ONLINE FIRST

Predicting Treatment Response in Social Anxiety Disorder From Functional Magnetic Resonance Imaging

Oliver Doehrmann, PhD; Satrajit S. Ghosh, PhD; Frida E. Polli, PhD; Gretchen O. Reynolds, BA; Franziska Horn, BSc; Anisha Keshavan, BSc; Christina Triantafyllou, PhD; Zeynep M. Saygin, PhD; Susan Whitfield-Gabrieli, PhD; Stefan G. Hofmann, PhD; Mark Pollack, MD; John D. Gabrieli, PhD

Context: Current behavioral measures poorly predict treatment outcome in social anxiety disorder (SAD). To our knowledge, this is the first study to examine neuroimaging-based treatment prediction in SAD.

Objective: To measure brain activation in patients with SAD as a biomarker to predict subsequent response to cognitive behavioral therapy (CBT).

Design: Functional magnetic resonance imaging (fMRI) data were collected prior to CBT intervention. Changes in clinical status were regressed on brain responses and tested for selectivity for social stimuli.

Setting: Patients were treated with protocol-based CBT at anxiety disorder programs at Boston University or Massachusetts General Hospital and underwent neuroimaging data collection at Massachusetts Institute of Technology.

Patients: Thirty-nine medication-free patients meeting *DSM-IV* criteria for the generalized subtype of SAD.

Interventions: Brain responses to angry vs neutral faces or emotional vs neutral scenes were examined with fMRI prior to initiation of CBT.

Main Outcome Measures: Whole-brain regression analyses with differential fMRI responses for angry vs neutral faces and changes in Liebowitz Social Anxiety Scale score as the treatment outcome measure.

Results: Pretreatment responses significantly predicted subsequent treatment outcome of patients selectively for social stimuli and particularly in regions of higher-order visual cortex. Combining the brain measures with information on clinical severity accounted for more than 40% of the variance in treatment response and substantially exceeded predictions based on clinical measures at baseline. Prediction success was unaffected by testing for potential confounding factors such as depression severity at baseline.

Conclusions: The results suggest that brain imaging can provide biomarkers that substantially improve predictions for the success of cognitive behavioral interventions and more generally suggest that such biomarkers may offer evidence-based, personalized medicine approaches for optimally selecting among treatment options for a patient.

Arch Gen Psychiatry.
Published online September 3, 2012.
doi:10.1001/2013.jamapsychiatry.5

Author Affiliations are listed at the end of this article.

SOCIAL ANXIETY DISORDER (SAD), one of the most common psychiatric conditions in the United States,[1] is a chronic and disabling disorder associated with substantial impairment, decreased quality of life, and psychiatric comorbidity.[2-5] The 2 gold-standard treatments for SAD are cognitive behavioral therapy (CBT) and pharmacotherapy. Both treatment modalities are similarly but only moderately effective, with a large proportion of patients remaining symptomatic after the initial intervention.[6-8] Although such treatments are superior to placebo on average, no reliable predictor of treatment response has been identified.

Possibly the major reason for the large interindividual differences in treatment responsiveness are variations within current psychiatric disease categories, which are present at all levels (genetic, neurobiological, and phenotypic). This fundamental variability is not well understood but is likely to be essential for understanding etiologies and enhancing treatments for these diseases.[9] Noninvasive neuroimaging measures may provide important indices of patient variation (biomarkers or neuromarkers) because psychiatric diseases can be conceptualized as brain disorders, and brain structure and function reflect both genetic and environmental influences on current behavior.

Some studies using neuromarkers have reported promising findings that likely captured meaningful variations across individuals who shared a diagnosis and that could allow for improved prognosis in patients with a range of behavioral disorders. For instance, in schizophrenia, neuromarkers have been used to identify individuals at high risk for the disease, predict onset of psychosis in high-risk individuals,[10] and predict treatment outcome.[11] In depression, neuromarkers have predicted recovery from the disease 8 months later[12] and CBT or drug treatment response.[13-15] Furthermore, neuromarkers have been used to predict the likelihood of relapse in drug addiction.[16] Finally, neuromarkers have also been successfully applied outside the domain of psychiatry. In dyslexia, evoked-response potentials measured in newborns[17] and prereading children[18] with familial risk have predicted language and reading scores years later. Similar prediction success over multiple years was reported with functional magnetic resonance imaging (fMRI) in dyslexic participants.[19]

Considering the high prevalence of anxiety disorders, surprisingly few studies have thus far correlated neuroimaging with treatment outcome for this class of disorders. Generalized anxiety disorder has been studied most extensively in this context[20,21] with a focus on predictions for pharmacological treatment outcome. These outcome predictions for generalized anxiety disorder and other anxiety disorders[22] were reported primarily for a priori regions of interest in the amygdala and anterior cingulate cortex.

In the present study, we asked whether fMRI could better predict treatment outcome of CBT in SAD than current clinical measures alone. To this end, 39 patients with generalized SAD underwent an fMRI session in which they viewed faces or scenes with either neutral or negative emotional valence (anger in the case of faces). Given the dissociable representations of faces and scenes in the extrastriate visual cortex both for neutral and emotional stimuli,[23] this paradigm allowed for assessing the category selectivity of outcome-predictive brain responses. Based on previous findings using face stimuli with patients with SAD[24,25] and because of the social nature of the disorder, we hypothesized that stimuli with social content (faces) would be of higher relevance for treatment prediction than those lacking this content (scenes without people). Further, we expected that brain regions identified as dysfunctional in prior neuroimaging studies of SAD might provide predictive information about treatment response. These brain regions include the amygdala and other limbic brain structures[26] and cortical regions in the occipital, temporal, and frontal lobes, which have been implicated in emotion processing.[24,25,27,28]

Patients participated in 12 weekly CBT sessions according to a standardized protocol-based group treatment.[29] Measures of social anxiety, obtained prior to and after therapy sessions to assess treatment-related changes, were correlated with brain-activation data collected at pretreatment. Based on findings from previous studies comparing patients with SAD and controls, we hypothesized that a regression analysis based on the differential signal for angry vs neutral faces would allow the most successful treatment response prediction. Angry faces, relative to neutral faces, convey disapproval and are likely to evoke excessive fear responses and negative cognitions in patients with SAD. Also, means to downregulate these responses are learned during CBT.

A robust, clinically useful model should predict improvement for any individual prior to treatment selection. We used cross-validated machine-learning techniques to develop and test such a prediction model that can predict CBT outcome based on an individual's brain activation and score on the Liebowitz Social Anxiety Scale (LSAS).[30] We also examined the specificity of findings by comparing brain activation responses to social stimuli (faces) with those to nonsocial emotional scene stimuli and how much prediction accuracy is improved by using brain activation values relative to a standard rating scale, namely initial SAD severity.

Taken together, to our knowledge, we report the first data on neuromarkers for treatment responses to CBT in a large sample of patients with SAD. Based on the hypothesis that brain activation could be a more sensitive measure for revealing interindividual variability in SAD pathology relevant for treatment response, we expected fMRI-guided predictions of treatment responsiveness to exceed those based on conventional clinical assessments and self-reports.

METHODS

SUBJECTS

Outpatients were recruited from 2 recruitment sites, the Center for Anxiety and Related Disorders at Boston University (n = 23) and the Center for Anxiety and Traumatic Stress at the Massachusetts General Hospital (n = 18). Patients gave written informed consent to all procedures, which were approved by the internal review boards of all 3 sites. Data from all 41 patients with SAD (generalized subtype) who were scanned and who completed the CBT study were included in these analyses. Nine additional scanned patients (<20%) dropped out of treatment early.

Patients were not taking concurrent psychotropic medication for at least 2 weeks prior to the scan session and CBT initiation. Consistent with an earlier study involving both clinical sites,[31] diagnoses were confirmed at the Massachusetts General Hospital with the Structured Clinical Interview for *DSM-IV*[32] or at the Center for Anxiety and Related Disorders with the Anxiety Disorders Interview Schedule for *DSM-IV*.[33] Severity of social anxiety was measured using the clinician-administered version of the LSAS,[30] which was also used as the dependent variable for analyses. Clinical assessments took place both immediately prior to and after 12 weekly treatment sessions with group-based CBT (see eAppendix [http://www.archgenpsychiatry.com] for details of clinical assessments). Neuroimaging data for 1 participant were discarded from analysis because of a suboptimal slice prescription resulting in incomplete coverage of the most dorsal and ventral portions of the brain. Treatment gain (LSAS score at pretreatment [LSAS-pre] minus LSAS score at posttreatment [LSAS-post] = change in LSAS score [LSAS-change]) for 1 participant was more than 3 SDs higher than the average in our sample. Because of the high sensitivity of regression analyses to outliers, this participant was also excluded, leaving an overall sample size of 39 patients (14 female; additional information provided in eTable 1).

Unrelated to the objective of this analysis, patients were randomized to receive either placebo or the antibiotic D-

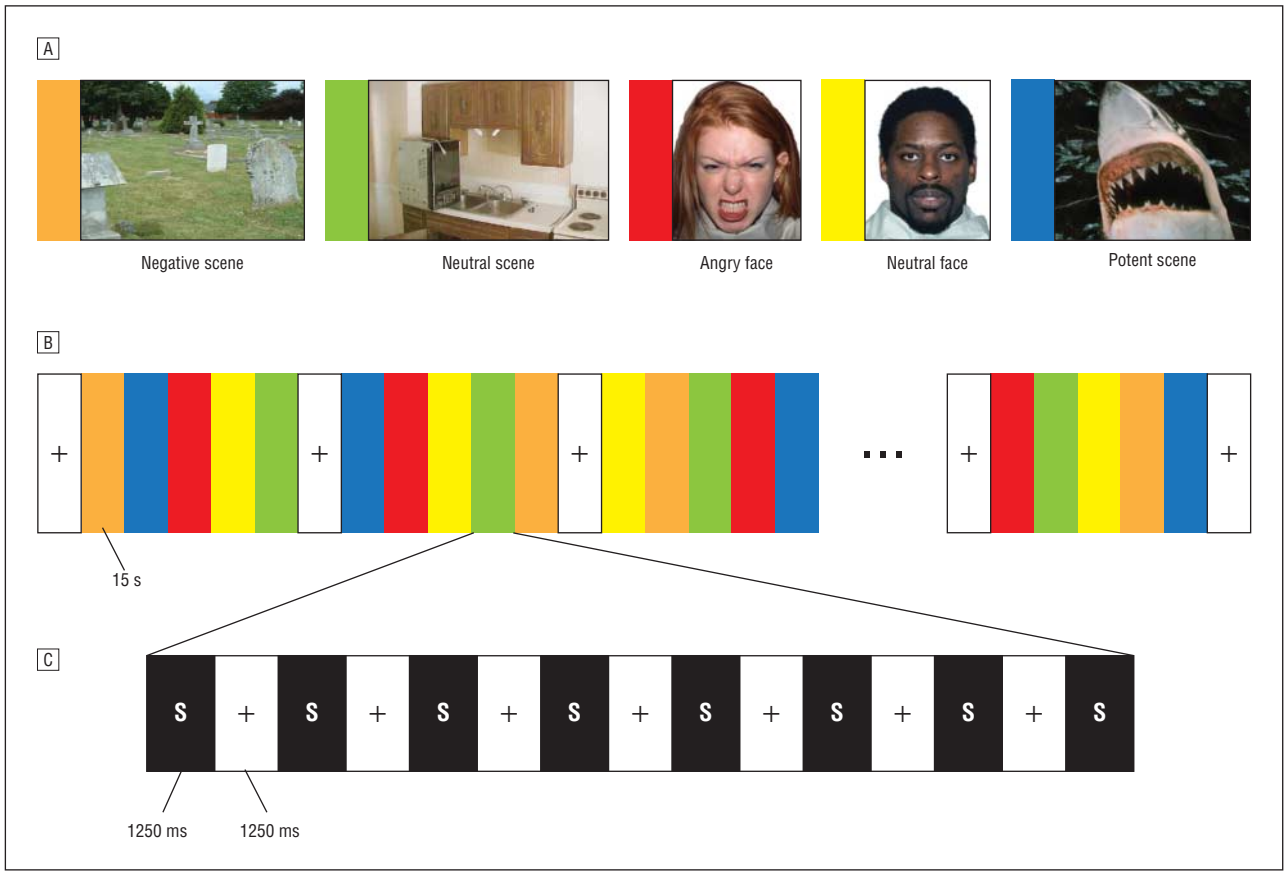

Figure 1. The functional magnetic resonance imaging task. A, Examples of stimuli for each category and color code. B and C, Visualization of stimulation blocks that cycled through all 5 experimental conditions, block timing within a block, and visualization of stimulus (S) timing within a block.

cycloserine prior to 5 of the CBT sessions. D-Cycloserine has been shown to have a facilitative effect on the outcome of CBT for a variety of anxiety disorders including SAD.[31] In all analyses, the effect of treatment group (D-cycloserine or placebo) was explicitly accounted for.

STIMULI AND TASK

For the fMRI task (**Figure 1**), color face images came from the NimStim stimulus set[34] and color images of scenes, from the International Affective Picture System.[35] Overall, 5 different types of images were included in the experiment: (1) negative emotional (angry) faces, (2) neutral faces, (3) negative emotional scenes, (4) neutral scenes, and (5) more intensively negative emotional scenes. Details on properties and assessments of the stimuli are in the eAppendix and eTable 2.

During the imaging experiment, stimuli were projected using a Hitachi (CP-X1200 series) projector and displayed on a rear projection screen that was visible for the subject in a supine position via a tilted mirror fixed to the head coil. Each of the 5 experimental conditions consisted of 30 stimuli presented in six 15-second blocks of 6 stimuli. Each image was presented for 1250 milliseconds, followed by 1250 milliseconds of fixation. The experimental run started and finished with 1 fixation block, and each full cycle of 5 blocks (1 for each condition) was separated by 1 fixation block. The whole run comprised 37 blocks: 6 blocks per condition plus 7 blocks of fixation. One of 2 fixed orders of experimental blocks was used for each participant with 1 block order being the reverse of the other.

Participants performed a 1-back task while in the scanner. For each stimulation block, participants had to indicate via button press the repetition of 1 stimulus. Participants performed at ceiling (mean [SD] correct, 96.1% [0.08]) for this task with little variation between experimental conditions ($P > .10$ for all paired t tests).

IMAGING

Structural and Functional Image Acquisition

Imaging was conducted with a 3-T Siemens TIM Trio system at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research, Massachusetts Institute of Technology. A 32-channel birdcage head coil was used for image acquisition.

One high-resolution structural image was acquired using a T1-weighted 3-dimensional radio-frequency spoiled gradient-echo magnetization-prepared rapid acquisition with gradient echo sequence that optimized the contrast for a range of tissue properties. The pulse sequence was configured as follows: repetition time = 2530 milliseconds, echo time = 3.39 milliseconds, flip angle = 9°, field of view = 256 × 256 mm, one hundred seventy-six 1 × 1 mm in-plane sagittal slices, and 1 mm thickness. Total scan time for this was approximately 8 minutes.

Functional images were collected using a gradient-echo T2*-weighted sequence (repetition time = 2500 milliseconds, echo time = 30 milliseconds, and flip angle = 90°). Twenty-seven contiguous oblique slices (voxel size: 1.7 × 1.7 × 4.5 mm) were acquired interleaved; oblique orientation was defined as a −30° to −40° tilt from a slice parallel to the intercomissural plane. Sequences included prospective acquisition correction for head motion.[36]

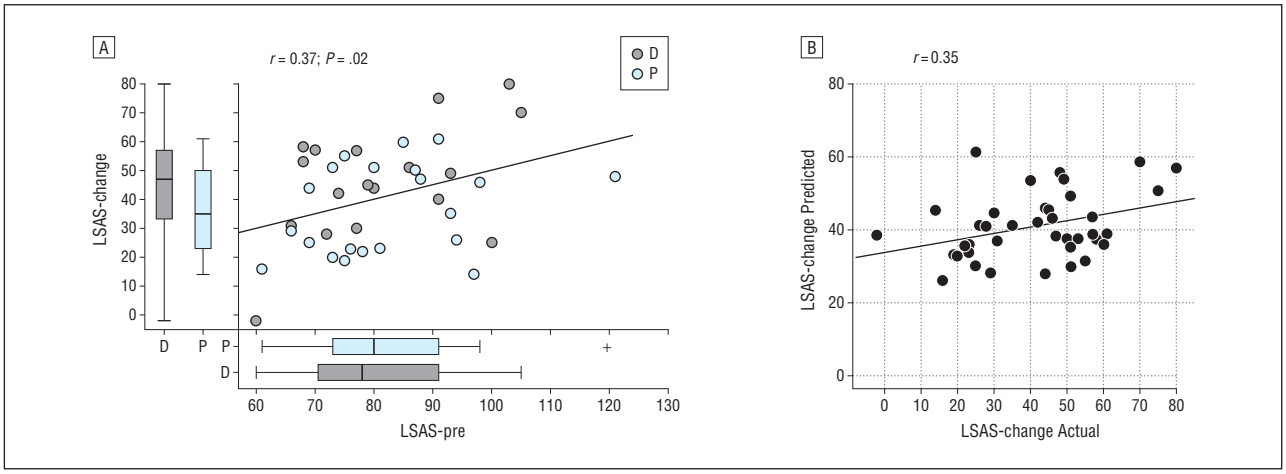

Figure 2. Relation and prediction using Liebowitz Social Anxiety Scale[30] (LSAS) scores. A, Relation of initial social anxiety disorder severity score (LSAS-pre) to treatment effectiveness (change in LSAS score [LSAS-change]). D indicates D-cycloserine; and P, placebo. Left and bottom panels of part A: box plots of LSAS-change and LSAS-pre for each group. B, Relation between predicted LSAS-change from cross-validated model and actual LSAS-change using LSAS-pre and group information only.

Data Preprocessing

Data analysis was done using Statistical Parametric Mapping version 8 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm). The analysis was implemented in Nipype,[37] a Python-based framework that permits efficient batch processing and integration of several neuroimaging analysis packages (http://nipy.org/nipype).

Functional images from each participant were realigned using a 2-pass procedure to the mean functional image and coregistered to the anatomical image using a rigid-body transformation. Structural data were segmented and normalized to Montreal Neurological Institute space using the Statistical Parametric Mapping unified segmentation algorithm.[38] A Python implementation of the Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect) available via Nipype was used to detect outliers (composite volume-to-volume motion >1 mm and intensity >3 SDs) in the functional time-series data and remove them from the analysis. On average, only 5.2 (SD, 9.7) time points per subject were excluded as outliers so that across the 39 subjects, 202 time points (2.3%) were excluded. A spatial smoothing kernel of 6 mm (full width at half maximum) was applied to the functional data. The time series in each voxel was high-pass filtered with a cutoff at 1/128 Hz.

Subject-specific first-level analysis was then applied using a general linear model approach. Regressors for each of the 5 experimental conditions were entered into the design matrix after convolving with the canonical Statistical Parametric Mapping hemodynamic response function. Motion parameters and outliers as detected by Artifact Detection Tools were included in the model as nuisance variables. Beta images modeling the contribution of each experimental condition were submitted to further analysis for contrasts of interests, in particular for responses to angry vs neutral faces and emotional vs neutral scenes.

Details of the experimental approach are specified in the eAppendix and eFigure 1. Subject-specific contrast images were submitted to random-effects second-level statistics. We entered the contrast images into an analysis of covariance regressing LSAS-change onto brain responses, controlling for the effect of initial severity (LSAS-pre) and treatment group (D-cycloserine vs placebo). The treatment group was controlled through an interaction with both LSAS-change and LSAS-pre using a design matrix with separate columns for D-cycloserine and placebo (eFigure 2) and a contrast computing the mean LSAS-change across these 2 patient groups. A voxelwise threshold of $P<.001$ plus a topological correction procedure[39] was applied to account for false positives and limit the false discovery rate (FDR) of the resulting clusters to q(FDR)=0.05.

To create a robust and generalizable prediction model, the subject-specific contrast images were used in a nested cross-validation analysis that ensured separation between training and testing data (procedure schematized in eFigure 1). Prediction analysis was performed using scikit.learn[40] and its significance was assessed using an approximate permutation test.[41]

RESULTS

TREATMENT RESPONSE AND PREDICTION FROM INITIAL SEVERITY

Patients' LSAS scores after CBT were reduced significantly ($t_{38}=14.13$; $P<.001$) (eTable 1). The reductions occurred for both LSAS subscales (fear: $t_{38}=11.76$; $P<.001$; avoidance: $t_{38}=13.94$; $P<.001$) but were significantly greater for the avoidance than the fear subscale ($t_{38}=4.04$; $P<.001$).

The LSAS-pre was positively and significantly ($r=0.37$) correlated with LSAS-change (the difference between LSAS-pre and LSAS-post) (**Figure 2**A), accounting for approximately 12% of the variance in treatment response (adjusted $R^2=0.1162$; $P=.02$). The LSAS-pre scores were similar for the D-cycloserine and placebo groups ($F_{1,37}=0.08$; $P=.77$), and there was a trend for greater improvement in the D-cycloserine group ($F_{1,37}=3.02$; $P=.09$). Adding the interaction of treatment group and LSAS-pre to the regression analysis explained an additional 8% of variance (adjusted $R^2=0.20$; $P=.01$), and this increase was significant ($F_{1,37}=4.63$; $P<.04$). The addition of other potentially relevant parameters such as sex, initial depression scores (from the Montgomery-Åsberg Depression Rating Scale), and the presence or absence of comorbid anxiety disorders to the regression analysis did not significantly change the amount of explained variance (adjusted $R^2=0.21$; $P<.05$).

This model was built and tested on the same data, but it is uncertain how the model would generalize to new

patients. To more accurately estimate the predictive power of the model, we used a stratified cross-validation procedure (maintaining equal numbers of placebo and D-cycloserine patients in each training set) that builds and tests models on independent subsets of data. This more conservative, but generalizable, approach yielded a significant decrease in explained variance (adjusted R^2=0.13 vs 0.20 in the earlier-mentioned model; P=.01 from approximate permutation test) (Figure 2B).

REGRESSION ANALYSES WITH BRAIN RESPONSES

Patients exhibited widespread brain responses to angry vs neutral faces, especially in occipital and ventral temporal regions, and, to a lesser degree, in subcortical structures (eFigure 3). We regressed LSAS-change on the contrast of angry vs neutral faces. Covariates to control for initial severity (LSAS-pre) and treatment group (D-cycloserine or placebo) were included in this whole-brain regression analysis ("Methods" section and eAppendix).

Greater treatment response correlated significantly with greater pretreatment activation in 2 clusters of activation that both survived topological FDR correction at q(FDR)=0.05 (**Figure 3** and eTable 3). The larger of these clusters extended across the right cuneus, superior occipital gyrus, and posterior aspects of the middle temporal gyrus (Figure 3A). A second cluster was located more ventrally on the right lateral cortical surface of the middle occipital gyrus extending into the inferior temporal gyrus (Figure 3B). Because of their locations in more superior and more inferior portions of the occipitotemporal cortex, we refer to these clusters as the dorsal and ventral occipitotemporal cortex, respectively. The relation between the magnitudes of activation and LSAS-change and LSAS-pre is shown in Figure 3C and D. Neither cluster correlated significantly with LSAS-pre (all P>.26).

Several additional clusters exhibited substantial correlations with LSAS-change but did not survive the correction for multiple comparisons (eTable 3), including clusters in the right dorsolateral and right and left ventrolateral prefrontal cortex. No correlation with LSAS-change was found in either the left or right structurally defined amygdala[42] (eAppendix and eFigure 4). Adding the amygdala responses from each condition to a multiple regression model including LSAS-pre and group information did not result in a significant prediction of LSAS-change (multiple R^2=0.43; adjusted R^2=–0.02; P=.53) and did not significantly differ from a model that only included LSAS-pre and group information.

To examine for the category selectivity of these effects, regression analysis was performed for LSAS-change and the contrast of emotional vs neutral scenes. Despite robust and widespread activation for emotional relative to neutral scenes (eFigure 5), this regression analysis did not reveal any clusters at the same threshold as for the face contrast. The same was true for a regression analysis with the intensively negative scenes, which were more negative and more arousing than the angry faces, vs neutral scenes. Thus, the association between pretreatment activation and treatment response was selective for face stimuli.

NESTED CROSS-VALIDATION ANALYSIS

The above analyses revealed that consideration of initial (pretreatment) LSAS score and group (placebo or D-cycloserine) accounted for 20% of treatment outcome variance (adjusted R^2=0.20; P=.01). The addition of neuroimaging (activation values) in the 2 occipitotemporal regions resulted in an improved accounting of 57% of the variance (adjusted R^2=0.57; P<.001). However, selecting clusters using multiple regression on the entire data for model creation biases its predictions[43] and makes uncertain its generalizability. Therefore, using a nested cross-validation approach, we performed an analysis creating a prediction model that separated, for each calculation, the training data set that created the model and the test of that model on an independent data set (see eAppendix for details). The correlation between actual and predicted treatment response using this method was r=0.64, which corresponds to 41% of explained treatment outcome variance (adjusted R^2=0.41; P=.005 from approximate permutation test) (**Figure 4**). Using the same prediction analysis that separates training and test data, the combination of LSAS-pre and group accounted for 12% of the variance (adjusted R^2=0.12; P=.01). As would be expected, the use of a prediction model lowered the accounted for variance in all analyses, but inclusion of the neuroimaging data tripled the amount of variance accounted for in treatment outcome. The cross-validated neuroimaging-based model performed significantly better than the cross-validated LSAS-pre model (Wilcoxon test of mean square errors: z=44; P<.04, 1-tailed).

COMMENT

To our knowledge, the present study is the first to apply neuroimaging-based treatment response prediction to patients with SAD. Pretreatment brain responses for angry vs neutral faces in 2 occipitotemporal brain regions were significantly and positively associated with CBT outcome. The neuroimaging measures in combination with pretreatment severity scores (LSAS-pre) predicted CBT outcome significantly better, accounting for about 40% of the variance in treatment response, than predictions based on LSAS-pre alone, which accounted for about 12% of the variance in treatment response.

Pretreatment disorder severity has previously been suggested to be a predictor of treatment outcome[44] and this was the case in the present study. However, treatment prediction that additionally included neuromarkers substantially outperformed predictions based on conventional clinical measures alone. Further, our findings suggest that the specifically social nature of the face stimuli was relevant to their predictive value because activations to emotional scenes, although extensive and robust, did not predict treatment outcome. Finally, even when controlling for several potentially relevant factors, such as initial severity of SAD and whether patients received D-cycloserine or placebo in addition to CBT,

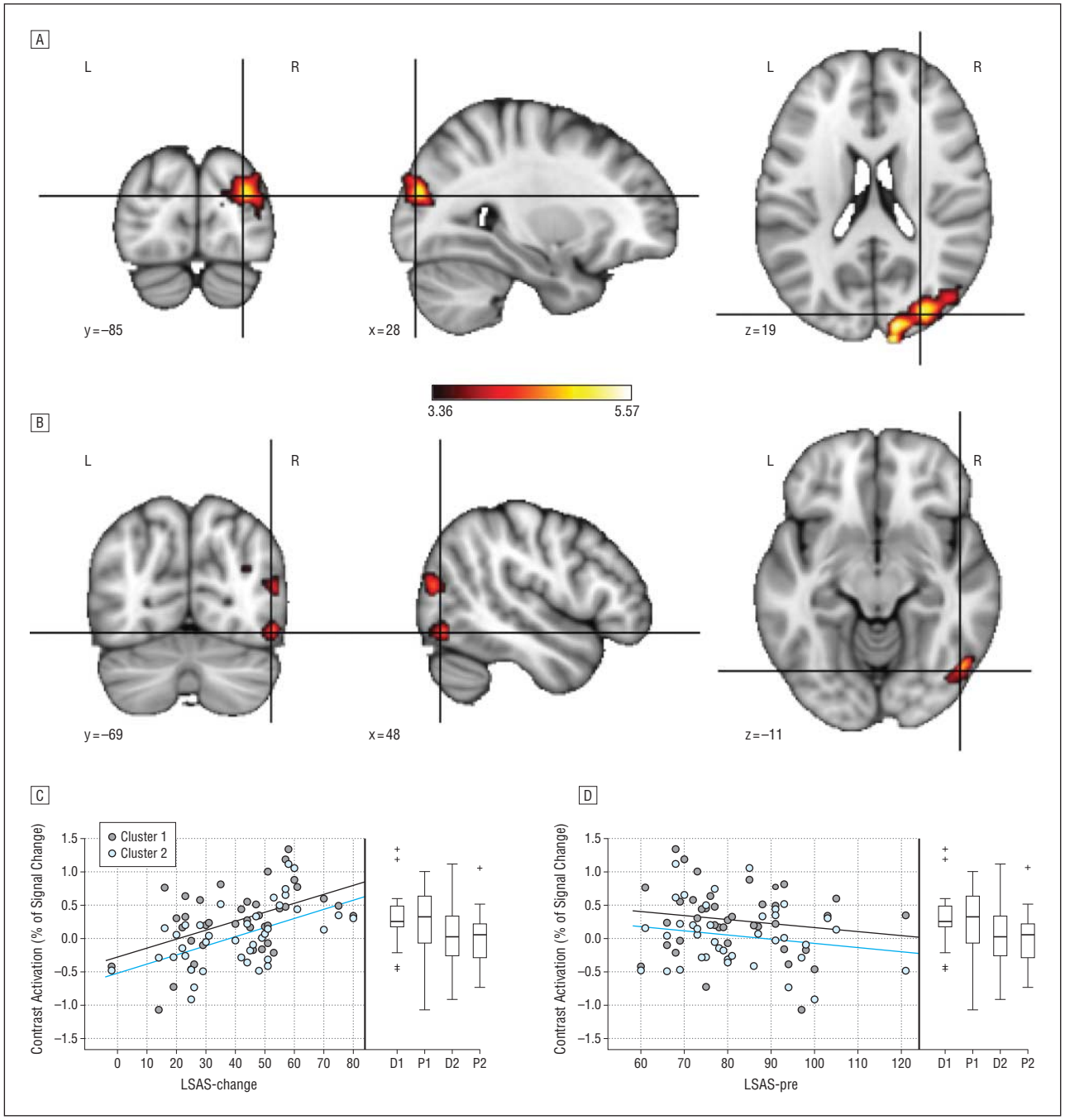

Figure 3. Two right-hemisphere occipitotemporal regions in which initial activation for angry vs neutral faces significantly predicted treatment effectiveness. A and B, *t* Values and locations of clusters showing positive relations with change in Liebowitz Social Anxiety Scale[30] scores (LSAS-change). C, Cluster activation means of each participant vs LSAS-change. Right panel of parts C and D: box plots of cluster means grouped by treatment group (D indicates D-cycloserine; P, placebo) showing similar results in both groups. D, Cluster activation means vs initial LSAS scores (LSAS-pre) showing no significant relation. Color bar represents *t* values.

the predictive power of the brain activations remained significant.

COGNITIVE NEUROSCIENCE OF TREATMENT RESPONSE PREDICTION IN SAD

The specific pattern of functional brain responses that predicted treatment response had both expected and unexpected aspects. The finding that functional brain responses to faces (angry vs neutral) but not scenes (negative vs neutral) predicted treatment response, despite the equating of faces and scenes for emotional valence and arousal, is consistent with the specifically social basis of SAD. However, the locations of activations that predicted response were not the regions most consistently reported in studies comparing brain responses in patients with SAD and typical control groups, such as the amygdala and other limbic areas.[24,45] In the present study, even when using a specific region of interest, no association with treatment response was found in the amygdala despite its robust activation to

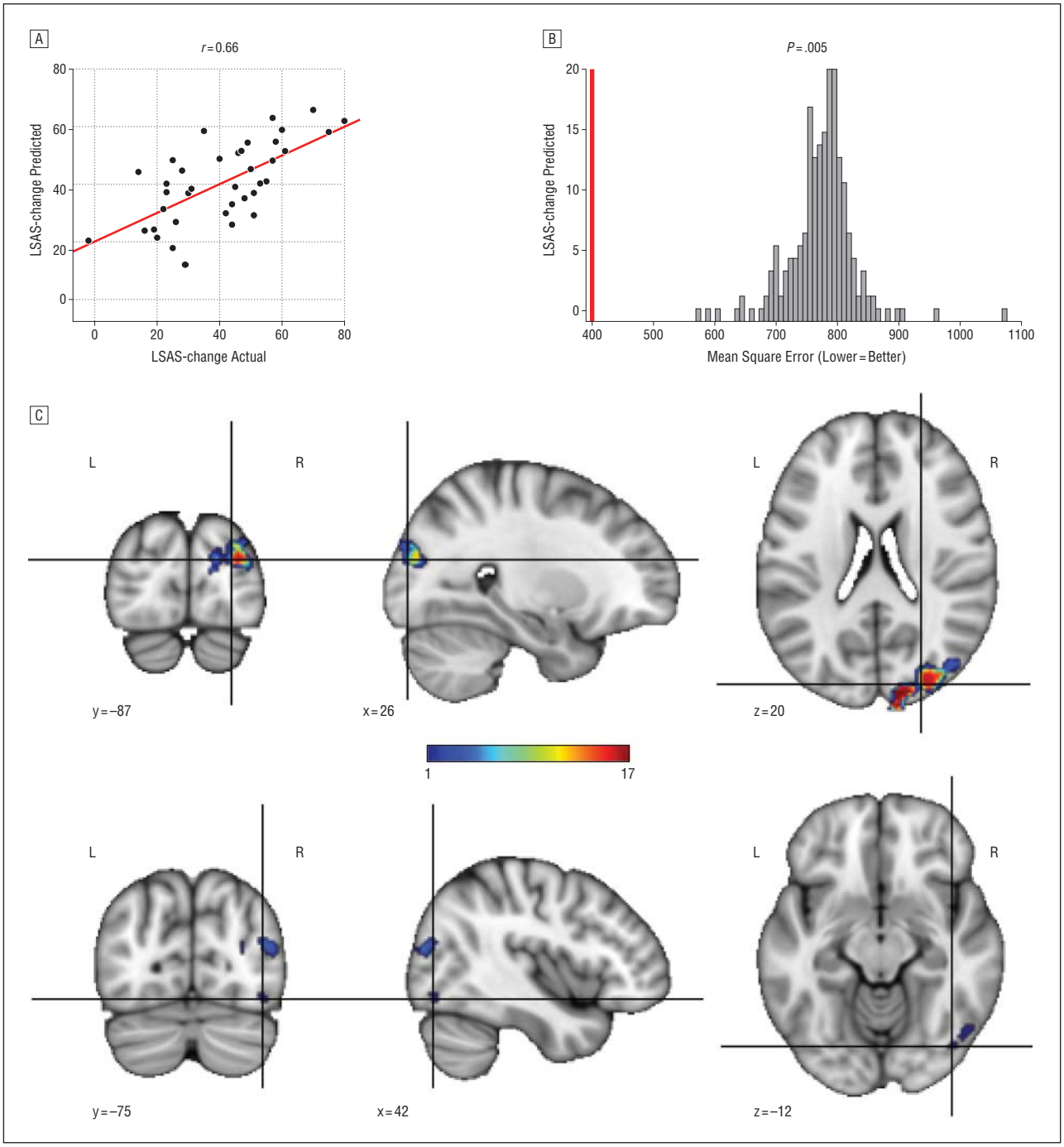

Figure 4. Results from the prediction model created via nested cross-validation using Liebowitz Social Anxiety Scale[30] (LSAS) scores, group information, and brain imaging data. A, Relation between predicted change in LSAS score (LSAS-change) using this model and actual LSAS-change. B, Approximate permutation test results: null distribution (gray), actual value (red). C, Voxels selected in at least 1 fold of the cross-validation. Color bar indicates the number of folds in which a particular voxel was selected.

all experimental conditions. This may be consistent with a prior study reporting no abnormality in the amygdala response to angry faces in SAD.[46] Furthermore, although the amygdala is important for affect, there is evidence for multiple pathways for affective processing with little or no contribution of the amygdala.[47] Consistent with the present findings, 1 study found that in healthy participants processing of angry faces was associated with increased effective connectivity from inferior occipital to ventrolateral prefrontal regions, bypassing the amygdala.[48]

Multiple neuroimaging studies have reported differences between SAD and control groups in similar visual regions for responses to emotional faces, although these cortical activation differences have not received as much attention as the limbic differences.[49,50] Further, connectivity between higher-order visual areas and limbic areas is altered in SAD.[51] In relation to treatment, changes in both higher-order visual and limbic areas correlated with effects of behavioral[52,53] and pharmacological[54] interventions in SAD. All these studies reported increased acti-

vations after treatment, particularly in occipital and temporal regions, in response to anxiety-provoking stimuli. In our study, greater activation in these regions prior to treatment predicted greater treatment effects. Therefore, the high-order visual cortical regions, where activation predicted CBT response in our sample, are implicated in both basic and treatment studies of brain dysfunction in SAD.

Activations in 3 prefrontal cortical regions were also related to treatment outcome, although not significant after correction for multiple comparisons. These prefrontal regions are associated with emotion regulation.[55] The ventrolateral prefrontal cortex has also exhibited differential activations in patients with SAD for faces with negative emotional expressions.[24] Thus, activation of this region could be predictive for treatment response because of its role in stimulus reappraisal and selection of appropriate emotion regulation strategies, which might be dysfunctional in SAD.[28]

POSSIBLE MECHANISMS RELATING IMAGING AND CLINICAL OUTCOME FINDINGS

The specific finding that greater response to angry relative to neutral faces in high-order visual cortices predicts clinical response to CBT can be related to prior findings about SAD. Patients with SAD display reduced activation in similar occipital clusters (along with additional temporal, parietal, and frontal clusters) during emotion regulation tasks on disapproving face stimuli.[28] A fundamental goal of CBT is to enhance emotion regulation in SAD, so perhaps CBT was particularly successful in patients with superior emotion regulation capacities, which was correlated with already stronger responses to angry faces in visual regions. Thus, patients with particularly low responses to angry faces (even less than for neutral faces) might have benefited less from treatment because of poorer emotion regulation capacities. This interpretation is consistent with findings in mood disorders, such as major depressive disorder, where activation changes in occipital cortices were found after CBT[13] and pharmacological treatment[56] and where the rate of change in treatment correlated with gray matter density in occipital regions.[14]

Most salient to SAD are the observations that, by electrophysiological measures, patients with SAD show abnormally reduced attentional enhancement of visual regions similar to the ones reported in the present article,[57] which may reflect avoidance of angry faces.[58] Based on these findings, a behavioral treatment approach for SAD that yields clinical benefits[59] has been attention retraining, in which patients are specifically trained to reallocate their attention to faces. An fMRI study in healthy participants found that a comparable experimentally induced modification of attentional bias to threatening faces was associated with activation changes in a brain region similar in location to our ventral occipitotemporal cortex cluster[60] (without measureable changes in limbic regions). Furthermore, changes in clinical measures of SAD induced by another cognitive-behavioral intervention, a mindfulness-based stress-reduction program, were associated with activation increases during emotion regulation also in occipital regions implicated in attentional deployment.[53] Overall, these findings suggest that attentional mechanisms related to visual perception of social stimuli may be mediated, in part, by activation of occipitotemporal regions and that the status of these mechanisms prior to treatment is important in determining whether CBT is an effective treatment for a patient with SAD.

CLINICAL IMPLICATIONS AND LIMITATIONS OF NEUROMARKERS PREDICTING TREATMENT RESPONSE IN SAD

Most prior imaging studies of SAD have focused on what brain differences are in common among patients relative to controls, whereas the present study focused on variation among patients that is relevant to treatment efficacy. By definition, analyses that focus on homogeneity vs heterogeneity in SAD will reveal different brain regions. For example, the scatterplots (Figure 3) show that patients with greater activation for angry than neutral faces also gained greater benefits from CBT, whereas patients showing the reverse activation (greater activation for neutral than angry faces) gained lesser benefits from CBT. A standard analysis that combines these opposite patterns of activation by treating patients with SAD as a homogenous group would find little or no activation in this region (although we found in adjacent, nonoverlapping regions exactly such an increased response to angry vs neutral faces for the patients as a group).

Conversely, an analysis of the kind reported here can provide a new avenue for the identification of treatment-relevant subtypes in SAD that is based on brain measures and, to a lesser extent, conventional clinical measures. In line with this reasoning, most studies examining interventions to treat SAD[6-8] considered patients as a single, homogeneous group with no evidence as to whether a particular patient was more or less likely to benefit from CBT or pharmacological treatment. However, in most treatment studies with either modality, interventions were effective in only approximately half of the sample, with little additional gain for combination treatment.[7] Accordingly, there is a large demand for evidence-based criteria to determine whether a patient should receive CBT or pharmacotherapy to maximize treatment response. Neuroimaging may offer an evidence-based path toward selection of optimal treatments, such that neuromarkers could selectively identify which patients are most likely to benefit from which treatment option. An integration of neuromarkers with genetic, behavioral, and other biomarkers is likely to further refine the prediction for individual patients[61-63]

Neuroimaging studies of SAD and other neuropsychiatric disorders have identified brain differences in these disorders, but these observations have had limited clinical implications so far. Neuromarkers may become a practical clinical tool to guide the selection of optimal treatments for individual patients. However, several limitations of the present study would need to be addressed in further studies before such practical application is possible. First, although we

used analytic methods that prioritized generalizability (eg, cross-validation techniques), a larger study is needed in which a model derived from a particular group is applied to a completely independent group to determine the true model generalizability. Second, although statistically it appeared to make no difference, a larger study would not divide patients into drug and placebo groups. Third, it is unknown whether fMRI activation to angry vs neutral faces is the optimal neuromarker. Perhaps other facial expressions (eg, disgust or fear), or multimodal combinations of functional and structural measures, may be better predictors. Fourth, direct comparison of participants with SAD and typical participants would be useful in determining the typical pattern of activation in these predictive brain areas and may reveal the pathophysiological mechanism related to prediction (eg, whether these areas typically do or do not have activations greater for angry than neutral faces). Fifth, it will be essential to perform studies that contrast alternative treatments and thus discover whether neuromarkers can differentially predict which treatment is optimal for a patient. The positive finding that neuromarkers predicted treatment outcome significantly better than currently used clinical scales for SAD, however, provides evidence that treatment selection for a patient with SAD can move toward evidence-based neurobiological approaches that may guide toward optimal, individualized clinical benefits.

Submitted for Publication: April 10, 2012; final revision received June 27, 2012; accepted July 5, 2012.
Published Online: September 3, 2012. doi:10.1001/2013.jamapsychiatry.5
Author Affiliations: McGovern Institute for Brain Research and Poitras Center for Affective Disorders Research (Drs Doehrmann, Ghosh, Polli, Triantafyllou, Saygin, and Gabrieli and Mss Reynolds, Horn, and Keshavan) and Department of Brain and Cognitive Sciences (Drs Doehrmann, Whitfield-Gabrieli, and Gabrieli), Massachusetts Institute of Technology, Cambridge, and Department of Radiology, Massachusetts General Hospital Athinoula A. Martinos Center, Harvard Medical School (Dr Triantafyllou), and Department of Psychology, Boston University (Drs Doehrmann and Hofmann), Boston; and Department of Psychiatry, Rush University Medical Center, Chicago, Illinois (Dr Pollack).
Correspondence: Oliver Doehrmann, PhD, McGovern Institute for Brain Research, Massachusetts Institute of Technology, 43 Vassar St, Room 46-4033D, Cambridge, MA 02139 (oldoe@mit.edu).
Author Contributions: Drs Doehrmann and Ghosh contributed equally to this article and confirm that they had full access to all of the data in the study, performed the statistical analyses for this article, and take responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: Dr Doehrmann was supported by postdoctoral fellowship DO-1469/1-1 from the Deutsche Forschungsgemeinschaft. Neuroimaging was supported by the Poitras Center for Affective Disorders Research. Dr Hofmann is a paid consultant for Merck/Schering-Plough and is supported by National Institutes of Mental Health grant MH078308. Dr Pollack is supported by National Institute of Mental Health grant MH075889. He additionally is a member of the advisory boards or a consultant for BrainCells, Eli Lilly, Johnson & Johnson, MedAvante, Labopharm, Mindsite, Otsuka, Targia Pharmaceuticals, and Pfizer. He has received research grants from Bristol-Myers Squibb, Euthymics, Forest Laboratories, GlaxoSmithKline, Eli Lilly, National Center for Complementary and Alternative Medicine, National Institute on Drug Abuse, and National Institute of Mental Health. Continuing Medical Education–supported activities of Dr Pollack were sponsored by AstraZeneca, Sepracor, and Pfizer. He holds equity in MedAvante, Mensante Corporation, Mindsite, and Targia Pharmaceuticals and receives royalties for SIGH-A, SAFER interviews.
Previous Presentations: Parts of the data from this article were presented at the 44th Annual Convention of the Association for Behavioral and Cognitive Therapy; November 20, 2010; San Francisco, California; the 2011 Annual Conference of the Anxiety Disorders Association of America; March 26, 2011; New Orleans, Louisiana; and the 17th Annual Meeting of the Organization for Human Brain Mapping; June 26, 2011; Quebec City, Quebec, Canada.
Online-Only Material: The eTables, eFigures, and eAppendix are available at http://www.archgenpsychiatry.com.
Additional Information: Data were collected from a subsample of subjects who took part in a clinical trial registered at clinicaltrials.gov (NCT00515879). However, the present article does not report findings from this clinical trial.
Additional Contributions: We gratefully acknowledge the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research for providing an excellent neuroimaging environment.

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):768]. *Arch Gen Psychiatry*. 2005;62(6):593-602.
2. Katzelnick DJ, Kobak KA, DeLeire T, Henk HJ, Greist JH, Davidson JR, Schneier FR, Stein MB, Helstad CP. Impact of generalized social anxiety disorder in managed care. *Am J Psychiatry*. 2001;158(12):1999-2007.
3. Magee WJ, Eaton WW, Wittchen HU, McGonagle KA, Kessler RC. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1996;53(2):159-168.
4. Stein MB, Kean YM. Disability and quality of life in social phobia: epidemiologic findings. *Am J Psychiatry*. 2000;157(10):1606-1613.
5. Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia: comorbidity and morbidity in an epidemiologic sample. *Arch Gen Psychiatry*. 1992;49(4):282-288.
6. Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, Holt CS, Welkowitz LA, Juster HR, Campeas R, Bruch MA, Cloitre M, Fallon B, Klein DF. Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. *Arch Gen Psychiatry*. 1998;55(12):1133-1141.
7. Davidson JR, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, Zhao N, Connor KM, Lynch TR, Gadde KM. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry*. 2004;61(10):1005-1013.
8. Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, Vermes D, Erwin BA, Schmidt AB, Juster HR, Campeas R, Liebowitz MR. A placebo-controlled

trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Arch Gen Psychiatry*. 2010;67(3):286-295.
9. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol*. 2010;6:155-179.
10. Koutsouleris N, Meisenzahl EM, Davatzikos C, Bottlender R, Frodl T, Scheuerecker J, Schmitt G, Zetzsche T, Decker P, Reiser M, Möller HJ, Gaser C. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Arch Gen Psychiatry*. 2009;66(7): 700-712.
11. Kumari V, Peters ER, Fannon D, Antonova E, Premkumar P, Anilkumar AP, Williams SC, Kuipers E. Dorsolateral prefrontal cortex activity predicts responsiveness to cognitive-behavioral therapy in schizophrenia. *Biol Psychiatry*. 2009; 66(6):594-602.
12. Canli T, Cooney RE, Goldin P, Shah M, Sivers H, Thomason ME, Whitfield-Gabrieli S, Gabrieli JD, Gotlib IH. Amygdala reactivity to emotional faces predicts improvement in major depression. *Neuroreport*. 2005;16(12):1267-1270.
13. Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, Donaldson C, Suckling J, Andrew C, Steiner H, Murray RM. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biol Psychiatry*. 2008;64(6):505-512.
14. Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, Bullmore E. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry*. 2007;62 (5):407-414.
15. Siegle GJ, Carter CS, Thase ME. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. *Am J Psychiatry*. 2006;163(4): 735-738.
16. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry*. 2005;62(7):761-768.
17. Molfese VJ, Molfese DL, Modgline AA. Newborn and preschool predictors of second-grade reading scores: an evaluation of categorical and continuous scores. *J Learn Disabil*. 2001;34(6):545-554.
18. Maurer U, Bucher K, Brem S, Benz R, Kranz F, Schulz E, van der Mark S, Steinhausen HC, Brandeis D. Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biol Psychiatry*. 2009; 66(4):341-348.
19. Hoeft F, McCandliss BD, Black JM, Gantman A, Zakerani N, Hulme C, Lyytinen H, Whitfield-Gabrieli S, Glover GH, Reiss AL, Gabrieli JD. Neural systems predicting long-term outcome in dyslexia. *Proc Natl Acad Sci U S A*. 2011;108 (1):361-366.
20. Nitschke JB, Sarinopoulos I, Oathes DJ, Johnstone T, Whalen PJ, Davidson RJ, Kalin NH. Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *Am J Psychiatry*. 2009;166(3):302-310.
21. Whalen PJ, Johnstone T, Somerville LH, Nitschke JB, Polis S, Alexander AL, Davidson RJ, Kalin NH. A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. *Biol Psychiatry*. 2008;63(9):858-863.
22. Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychol Med*. 2008;38(4):555-561.
23. Sabatinelli D, Fortune EE, Li Q, Siddiqui A, Krafft C, Oliver WT, Beck S, Jeffries J. Emotional perception: meta-analyses of face and natural scene processing. *Neuroimage*. 2011;54(3):2524-2533.
24. Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry*. 2002;59(11):1027-1034.
25. Straube T, Mentzel HJ, Miltner WH. Common and distinct brain activation to threat and safety signals in social phobia. *Neuropsychobiology*. 2005;52(3):163-168.
26. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476-1488.
27. Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci*. 2009;34 (6):418-432.
28. Goldin PR, Manber T, Hakimi S, Canli T, Gross JJ. Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. *Arch Gen Psychiatry*. 2009;66(2):170-180.
29. Hofmann SG, Otto MW. *Cognitive Behavioral Therapy for Social Anxiety Disorder: Evidence-Based and Disorder-Specific Treatment Techniques*. New York, NY: Routledge; 2008.
30. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, Liebowitz MR. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med*. 1999;29(1):199-212.
31. Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, Shiekh M, Otto MW. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry*. 2006;63(3):298-304.
32. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for* DSM-IV *Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/PSY SCREEN)*. New York: Biometrics Research, New York State Psychiatric Institute; 1997.
33. DiNardo PA, Brown TA, Barlow DH. *Anxiety Disorders Interview Schedule for* DSM-IV*: Lifetime Version (ADIS-IV-L)*. San Antonio, TX: Psychological Corp; 1994.
34. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, Marcus DJ, Westerlund A, Casey BJ, Nelson C. The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res*. 2009;168(3):242-249.
35. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. Gainesville, FL: NIMH Center for the Study of Emotion and Attention; 1997.
36. Thesen S, Heid O, Mueller E, Schad LR. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magn Reson Med*. 2000;44(3):457-465.
37. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, Ghosh SS. Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Front Neuroinform*. 2011;5:13.
38. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839-851.
39. Chumbley JR, Friston KJ. False discovery rate revisited: FDR and topological inference using gaussian random fields. *Neuroimage*. 2009;44(1):62-70.
40. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, Blondel M, Prettenhofer P, Weiss R, Dubourg V, Vanderplas J, Passos A, Cournapeau D, Brucher M, Perrot M, Duchesnay E. Scikit-learn: machine learning in Python. *J Mach Learn Res*. 2011;12(Oct):2825-2830.
41. Dwass M. Modified randomization tests for nonparametric hypotheses. *Ann Math Stat*. 1957;28(1):181-187. doi:10.1214/aoms/1177707045.
42. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19(3):1233-1239.
43. Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. *Nat Neurosci*. 2009;12(5): 535-540.
44. Scholing A, Emmelkamp PM. Prediction of treatment outcome in social phobia: a cross-validation. *Behav Res Ther*. 1999;37(7):659-670.
45. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry*. 2006;59(5):424-429.
46. Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, Stout JC, Nathan PJ. Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology*. 2010;35(12):2403-2413.
47. Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat Rev Neurosci*. 2010; 11(11):773-783.
48. Dima D, Stephan KE, Roiser JP, Friston KJ, Frangou S. Effective connectivity during processing of facial affect: evidence for multiple parallel pathways. *J Neurosci*. 2011;31(40):14378-14385.
49. Brühl AB, Rufer M, Delsignore A, Kaffenberger T, Jäncke L, Herwig U. Neural correlates of altered general emotion processing in social anxiety disorder. *Brain Res*. 2011;1378:72-83.
50. Evans KC, Wright CI, Wedig MM, Gold AL, Pollack MH, Rauch SL. A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder. *Depress Anxiety*. 2008;25(6):496-505.
51. Liao W, Qiu C, Gentili C, Walter M, Pan Z, Ding J, Zhang W, Gong Q, Chen H. Altered effective connectivity network of the amygdala in social anxiety disorder: a resting-state FMRI study. *PLoS One*. 2010;5(12):e15238.
52. Furmark T, Tillfors M, Marteinsdottir I, Fischer H, Pissiota A, Långström B, Fredrikson M. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry*. 2002;59(5):425-433.
53. Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion*. 2010;10(1):83-91.
54. Kilts CD, Kelsey JE, Knight B, Ely TD, Bowman FD, Gross RE, Selvig A, Gordon A, Newport DJ, Nemeroff CB. The neural correlates of social anxiety disorder and response to pharmacotherapy. *Neuropsychopharmacology*. 2006;31(10):2243-2253.
55. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-

subcortical pathways mediating successful emotion regulation. *Neuron*. 2008; 59(6):1037-1050.
56. Fu CH, Williams SC, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM, Bullmore ET. Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am J Psychiatry*. 2007;164(4):599-607.
57. Mueller EM, Hofmann SG, Santesso DL, Meuret AE, Bitran S, Pizzagalli DA. Electrophysiological evidence of attentional biases in social anxiety disorder. *Psychol Med*. 2009;39(7):1141-1152.
58. Mansell W, Clark DM, Ehlers A, Chen YP. Social anxiety and attention away from emotional faces. *Cogn Emotion*. 1999;13(6):673-690. doi:10.1080/026999399379032.
59. Amir N, Beard C, Taylor CT, Klumpp H, Elias J, Burns M, Chen X. Attention training in individuals with generalized social phobia: a randomized controlled trial. *J Consult Clin Psychol*. 2009;77(5):961-973.
60. Monk CS, Nelson EE, Woldehawariat G, Montgomery LA, Zarahn E, McClure EB, Guyer AE, Leibenluft E, Charney DS, Ernst M, Pine DS. Experience-dependent plasticity for attention to threat: behavioral and neurophysiological evidence in humans. *Biol Psychiatry*. 2004;56(8):607-610.
61. Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S, Kohli MA, Hennings JM, Horstmann S, Kloiber S, Menke A, Bondy B, Rupprecht R, Domschke K, Baune BT, Arolt V, Rush AJ, Holsboer F, Müller-Myhsok B. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *Arch Gen Psychiatry*. 2009;66(9):966-975.
62. Kemp AH, Gordon E, Rush AJ, Williams LM. Improving the prediction of treatment response in depression: integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. *CNS Spectr*. 2008;13(12):1066-1086, quiz 1087-1088.
63. Siegle GJ, Steinhauer SR, Friedman ES, Thompson WS, Thase ME. Remission prognosis for cognitive therapy for recurrent depression using the pupil: utility and neural correlates. *Biol Psychiatry*. 2011;69(8):726-733.