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A pilot study of gray matter volume changes associated with paroxetine treatment and response in social anxiety disorder

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ABSTRACT

Social anxiety disorder (SAD) has received relatively little attention in neurobiological studies. We sought to identify neuro-anatomical changes associated with successful treatment for the disorder. Fourteen patients (31 years; 57% female) with *DSM-IV* generalized SAD were imaged before and after 8-weeks of paroxetine treatment on a 1.5 T GE Signa MRI scanner. Symptoms were assessed by a clinician using the Liebowitz Social Anxiety Scale (LSAS). Longitudinal changes in voxel based morphometry (VBM) were determined using the VBM8 Toolbox for SPM8. Symptom severity decreased by 46% following treatment ($p < 0.001$). At week 8, significant gray matter reductions were detected in bilateral caudate and putamen, and right thalamus, and increases in the cerebellum. Gray matter decreases in left thalamus were correlated with clinical response. This is the first study to our knowledge to identify treatment related correlates of symptom improvement for SAD. Replication in larger samples with control groups is needed to confirm these findings, as well as to test their specificity and temporal stability.

1. Introduction

Social anxiety disorder (SAD) is among the most commonly occurring psychiatric disorders, with lifetime prevalence of 5–12% (Weissman et al., 1996; Grant et al., 2005; Kessler et al., 2005). Cardinal features include fear of social situations, particularly those involving exposure to unfamiliar persons, which is associated with avoidance and significant functional impairment (Filho et al., 2010). SAD also shares a number of clinical features with other anxiety syndromes (Bienvenu et al., 2011; Stein et al., 2011), and one of the aims of neuroimaging studies has been to identify similarities and differences at the brain level that may guide more precise understanding of etiology, pathophysiology, and mechanisms of treatment response. Well-established treatments for SAD include cognitive-behavioral therapy and selective serotonin reuptake inhibitor (SSRI) medications; however, as many as half of patients do not respond to a course of either treatment (Stein and Stein, 2008). There is a need for better understanding of mechanisms of treatment, in order to inform treatment selection and improvement.

Most paradigms in imaging studies of SAD to date have compared neural activity in persons with and without the disorder performing tasks related to the core psychopathology, such as viewing of threatening faces (Freitas-Ferrari et al., 2010; Pietrini et al., 2010), performance anticipation (Lorberbaum et al., 2004; Tillfors et al., 2001), eye contact (Schneier et al., 2011), and self-judgment (Andrews-Hanna et al., 2010; Whitfield-Gabrieli et al., 2011). Evidence from these studies have implicated hyperactivation of neural circuits serving emotion, particularly the amygdala, striatum, insula, hippocampus, fusiform and parahippocampal region (Bruhl et al., 2014a, 2011; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010). Disturbances in cingulate and prefrontal circuitry are also reported, but directionality of these results is less consistent (Freitas-Ferrari et al., 2010). Studies examining structural morphology have been fewer, and with findings less consistent. A pilot study of 13 unmedicated SAD patients found cortical thinning in bilateral fusiform and postcentral, and right hemisphere frontal, parietal and temporal pole regions associated with the disorder (Syal et al., 2012). A larger study of 46 patients and matched controls, however, found no thinning but increased thickness in the left insula and right anterior cingulate and temporal pole (Bruhl et al., 2014b). Finally,

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thicker left inferior temporal cortex was reported in a study of 14 SAD patients, compared to 12 healthy controls (Frick et al., 2013a, 2013b). Within the patient group, rostral cingulate thickness was inversely associated with symptom severity.

The above studies are based on comparisons of cases to controls at a single time-point. A complementary approach to mapping neural correlates is to follow persons with the disorder longitudinally through treatment, and to examine associated changes in morphology or function. Regions that change with clinical improvement are more likely to be related to the underlying pathophysiology than those that do not. Whereas case-control designs target abnormalities that are *shared* across cases (relative to controls), treatment designs seek to model the individual variation between cases, and can thus be particularly informative for identifying clinical or biological markers of change in illness severity (Hofmann, 2013). A methodological advantage of such an approach is that because each subject in essence serves as their own comparison group, heterogeneity resulting from variation between subjects in demographics, psychiatric and medical history, and gross brain morphology is minimized (Cohen, 1988).

Applying this approach, functional MRI studies of SAD patients undergoing SSRI treatment have identified post-treatment reductions in regions including the amygdala, ventromedial prefrontal cortex, insula, thalamus, anterior and posterior cingulate cortices, during SAD-probing paradigms (viewing of threatening faces, eye contact, and scrutiny by others) (Gimenez et al., 2013; Phan et al., 2013; Schneier et al., 2011). Similar reductions have been reported in positron emission tomography (PET) and single photon emission tomography (SPECT) studies (Furmark et al., 2002). Though specific regions vary across the studies (potentially attributable to differences in comorbidity, selected regions of interest, and imaging paradigms), the overall direction is consistent with a treatment-based normalization of hyperactive fear circuitry. Finally, these brain changes have been also identified when treating with cognitive behavioral therapy (Goldin et al., 2013; Klumpp et al., 2013; Mansson et al., 2013), making it unlikely that the findings are pharmacological-specific sequelae unrelated to SAD.

The above examples target *task-induced* changes in the brain. Anatomical changes can be provide complementary information as unlike functional measures, detection of structural changes is not modulated by a subject's current state or performance metrics. Only one study to our knowledge has directly probed treatment effects on neuroanatomy (Cassimjee et al., 2010). In that study, reductions in left cerebellar and bilateral superior temporal volumes in 11 SAD patients were noted following 12 weeks of treatment with escitalopram, but correlations between anatomical changes and clinical course were not reported.

The present study seeks to further examine the relationships between treatment, clinical severity, and gray matter in social anxiety. Specifically, we test among patients with *DSM-IV* generalized SAD, whether (1) 8 weeks of treatment with paroxetine is associated with neuroanatomical changes, and (2) whether neuroanatomical changes are associated with clinical response.

2. Methods

2.1. Sample

The research was approved by the Institutional Review Board of the New York State Psychiatric Institute, and all subjects provided informed written consent. The sample has been detailed elsewhere (Schneier et al., 2011). Briefly, subjects were recruited through media advertisements and clinical referrals, and interviewed using the Structured Clinical Interview for *DSM-IV* Axis I disorders (SCID IV) (First et al., 1997). Subjects were required to have a current diagnosis of generalized SAD, and no other current Axis I disorder (except secondary diagnoses of generalized anxiety, dysthymia, or specific phobia). The present analysis is based on 14 of 17 enrolled patients [two subjects failed to return for the post-treatment scan, and one subject had unusable post-treatment scan data]. For corollary analyses to rule out temporal artifacts unrelated to treatment, we incorporated data from a separate group of seven healthy participants free of any psychiatric diagnoses (3 female, mean age, 33.2 years) who were also imaged at the same time-points.

2.2. Treatment

At baseline, all subjects were medication-free for ≥ 4 weeks. Following the baseline scan, subjects started open label paroxetine treatment and were seen by the treating psychiatrist weekly (first 2 weeks) and then biweekly. Dose was adjusted as clinically indicated between 0 and 60 mg/day; no other medications or psychotherapy were permitted during treatment. Social anxiety severity was rated by a clinician (F.R.S.) using the Liebowitz Social Anxiety Scale [LSAS] (Liebowitz, 1987), before and following treatment. The LSAS has high reliability, convergent validity, and treatment sensitivity, and is a gold standard in clinical trials of SAD (Heimberg et al., 1999). Response was operationalized as the difference in pre-and post-treatment scores.

2.3. Imaging and data analysis

Structural data were acquired on a 1.5 T GE Signa MRI scanner using a 3D T1-weighted spoiled gradient recalled (SPGR) pulse sequence with isomorphic voxels ($1 \times 1 \times 1$ mm^3) in a 24-cm field of view (256×256 matrix, ~186 slices, TR 34 ms, TE 3 ms). Anatomical data were processed using longitudinal whole-brain voxel based morphometry (VBM) (Ashburner and Friston, 2000, 2001) analyses, as implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/467/) for SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm) using Matlab v7.13. Preprocessing followed the default procedures for longitudinal data in the VBM8 toolbox http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf. After initial within-subject realignment, the mean of the realigned images was calculated and used as a reference image in a subsequent realignment. The realigned images were then corrected for signal inhomogeneities with regard to the reference mean image. Spatial normalization parameters (using DARTEL) were estimated in the next step using the segmentations of the mean image. These normalization parameters were applied to the segmentations of the bias-corrected images. The resulting normalized segmentations were finally again realigned. The images were modulated with the individual Jacobian determinants to preserve the local amount of gray matter (GM) and white matter (WM) (Keller et al., 2004).

For whole-brain analyses, tables and maps were thresholded at $p=0.001$ and cluster-size of 10 (Silver et al., 2011). Significant clusters were identified by non-stationary cluster extent correction using random fields (Hayasaka et al., 2004) as implemented using the NS-toolbox (http://fmri.wfubmc.edu/cms/software#NS) for SPM5. This correction method confers increased sensitivity to spatially extended signals while remaining valid when cluster-size distribution varies depending on local smoothness as is the case in VBM data (Hayasaka et al., 2004).

Because of the repeated-measures design, each subject served as her/his own control, and no adjustments for age, gender, and total intracranial volume were made. For the primary analyses, smoothing across voxels was not performed in order to maintain anatomical resolution of the resulting differences. However, smoothed results are presented in Table S2 for comparison. Models were estimated as follows. First, pre- versus post-treatment GM matter differences were determined with a repeated measures analysis of variance in the group of 14 SAD patients (Model 1). Second, pre–post GM differences versus changes in LSAS total score were determined in the 14 SAD patients. This was done by generating pre–post subtraction images and regressing these along pre–post differences in LSAS scores, while adjusting for overall mean change (Model 2). This model was conducted both with and without inclusion of pre-treatment LSAS severity scores as a covariate in the model. Finally, pre–post GM differences in the 14 SAD patients were compared to the equivalent time 1 – time 2 GM differences in the seven comparison group subjects using a two sample *t*-test ('corollary analysis', model 3). Regions which were deemed significant in Model 1 were used as regions of interest (ROIs) in Model 3 in order to provide further confirmation that the magnitude of the observed pre–post differences in cases was significantly greater than those observed under no treatment conditions.

3. Results

3.1. Baseline and treatment characteristics

Mean age was 30.9 years; 57% of subjects were female, and 71% were Caucasian. Most subjects had moderate to severe social anxiety at baseline (mean LSAS total score: 82.5 [95% CI, 74.1–90.1]). Two subjects also had a secondary diagnosis of generalized anxiety disorder.

The mean dose of paroxetine was 33.5 ± 8 mg (range, 20–40 mg). Following treatment, there was a significant overall reduction in social