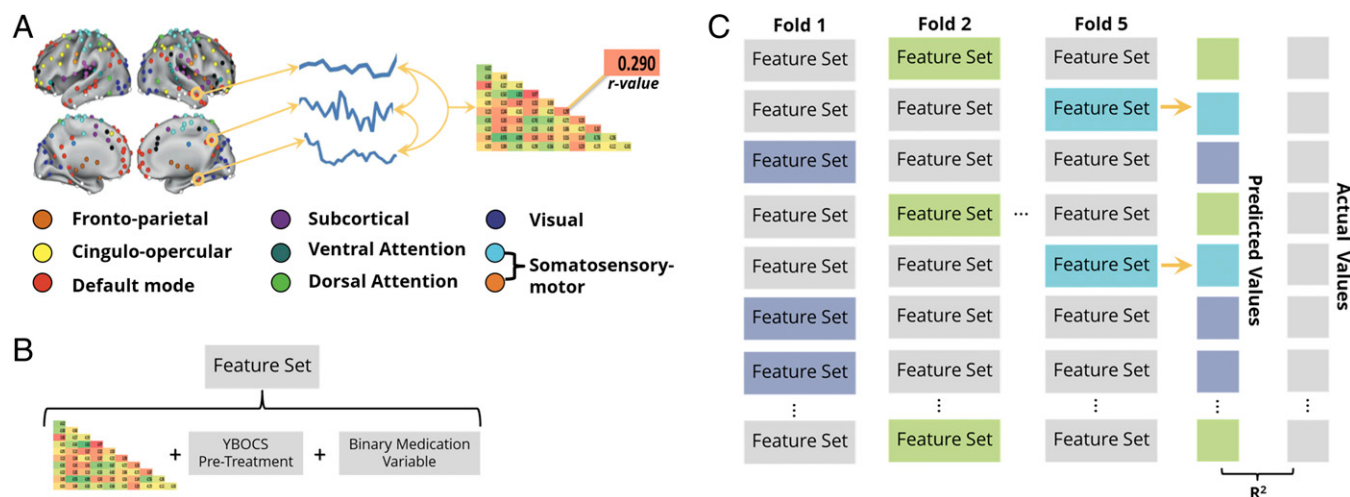


Fig. 1. (A) The average resting-state activity within ROIs from eight functional brain networks defined by Power et al. (24) was used to create a mean BOLD time course. A pairwise Pearson correlation of these time courses resulted in a functional connectivity (FC) matrix specific to each network. (B) The lower diagonal of each participant's network-specific FC matrix was concatenated with the participant's pretreatment YBOCS score and a binary variable indicating whether or not the participant was on medication to create a feature set for that participant. (C) A LASSO regression model was trained on $n - 10$ participants' feature sets and their associated posttreatment YBOCS values and used to predict each of the left-out participant's posttreatment YBOCS scores. Left-out participants are denoted as shaded feature sets (only three shown here due to space constraints). This process was repeated until all participants had been left out in a fold of the cross-validation and had been assigned a predicted posttreatment YBOCS ($\hat{Y}$). We correlated the array of predicted values ($\hat{Y}$) with the actual values (Y), yielding Pearson's R and R^2 , a measure of our model's feature-dependent ability to capture the behavioral variance across participants. Note that due to our participant sample size ($n = 42$), one fold of the cross-validation left out two participants, exemplified in fold 5.

correct classifications of the total number of classifications (number of participants raised to the power of the number of groups in the classification), where the distribution was centered around the chance value by randomly shuffling the labels before classification (49).

Top Connections. For each fold of the cross-validation, the betas used to predict the left-out participants were stored. The average beta for each FC feature was calculated and sorted as a function of magnitude. For visualization purposes, the top 5% of connections in each network that reached significance can be seen in Figs. S1 and S2.

Results

Participants. Fifty-one right-handed adults ages 18–60 with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* (50) OCD were enrolled. Four waitlist-first participants withdrew before completing waitlist, and one was withdrawn due to medication protocol violation. The study physician withdrew two treatment-first participants, and two completed the study but had inadequate fMRI data due to head motion. Ultimately, data from 42 OCD participants were analyzed. Thirteen were medicated: six with fluoxetine, one with fluvoxamine, two with escitalopram, and three with sertraline. Twenty-nine had one or more comorbid psychiatric diagnoses (Table 1 and Table S1).

Symptom Changes. YBOCS improved pre- to post-CBT in 41 of 42 OCD participants [pre-CBT mean: 24.6 ± 4.7 , post-CBT: 15.0 ± 5.3 ; improvement 9.6 ± 5.9 (39.0%), 95% CI, 8.8–11.3; $t_{41} = 10.5$, $P < 0.001$] (Table 1). Prewaitlist to postwaitlist, there was little change in YBOCS [prewaitlist: 25.8 ± 4.9 , postwaitlist 25.0 ± 5.4 ; 0.90 ± 3.1 (3.2%) improvement: $t_{41} = 1.21$, $P = 0.24$]. Pretreatment and posttreatment YBOCS scores were only moderately associated ($R^2 = 0.095$, $P = 0.047$).

Functional Connectivity. Two of the pretreatment FC feature sets strongly and reliably predicted a participant's posttreatment YBOCS (Fig. 2). When the DMN's pretreatment FC values were used in the feature set, the classification was most powerful, capturing 67% of the variance in posttreatment YBOCS ($R^2 = 0.67$; RMSE = 3.32; $p_t < 0.001$; $p_{bs} < 0.001$). Pretreatment

FC within the visual network also accounted for significant variance ($R^2 = 0.51$; RMSE = 3.69; $p_t < 0.001$; $p_{bs} < 0.001$). No other networks reached statistical significance (Table 2).

For networks whose pretreatment FC was informative when predicting posttreatment YBOCS, we examined the effect of including bilateral amygdala ROIs with each network. Neither the DMN nor the visual network saw an increase in predictive ability from the inclusion of the amygdala. To determine the effect of the additional features (pretreatment YBOCS and the binary medication variable), we reran the LASSO cross-validation without these features (relying only on FC patterns within the networks of interest) and observed moderately higher predictive

Table 1. Demographic and psychometric characteristics of the sample ($N = 42$)

Characteristic	Value	SD	P value
Female/male	22/20		
Age	32.4	9.9	
Education, y	15.6	2.4	
WASI IQ	108.4	9.1	
Number on serotonin-reuptake inhibitor	13		
Number with psychiatric comorbidities	29		
Number without psychiatric comorbidities	13		
YBOCS total pre-CBT	24.6	4.7	
YBOCS total post-CBT	15.0	5.3	<0.001*
YBOCS obsessions (1–5) pre-CBT	12.0	2.7	
YBOCS obsessions (1–5) post-CBT	7.9	3.1	<0.001*
YBOCS compulsions (6–10) pre-CBT	12.6	2.3	
YBOCS compulsions (6–10) post-CBT	7.1	2.7	<0.001*
HAMA pre-CBT	12.5	5.3	
HAMA post-CBT	8.5	5.1	<0.001*
MADRS pre-CBT	15.6	9.3	
MADRS post-CBT	11.0	8.9	<0.001*
GAS pre-CBT	57.7	8.6	
GAS post-CBT	69.5	13.4	<0.001*

*Paired t test, comparing pre- versus post-CBT.

disorders and in other obsessive-compulsive related disorders, similar brain activity and connectivity relationships have been observed in visual regions. A study in social anxiety disorder found right visual cortex activity in response to angry faces to be associated with improved symptoms post-CBT (59). Also in social anxiety disorder, FC between amygdala and inferior temporal/occipital cortex and fractional anisotropy in inferior longitudinal fasciculus (connecting the amygdala with visual regions) both predicted symptom response to CBT (60). Activity in the visual stream, mediated by amygdala activity, was associated with anxiety in individuals with body dysmorphic disorder (61).

The current investigation adds to evidence for a role of visual ROIs in CBT response across disorders. A rationale exists for an association of visual network connectivity with CBT response in OCD. OCD trigger stimuli are frequently visual or evoke visual imagery. Early theories about potential mechanisms of exposure and response prevention exercises in CBT described corrective learning occurring as a result of emotional desensitization (fear extinction) when one is exposed to a feared stimulus and compulsive behaviors are not performed (62). More recent theories posit that successful exposure and response prevention may not require extinction but rather the acquisition of secondary inhibitory learning (63). With either model, reorganization of visual networks may accompany these evolving responses to OCD-relevant signals.

Emotionally charged stimuli can up-regulate visual processing (64–68). In most cases, e.g., ref. 69, such up-regulation is adaptive. However, misattribution of emotional valence to non-threatening or non-task-related stimuli could cause pathological up-regulation of visual processing dedicated to those stimuli. In OCD, hypervigilance-related up-regulation could enhance visual attention, contributing to obsessional preoccupation with environmental stimuli that are not inherently salient (e.g., a dirty doorknob) or with irrelevant details (70). Because visual awareness has been shown to modulate detection of fearful stimuli (71), visual activation could facilitate an arousal feedback loop within and across the visual network and amygdalae. In the current study, OCD participants who achieved lower post-CBT YBOCS may be those who started treatment with visual systems that were more amenable to a “rewiring” that could help impede such circularities. As such, we suspected that including an amygdala ROI to our visual network might result in a FC feature set that outperformed the visual network alone. However, we witnessed no increase in model performance—accuracy stayed the same. This suggests that FC within the visual network may already contain information relayed by the amygdala or that the amygdala does not meaningfully modulate visual activity, as related to OCD treatment response, during rest. Future studies

using task-based fMRI are needed to test such hypotheses. However, our finding that posttreatment FC in the visual network is only informative in predicting posttreatment YBOCS scores when bilateral amygdala ROIs are included raises the possibility that one of the effects of CBT might be to significantly adjust the interplay between the visual network and amygdala.

One limitation of the current study is sample size. Our cross-validation approach of leaving out ~25% of participants for model testing helped minimize overfitting, yet much larger datasets that can be randomly split and still contain larger numbers for both training and testing the model may provide more optimal internal validation. Beyond that, there is need for validation in a fully independent sample to ensure robustness and generalizability across samples that differ slightly, because prediction analyses in smaller studies may fail to generalize when applied to independent samples. Another limitation is that some participants ($n = 13$) were medicated. The small size of this subsample precluded separate analyses of medicated and unmedicated participants, so to account for possible medication effects we used a binary medication variable in the model. A further limitation is that although multivariate regression analyses capitalize on complex data patterns to make predictions, the specific nature of the patterns that lead to predictions can be challenging to interpret. Future work is required to obtain a deeper mechanistic understanding of which sets of regions and directions of interactions within the DMN and visual network are driving the classifier's predictions and why.

This study marks a success in predicting response to CBT for OCD on the individual participant level. Using machine learning and cross-validation, we demonstrated the ecological validity of FC in assessing potential treatment efficacy. Such measures yield a quantifiable benchmark of confidence when determining treatment plans. Specifically, for a new OCD patient undergoing a single 7-min resting-state scan, network connectivity patterns could predict post-CBT YBOCS (or responder vs. nonresponder status) with relatively high confidence. This could assist in developing treatment plans that optimize time, cost, and available resources.

Finally, this study makes significant contributions to mapping the neural correlates of responsiveness to OCD treatment. Such insights could, for example, guide future studies of neuro-modulatory treatment alongside behavioral therapy to expedite patient recovery.

ACKNOWLEDGMENTS. This work was supported by a National Institute of Mental Health Grant (R01MH085900, to J.O. and J.D.F.). [ClinicalTrials.gov](https://www.clinicaltrials.gov) identifier is NCT01368510.

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