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Neural response to eye contact and paroxetine treatment in generalized social anxiety disorder

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Abstract

Generalized social anxiety disorder (GSAD) is characterized by excessive fears of scrutiny and negative evaluation, but neural circuitry related to scrutiny in GSAD has been little-studied. In this study, 16 unmedicated adults with GSAD and 16 matched healthy comparison (HC) participants underwent functional MRI to assess neural response to viewed images of faces simulating movement into eye contact versus away from eye contact. GSAD patients were then treated for eight weeks with paroxetine and 15 patients were re-imaged. At baseline, GSAD patients had elevated neural response to eye contact in parahippocampal cortex, inferior parietal lobule, supramarginal gyrus, posterior cingulate and middle occipital cortex. During paroxetine treatment, symptomatic improvement was associated with decreased neural response to eye contact in regions including inferior and middle frontal gyri, anterior cingulate, posterior cingulate, precuneus and inferior parietal lobule. Magnitude of GSAD symptom reduction with paroxetine treatment, and GSAD diagnosis in comparison to HCs at baseline, were both associated with neural processing of eye contact in distributed networks that included regions involved in self-referential processing. These findings demonstrate that eye contact in GSAD engages neurocircuitry consistent with the heightened self-conscious emotional states known to characterize GSAD patients during scrutiny.

Keywords

fMRI; social phobia; self-referential processing

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1. Introduction

Social anxiety disorder (SAD) has a lifetime prevalence of 5 - 13% (Kessler et al., 1994, 2005) and is characterized by excessive fear of situations involving potential scrutiny by others, and by self-conscious emotions of embarrassment and humiliation. Generalized SAD (GSAD) is a subtype characterized by fear and avoidance of most social situations. It is associated with greater severity of symptoms, social and occupational impairment, depression, substance abuse and suicide (Schneier, 2006). Cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs) have established efficacy for SAD, but neural mechanisms of treatment response are not well-understood (Schneier, 2006).

Fears of making eye contact or being looked at, which evoke feelings of scrutiny and self-consciousness in persons with SAD, are associated with severity of SAD (Schneier et al., 2011). Leading explanatory models of SAD highlight the role of self-focused attention (Clark and Wells, 1995; Schultz and Heimberg, 2008) and biased attention to threat (Bögels and Mansell, 2004), and factor analyses of the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987), which includes a “fear of eye contact” item, are consistent with this fear being a core feature of SAD (Safren et al., 1999; Baker et al., 2002; Stein et al., 2004). Eye contact functions more generally across primate species as an essential social signal, providing information on identity, status, interest, and intent (Emery, 2004).

Eye contact in SAD might be expected to engage brain regions involved in processing gaze direction, self-referential processing, and fear. Functional magnetic resonance imaging (fMRI) studies in monkeys and healthy subjects have most consistently identified the superior temporal sulcus to be involved in normal processing of others’ gaze direction (Nummenmaa and Calder, 2009). A meta-analysis of neuroimaging studies utilizing a variety of stimuli related to the self found that self-referential processing is mediated by cortical midline structures (Northoff et al., 2006). These include the ventromedial prefrontal cortex, dorsomedial prefrontal cortex, and posterior cingulate cortex/precuneus.

Neurocircuitry associated with eye contact or scrutiny fears has been little studied in SAD or other disorders. Most fMRI studies in SAD have used harsh facial expressions as threat stimuli, and a meta-analysis has documented increased activation of fear-related circuitry including amygdala, insula, hippocampus, and anterior cingulate (Etkin and Wager, 2007). These regional activations to facial expressions are also observed in other anxiety disorders, and during fear learning in healthy subjects (HCs) (Etkin and Wager, 2007). A limitation of prior imaging studies using threat stimuli has been lack of controls for individual differences in attention paid to stimuli, a known modulator of neural responses to facial expressions in anxiety disorder patients and HCs (Pessoa et al., 2002, 2005; Mitchell et al., 2007). Additionally, few studies have examined changes in neural activity in response to treatment of SAD, and none of these treatment studies have used fMRI, which offers advantages of high resolution, sensitivity to pharmacodynamic effects, and ability to assess neural function during performance of an ecologically valid task (Furmark et al., 2002; Kilts et al., 2006; Evans et al., 2008).

This study of GSAD patients and HCs used fMRI to contrast neural responses to viewing direct gaze from another person (i.e. involuntary eye contact, known to be feared by many GSAD patients, but inherently neutral in emotional valence) versus viewing averted gaze. Eye position of participants was monitored to assess visual attention to gaze stimuli in the scanner. Goals of this study were to compare neural response to direct vs. averted gaze stimuli in GSAD patients and HCs, and within the GSAD group to assess the relationship of changes in activations to changes in symptom severity during 8 weeks of treatment with the SSRI paroxetine.

2. Methods

2.1 Participants

Eighteen adults with a primary diagnosis of GSAD (age 20-52) and 17 HCs were recruited through media notices and clinical referrals. Diagnoses were based on psychiatric interview and confirmed by the Structured Clinical Interview for *DSM-IV* Axis I disorders (First et al., 1995). Exclusion criteria for GSAD participants included having a current Axis I disorder (other than secondary diagnoses of generalized anxiety disorder, dysthymia, or specific phobia), major depressive episode in the past year, substance abuse in the past six months, and clinically significant general medical conditions. HCs did not meet criteria for any lifetime Axis I disorder. Health status was confirmed by a physical examination including drug toxicology screen. All subjects were free of psychotropic medications for at least four weeks prior to study entry.

Data from two GSAD patients were excluded from analyses (one subsequently revealed a recent history of major depression, and one failed to follow imaging task instructions), yielding 16 evaluable GSAD patients. HCs were matched to patients by age, sex, and race. One HC failed to follow task instructions and was replaced, yielding 16 evaluable HCs.

Secondary comorbid diagnoses in participants with GSAD consisted of current generalized anxiety disorder (N=3), past major depression (N=6), and past alcohol abuse (N=1). Six GSAD subjects had taken medication for anxiety or depression prior to the past four weeks.

All subjects provided written informed consent after discussion of study procedures. This study was approved by the Institutional Review Board of New York State Psychiatric Institute.

2.2 Experimental Design

All participants underwent fMRI imaging at baseline, and GSAD patients were asked to return for a repeat imaging session after 8 weeks of treatment with paroxetine. Prior to each imaging session, participants were familiarized with study stimuli and tasks outside the scanner.

GSAD patients started paroxetine treatment after the first imaging session. The treating psychiatrist saw patients weekly for the first 2 weeks, then biweekly. Paroxetine dose was adjusted as clinically indicated within the range of 10-60 mg/day, and participants did not receive other psychoactive medications or any psychotherapy.

Clinical assessments were performed before each imaging session by a study clinician. Primary clinical assessment measures were the Liebowitz Social Anxiety Scale (LSAS), widely used in clinical trials to assess severity of SAD, and the Clinical Global Impression - Improvement scale (CGI-I) (Guy, 1976), which provides 7-point ratings of change from baseline, adapted for SAD with specific anchors (Zaider et al., 2003). The 17-item Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1967) was administered to confirm the absence of clinically significant depression. Participants also completed the self-rated Gaze Anxiety Rating Scale (GARS), which assesses fear and avoidance of eye contact in 17 interpersonal situations (Schneier et al., 2011).

Stimuli were produced from photographs of faces of 12 male and 12 female adults with neutral expressions and three directions of eye gaze (neutral, direct, and averted) for each individual, modified from Schneier et al. (2009). Each face was displayed against a black background, with the chin aligned 30 degrees from the frontal plane (to the subject's right). Each trial consisted of a sequence of two photographs of the same individual, beginning

with a 1000 msec image showing neutral direction of eye gaze, aligned with the viewed individual's face (i.e., gazing to the subject's right). In the "averted gaze" trial the first image was immediately followed by a 1000 msec image of the same face identically aligned, but with eyes gazing upward. The "direct gaze" trial differed in that eyes in the second image align directly toward the subject, giving the illusion that gaze moves into eye contact. Thus direct and averted gaze stimuli varied only in path of apparent movement of gaze.

The run consisted of 16 blocks, eight of direct gaze and eight of averted gaze, presented in random order, with 10 sec intervals of viewing crosshair between blocks. Each block consisted of three face trials. Individual faces were presented in random order, and each individual face was presented in one direct gaze trial and one averted gaze trial. Subjects used a keypad to report for each face trial whether gaze was directed toward the subject or away.

2.3 Eye tracking data acquisition and processing

Subjects viewed the stimuli through goggles (Avotec Silent Vision™ SV-4021 Fiber Optic Visual System, Avotec, Inc., Stuart, FL) mounted to the head coil. Goggles were equipped with an eye-tracking device (Avotec Real Eye™ RE-4501 Fiber Optic Eye Imaging System) combined with iViewX Tracking System (SensoMotoric Instruments, Inc., Boston, MA), which continually recorded gaze position at a sample rate of 60 Hz through simultaneous pupil and corneal reflex tracking. The eye-tracking device was triggered simultaneously with the scanner, and to minimize distortion in gaze-position measurement, the built-in 9-point calibration procedure of the iViewX system was augmented by a 4-by-4 point calibration prior to each experimental run.

Eye tracking data analysis utilized the iView X bundled analysis package for fixation analysis. Data from the additional calibration procedure were processed by an artificial neural network interface using a Parameterized Self-Organizing Map, variants of which have previously been shown to considerably reduce distortions in gaze-position measurement (Pomplun et al., 1994; Essig et al., 2006). Pictorial analysis was performed with data for each stimulus block overlaid onto a sample stimulus image, giving scanpaths and eye fixations displayed with raindrop analysis (fixation duration directly proportional to diameter of circle). During post-processing, a rectangular "object" was created to encompass the eye region, which was previously aligned for all stimulus images during the stimulus development phase. Fixation analyses were further processed using Matlab (The MathWorks, Inc., Natick, MA) to give fixation duration and position for each stimulus condition. This analysis revealed the number and length of the subject's gaze fixations within the defined object area for each condition. Eye fixations were defined as eye position maintained within a 30-pixel diameter region for at least 83 ms (five consecutive gaze-position samples). Percent of fixations in the eye region was calculated by dividing fixations within the eye region by total number of fixations. Scanpath length was computed as the sum (in pixels) of the Euclidean distances between all consecutive fixations within a trial.

2.4 Image acquisition and analysis

Images were obtained on a 1.5 T GE Signa Twin Speed MRI scanner. Functional images were acquired parallel to the anterior-posterior commissure line with a T_2*-weighted sequence of twenty-seven contiguous axial slices (time repetition [TR] = 2000 ms, time echo [TE] = 40 ms, flip angle = 60°, field of view [FoV] = 190 × 190 mm, array size 64 × 64) of 4.5 mm thickness and 3.13 × 3.13 × 4.5 mm. Structural images were acquired with a T1-weighted SPGR sequence (TR = 19 ms, TE = 5 ms, flip angle = 20°, FoV = 220 × 220 mm) recording slices at a thickness of 1.5 mm with in-plane resolution of 0.86 × 0.86 mm.

Preprocessing and statistical analyses were carried out using Statistical Parametric Mapping 5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). The first three volumes of each functional run were discarded to eliminate onset transients. The remaining volumes were then spatially realigned to the first volume of the first run. The mean image of the realigned volumes was normalized to a standardized EPI template and resampled at a voxel size of 2 mm^3. Finally, the normalized images were spatially smoothed with a Gaussian kernel of 8-mm^3. In order to remove low-frequency confounds, data were high-pass filtered (128 s).

Using the general linear model within SPM5, voxelwise statistical parametric maps (SPMs) convolved with the hemodynamic response function were generated for direct and averted gaze stimuli. The parameters from each subject were entered into group level analyses contrasting the two conditions. Group-level comparisons consisted of independent and paired t tests at a voxel threshold of $P < 0.01$ corrected by a cluster extent threshold of 10 voxels (Forman et al., 1995). Whole brain analyses and statistical levels appropriate for such low-power approaches were selected as a first step because the novelty of the gaze task did not offer sufficient basis to prespecify regions of interest and sample sizes were not large, we focused on whole brain analyses as a first step.

3. Results

3.1 Sample

Demographic and clinical features of the evaluable sample are presented in Table 1. GSAD patients evidenced elevated levels of anxiety and avoidance related to eye contact compared to HCs, moderate to severe social anxiety, and mild, subsyndromal levels of depressive symptoms. One GSAD patient completed the first scan and was dispensed paroxetine but did not return for any subsequent appointments. Fifteen GSAD patients completed the study.

3.2 Treatment response and behavioral response

Patients evidenced statistically significant and clinically meaningful improvement in GSAD symptoms during paroxetine treatment, as evidenced by a 36-point decrease in the mean score of the LSAS, similar to change reported in randomized clinical trials of paroxetine (Stein et al., 1998). At week 8, among the 15 GSAD completers, 12 were rated responders to treatment (three were rated “very much improved” and nine were “much improved”), and 3 were classified as nonresponders (all rated “minimally improved”). Self-reported anxiety and avoidance related to eye contact (GARS) also improved significantly (Table 2). Mean paroxetine dosage at week 8 was 34.0 +/− 8.3 mg/day (range 20 – 40 mg/day).

At baseline, there were no significant between-group differences in visual attention to stimuli (Table 1). From pre- to post-treatment (week 0 to week 8), GSAD patients evidenced no changes in the difference in percent of fixations on the eye region in response to direct vs. averted gaze (direct – averted, Table 2). However, percent of fixations on the eye region in response to direct gaze and percent of fixation on the eye region in response to averted gaze stimuli each decreased significantly pre- to post-treatment. These decreases were not significantly associated with improvement in GSAD symptoms ($R_S = -0.02$ for direct gaze and $R_S = -0.04$ for averted gaze).

3.3 Imaging results

To address the question of what neural regions are activated during the processing of direct gaze in persons with symptoms of GSAD, we report directional findings at week 0 for GSAD > HC, direct > averted gaze; and at weeks 0 and 8, within GSAD patients, for direct>averted gaze, week 0 > week 8.

3.3.1 Baseline Analyses—Group differences in BOLD at baseline (see Table 3 and Figure 1) were present in regions associated with emotion and place perception (parahippocampal cortex), self-referential processing (inferior parietal lobule, supramarginal gyrus, and posterior cingulate), and high level visual processing (middle occipital cortex) (Russ et al., 2003; Sugiura et al., 2005; Platek et al., 2006; Uddin et al., 2006). The 2 × 2 ANOVA for group vs. gaze direction was consistent with a differential response to gaze direction ($P < 0.01$) for ROIs including inferior parietal lobule and posterior cingulate.

Secondary within-group analyses (direct > averted) for the HC group demonstrated BOLD responses to eye contact ($P < 0.01$) bilaterally in superior temporal sulci, the region most associated with response to gaze direction (Hooker et al., 2003; Pelphrey et al., 2004; Materna et al., 2008) (L temporal cortex, 400 voxels, $x = -38$, $y = 0$, $z = -12$, t = 4.44; and right temporal cortex, 578 voxels, $x = 36$, $y = 6$, $z = -16$, t = 4.09). These areas were not significantly activated within the GSAD group, which instead demonstrated significant BOLD responses in left globus pallidus, 23 voxels, $x = -24$, $y = -16$, $z = 0$, t = 4.02; L insula, 38 voxels, $x = -36$, $y = -18$, $z = 14$, t = 4.43; bilateral cingulate gyrus, 58 voxels, $x = -2$, $y = -10$, $z = 28$, t = 3.17 and 21 voxels, $x = 8$, $y = -12$, $z = 40$, t = 3.26; and right inferior parietal lobule, $x = 54$, $y = -54$, $z = 48$, t = 3.63.

Secondary within-group contrasts of fixation cross vs. direct and averted gaze stimuli conditions were used to evaluate response polarity in selected ROIs, identified with MarsBaR (Brett et al., 2002). These included regions previously shown to be activated by social threat in SAD (Stein et al., 2002) (amygdala and insula, defined anatomically) and regions activated by direct vs. averted gaze at baseline in this study (inferior parietal lobule and posterior cingulate cortex, defined functionally). BOLD signal in amygdala, insula, and inferior parietal lobule was significantly greater for both direct and averted gaze stimuli (relative to fixation cross) in both SAD and HCs, but for posterior cingulate cortex there were no significant differences.

3.3.2 Pre- vs. post-treatment—Within the GSAD group, regions showing a stimulus gaze direction by time interaction (week 0 > week 8, direct > averted, see Table 4) included regions associated with interoception and emotion (insula), high level visual processing (middle temporal gyrus, occipital cortex) and self-referential processing (posterior cingulate cortex and precuneus)(Vogt and Laureys, 2005; Paulus and Stein, 2006). The 2 × 2 ANOVA for stimulus gaze direction vs. time (pre-treatment and post-treatment) is consistent with a post-treatment reduction in the effect of direct eye gaze relative to averted gaze ($P < 0.01$) for ROIs including occipital cortex and middle temporal gyrus.

3.3.3 Correlates of Symptomatic Improvement—Within the GSAD group, regions in which changes in activations (direct > averted gaze) covaried with reductions in social anxiety during treatment (see Table 5 and Figure 1) included areas with functions that include emotion regulation and self -referential processing (subgenual anterior cingulate, ventromedial prefrontal cortex, inferior frontal gyrus, posterior cingulate cortex, precuneus, and inferior parietal lobule) (Buccino et al., 2001; Castelli et al., 2002, Vogt et al., 2006; Morita et al., 2008).

4. Discussion

This study investigated responses to eye contact in patients with GSAD, a disorder known to be associated with fear of scrutiny. GSAD patients preferentially activated regions that have been associated with self-referential processing, including inferior parietal lobule and cortical midline structures of ventromedial prefrontal cortex and posterior cingulate cortex (Northoff et al., 2006), and regions associated with visual attention (occipital cortex,

thalamus), and regions associated with emotion regulation and place perception (ventromedial prefrontal cortex, parahippocampal gyrus), compared to HCs. Of these regions, inferior parietal lobule and posterior cingulate also showed decreases in activation associated with improvement in SAD symptoms after paroxetine treatment. Decreases in activation associated with improvement in SAD symptoms also occurred in other regions that share an association with self-referential processing (inferior, medial and middle frontal gyri, precuneus, and subgenual anterior cingulate, as well as other regions with diverse functions (anterior and dorsal cingulate, lentiform nucleus, thalamus, paracentral lobule). The association of these regions with SAD symptoms is consistent with the centrality of excessive feelings of scrutiny and self-conscious emotions of embarrassment and humiliation to mechanisms of SAD, as well as the response to direct gaze as a threat. These regions are also associated with many other functions, including executive functions (inferior and middle frontal gyri)(Chikazoe, 2010), fear extinction (medial frontal gyri)(Kim et al., 2011), episodic memory (precuneus)(Cavanna and Trimble, 2006), depression (subgenual anterior cingulate)(Walter et al, 2009), reward processing (anterior and dorsal cingulate) (Liu et al., 2011), action selection (lentiform nucleus)(Stocco et al, 2010), and sensory processing (thalamus)(Wurtz et al., 2011).

Among the regions associated with SAD in this study, the inferior parietal lobule has been linked with own-body perception including self-face recognition (Sugiura et al., 2005; Platek et al., 2006; Uddin et al., 2006), and it is adjacent to the intraparietal sulcus, associated with spatial attention processes including response to gaze direction (Puce et al, 1998; Wicker et al., 1998; Hoffmann and Haxby, 2003). The supramarginal gyrus has been associated with the enactment effect, or facilitation of learning by performing actions (Russ et al., 2003). The predominance of right-sided differences are consistent with literature on right hemisphere role in self-related cognition (Decety and Chaminade, 2003; Platek et al., 2004), self-awareness (Andelman et al., 2004; Barnacz et al., 2004), and own-body perception (Blanke et al., 2002, 2005). These regional activations are consistent with heightened self-consciousness in GSAD patients, which may include elements of increased attention and visual processing, and the experience of viewing oneself from another's perspective.

Within HCs, direct gaze stimuli (vs. averted) activated bilateral superior temporal sulci, the region most closely associated with processing of others' eye movements in healthy subjects and in nonhuman primates (Heide et al., 2001; Hooker et al., 2003; Pelphrey et al., 2004; Nummenmaa and Calder, 2009). GSAD patients, in contrast, activated insula and cingulate, areas associated with monitoring and regulation of negative emotions (Paulus and Stein, 2006; Mohanty et al., 2007), and inferior parietal lobule. These differences in GSAD patients suggest interference in the normal processing of gaze direction stimuli.

Symptomatic improvement during paroxetine treatment correlated significantly with magnitude of decrease in BOLD response to direct (vs. averted) gaze in the inferior parietal lobule and other regions that share an association with self-referential processing (posterior cingulate, inferior frontal, medial prefrontal cortex). The posterior cingulate is involved in visuospatial orientation of the body in space (Vogt et al., 2004) and self-reflection (Johnson et al., 2002; Kelley et al., 2002). Both inferior parietal lobule and inferior frontal gyrus have been considered part of the "mirror system" that activates equally to the execution of or observation of a motor action (Buccino et al., 2001), and inferior frontal gyrus activation has been associated with embarrassment (Morita et al., 2008). Medial prefrontal cortex has been associated with inferring intentions of others (Castelli et al., 2002). Improvement also correlated with decreased BOLD response in subgenual anterior cingulate, which is connected to ventral posterior cingulate and involved in self-relevant information and self-

reflection (Vogt et al., 2006), as well as processing of emotional stimuli (Gottlib et al., 2005).

Prior studies that have imaged SAD patients during task performance have rarely focused on regions associated with self-referential processing, possibly due to predominant use of paradigms comparing emotional expressions that are not designed to trigger self consciousness. A paradigm using self-referential (verbal) stimuli, however, did result in activation of medial prefrontal cortex and precuneus in one study (Blair et al., 2008), and persons with SAD have previously been noted to differ in activation of posterior cingulate/precuneus during viewing of faces or nonsense pictures (Gentili et al., 2009). Studies of public speaking or facial expression stimuli in SAD have sometimes reported activation of some of these regions, including medial and inferior prefrontal cortex (Tillfors et al., 2001; Stein et al., 2002; Straube et al., 2004; Blair et al., 2008), supramarginal gyrus (Evans et al., 2009), posterior cingulate (Evans et al., 2009), and precuneus (Warwick et al., 2008). Understanding of neural processes in SAD may benefit from study of both fear processing that may have dysfunction shared with other anxiety disorders, and self-referential processing that may be relatively specific to SAD.

A few imaging studies have examined changes in response to treatment of SAD. In O-15 PET studies, symptomatic improvement during treatment with the SSRI citalopram and cognitive-behavioral therapy was associated with reduced regional cerebral blood flow (rCBF) mainly in the medial temporal lobe, including the amygdala, hippocampus, and rhinal and parahippocampal cortices (Furmark et al., 2002), and improvement during treatment with citalopram and an NK1-antagonist reduced rCBF response to public speaking in the same regions, with citalopram also reducing activity in the posterior cingulate (Furmark et al., 2005). Citalopram also decreased resting-state neuronal activity in the left temporal cortex in a SPECT study (Van der Linden et al., 2000). Another O-15 PET study found that treatment with the antidepressant nefazodone was associated with reductions in rCBF in the precentral gyrus, insula, midbrain/hypothalamus, and middle frontal and anterior cingulate cortex, and increases in the middle occipital and lingual gyri, postcentral gyrus, gyrus rectus, and hippocampus (Kilts et al., 2006). Treatment with the GABA reuptake inhibitor tiagabine was associated with increased glucose metabolism in the ventromedial prefrontal cortex in a study using resting state 18-FDG PET (Evans et al., 2009). The heterogeneity of these imaging findings reflects marked differences in imaging methods, tasks, and treatments, but does overlap with our findings of decreased BOLD response in insula and posterior cingulate after paroxetine treatment, and the correlation of medial frontal cortex activation with symptomatic improvement during paroxetine treatment.

Absent from our findings, in both whole brain and ROI analyses, is evidence of differential activation to direct vs. averted gaze for amygdala, which has been shown to engage in response to threat in animals (LeDoux, 2000) and in healthy humans (Phelps and LeDoux, 2005), and to be hyperresponsive in persons with SAD and other anxiety disorders (Etkin and Wager, 2007). The absence of amygdala findings may be in part due to the nature of the stimuli and comparisons used in this study, where both the direct and averted stimuli activated the amygdala relative to fixation cross.

Eye tracking data showed that this study's BOLD findings at baseline and during treatment were not attributable to differences in gaze behavior. Percentage of fixations to the eye region of direct vs. averted stimuli did not differ between groups, nor pre- vs. post-treatment in GSAD. Treatment was associated, however, with decreased fixations to the eyes for direct and averted stimuli, considered separately. In post hoc tests these decreases were not correlated with clinical improvement, suggesting that decreased fixations on the eyes may be

a general effect of paroxetine treatment, unrelated to symptom reduction, but consistent with a report of subchronic paroxetine treatment reducing vigilance in healthy volunteers (Schmitt et al., 2002).

Our findings must be considered in the context of several other limitations. A limitation of the eye contact paradigm was that the nature of the "control" stimulus of averted gaze (eyes looking up) may have also contributed to differences in activation. Additionally, the attribution of neural differences to self-referential processing was inferred from the nature of the task, known features of SAD, and functions previously associated with these neural regions. Each of these regions is believed to have multiple functions, however, and self-referential mental processes were not directly measured, so the reported associations could have also been related to other mental processes.

The potential specificity to GSAD of the activation of self-referential processing regions by the direct gaze paradigm requires confirmation by further study. Gaze aversion may also be related to other disorders, non-pathological temperaments such as behavioral inhibition, or sociocultural influences. In the absence of a placebo-treated GSAD group and of re-test data on the HC group, it is unknown to what extent observed changes during paroxetine treatment may have been due to nonspecific effects, including expectancy, time, learning, and limits on test-retest reliability of the paradigm.

Future investigations of specific responses to the treatment and of prespecified ROIs can test for relationships between regional BOLD responses and treatment effects. The limited sample size (n=16 GSAD subjects) of this study constrains such analyses and the levels of statistical significance employed in this study, given the variability in a patient sample. These findings, however, may guide subsequent fMRI studies of treatment.

In summary, using a paradigm focused on the ecologically salient stimulus of direct eye gaze in patients with GSAD before and after paroxetine treatment, we found GSAD symptoms to be associated with increased activation of a distributed network, involving posterior midline structures, inferior parietal lobule, and inferior and medial frontal cortex that have been identified in animal and human studies as mediating self-referential processing. Other areas of activation reflected high level visual processing (occipital and parahippocampal cortex), and processing and regulation of negative affect (insula and subgenual cingulate cortex). Response to treatment with paroxetine was associated with decreased activation to direct gaze in many of the same regions, including inferior parietal lobule, posterior cingulate, inferior frontal, and medial prefrontal cortex, suggesting a possible normalization of activity in this system. Studies in other patient populations utilizing other treatments may help clarify the specificity of these findings to GSAD and its treatment.

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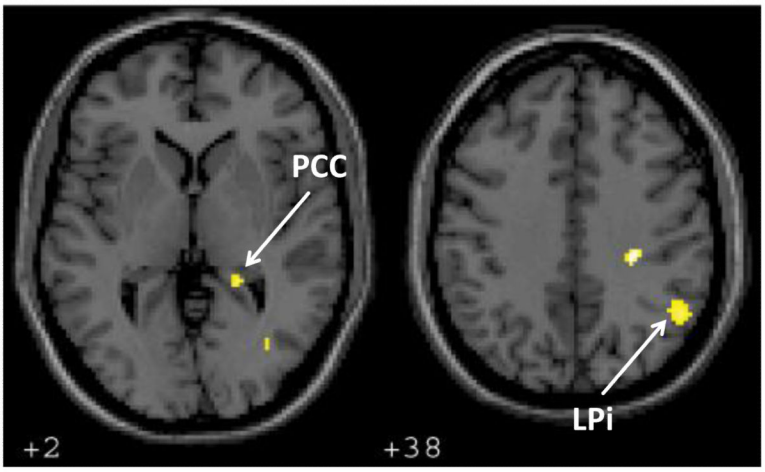

Figure 1.
Group differences at baseline.
Participants with generalized social anxiety disorder had significantly greater blood oxygen-level dependent responses than healthy comparison participants for direct vs averted gaze in posterior cingulate cortex (PCC) and inferior parietal lobule (LPi). Numbers below each image refer to z-coordinates.

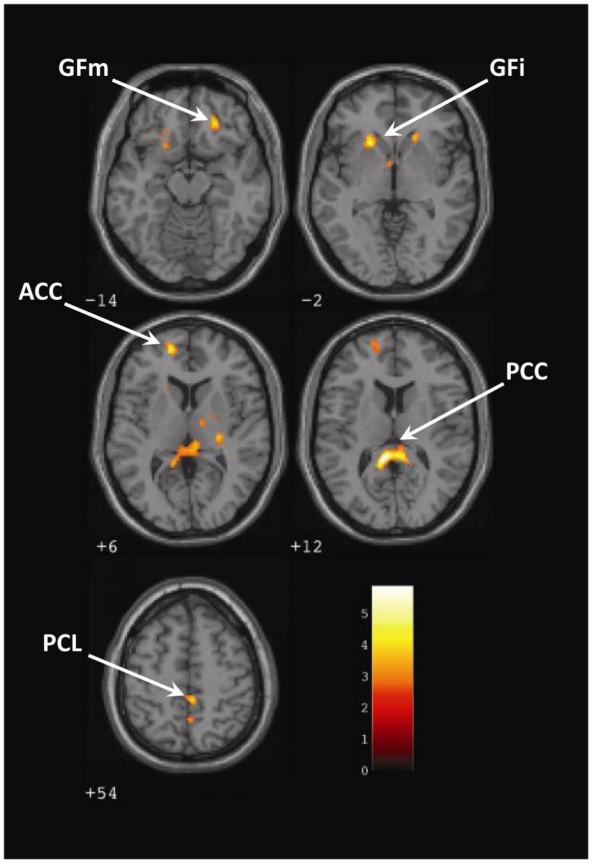

Figure 2.
Among participants with generalized social anxiety disorder, magnitude of symptomatic improvement during paroxetine treatment was associated with decreases in blood oxygen-level dependent responses for direct vs averted gaze. GFm and GFi indicate middle and inferior frontal gyri, ACC and PCC anterior and posterior cingulate cortices, PCL paracentral lobule. Numbers below each image refer to z-coordinates.

Table 1

Demographic, Clinical, and Gaze Behavior Characteristics at Baseline

	GSAD participants (n=16) No. (%) or Mean (SD)	**HC participants (n=16) No. (%) or Mean (SD)**	***t* or X^2**	***df***	***P***
Age, y	29.8 (9.0)	30.3 (9.7)	0.2	29.8	0.88
Sex					
F	10 (62.5%)	10 (62.5%)	0.0		1.00
M	6 (37.5%)	6 (37.5%)			
Race					
White non-Hispanic	11 (68.8%)	13 (81.3%)			
Asian	2 (12.5%)	1 (6.3%)			0.73[1]
Hispanic	3 (18.8%)	2 (12.5%)			
Education, y	16.2 (1.9)	16.5 (2.1)	0.5	29	0.64
LSAS	81.4 (15.6)	8.2 (5.4)	17.7	18.5	<0.001
GARS	49.8 (16.2)	6.9 (6.9)	9.8	20.3	<0.001
HRSD-17	6.4 (3.3)	0.3 (0.7)	7.4	16.4	<0.001
% fixations on eye region, direct stimuli	60.4 (25.0)	48.4 (22.2)	−1.4	28	0.18
% fixations on eye region, averted stimuli	60.3 (23.6)	50.1 (26.6)	−1.1	28	0.28
% fixations on eye region, direct – averted	0.1 (7.2)	−1.8 (9.0)	−0.6	28	0.54
Scanpath length (pixels), direct stimuli	3038.8 (998.3)	2578.4 (1216.4)	−1.1	28	0.27
Scanpath length (pixels), averted stimuli	2836.2 (1041.7)	2660.7 (1078.7)	−0.5	28	0.65
Scanpath length (pixels), direct – averted	202.6 (498.4)	−82.3 (430.3)	−1.7	28	0.11

LSAS = Liebowitz Social Anxiety Scale; GARS = Gaze Anxiety Rating Scale; HRSD-17 = Hamilton Rating Scale for Depression, 17-Item Version;

[1] Fishers Exact Test

Table 2

Symptom and Gaze Behavior Measures Pre- vs. Post-treatment in GSAD Group Completers (n=15)[1]

	Week 0 Mean (SD)	**Week 8 Mean (SD)**	***T***	***df***	***P***
LSAS	82.6 (15.5)	45.9 (25.6)	5.9	14	<0.001
GARS	51.2 (15.7)	29.6 (14.5)	5.3	14	<0.001
HRSD-17	6.3 (3.3)	3.9 (3.5)	1.9	14	0.076
% fixations on eye region, direct stimuli	60.0 (23.4)	39.2 (27.4)	4.8	11	<0.001
% fixations on eye region, averted stimuli	60.8 (20.9)	40.9 (25.2)	4.0	11	0.002
% fixations on eye region, direct – averted	−0.8 (7.7)	−1.6 (8.4)	0.3	11	0.76
Scanpath length (pixels), direct stimuli	3154.0 (1077.1)	4063.3 (1747.1)	1.3	11	0.22
Scanpath length (pixels), averted stimuli	2842.2 (1167.8)	4191.1 (2050.0)	1.7	11	0.11
Scanpath length (pixels), direct – averted	311.8 (491.1)	−127.9 (945.2)	1.5	11	0.17

LSAS = Liebowitz Social Anxiety Scale; GARS = Gaze Aversion Rating Scale; HRSD-17 = Hamilton Rating Scale for Depression, 17-Item Version

[1]Eye gaze data for 3 patients were excluded from analysis due to technical problems with acquisition.

Table 3

Group Differences at Baseline: Areas of Significant Activation for Group (GSAD>HC) by Stimuli (Direct > Averted Gaze) at Week 0

Region	Voxels	x	y	z	T
R parahippocampal gyrus	21	22	−40	2	2.97
R inferior parietal lobule	11	40	−30	28	2.95
R inferior parietal lobule, supramarginal gyrus	160	52	−58	44	3.22
R posterior cingulate gyrus	32	28	−30	38	3.44
R middle occipital gyrus	13	36	−72	−2	3.15

All activations are effects observed in whole-brain analyses and are significant at $P < 0.01$

Table 4

Pre- vs. Post-Treatment: Areas of Significant Activation for Treatment (Wk 0 > Wk 8) by Stimuli (Direct > Averted Gaze), Within GSAD Group

Region	Voxels	x	y	z	T
L insula	48	−34	−12	14	3.61
R middle temporal gyrus	18	40	−52	−2	3.46
R precentral gyrus	29	50	−4	18	3.54
R posterior cingulate gyrus, precuneus	88	6	−40	48	4.28
L superior occipital gyrus	29	−26	−72	28	3.90

All activations are effects observed in whole-brain analyses and are significant at $P < 0.01$

Table 5

Correlates of Symptomatic Improvement: Areas of Change in Activation Significantly Associated with Change in LSAS During Treatment, Within GSAD Group

Region	Voxels	x	y	z	T
L inferior frontal gyrus	261	−20	20	−2	4.69
L subgenual anterior cingulate	100	−14	54	6	4.62
R middle frontal gyrus	77	24	36	−14	4.35
L caudate	53	−2	2	0	3.26
R anterior cingulate	52	20	24	−6	3.98
R dorsal cingulate gyrus	49	4	−4	34	2.97
L lentiform nucleus	47	−22	−12	−8	4.73
R lentiform nucleus	20	16	−2	2	3.06
R thalamus	40	28	−22	4	4.14
R thalamus	29	14	−8	8	3.23
R&L posterior cingulate	493	−6	−38	12	5.87
R paracentral lobule	43	4	−38	54	3.91
R&L precuneus	89	4	−54	50	3.48
L inferior parietal lobule	97	−30	−52	62	3.89

All activations are effects observed in whole-brain analyses and are significant at $P < 0.01$