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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 magnetic resonance imaging 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 8 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. Both the magnitude of GSAD symptom reduction with paroxetine treatment and the baseline comparison of GSAD vs. HCs were 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.

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1. Introduction

Social anxiety disorder (SAD) has a lifetime prevalence of 5–13% (Kessler et al., 1994, 2005); the disorder 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 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

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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 6 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 4 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 GSAD patients. HCs were matched to patients by age, sex, and race. One HC failed to follow task instructions and was replaced, yielding 16 suitable 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 4 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° 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-ms 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-ms 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-s intervals of viewing the crosshairs 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

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