



## Atypical modulation of medial prefrontal cortex to self-referential comments in generalized social phobia

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### ABSTRACT

Generalized social phobia (GSP) involves the fear of being negatively evaluated. Previous work suggests that self-referentiality, mediated by the medial prefrontal cortex (MPFC), plays an important role in the disorder. However, it is not clear whether this anomalous MPFC response to self-related information in patients with GSP concerns an increased representation of their own or others' opinions. In this article, we examine whether GSP is associated with increased response to own (1st person) or other individuals' (2nd person) opinions relative to healthy individuals. Unmedicated individuals with GSP ( $n = 15$ ) and age-, IQ-, and gender-matched comparison individuals ( $n = 15$ ) read 1st (e.g., *I'm ugly*), and 2nd (e.g., *You're ugly*) person viewpoint comments during functional magnetic resonance imaging. We observed significant group-by-viewpoint interactions within the ventral MPFC. Whereas the healthy comparison individuals showed significantly increased (or less decreased) BOLD responses to 1st relative to 2nd person viewpoints, the patients showed significantly increased responses to 2nd relative to 1st person viewpoints. The reduced BOLD responses to 1st person viewpoint comments shown by the patients correlated significantly with severity of social anxiety symptom severity. These results underscore the importance of dysfunctional self-referential processing and MPFC in GSP. We believe that these data reflect a reorganization of self-referential reasoning in the disorder with a self-concept perhaps atypically related to the view of others.

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### 1. Introduction

Generalized social phobia (GSP) involves a strong and persistent fear of social or performance situations that have the potential for negative evaluation. It is a relatively common disorder associated with a high risk for alcohol and drug abuse, depression, and suicide (Kaufman and Charney, 2000; Kessler, 2003; Beesdo et al., 2007).

Functional magnetic resonance imaging (fMRI) studies in GSP have focused on examining responses to social stimuli. In particular, extensive work has examined the response to facial expressions, including harsh (Phan et al., 2006), angry (Stein et al., 2002; Straube et al., 2004; Straube et al., 2005; Blair et al., submitted for publication), fearful (Stein et al., 2002; Blair et al., 2008b; Blair et al., submitted for publication), disgusted (Amir et al., 2005), happy (Straube et al., 2005) and neutral (Birbaumer et al., 1998; Stein et al., 2002) expressions. This work finds increased amygdala response in GSP (Stein et al., 2002; Straube et al., 2005; Phan et al., 2006), though the dorsal medial prefrontal cortex (MPFC) has also been implicated

(Stein et al., 2002; Straube et al., 2004; Amir et al., 2005; Blair et al., 2008b).

However, the response to facial expressions in both healthy individuals (Pessoa et al., 2002; Pessoa et al., 2005; Mitchell et al., 2007) and patients (Pine et al., 2005; McClure, et al., 2007) is under considerable attentional control; increased attention to other features in the environment reduces the representation of facial expressions and thus the emotional response to them (Pessoa and Ungerleider, 2004; Mitchell et al., 2007; Luo et al., 2010). Moreover, the intent and self-relevance of facial expressions can be difficult to ascertain (i.e., "Are you laughing at me or smiling with me? Angry with me or somebody else?"). Given that fears of other people's scrutiny and judgment lie at the core of GSP (First et al., 1995), aberrant processing of self-referential information may play a role in the disorder.

In the first study to directly examine self-referential processing in GSP using fMRI, patients were assessed when processing self- vs. other-referential criticism (e.g., "*You're ugly*" vs. "*He's ugly*") and praise (e.g., "*You're beautiful*" vs. "*He's beautiful*") (Blair et al., 2008a). This study revealed selectively increased BOLD responses within both the amygdala and the dorsal MPFC in patients with GSP to self-referential criticism. In short, these data indicated that the heightened sensitivity to self-referential criticism in patients with GSP reflects dysfunction in the dorsal MPFC as well as the amygdala (see also

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recent work by Goldin and colleagues that examines emotion regulation in social phobia to criticism [Goldin et al., 2009; Goldin and Gross, 2010]). The MPFC finding is of particular relevance given the extensive data implicating dorsal as well as ventral MPFC in self-referential processing (Johnson et al., 2002; Fossati et al., 2003; Phan et al., 2004; Seger et al., 2004; Mitchell et al., 2005; Moran et al., 2006; for review see Gillihan and Farah, 2005; Northoff et al., 2006; Schmitz and Johnson, 2007; Legrand and Ruby, 2009; van der Meer et al., 2010). Specifically, both regions show increased responses during self-related as opposed to non-self-related reasoning. Moreover, in addition to the MPFC, recent work has also highlighted the role of the amygdala in the response to praise and criticism in healthy individuals (Frewen et al., 2010). Taken together, these findings suggest that the MPFC might make independent contributions to GSP but may also interact as part of a circuit.

The goal of the current study was to extend our earlier work (Blair et al., 2008a) and to specifically examine whether patients with GSP show aberrant responding to self-referential comments depending on whether the origin of those comments is another individual (e.g., hearing “You’re ugly”) or the self (e.g., thinking “I’m ugly”). Our aim is to go beyond describing the regions implicated in GSP and rather to probe the nature of information-processing perturbations that occur within these regions. Without this information, it will be difficult to optimize treatments for this disorder, particularly when they are targeted towards specific cognitive processes. As such, we used a novel verbal-comment paradigm to implement a 2(Viewpoint: 1st or 2nd Person) by 3 (Valence: negative, neutral and positive) by 2(Group: GSP, healthy comparison) design.

On the basis of our earlier data, which found these stimuli to elicit GSP-related perturbations in dorsal and ventral MPFC (Blair et al., 2008a; Blair et al., 2010), we hypothesize that GSP involves hyper-responsiveness to social feedback from others. Thus, we expect patients with GSP to show (to 2nd person point-of-view comments) increased responses within MPFC (i.e., there will be a group-by-viewpoint interaction). This might be particularly marked for others’ criticism (i.e., there will be a group-by-viewpoint-by-valence interaction). Alternatively, given that GSP is associated with an increased level of self-criticism (Cox et al., 2002; Cox et al., 2004), it could be hypothesized that it involves hyper-responsiveness to self-referential comments whether these are generated internally or externally (i.e., there will be a main effect of group within the MPFC).

## 2. Materials and methods

### 2.1. Subjects

This study included 15 patients with GSP and 15 healthy comparison (HC) individuals, group-matched on age, gender, and IQ (see Table 1). Subjects were recruited from NIMH Institutional-Review-Board (IRB) approved advertisements. Subjects with GSP met criteria for GSP according to the DSM-IV (1994) criteria based on the Structural Clinical interview for DSM-IV Axis I disorders (SCID) (First et al., 1997) and a confirmatory clinical interview by a board-certified psychiatrist (DSP). No GSP patient had another Axis-1 diagnosis; all were currently medication-free >6 months. Specifically, 14 of the 15 patients reported that they were medication-naïve, and two reported past medication use (one patient reported taking Xanax for 6 months 22 years ago and Zoloft for 2 months 9 years ago). No patient reported receiving past cognitive behavior therapy. HCs were excluded if they had a history of any psychiatric illness. All subjects were in good physical health, as confirmed by a complete physical exam, and provided written informed consent. Further, as part of the assessment, all subjects completed the Liebowitz Social Anxiety Scale – Self Report (LSAS-SR), and the Inventory of Depressive Symptomatology – Self Report (IDS-SR). In addition, for the patients with GSP, the level of

**Table 1**  
Subject characteristics: S.D. in parentheses ( ).

	Patients with GSP (N = 15)	Healthy subjects (N = 15)	p
Age	30.3 (8.49)	31.1 (6.37)	n.s.
Gender	8 M/7 F	9 M/6 F	n.s.
Race			
Caucasian	9	9	–
African-American	5	5	
Asian	1	1	
IQ	115.4 (12.54)	111.9 (8.9)	n.s.
LSAS	67.7 (21.82; range 40–120)	17.5 (11.81; range 0–23)	p < 0.001
IDS	5.1 (4.78)	9.2 (6.30)	n.s.
GAF	61.3 (4.50)	–	

Key to Table 1: M = Male; F = Female; LSAS = Liebowitz Social Anxiety Scale; IDS = Inventory of Depressive Symptomatology; GAF = Global Assessment of Functioning.

overall social, occupational and psychological functioning was assessed by the Global Assessment of Functioning (GAF). Scores on these measures characterized the GSP group as having moderate levels of social anxiety with some associated impairment in functioning; Table 1.

### 2.2. Task

Subjects viewed comments that varied according to whether they were 1st person viewpoints (e.g., “I’m beautiful”) or 2nd person viewpoints (e.g., “You’re beautiful”). Thirty-two negative (e.g., idiot, ugly, hated), thirty-two neutral (e.g., human, average, OK), and thirty-two positive comments (e.g., genius, beautiful, loved), matched on number of letters and words, were used. Thus, the task involved a 3(Valence: Negative, Neutral, Positive) by 2(Viewpoint: 1st Person, 2nd Person) design. In addition, the comments could be negative (e.g., I’m an idiot; You’re an idiot), neutral (e.g., I’m a human; You’re a human), or positive (I’m a genius; You’re a genius). The 3rd person point of view was not included as our earlier study had shown that patients with GSP do not show increased responses to self-referential comments originating from a 3rd person perspective. The valence words used (available per request from the corresponding author) were identical to those used in the Blair et al. (2008a) study. Prior to scanning, subjects were told that they would view different comments that were always about them, but that they would appear either as 1st or 2nd person viewpoints. For the 2nd person comments they were told to imagine that they were coming from somebody whose opinion they really care about. Following our earlier design, for each comment and regardless of speaker, subjects simply pressed a button with their left hand when they had read each comment. Each comment was presented for 2500 ms with a 500-ms interstimulus interval and was presented in a fully randomized order within each run. In addition, for each run, 44 trial-length fixation points were presented between the stimuli (four at the beginning and end, and 36 randomized throughout the run), providing an implicit baseline against which the other events could be contrasted.

There were two runs. In addition to 44 null events, each run included 16 negative 1st person, 16 negative 2nd person, 16 neutral 1st person, 16 neutral 2nd person, 16 positive 1st person, and 16 positive 2nd person comments, resulting in a total of 96 comments per run. In short, subjects received 32 comments of each of the six conditions.

Following EPI acquisition, subjects rated each individual comment on a 7-point Likert scale, according to how the comments made them feel where 1 = Extremely unhappy, 4 = Neither unhappy nor happy, and 7 = Extremely happy.

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