Molecular Psychiatry (2015), 1–6

www.nature.com/mp

ORIGINAL ARTICLE

# Brain connectomics predict response to treatment in social anxiety disorder

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We asked whether brain connectomics can predict response to treatment for a neuropsychiatric disorder better than conventional clinical measures. Pre-treatment resting-state brain functional connectivity and diffusion-weighted structural connectivity were measured in 38 patients with social anxiety disorder (SAD) to predict subsequent treatment response to cognitive behavioral therapy (CBT). We used *a priori* bilateral anatomical amygdala seed-driven resting connectivity and probabilistic tractography of the right inferior longitudinal fasciculus together with a data-driven multivoxel pattern analysis of whole-brain resting-state connectivity before treatment to predict improvement in social anxiety after CBT. Each connectomic measure improved the prediction of individuals' treatment outcomes significantly better than a clinical measure of initial severity, and combining the multimodal connectomics yielded a fivefold improvement in predicting treatment response. Generalization of the findings was supported by leave-one-out cross-validation. After dividing patients into better or worse responders, logistic regression of connectomic predictors and initial severity combined with leave-one-out cross-validation yielded a categorical prediction of clinical improvement with 81% accuracy, 84% sensitivity and 78% specificity. Connectomics of the human brain, measured by widely available imaging methods, may provide brain-based biomarkers (neuromarkers) supporting precision medicine that better guide patients with neuropsychiatric diseases to optimal available treatments, and thus translate basic neuroimaging into medical practice.

*Molecular Psychiatry* advance online publication, 11 August 2015; doi:10.1038/mp.2015.109

## INTRODUCTION

Although there are a number of treatment alternatives available for major neuropsychiatric disorders, there is remarkably little scientific evidence about which treatment would be optimal for a particular patient. Because neuropsychiatric diseases reflect brain differences in structure and function, neuroimaging could provide neuromarkers supporting selection of optimally personalized or precision medicine. One such disorder is social anxiety disorder (SAD), one of the most common psychiatric conditions in the United States,[1] which is characterized by intense fear of social situations and associated with substantial impairment, decreased quality of life and psychiatric comorbidity.[2–5] The standard treatments for SAD, cognitive behavioral therapy (CBT) and pharmacotherapy, are similarly but only moderately effective, with a large proportion of patients remaining symptomatic after initial intervention.[6–8] Although such treatments are superior to placebo on average, no reliable predictor of treatment response has been identified.

Here we asked whether the intrinsic functional and structural organization of the brain (connectomics), as measured through resting-state functional magnetic resonance imaging (rsfMRI) and diffusion-weighted magnetic resonance imaging (dMRI), respectively, predicts therapeutic response to CBT in SAD patients. Resting-state functional connectivity reveals intrinsic functional brain organization by identifying networks as defined by regions exhibiting correlated, low-frequency functional magnetic resonance imaging (fMRI) signals in the absence of external stimuli.[9,10] Structural connectivity can be measured with dMRI, which characterizes the microstructure of white-matter pathways. Both rsfMRI and dMRI have broad clinical appeal because they can be acquired easily and similarly across different sites, involve no task demands and minimal compliance during a brief scan, and do not have behavioral confounds. Such measures would have potential clinical value if they predict treatment response better than current behavioral and clinical assessments of SAD.

Prior studies of SAD have reported alterations of both resting-state functional connectivity[11–13] and structural connectivity.[14–16] The rsfMRI studies have focused on connectivity between the amygdala and orbitofrontal cortex with inconsistent findings in SAD patients of hypoconnectivity[12] or hyperconnectivity.[11] One study[17] reported that greater resting-state amygdala-orbitofrontal cortex functional connectivity at baseline correlated with better response to CBT in SAD patients, but this study did not use statistics allowing for the calculation of prediction (the model was not tested on independent data), and the correlations were inflated due to the recalculation of statistics on already identified clusters.[18] Three dMRI studies of SAD reported altered microstructure of the uncinate fasciculus, which connects frontal and limbic regions.[15,19]

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Received 13 January 2015; revised 6 May 2015; accepted 25 June 2015

In the present study, SAD patients participated in 12 weekly sessions with CBT according to a standardized protocol-based group treatment.[20] Treatment-related improvement in SAD was measured by pre-post change in the Liebowitz Social Anxiety Scale (LSAS).[21] A higher initial LSAS score (more severe SAD) has correlated modestly with greater treatment benefit.[21] Here we asked whether connectomic measures would significantly improve the prediction of treatment benefit relative to conventional initial LSAS scores.

We performed three connectomic measures, and then combined them in a multimodal analysis. First, because the amygdala has been the most common brain locus of dysfunction in SAD,[22] we examined whether amygdalae seed-driven rsfMRI could better predict treatment outcome for CBT than current behavioral or subjective assessment for SAD. Second, we implemented an agnostic data-driven approach, resting-state multi-voxel pattern analysis (MVPA), in order to try to maximize prediction of clinical improvement. Third, using dMRI, we examined the right inferior longitudinal fasciculus (ILF) because it is the tract most associated with right-hemisphere occipital-temporal regions in which activation predicted the efficacy of CBT in SAD patients.[23] The right ILF is thought to mediate the fast transfer of visual emotional signals to anterior temporal regions and neuromodulatory back-projections from the amygdala to early visual areas.[24] Finally, we implemented a multimodal predictive model to investigate whether the combination of the different imaging measures (rsfMRI and dMRI) would improve prediction or whether these imaging measures contained redundant information.

To test the generalizability of the connectivity models, we implemented leave-one-out cross-validation. This cross-validation step was used to minimize potential biases due to voxel-selection in the predictive models. $R^2$ values represent the estimated percent variance explained in CBT outcome (change in LSAS) for SAD patients. We calculated adjusted $R^2$ values ($R^{2*}$)[25] to minimize potential biases because of model selection or overfitting, and to better compare across models with different numbers of predictors. We report results as the estimated percent variance in CBT outcome explained in the general SAD patient population as calculated by $R^{2*}$. Finally, we divided patients into two groups based on their greater or lesser response to CBT, and calculated how accurately individual patients could be classified into those two groups on the basis of connectomics and initial severity.

## MATERIALS AND METHODS

### Participants

The participants (24 men and 14 women; 32 right-handed) had a mean age of 29.2 years (range 18–49 years) and had an above average intelligent quotient as measured with the American National Adult Reading Test (mean American National Adult Reading Test score of 117.9).[26] The mean estimated age of onset of SAD was 12.2 years, and the mean illness duration was 17.4 years. Participants were recruited from the Center for Anxiety and Related Disorders at Boston University and the Center for Anxiety and Traumatic Stress at the Massachusetts General Hospital. All patients gave written informed consent to all procedures, which were approved by the Internal Review Boards of the two clinical sites and the imaging site.

Patients were off concurrent psychotropic medication for at least 2 weeks before the scan session, which is a commonly used criterion in clinical trials to balance the need for scientific rigor and ethical considerations. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV [27] or the Anxiety Disorders Interview Schedule for DSM-IV.[28] Severity of social anxiety was measured using the clinician administered version of the LSAS with a minimal LSAS score of 60 as an additional inclusion criterion. Thus, the sample consisted of patients with a comparatively high severity of SAD.

Exclusion from the study occurred in the case of a lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders or obsessive-compulsive disorder; an eating disorder in the past 6 months; a history of substance or alcohol abuse or dependence (other than nicotine) in the last 6 months and posttraumatic stress disorder within the past 6 months. Entry of patients with other mood or anxiety disorders was permitted if the SAD was judged to be the predominant disorder. In addition to the primary diagnosis of SAD, 15 patients also qualified for a comorbid mood disorder and 15 patients for a comorbid anxiety disorders. Patients additionally completed the Social Phobia and Anxiety Inventory[29] and the State and Trait Anxiety Inventory.[30] Participants were excluded in the case of neurological disorders or serious medical illnesses.

Patients participated in 12 weekly sessions with CBT according to a standardized protocol-based group treatment. Measures of social anxiety, obtained before and after therapy sessions, were collected to assess treatment-related changes. Unrelated to the objective of this analysis, patients were randomized to receive either placebo or d-cycloserine before 5 of the 12 CBT sessions because some research suggests that d-cycloserine may increase CBT effectiveness.[31] However, this was accounted for in the current analysis and there was no main effect between the larger placebo and d-cycloserine groups.[32]

### Imaging

*Data acquisition*. Data were acquired on a 3 T Siemens Trio Tim MRI scanner with a standard Siemens 32-channel phased array head coil. One 6-min resting-state scan was collected while participants fixated on a cross (T2* weighted gradient echo repetition time/echo time/Flip = 6000 ms/30 ms/90°, 67 contiguous interleaved oblique slices, voxel size: 2.0 $mm^3$). The diffusion-weighted scan (10 min total) included 10 non-diffusion weighted volumes ($b = 0$) and 60 diffusion-weighted volumes acquired with non-collinear gradient directions ($b = 700\ s\ mm^{-2}$), all at $128 \times 128$ base resolution and isotropic voxel resolution of 2.0 $mm^3$.

### Data analysis

*Resting-state functional magnetic resonance imaging*. We used methods that both minimize the influence of motion and artifacts, and that allow for valid identification of correlated and anti-correlated networks[33] (see Supplementary Information).

We implemented an *a priori* bilateral anatomical amygdala seed-driven approach as well as MVPA, a data-driven agnostic approach motivated to maximize clinical prediction, with *Conn*.[33]

To create a robust prediction model that can be generalized to new cases, we performed leave-one-out cross-validation. See Supplementary Information for a detailed description of rsfMRI analyses.

*Diffusion-weighted magnetic resonance imaging*. We performed probabilistic tractography with TRACULA, Tracts Constrained by UnderLying Anatomy,[34] an automated method that reconstructs probabilistic distributions of major white matter tracts from each participant's native diffusion images. This method has been shown to accurately reconstruct tracts in individual participants and thus preserves individual variation while maintaining confidence in choosing the same tract across individuals. See Supplementary Information for a detailed description of dMRI analyses.

*Logistic regression*. We divided patients into two categories: the better responders who were the 19 patients with an LSAS improvement of 50% or greater, or the worse responders who were the other 19 patients with less than a 50% improvement. We used logistic regression of initial severity (initial LSAS scores) and the three connectomic measures combined with leave-one-out cross-validation (that is, all participants except one were fit and predicted the out-of-sample participants outcome category; this was iterated for each participant and used to build cross-validated predictions and estimate specificity/sensitivity from the out-of-sample predictions).

## RESULTS

### Initial anxiety severity

Initial LSAS (pre-treatment severity) accounted for 12% of the variance in treatment outcome (Null Model (Initial LSAS), $T(36) = 2.48$, $P = 0.018$) with more severe patients exhibiting greater gains on LSAS scores.

### Resting-state functional magnetic resonance imaging

The amygdalae resting state functional connectivity measures together with initial LSAS scores accounted for 33% of the

variance in treatment outcome. This model performed significantly better than the model with initial LSAS alone ($T(35) = 3.45$, $P = 0.001$; Figure 1). These analyses identified four regions of significant correlation with the amygdala that were associated with LSAS change scores: (1) subgenual ACC/caudate/putamen, (2/3) left and right central sulcus and (4) right inferior temporal/occipital (cluster-level FDR-corrected $P < 0.05$; height threshold uncorrected $P < 0.01$). Greater amygdala connectivity with the subgenual ACC/caudate/putamen cluster and lesser amygdala connectivity with the bilateral central sulcus and right temporal-occipital clusters predicted better treatment gain. Resting-state MVPA together with initial LSAS scores accounted for 34% percent of the variance in treatment outcome ($T(35) = 3.62$, $P = 0.001$; Figure 2). Combined, the resting-state data (amygdalae and MVPA) together with initial LSAS accounted for 50% of the variance in treatment outcome ($F(2,34) = 14.33$, $P < 0.001$).

### Diffusion-weighted magnetic resonance imaging

The first principal component of the four dMRI measures (fractional anisotropy (FA), radial diffusivity, mean diffusivity and axial diffusivity (AD)) of the right ILF in combination with pre-treatment LSAS accounted for 28% of the variance in treatment outcome. This model performed significantly better than a model with initial LSAS scores alone ($T(34) = 3.00$, $P = 0.005$). The correlation of FA and treatment outcome is depicted in Figure 3.

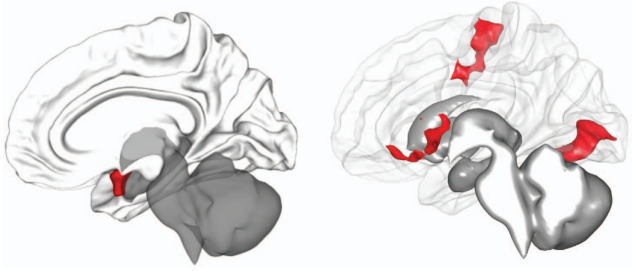

**Figure 1.** Seed-based brain regions predicting clinical response in social anxiety disorder to cognitive behavioral therapy. Anatomically based amygdala seed region is displayed in red (left). Clusters in red identify brain regions that predicted clinical outcome as a function of temporal correlations with bilateral amygdalae seed regions (right). Clusters from left to right include (1) subgenual anterior cingulate/caudate/putamen, (2) bilateral central sulcus and (3) inferior temporal/occipital cortex.

### Multimodal prediction

Combining all connectomic predictors (dMRI, amygdala rsfMRI and MVPA) with initial LSAS scores accounted for 60% of variance in treatment response (Figure 4), which was a significant improvement over the model with initial LSAS scores alone ($F(3,32) = 14.73$, $P < 0.001$). Each predictor carried different information (that is, there were significant effects for each predictor that *uniquely* explained variance after discounting the variance explained by the other predictors): whole-brain MVPA rsfMRI ($T(32) = 3.71$, $P = 0.001$), amygdala rsfMRI ($T(32) = 3.26$, $P = 0.003$) and dMRI ($T(32) = 3.00$, $P = 0.005$). Adding patient demographics (age, intelligent quotient and gender) did not significantly improve the model predictions ($F(3,29) = 1.35$, $R^{2^*} = 0.61$, $P = 0.278$).

### Logistic regression

Using initial LSAS and the three connectomic measures, individual patients could be categorized into better (or worse) responders with 81% accuracy, 84% sensitivity and 78% specificity.

## DISCUSSION

The major finding was that neuromarkers from two widely available connectomics neuroimaging methods, rsfMRI and dMRI, predicted response to CBT treatment for SAD patients substantially better than a current clinician-administrated measure of disease severity. Baseline SAD severity accounted for 12% of the variance in clinical benefit, whereas the combination of neuromarkers and baseline SAD severity accounted for 60% of the variance in clinical benefit. Further, individual patients could be categorized as likely to have better or worse clinical benefit from CBT with over 80% accuracy. These findings indicate that connectomics-based neuromarkers may provide a major improvement in precision treatment for SAD, and perhaps other neuropsychiatric disorders.

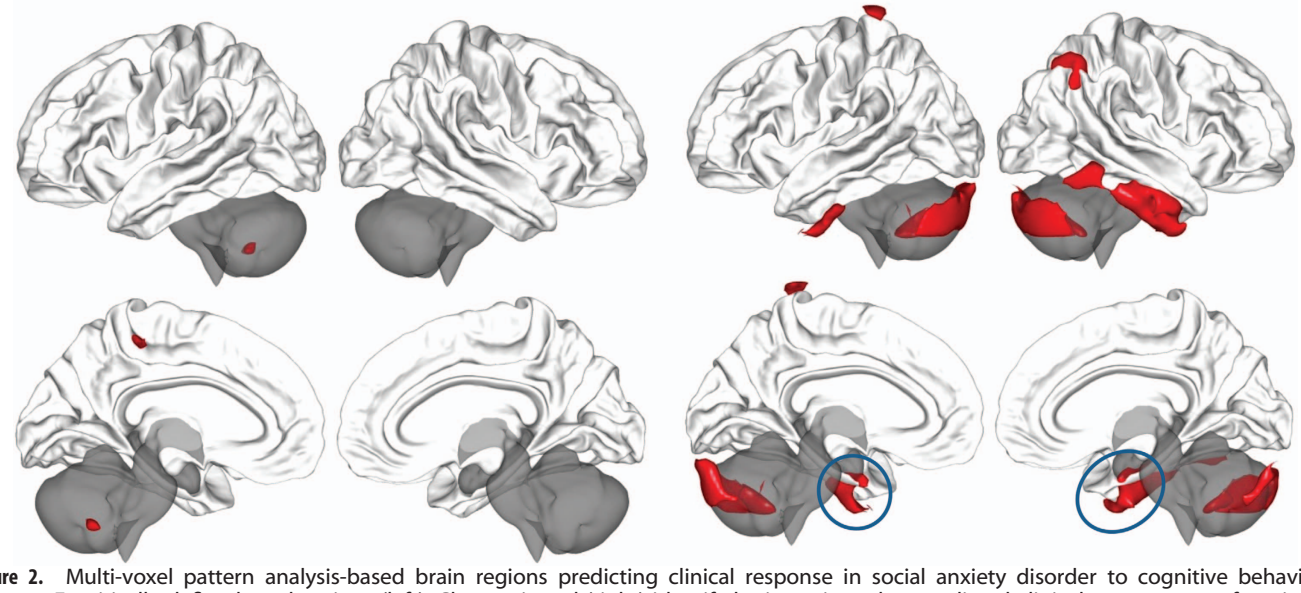

**Figure 2.** Multi-voxel pattern analysis-based brain regions predicting clinical response in social anxiety disorder to cognitive behavioral therapy. Empirically defined seed regions (left). Clusters in red (right) identify brain regions that predicted clinical outcome as a function of temporal correlations with the seed regions. Blue circles highlight bilateral inferior temporal/amygdala clusters (right).

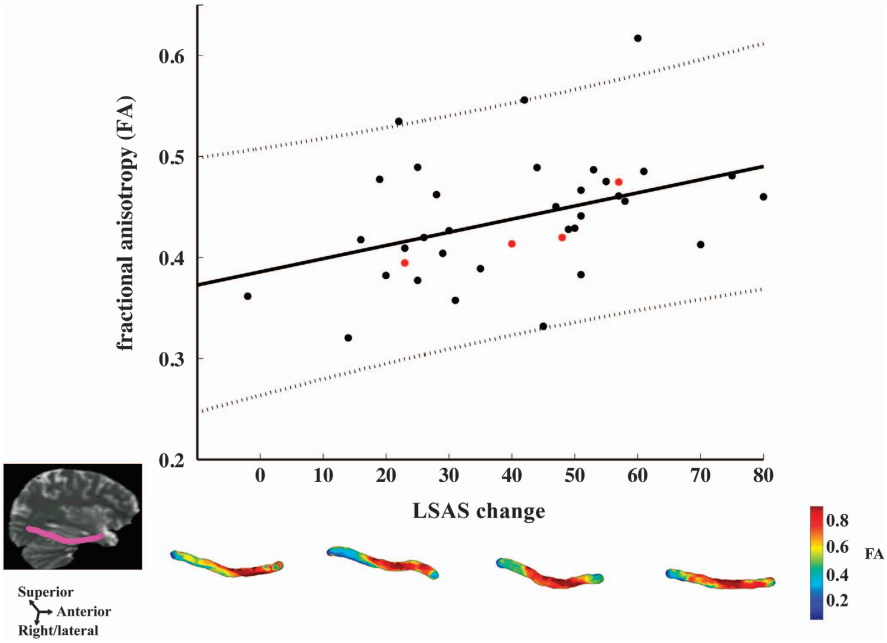


**Figure 3.** Pretreatment diffusion-weighted magnetic resonance imaging (dMRI) of the right inferior longitudinal fasciculus (ILF; bottom left) predicting clinical response in social anxiety disorder to cognitive behavioral therapy. Fractional anisotropy (FA) is plotted against clinical change (Liebowitz Social Anxiety Scale (LSAS) change); the thick line represents the best fit and the thin dotted lines represent the 95% confidence intervals. To illustrate the relation between initial FA and LSAS change, ILF tracts were 3D reconstructed from four example participants (filled red circles in scatter plot) and colored according to FA (bottom). The tracts are ordered by increasing clinical benefit or LSAS change from left to right. Increased FA along the ILF predicted better clinical response.

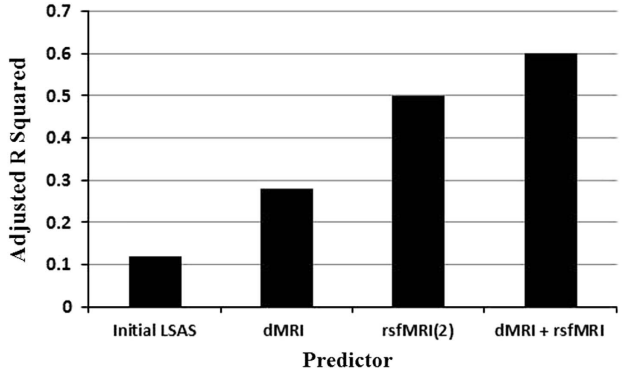


**Figure 4.** Multimodal neuroimaging best predicts clinical response in social anxiety disorder to cognitive behavioral therapy. From left to right, percent variance in treatment effect accounted for by (1) initial clinical interview (initial Liebowitz Social Anxiety Scale (LSAS)); (2) diffusion-weighted magnetic resonance imaging (dMRI) and LSAS; (3) resting-state functional magnetic resonance imaging (rsfMRI; both amygdala-seed and multi-voxel pattern analysis (MVPA) analyses) and LSAS and (4) all dMRI and rsfMRI measures and LSAS. Multimodal neuroimaging yielded a fivefold improvement over initial LSAS in predicting clinical response.

A prior study with some of the same patients reported that fMRI task activation also predicted clinical response to CBT treatment.[23] In that study, patients viewed angry and neutral facial expressions, and greater activation for angry expressions in two right-hemisphere posterior visual regions predicted better clinical gains. The present neuromarkers have three major advantages relevant to fMRI task activations. First, the fMRI task activations accounted for about 40% of variance in treatment response, which was superior to the 14% derived from baseline severity, but substantially less than the 60% achieved with the connectomics measures. Second, because there is no activation task with specific stimuli and task instructions, rsfMRI and dMRI can more readily be measured in a consistent fashion across settings and they hold promise for reliability.[35] Finally, connectomic measures can be performed with a broad range of participants (including infants), and are independent of task performance confounds.

Resting-state fMRI was approached in two related ways. A seed-driven analysis was motivated by evidence that the amygdala is the most frequent locus of dysfunction in SAD.[14] The finding that greater resting-state amygdala-prefrontal connectivity (including subgenual ACC) predicted greater response to CBT is consistent with prior evidence for generalized SAD.[17] The finding that greater amygdala-right temporal-occipital cortex correlation was associated with less treatment response to CBT is consistent with evidence that task activation in right temporal-occipital cortex predicted response to CBT in SAD patients.[23] A second data-driven analysis examined the functional connectivity of all voxels in the brain, independent of *a priori* anatomical hypotheses, using MVPA. Both rsfMRI measures similarly predicted treatment efficacy with the seed-driven amygdala analysis accounting for 33% of the variance and the MVPA analysis accounting for 34% of the variance. The strength of MVPA is its utilization of a massive data set (connectivity between all pairs of recorded voxels) for purposes of prediction, but such an analysis often lacks sensitivity to illuminate the role of specific *a priori* neuroanatomical structures or circuits in a disease. It is noteworthy, however, that the amygdala, which is the most common locus of activation differences in SAD,[20] was predictive of treatment outcome in both seed-based and data-driven (MVPA) analyses.

Diffusion MRI analysis of the right ILF white-matter microstructure also contributed to enhancing prediction accuracy. The right ILF was investigated because it was anatomically consistent with the right-hemisphere posterior cortical locus of fMRI activation that also predicted treatment outcome[23] (and

turned out to be consistent with the right temporal/occipital cluster correlated with the amygdala in the present study). Because we did not have an *a priori* hypothesis as to which measure would be relevant in relation to clinical change, we were agnostic and included the first principal component of all four dMRI (FA, radial diffusivity, axial diffusivity and mean diffusivity) measures.

There are two different uses of the term 'prediction', and the present study used the more rigorous and generalizable sense of that term. In many studies, 'prediction' refers to a correlation between initial or baseline measures and future outcomes. These correlational studies have value in identifying such relations, but they are known to overestimate (be overly optimistic) how a finding in a given data set will apply to a new data set (for example, another set of patients). If neuromarkers were to become a useful part of clinical practice for brain disorders, they would need to be optimized to have a high generalization that would be applicable to a single new case with an as yet unknown outcome. In the long run, this is best accomplished by having larger patient groups in which a model developed for one group transfers usefully to a second, independent group. Within groups, however, a method such as the leave-one-out cross-validation used in present study, in which a prediction for each individual patient was made on the basis of data from the other patients, supports the likely generalizability of findings.

Developing neuromarkers predicting treatment outcomes for neuropsychiatric diseases differs fundamentally in its purposes from the many neuroimaging studies that have compared a patient group to a healthy control group. Comparisons between groups, both conceptually and statistically, highlight differences in which there tends to be homogeneity among patients that distinguish them from a control group (for example, reduced volume or activation of a brain structure). In contrast, predicting treatment outcome capitalizes on heterogeneity among brains of patients that corresponds to heterogeneity in treatment outcomes among patients. In other words, neuromarkers reflect the brain bases of treatment responsivity and not necessarily the brain bases of the etiology or manifestation of a neuropsychiatric disorder.

There is growing evidence that neuromarkers may usefully identify individual differences in future treatment response that can support precision medicine for brain disorders, although most studies to date are correlational rather than predictive in nature.[36] There is evidence that baseline neuromarkers can correlate with or predict treatment outcome in depression,[37–39] schizophrenia,[40] obsessive compulsive disorder,[41] generalized anxiety[42] and addiction.[43] There is also evidence that neuromarkers can predict clinical courses in dyslexia[44] and behaviors that lead to poor health outcomes, such as future abuse of alcohol in adolescence[45,46] or weight gain.[47]

Future neuromarker studies of SAD, or other disorders, will need to approach three criteria. First, patients and clinicians making decisions about treatment options need to know not only whether a particular treatment (for example, CBT) is more or less likely to be efficacious, but also whether an alternative treatment (for example, a drug) is a better or worse choice. Indeed, there is evidence that positron emission tomography can identify neuromarkers that simultaneously indicate whether behavioral or pharmacological treatment is more likely to be effective for depression.[48] It is unknown as yet whether positron emission tomography or MRI imaging provides more sensitive prediction of treatment outcome, but positron emission tomography imaging is relatively rare and invasive, so it would be useful if widely available and non-invasive MRI measures such as rfMRI and dMRI connectomics could also identify which among alternative treatments is optimal for an individual patient. Second, a future study ought to have a larger sample than the 38 patients in the present study to determine the reliability of a connectomic approach for a large and diverse patient sample. Third, for practical clinical use, a choice for treatment must occur for an individual patient. Therefore, neuromarkers must have considerable accuracy for a single patient. Indeed, the combination of initial severity and connectomic measures yielded 81% accuracy (84% sensitivity and 78% specificity) in predicting for each individual patient a better or worse clinical benefit from CBT. There are other examples of such individualized predictive accuracies from neuromarkers for future outcomes in addiction,[49] panic disorder,[50] generalized anxiety and panic disorders,[51] and dyslexia.[52] A limitation of this analysis is that there is no conventional criterion for categorizing the efficacy of CBT treatment for SAD, so that the 50% improvement criterion is somewhat arbitrary. Nevertheless, it can serve as a benchmark in relation to alternative therapies in future studies.

To our knowledge, this is the first multimodal brain imaging study predicting treatment outcome. Because the structural and functional connectivity measures did not carry redundant information, combining these connectomic measures improved the prediction of treatment response with a high degree of accuracy for individual patients. Connectomics may provide neuromarkers that substantially improve predictions for success of clinical interventions, and such neuromarkers may offer evidence-based, precision medicine approaches for optimally selecting treatment options. This approach can lead to a more clinically useful classification of patients, which is in line with the Research Domain Criteria initiative of the National Institute of Mental Health.[52]

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGMENTS

This study was funded in part by NIH grants R01MH078308 and R01MH075889 from the National Institute of Mental Health and the Poitras Center for Affective Disorders Research, Massachusetts Institute of Technology, Cambridge, MA, USA.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)