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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 Tesla 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 grey 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.

Keywords

Social anxiety; Paroxetine; Thalamus; Caudate; Cerebellum; Structural MRI

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Contributors

All authors played a central role in preparation and critical revision of the manuscript.

Conflict of Interest

Dr. Schneier receives research funding from Forest Laboratories. This does not present a conflict of interest with the present study. Drs. Talati, Pantazatos and Hirsch have no conflicts of interest to report.

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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., 2011a), and self-judgment (Andrews-Hanna et al., 2010; Whitfield-Gabrieli et al., 2011). Evidence from these studies have implicated hyper-activation of neural circuits serving emotion, particularly the amygdala, striatum, insula, hippocampus, fusiform and parahippocampal region (Bruhl et al., 2014a; Bruhl et al., 2011; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010). Disturbances in cingulate and pre-frontal 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 post-central, 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, thicker left inferior temporal cortex was reported in a study of 14 SAD patients, compared to 12 healthy controls (Frick et al., 2013a; Frick et al., 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, scrutiny by others) (Gimenez et al., 2013; Phan et al., 2013; Schneier et al., 2011b). 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., 2013b), 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 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., 2010b). 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 neuro-anatomical 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., 2011b). 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, 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 0–60 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 Tesla GE Signa MRI scanner using a 3D T1-weighted spoiled gradient recalled (SPGR) pulse sequence with isomorphic voxels (1×1×1 mm) 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 yrs; 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 anxiety symptoms [mean reduction, 38 points (45.6%); paired *t*-test, d.f. = 13, *p* < 0.001]. [Individual reductions in LSAS total scores for the 14 subjects were 84%, 84%, 67%, 63%, 60%, 54%, 50%, 48%, 44%, 39%, 27%, 27%, 1%, –14%].

3.2. Gray matter differences following treatment

We examined whether eight weeks of treatment with paroxetine was associated with anatomical changes in the brain. There were no changes in either *total* grey (*t* = 1.55, *p* = 0.15) or white (*t* = –0.69, *p* = 0.50) matter across the two scans. There were however a number of *regional* GM changes. As illustrated in Fig 1 (coordinates and statistical parameters are presented Table 1), there was a significant reduction in GM volumes in bilateral caudate and putamen, and right thalamus (shown in red), and increases in cerebellum (*k* = 10, *p* < 0.001). Findings within the putamen, caudate, and cerebellar findings remained significant after further correcting for multiple comparisons (asterisked clusters).

As an unrelated group of seven healthy participants (3 female, mean age 33.2 years, no current psychopathology) had also been imaged at the same two time points, we included these participants as a comparison group in a corollary analysis to test whether our findings could be a temporal artifact unrelated to treatment. The comparison group showed no significant differences in any region from the first to the second scan. Formal comparisons between our 14 SAD cases and the seven comparison subjects found significant group differences within the caudate (*t* = –2.55, d.f. = 19, *p* = 0.02), cerebellum (*t* = –2.55, d.f. = 19, *p* = 0.02), and thalamus (*t* = 2.82, d.f. = 19, *p* = 0.005). Although these findings should be

interpreted cautiously given the small comparison sample, they suggest that the changes observed in the SAD group are not related to temporal factors alone.

3.3. Associations between gray matter changes and symptom changes

We next investigated whether changes in GM volume were associated with changes in symptoms. Pretreatment GM alone did not predict treatment response within any brain region. However, when changes in GM were regressed on changes in symptoms, a cluster was identified in the left thalamus where greater volume loss following treatment was associated with greater reduction in social anxiety symptoms (95 voxels, $x=-10.5$, $y=-24$, $z=-1.5$, $t=-7.12$, d.f. = 12, $p_{uncorrected} < 0.001$; $p_{corrected} = 0.018$). We then further adjusted for baseline symptom severity to guard against the possibility that the findings were being driven by pre-treatment illness severity. Again, the left thalamus remained the only significant region (85 voxels, peak: $x=-13.5$, $y=-24$, $z=1.5$; $t = 7.27$; d.f. = 11, cluster corrected $p = 0.054$) (Fig. 2). Finally, we conducted a post hoc examination of the peak of this cluster to determine whether outliers might account for this effect, and to estimate the percent variance in LSAS reduction explained by GM volume loss. As shown in Fig. 2, there was a significant, overall linear pattern, with more than half ($r^2 = 0.86$) of the variation in symptom improvement explained by loss of thalamic gray matter at this location.

For exploratory purposes, we loosened the threshold to identify additional GM changes that were associated with symptom change ($k=10$, $p<0.005$; Table S1). In addition to the left thalamus, reductions in the right hemisphere were also associated with symptom improvement, as were reductions within cerebellar, bilateral inferior temporal and caudate, left putamen, and right parahippocampal volumes. Conversely increases in right cerebellar and midbrain volumes were associated with symptom improvement. As with the primary results, the results were similar regardless of whether they were adjusted for baseline severity.

4. Discussion

4.1 Summary

Treatment with paroxetine for 8-weeks was associated with a significant (46%) reduction in clinical symptoms of social anxiety, comparable to findings in published clinical trials (Stein et al., 2006). Gray matter volumes in SAD patients following treatment were reduced in the striatum and thalamus, and increased in posterior cerebellum. Decreased volumes in left thalamus following treatment were correlated with clinical response; at the peak of the cluster, grey matter changes explained more than half of the clinical response. The correlation was invariant to whether or not we regressed out baseline symptom severity, making it unlikely that the findings are being driven by the most severely ill subjects.

These are to our knowledge, the first data to correlate the neuro-anatomical changes with clinical response in social anxiety. Because of the modest sample size and the lack of an untreated control group, findings should be interpreted cautiously (see limitations). The overall direction of the evidence is however consistent with prior findings in SAD of reduction of baseline thalamic and striatal hyperactivity with successful treatment (Freitas-Ferrari et al., 2010; Schneier et al., 2011b; Gimenez et al., 2013).

4.2. Gray matter changes following treatment

Post-treatment thalamic volume reductions were primarily located in the pulvinar nuclei (PN). The PN play a critical role in visual salience and attention (Grieve et al., 2000), and they are directly connected to the amygdala via a sub-cortical pathway that bypasses cortical involvement, thus allowing for rapid responses to a perceived threat (LeDoux, 1996). Heightened reactivity of this pathway may thus favor rapid automatic activation of the fight-or-flight response over cortically-mediated down-regulation of amygdala activity. This finding is consistent with neurobehavioral evidence in SAD for increased attention and reactivity to social threat stimuli. It is also consistent with our clinical observations that patients often report treatment response as dampening their physical symptoms of anxiety in social situations and allowing for more reasoned assessments of risk. Comporting with the above finding of thalamus involvement in SAD symptoms is evidence of baseline abnormalities in SAD of neurotransmitter systems in the thalamus: increased serotonin transporter binding (van der Wee et al., 2008), as well as increased levels of glutamate and decreased levels of gamma-aminobutyric acid (Pollack et al., 2008). Previous functional studies have reported thalamic hyperactivation in SAD patients in response to viewing emotional faces (Klumpp et al., 2010; Bruhl et al., 2014), and, paralleling our finding here, a functional MRI treatment study of SAD patients found paroxetine to reduce thalamic activation and default mode connectivity during performance of a public exposition task (Gimenez et al., 2014). An unrelated 12-week cognitive behavioral therapy treatment paradigm also found similar post-treatment reductions in thalamic, as well as caudate (discussed below) volumes (Mansson et al., 2013a). Finally, lesions to the thalamus have also been linked to the development of phobias (Kazui et al., 2001).

Overall treatment related decreases were detected only within the right thalamus; associations between GM reduction and symptomatic improvement were however observed primarily within the left hemisphere (although homologous right hemisphere regions were also identified when statistical criteria were relaxed, as seen in Table S1). Given the limited statistical power, it is premature to ascribe etiological meaning to this apparent asymmetry. Some imaging studies of SAD and other anxiety disorders have also reported right-hemisphere only reductions in thalamic activation, connectivity, and metabolism following paroxetine treatment (Gimenez et al., 2014; Saxena et al., 2002). On the other hand, animal work suggests a lack of hemispheric specialization at the thalamic level for fear processing, and perturbations of either thalamic hemisphere induce similar behavioral changes (Kim et al., 2012).

The neostriatum (which encompasses caudate and putamen) is densely interconnected with the limbic system as well the intralaminar nuclei of the thalamus (Stathis et al., 2007) and is part of the circuitry alerting the brain to potential threat (Berns et al., 1997). Persons with SAD manifest resting state hyperconnectivity between caudate/putamen and pre-frontal and anterior cingulate cortices (Arnold Anteraper et al., 2014) and increased activation in these regions when performing paradigms intended to elicit core symptoms of the disorder (Bruhl et al., 2014). The caudate is also particularly associated with detecting subliminal (masked) versus overt threat, and there is a correlation between heart rate variation and caudate activation in SAD patients that is not observed in healthy controls (Gaebler et al., 2013). A

previous functional MRI (Schneier et al., 2011b) study based on a sample that overlaps with the present work found post-treatment reductions in BOLD signal in striatum (left caudate, bilateral lentiform nuclei) and right thalamus during an eye gaze task; these functional changes were also correlated with clinical response. Those observations, coupled with our present results, suggest a parallel structural and functional plasticity.

We previously identified increased cerebellar volume in an overlapping sample of persons with generalized SAD, when compared to either healthy controls or a panic disorder group (Talati et al., 2013). If treatment reduces symptoms via normalizing existing grey matter abnormalities, then decreases in cerebellar volumes would be anticipated. However, right hemisphere cerebellar volume was increased following paroxetine treatment. This is not only at odds with the above prediction but also with the aforementioned escitalopram treatment study (Cassimjee et al., 2010a) that showed a decrease in cerebellar volume post-treatment, albeit in a non-homologous left hemisphere region. The role of cerebellar abnormalities in the pathophysiology of anxiety remains unclear, although disturbances in autonomic regulation via circuits linking the cerebellar vermis to midbrain structures have been postulated as a mechanism (Baldacara et al., 2008). Recent studies show that resting-state perfusion in SAD patients is elevated in some cerebellar sub-regions, but decreased in others relative to healthy controls (Warwick et al., 2008), suggesting functional dissociations within cerebellum for anxiety. Thus, improvements in anatomical and functional resolution over that provided by current segmentation techniques may be needed to better understand the role of the cerebellum in anxiety pathology.

Because MRI indexes gross morphology—the signal is a composite of the collective size, quantity and density of neurons, glial cells, and regional vasculature (Frick et al., 2013a)—the present work cannot directly speak to molecular and cellular determinants of the observed GM changes. There is evidence that over time, continuous emotional and intellectual activity can lead to neuronal differentiation and synaptogenesis, thus modifying the underlying grey matter architecture (Draganski et al., 2004; Draganski et al., 2006). In persons with social anxiety, chronic hyper-stimulation of fear circuits could lead to regional synaptogenesis, which would register as increased local volumes. As treatment normalizes the clinical symptoms, these processes would be diminished, registering as a decrease (relative to baseline) in the MRI signal.

4.3. Limitations

A number of factors should be weighed when interpreting the significance of these findings. First, because subjects were imaged after only 8 weeks of treatment, the long-term stability of the findings—that is, whether these GM volume changes persist or revert to pre-treatment levels—are unclear. Most imaging studies of SAD treatment have used only an 8–12 week window and none to our knowledge have followed the participants over long-term. Second, the neural substrates identified cannot be attributed specifically to social anxiety, as studies of other anxiety syndromes including specific phobia, panic disorder, and obsessive compulsive disorder have reported abnormalities in the basal ganglia and thalamus, suggesting that these may reflect a more generalized disturbance in emotion regulation (Ferrari et al., 2008; Linares et al., 2012). And because anxiety disorders are served by

complex feedback circuits, the *functional* site of therapeutic action may not necessarily lie within the identified ROIs. It is possible, for example, that thalamic reductions do not directly affect symptoms, but alter projections from thalamic nuclei to the executive cortex, which in turn mediate the clinical response. Finally, though we conceptualize the findings as brain changes effecting clinical changes, the data, as from most imaging studies, do not allow us to rule out the converse process, where GM changes are driven by symptom changes.

There are also methodological limitations. The sample size is modest, leading to potential type II errors. However the repeated-measures design reduces noise, and findings were not due to outliers. Causality cannot be inferred, as in the absence of an untreated patient group, it is not possible to determine whether post-treatment changes were due to paroxetine or non-specific effects. VBM has inherent methodological limitations, particularly related to normalization, which may disproportionately impact smaller brain structures (Ashburner and Friston, 2001; Crum et al., 2003).

4.4. Conclusions and implications

This study is the first to our knowledge to identify a set of neuroanatomical changes that may mediate successful treatment response for social anxiety. Future work should be aimed at replicating these observations in larger and independent samples, as well as examining the specificity and post-treatment stability of these associations. Better understanding of the neural mechanisms of treatment response may help inform treatment selection and development of superior targeted treatments in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

We conducted a pilot longitudinal study examining neuroanatomical changes associated with successful treatment for the disorder.

14 patients were imaged both before and after 8 weeks of treatment with paroxetine and changes in grey matter were compared with changes in symptoms.

Treatment was associated with decreased volumes in the right thalamus and bilateral striatum. Reductions in left thalamic volumes were further correlated with clinical response.

Figure 1. Grey Matter Changes following Treatment
N = 14; T1 -weighted axial images; image left is brain left.
Images shown with an *a priori* threshold set at $p < 0.001$; $k = 10$. Differences that survived further non-stationary cluster correction ($p < 0.05$) are asterisked.
Blue indicates regions showing decreased gray matter, and orange increased gray matter, following eight weeks of treatment with paroxetine. Caudate, putamen, and thalamus showed decreased gray matter volumes post-treatment; cerebellum showed increased gray matter. Coordinates and statistical properties for each numbered cluster are described in Table 1.

A

B

Figure 2. Grey matter changes associated with treatment response

$N = 14$; T1-weighted axial images; image left is brain left. Representative images ($z = 0, +4, +8$ and $+12$) are illustrated; $p < 0.001$; $k = 10$.

Without adjusting for baseline (pre-treatment) symptom severity:

Left thalamus, cluster size, 95 voxels; $x = -10.5$, $y = -24$, $z = -1.5$, $t = -7.12$ (d.f. = 12)

Uncorrected p value: < 0.001 ; corrected p value: $p = 0.018$

Adjusting for baseline (pre-treatment) symptom severity:

Left Thalamus, cluster size, 85 voxels; $x = -13.5$, $y = -24$, $z = 1.5$, $t = -7.27$ (d.f. = 11)

Uncorrected p value: < 0.001 ; corrected p value: $p = 0.054$

To further understand the associations, we plotted the change in symptom severity (from week 0 to week 8) as a function of the gray matter (GM) change (also from week 0 to 8), within the peak voxel of the thalamus across subjects (panel b). GM changes are represented along the x-axis, with post-treatment increases represented by positive, and decreases, by negative, values. Clinical response is represented along the y-axis. Positive values indicate a decrease in symptoms, and a negative value, a worsening. The overall negative slope of the curve indicates that reduction in thalamic volume was associated with an improvement in

SAD symptoms across the eight weeks. At the peak voxel, 86.5% of the variance in clinical response was accounted for by change in GM.

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Table 1

Grey matter changes following 8 weeks paroxetine treatment

Contrast	Region	x	y	z	Cluster	Volume	t
Pre > Post							
	1 R Caudate, Putamen	21	14	-3	259	881	-6.7 *
	2 L Caudate, Putamen	-12	14	-5	66	224	-6.5 *
	3 R Thalamus	14	-29	3	18	61	-5.1
Post > Pre							
	4 L,R Cerebellum	15	-72	-29	1113	3784	8.9 *
		8	-66	-35	33	112	6.0

* Significant after correction for multiple comparisons using non-stationary cluster correction, $p < 0.05$

Pre > Post contrast indicates regions with reduction of grey matter volume following 8 week paroxetine treatment; Post > Pre indicates regions with increased volume.

Numbering in the table follows the numbering of the regions shown in Figure 1.

Cluster indicates the number of voxels; volume in mm^3 .