Increased Amygdala Activation to Angry and Contemptuous Faces in Generalized Social Phobia

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Background: Generalized social phobia (GSP) is characterized by fear of social interactions and sensitivity to disapproval by others. Given the established role of the amygdala as part of a distributed neural system for the processing of emotional cues, we hypothesized that subjects with GSP would exhibit greater amygdala activation in response to harsh (angry, fearful, and contemptuous) vs accepting (happy) facial emotional expressions compared with healthy control subjects (HCs).

Methods: Fifteen subjects with DSM-IV GSP and 15 age-, sex-, handedness-, and education-matched HCs, free of psychotropic medication for at least 12 weeks, viewed 60 color photographs from a standardized set of human facial stimuli, during which the task was to identify the sex of the person in the photograph. Data were collected across 3 functional (echo-planar) runs using a Siemens 1.5-T magnet, and analyzed using Analysis of Functional Neuroimaging software (Medical College of Wisconsin, Milwaukee).

Results: In the left allocortex (including the amygdala, uncus, and parahippocampal gyrus), subjects with GSP produced a significantly greater percent blood oxygen level–dependent signal change than did HCs for contemptuous compared with happy faces (GSP: 0.72% vs HC: −0.01%; F1,29=9.56, P= .004, Cohen d= 1.15) and for angry compared with happy faces (GSP: 0.45% vs HC: −0.09%; F1,29=6.78, P= .02, Cohen d= 1.00). Subjects with GSP and HCs did not produce a statistically different percent signal change for fearful or nonexpressive faces compared with the happy faces in this region.

Conclusions: These findings are consistent with a role for differential amygdala (and associated limbic) functioning in GSP. The pronounced response to contemptuous and angry facial expressions suggests that the amygdala in GSP may be particularly active in the processing of disorder-salient stimuli.

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Social phobia (also known as social anxiety disorder) is characterized by fear and avoidance of situations in which scrutiny by others is possible and in which embarrassment or humiliation is a dreaded outcome. Fear of interpersonal situations is especially pronounced in persons with generalized social phobia (GSP), a more pernicious form of the disorder that overlaps with avoidant personality disorder on Axis II. Persons with GSP frequently avoid making eye contact, are particularly sensitive to disapproval by others, and tend to view social events in a negative self-referential light. Functional impairment associated with social phobia rivals that seen in major depressive disorder and other chronic medical conditions.

Social phobia runs in families and a genetic contribution is presumed. Most twin studies support this contention. Although a neurobiologic basis for social phobia is therefore strongly suspected, including the possibility of dopamine dysfunction within the basal ganglia, its pathophysiologic mechanisms remain obscure.

New leads for understanding the etiologic substrates for social phobia have come from the basic and cognitive neurosciences. These studies have focused attention on the role of the amygdala and its rich network of connections with other cortical and subcortical regions in the mediation of fear and anxiety. Animal lesion and electrophysiologic studies collectively suggest that the amygdala mediates the acquisition of conditioned fear, a good model for some kinds of phobias. Of particular relevance to social phobia, the amygdala is also thought to play an important role in the neural circuitry of social intelligence. Humans with bilateral amygdala damage are unable to make accurate social judgments of others (eg, How trustworthy or approachable does this person appear?)
based on their facial appearance.\textsuperscript{21,22} Macaque monkeys with neonatal amygdala lesions show increased social fear, further emphasizing a potentially important role for the amygdala in the mediation of human social anxiety.\textsuperscript{23}

Early psychophysiological studies indicated an increased amygdala response in social phobia and other anxiety disorders.\textsuperscript{24} Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies confirm that the amygdala is activated during visual perception of some negative (eg, fearful) facial emotions in adults\textsuperscript{25,26} or adolescents,\textsuperscript{27} even at the subliminal level.\textsuperscript{28}

The presentation of faces with emotional expressions is being increasingly used as a probe of amygdala functioning in a range of anxiety and mood disorders. In an fMRI study, Rauch et al\textsuperscript{29} showed that, compared with combat veterans without posttraumatic stress disorder (PTSD), those with PTSD had an exaggerated amygdala response to the presentation of masked (ie, subliminally presented) fearful faces. Exaggerated amygdala response to masked fearful faces has also been seen in patients with major depression; this response seems to normalize with antidepressant treatment.\textsuperscript{30} Birbaumer and colleagues\textsuperscript{31} found that patients with social phobia, but not healthy controls (HCs), showed amygdala activation when presented with neutral faces. This research group also showed that patients with social phobia had increased activation in the amygdala (and hippocampus) when presented with neutral faces that had been previously paired with a noxious stimulus (an aversive odor), whereas deactivation was seen in these same regions in HCs.\textsuperscript{32} Taken together, these observations raise the possibility that anxious (and, possibly, depressed) patients might have an altered threshold for amygdala response to affective stimuli.

The face emotion processing probe of amygdala function has particular “face validity” for the study of GSP, a disorder characterized by fear of interpersonal situations and a tendency to avoid making eye contact. Information processing theory posits that individuals with social phobia manifest abnormalities in the way(s) in which they process social material.\textsuperscript{33,34} Persons with GSP show attentional bias for written threat-relevant information,\textsuperscript{33,34} and are more likely to remember faces with harsh (eg, angry) compared with accepting (eg, happy) emotional expressions.\textsuperscript{35}

It has recently been shown that an intact amygdala is critical for affective modulation of recollective experiences in humans.\textsuperscript{36} There is thus an a priori reason to expect that subjects with social phobia would differ from nonanxious comparison subjects in the way they process faces with harsh or critical emotional expressions, and that these processing differences would be reflected in alterations in neuronal activity of the amygdala and its connections.

To test this hypothesis, we presented a standard set of faces of varying affective content and measured the functional brain (blood oxygen level–dependent [BOLD]) response using fMRI. We hypothesized that subjects with GSP, compared with HCs, would exhibit a differential BOLD signal in limbic regions (eg, amygdala) in response to harsh (ie, angry, fearful, contemptuous) vs accepting (ie, happy) or nonexpressive (neutral) faces. To our knowledge, this is the first functional neuroimaging study to examine neural processing of varying facial emotional expressions in subjects with social phobia.

**METHODS**

**SUBJECTS**

Fifteen subjects (10 men, 5 women) diagnosed with GSP and 15 nonanxious HCs (10 men, 5 women), all recruited by advertisement, participated in this study. Potential subjects were screened by phone to determine potential group status and suitability for magnetic resonance (MR) scanning. Subjects were required to be right-handed as determined by the Edinburgh Handedness Inventory,\textsuperscript{37} nonsmokers, users of minimal caffeine (<200 mg/d), with no history of serious neurologic disorders, brain injury, loss of consciousness longer than 5 minutes, or regular medication use that would potentially interfere with cerebral blood flow. Furthermore, subjects had not used any psychotropic medication within the 3 months prior to scan. One HC was taking an angiotensin-converting enzyme inhibitor.

Subjects with GSP met DSM-IV criteria for that disorder as determined by an experienced interviewer using a version of the Structured Clinical Interview for DSM-IV\textsuperscript{39} that we modified by adding additional probes to permit the reliable diagnosis of the generalized subtype of social phobia and the Axis II disorder avoidant personality disorder\textsuperscript{40}; comorbid mood (nonbipolar) or other anxiety disorders were permitted, if deemed of lower priority. Avoidant personality disorder was present in 8 (72.7%) of 11 subjects with GSP (assessment unavailable in 4 subjects). Healthy comparison subjects were free of lifetime Axis I disorders (and avoidant personality disorder). Subjects with GSP and HCs were matched on a case-by-case basis on age, sex, and education. All subjects provided written informed consent for this study, which was approved by the University of California–San Diego School of Medicine Committee for the Protection of Human Subjects (La Jolla, Calif).

**CLINICAL MEASURES**

Subjects completed the Beck Depression Inventory,\textsuperscript{40} Liebowitz Social Anxiety Scale,\textsuperscript{41} and Benton Facial Recognition Test.\textsuperscript{42} State measures of sleepiness (Stanford Sleepiness Scale: a self-report rating from 1 [alert] to 7 [almost asleep])\textsuperscript{43} and anxiety (State Trait Anxiety Inventory, State Form)\textsuperscript{44} were administered immediately before and after the MRI scanning session.

**FACE EMOTION TASK**

Within the MRI magnet, subjects viewed color photographs of 60 human facial expressions from the Japanese and Caucasian Facial Expressions of Emotion standardized set developed by Matsumoto and Ekman,\textsuperscript{45} which has shown pancultural reliability.\textsuperscript{46} Test instructions and stimuli were back-projected onto a screen by a Polaroid projector (Polaroid Corp, Cambridge, Mass) using Micro Experimental Laboratory software (Psychology Software Tools, Pittsburgh, Pa).\textsuperscript{47} Images were viewed by means of a mirror attached to a head coil. The screen was 158 inches from the subject’s eyes, and the image was approximately 30 inches wide by 18 inches high. This resulted in subtended angles of 10.8° along the horizontal axis and 5.3° along the vertical axis. Each functional run included a random order of 36 blocks of 12 seconds’ duration each, including 16 expressive, 14 nonexpressive (neutral), and 6 asterisk fixation blocks in which the subject viewed an asterisk in the center of the screen (Figure 1). Each block consisted of 4 trials of 1 face stimulus type (either angry, fearful, contemptuous, happy, or nonexpressive), with each trial containing 1 facial stimulus presentation (2.5 seconds) followed by a black screen interstimulus interval (0.5 seconds). In each of the 3 functional runs, sets of 8 angry, 8 fearful, 8 contemptuous, 8 happy, and 28 nonexpressive faces were presented twice. This resulted in a total
of 48 trials of each type of expressive face (ie, angry, fearful, contemptuous, happy) and 168 trials of nonexpressive face stimuli. The face stimuli were counterbalanced for sex (male and female) and ethnicity (white and Japanese). Each set of emotion and neutral face stimuli were randomly ordered within their respective blocks, and blocks were randomly ordered within each functional run as well as across the 3 functional runs.

During the presentation of each face stimulus, subjects pressed 1 of 2 buttons (using their right index or middle finger) to indicate male or female. Each functional run was separated by a pause of approximately 3 minutes. Postscanning, all subjects viewed on a laptop computer each of the 60 unique face stimuli previously seen during the scanning session and were asked to make 2 decisions for each face stimulus: (1) choose the most accurate expression label from a list of 5 emotions (ie, anger, fear, contempt, neutral, and happy) and (2) rate the face on harshness from 1 (very approachable, warm) to 4 (neutral) to 7 (very critical, harsh). Accuracy and latency to response were recorded.

MR IMAGE ACQUISITION
Parameters of image acquisition were chosen to optimize the BOLD contrast. The BOLD signal is based on an endogenous contrast, namely, neural activity–related increases in the oxygenated to deoxygenated blood ratio, which rises to a peak level of intensity within 4 to 6 seconds after stimulus onset. In our study, 20 interleaved 7-mm-thick axial slices covering the whole brain were obtained in 3 separate functional runs, each consisting of 146 acquisitions, or repetitions. Gradient echo, echo-planar images (flip angle=90°, echo time=1029 ms, repetition time=3000 ms, field of view=220, 64×64 matrix, voxel size=3.44×3.44×3.44 mm in-plane resolution) were acquired using a Siemens 1.5-T magnet (Siemens AG, Erlangen, Germany) with an actively shielded magnet. The pulse sequence weighted the echo-planar images series toward T2* contrast. Also, high-resolution (magnetization prepared rapid acquisition with gradient echo sequence) structural images (180 1-mm3 sagittal slices, field of view=256) were acquired.

DATA ANALYSES
All data were transferred to a Sun Graphics (Sun Microsystems, Santa Clara, Calif) computer and analyzed using Analysis of Functional Neuroimaging (Medical College of Wisconsin, Milwaukee). To correct for movement, time series echo-planar images for each of the 3 face runs were aligned to a base image using a 3-dimensional, iterated, least-squares, coregistration algorithm provided in the Analysis of Functional Neuroimaging library. Fourier interpolation was used to resample images. The base image associated with the smallest shifts when coregistering the time series was chosen as the optimal base image for motion correction. Motion correction shifted images around 3 rotational axes, pitch, yaw, and roll, and in 3 directions, anterior to posterior, superior to inferior, and left to right. Estimates of these 6 parameters provide indirect measures of the extent of motion along the echo-planar time series.

Following a visual examination of signal dropout in areas of interest and of gross movement artifacts, the 3 functional face runs were combined into a single concatenated time series for each voxel and resampled into 3.5-mm3 voxels in Talairach coordinates. To obtain a functional signal, we used linear regression models to fit a stimulus reference vector to the echo-planar image time series values for each voxel. The stimulus reference vector coded when each type of face was presented in the experiment. In the primary analysis, linear contrasts were used to compare the brain's response to harsh faces (angry, fearful, contemptuous) with its response to accepting faces (happy). Although nonexpressive facial expressions have served as a control or comparison stimulus in several studies of affect recognition, some researchers have noted that they are often not viewed as “neutral” stimuli by subjects. When we assessed subjects' affective attributions of the faces on a post hoc basis outside of the magnet, we found that harshness ratings of the nonexpressive faces were judged to be intermediate between harsh and accepting faces.

In a secondary analysis, we used functionally derived “masks” to perform separate regression analyses comparing angry, fearful, contemptuous, and nonexpressive faces separately against happy faces in each brain region that showed a significant difference between subjects with GSP and HCs in the primary analysis. In addition to containing terms representing face contrasts, the regression models also included linear terms and additive constants for each of the 3 runs to control for differences in baseline signal across runs and to detect the trend for linear drifts. In each analysis, the stimulus reference function was shifted forward in the time series up to 6 seconds to account for the time delay in the hemodynamic response. The dependent variable chosen for all analyses was the fit coefficient of the stimulus reference vector derived from the regression analysis. The fit coefficient is a measure of task-related BOLD signal magnitude, with a threshold determined by its concomitant group t score distribution.

After transforming anatomical and functional images into Talairach coordinates, we performed t tests and generated maps of mean fit coefficients representing BOLD response to the various contrasts both within and between subjects with GSP and HCs. While within-group analyses show the magnitude and direction of significant areas of BOLD response, between-group analyses yield an interaction of group (subjects with GSP vs HCs) × task (target vs comparison condition, eg, perception of harsh faces vs accepting faces). These interactions isolate areas of significant differences between groups in the relative difference of MRI signal intensity between target and comparison faces.

To correct quantitatively for the multiple comparisons inherent in the statistical analysis of thousands of brain voxels, a Monte Carlo simulation method (10000 iterations) was em-
ployed to identify a joint voxel-wise threshold and cluster volume size combination to set a cluster-wise adjusted P value of less than .05. This included a voxel-wise threshold of P < 0.03, spatial blurring of FWHM (full width half maximum) = 7 mm (SD, 2.97 mm), and a cluster volume threshold of 8 original voxels (3.44 mm × 7 mm = 663 mm³), to protect against the probability of false positives (ie, type I error) at a cluster-wise level of P < 0.03.

Significant differential areas of BOLD signal are reported by location of the voxel with the highest signal magnitude using Talairach coordinates, Brodmann areas (BAs), and neuro-anatomical region labels. To provide a common metric interpretable across studies, differences in signal magnitude between groups are reported as Cohen d, an effect size measure. We used a percent difference score to plot graphical summaries across individuals.

Identification of neuroanatomical structures associated with areas of significant functional activation was determined using (1) Talairach and Tournoux atlas, (2) Talairach Daemon, and (3) Atlas of the Human Brain. Data are given as mean (SD) unless otherwise indicated.

RESULT

SUBJECT CHARACTERISTICS

Subjects with GSP and HCs did not differ significantly on age (GSP: 39.1 [14.3] vs HC: 39.3 [12.3] years; t28=−0.04, P = .97), sex (GSP: 5 of 15 women vs HC: 5 of 15 women), education (GSP: 13.5 [2.7] vs HC: 15.1 [2.3]; t28=−1.75, P = .09), right-handedness (Edinburgh Handedness Scale: GSP: 14.4 [5.9] vs HC: 12.1 [2.1]; t28=1.42, P <.17), facial recognition ability (Benton Facial Recognition: GSP: 47.0 [3.7] vs HC: 49.1 [2.9]; t28=1.39, P = .18), or habitual caffeine intake (GSP: 117 [87] mg/d; HC: 59 [69] mg/d; t28=2.02, P = .05).

Compared with HCs, subjects with GSP reported significantly greater symptoms of social anxiety on the Liebowitz Social Anxiety Scale (GSP: 87.7 [25.7] vs HC: 15.5 [13.4]; t28=9.05, P < .001), and symptoms of depression on the Beck Depression Inventory (GSP: 10.4 [7.5] vs HC: 2.1 [2.4]; t28=4.09, P < .001). Based on these measures, the GSP group would be characterized as moderately to severely socially anxious and minimally to mildly depressed.

Subjects with GSP and HCs did not differ significantly on prescanning and postscanning sleepiness (prescan: GSP: 1.9 [1.0] vs HC: 1.5 [0.6]; t28=1.33, P = .20; postscan: GSP: 2.9 [1.5] vs HC: 2.5 [1.3]; t28=0.78, P = .44). Although the GSP group reported significantly higher prescanning state anxiety (State Trait Anxiety Inventory, State Form) than the HC group (GSP: 38.4 [10.3] vs HC: 23.5 [6.5]; t28=5.03, P < .001), at postscanning the 2 groups were similar (GSP: 28.4 [9.7] vs HC: 25.7 [6.5]; t28=0.90, P = .38).

FACE IDENTIFICATION AND EMOTION LABELING TASK RESULTS

Accuracy on sex identification was equivalent both within and across all 3 functional runs for GSP and HCs (97.1% and 97.9%, respectively). There was also no evidence of a differential pattern of reaction times (data not shown, available in 12 subjects with GSP and 10 HCs) between groups.

Subjects with GSP and HCs did not differ significantly in the overall mean accuracy of face emotion labeling (GSP: 77.0% vs HC: 79.0%; P = .33), conducted immediately after the scanning session. The pattern of emotional ratings for each of the 5 types of facial emotions was also not significantly different (Table 1). Thus, GSP and HCs evinced the same pattern of facial emotion identification and intensity ratings. Any differential brain BOLD patterns cannot be accounted for by emotional processing as assessed by these behavioral results.

Analysis of harshness ratings comparing accepting, nonexpressive, and harsh faces revealed a large, significant linear effect across the face types, and a smaller but significant quadratic effect (linear: F1,28 = 95.48, P < .001, Cohen d = 3.66; quadratic: F1,28 = 5.90, P = .02, Cohen d = 0.91). The quadratic effect resulted from ratings of nonexpressive faces being more similar to harsh faces than to accepting faces. Group did not interact with face type, indicating that subjects and HCs rated faces similarly.

BOLD FMRI RESULTS

Analysis of Motion Artifacts

Analysis of the 3 rotational (roll, pitch, yaw) and 3 translational (anterior to posterior, superior to inferior, left to right) parameters yielded no significant differences in motion correction between subjects with GSP and HCs. Furthermore, correlations of the stimulus reference vector with each motion parameter did not reveal any significant group difference in stimulus-correlated motion.

Harsh vs Accepting Faces

Subjects with GSP produced significantly greater BOLD responses compared with HCs when harsh (angry, contemptuous, and fearful) facial expressions were contrasted with accepting (happy) facial expressions (Table 2 and Figure 2) in 4 brain areas: (1) left anterior medial temporal lobe (MTL), which included left amygdala (GSP: harsh > accepting; HC: accepting > harsh), left parahippocampal gyrus (GSP: harsh > accepting; HC: accepting > harsh), and left uncus (BA34, BA28; GSP: harsh > accepting; HC: accepting > harsh); (2) medial prefrontal cortex, which included bilateral dorsal medial frontal gyrus (BA9; GSP: harsh > accepting; HC: accepting > harsh) and right superior frontal gyrus (BA9; GSP: harsh > accepting; HC: accepting > harsh); (3) left inferior frontal gyrus (BA47; GSP: harsh > accepting; HC: accepting > harsh); and (4) right uncus (BA36; GSP: harsh > accepting; HC: accepting > harsh). There were no significant clusters for which the HCs produced greater BOLD responses compared with the subjects with GSP.

Percent Signal Change for Each Face Type vs Happy Faces

A more detailed analysis was conducted to examine the contrast of each face stimulus type (ie, angry, fearful, contemptuous, and nonexpressive), respectively, vs happy faces in the 4 brain areas on which subjects with GSP and HCs differed in the above analysis. In the left allocortical (anterior medial temporal lobe) region (which included the amyg-
Subjects with GSP produced significantly greater percent BOLD signal change than did HCs for contemptuous compared with happy faces (GSP: 0.72% vs HC: −0.01%; F1,29=9.56, P=.004, Cohen d=1.15) and for angry compared with happy faces (GSP: 0.45% vs HC, −0.09%; F1,29=6.78, P=.02, Cohen d=1.00). Subjects with GSP and HCs did not produce statistically different percent signal change for fearful or nonexpressive faces compared with happy faces. The pattern of response was similar in the other 3 brain areas of interest, with the largest differential responses generally seen for the angry and contemptuous vs happy face contrasts; the overall magnitude of responses was, however, smaller in the cortical regions (percent signal changes ranging from −0.12% to 0.14%) than in anterior allocortex (percent signal changes ranging from −0.47% to 0.72%).

### Table 2. Perception of Harsh Compared With Accepting Facial Expressions: Areas of Significantly Greater Relative Blood Oxygen Level–Dependent Activation in Subjects With Generalized Social Phobia vs Healthy Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann Area</th>
<th>Talairach XYZ</th>
<th>Effect Size (Cohen d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral dorsal</td>
<td>9</td>
<td>2L 55A 3S</td>
<td>1.09</td>
</tr>
<tr>
<td>MFC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left IFG</td>
<td>47</td>
<td>4L 31A 3S</td>
<td>0.88</td>
</tr>
<tr>
<td>Right SFG</td>
<td>9</td>
<td>18R 60A 27S</td>
<td>1.37</td>
</tr>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left amygdala</td>
<td>34</td>
<td>20L 5P 22I</td>
<td>1.22</td>
</tr>
<tr>
<td>Left uncus</td>
<td>28</td>
<td>18L 5P 25I</td>
<td>1.25</td>
</tr>
<tr>
<td>Right uncus</td>
<td>36</td>
<td>22R 3P 29I</td>
<td>1.34</td>
</tr>
<tr>
<td>Left PHG</td>
<td>20L 7P 21I</td>
<td>1.08</td>
<td></td>
</tr>
</tbody>
</table>

*MFC indicates medial frontal cortex; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; and PHG, parahippocampal gyrus. All activation clusters thresholded at P<.034 and cluster volume greater than or equal to 662 mm3 (≈8 × 3.5 mm3 voxels). Talairach coordinates specify the location of the maximum response within each cluster. Results are from 15 patients with generalized social phobia and 15 healthy control subjects.

**Figure 2. Areas of significantly greater blood oxygen level–dependent (BOLD) activation in subjects with generalized social phobia compared with healthy control subjects. Blood oxygen level–dependent activation was defined as the difference in the T2* signal for happy faces subtracted from the mean T2* signal averaged over harsh faces (contemptuous, angry, fearful). A between-group t test of BOLD activation was performed on a voxel-by-voxel basis. Only voxels showing significant (P<.05, 2-tailed) BOLD activation that formed a contiguous region of activation of at least 663 mm3 were presented. The color coding shows the effect size of the significant between-group difference, expressed as Cohen d. See the text for additional details.**

**Figure 3.**

This study is the first, to our knowledge, to evaluate the BOLD response to faces of varying emotional type in subjects with GSP and HCs. Whereas an earlier study showed that patients with social phobia, but not HCs, activated the amygdala when viewing neutral faces, an emotion-specific effect has not previously been demonstrated. In the present study, we found that subjects with GSP exhibited greater left-sided amygdala (and other anterior MTL structures, including uncus and parahippocampal gyrus) activation compared with HCs when viewing angry or contemptuous faces. The anterior MTL response to fearful and nonexpressive (neutral) faces was, however, similar in subjects with GSP and HCs. This finding may represent a difference in limbic processing of salient emotional cues that is integral to the pathophysiologic characteristics of GSP.

Our study has several limitations. Our inclusion of several different types of facial expressions—at the cost of fewer repetitions of each face type—limits our power for the contrasts across facial expression type. This would result in a type II error, wherein we might miss regions of differential activation. We also chose not to select regions of interest on an a priori basis, restricting ourselves to regions discerned from our data but employing a higher statistical threshold as a result; again, increased type II error risk is a potential consequence. Based on our results, future studies would be justified in focusing a priori on the amygdala and related anterior MTL structures. The inclusion of subjects with various comorbid conditions, even though GSP was in all cases the clinically predominant diagnosis, may have influenced the results in an unpredictable fashion. Replication in a more diagnostically pristine sample would be welcomed. Furthermore, given sex differences in amygdala activation during the perception of facial affect, future studies should be powered to detect possible interactions with sex. Finally, given the recent observation that amygdala responsivity to happy faces...
correlates with the degree of extraversion of the individual, and taking into consideration that GSP is associated with low extraversion, it will be important to evaluate additional types of emotional face contrasts in future studies to ensure that this does not present a confound to interpretation of the data.

Our finding of increased left amygdala activation for certain face-type contrasts is consistent with other studies that have used “unmasked” negatively valent faces as stimuli. It is unclear at this juncture whether this apparent laterality is meaningful with regard to physiologic processes. Given the difficulty in localizing the amygdala using our present technological resources, and the ambiguity in the field of what precisely constitutes the amygdala, we recommend caution in even assuming that our findings reflect true asymmetry of the amygdala.

Figure 3. Contrast of angry, contemptuous, fearful, and neutral (nonexpressive) faces with happy faces in subjects with generalized social phobia vs healthy comparison subjects in 4 functionally defined regions of interest. Mean values (with error bars showing SEM) expressed are percent signal change. Asterisk indicates P < .05; dagger, P < .005. PHG indicates parahippocampal gyrus; BA, Brodmann area; and IFG, inferior frontal gyrus.
dala response. This will require replication with additional attention paid to possible laterality effects.

It should be further understood that our findings do not label the amygdala in social phobia as wholly “abnormal.” There are subdivisions of the amygdala that are not resolvable at the field strength (1.5 T) and spatial resolution (3.5 × 3.5 × 7 mm with FWHM = 7 mm) used in this study. These subregions may carry the observed effects; additional studies at higher field strength (if susceptibility artifacts in this region can be overcome) may prove informative in this regard. Even more importantly, the amygdala and its distributed neural connections serve multiple functions that are not limited to the perception or processing of facial affect. Not all of these functions are abnormal, according to our findings. For example, the amygdala is required for accurate labeling of facial emotions,23 for making social judgments of others based on their facial appearance,24 and for the enhancement of perception that normally accompanies emotionally salient events.25 The first 2 of these functions—affect labeling and judging approachability—are, according to our findings, preserved in subjects with GSP; the latter function has yet to be studied. These observations—apparently normal amygdala-mediated “performance” in the context of a differential BOLD response to the task—may reflect relative insensitivity of the performance-based measures, genuine dissociation of this particular function from the BOLD response (ie, the increased activation does not result from differential performance of this particular aspect of the task), or another phenomenon that is not presently explainable. Choosing among these alternatives would be speculative at this juncture. But these findings do underscore the message that it is too simplistic (both in terms of neuroanatomical and functional precision) to speak of an “abnormal amygdala” in patients with GSP on the basis of our findings.

Several regions within the medial frontal cortex also showed increased BOLD responses in subjects with GSP compared with HCs for harsh vs accepting face contrasts. The medial prefrontal cortex has been implicated as a region important to the processing of emotionally salient stimuli, and is active in humans during the performance of anxiety-provoking tasks.69 Subjects with GSP differ from HCs with regard to attentional processing of such stimuli,33 as would be expected on the basis of their paramount concerns about being scrutinized and negatively evaluated.33 The increased responsiveness in GSP may, therefore, reflect increased processing demands placed on the medial prefrontal cortex when confronted with facial stimuli. If replicated, these results will offer evidence of an important convergence of clinically relevant structure and function. Other regions that showed increased responsiveness in GSP for the harsh vs accepting face contrast were several allocortical structures, including the parahippocampus and uncus. Each of these regions has been noted in 1 or more studies to form part of the neural circuitry for affect processing.16 Further research will be required to discern which element(s) of these circuits—and specifically which function(s) they subserve—are abnormal in social phobia.

Findings from a recent 15O water PET study in social phobia during performance of a public speaking task are convergent in also detecting increased amygdala activation in patients compared with HCs.65 Rauch and colleagues66 showed that combat veterans with PTSD have a heightened amygdala BOLD response to masked fearful faces compared with combat veterans without PTSD. It has been suggested that the amygdala response to emotionally noxious stimuli represents the activation of a phylogenetically archaic danger recognition system.66 As such, enhanced amygdala responding to “danger” signals may prove to be a feature shared by a number of anxiety disorders; selectivity of response to particular “danger” stimuli may be what differentiates them. These stimuli may be external (eg, someone with social phobia entering a crowded room) or, consistent with cognitive-behavioral theories of anxiety disorders, internal (eg, someone with panic disorder attends to an increase in their heart rate).

One need not infer from our findings that an enhanced amygdala response reflects an abnormality intrinsic to the amygdala. An equally persuasive case could be made that the amygdala is merely responding appropriately to cortical input that signals danger. As such, the abnormality in anxiety disorders could well be at the level of risk appraisal, a more evolved component (presumably involving links to the prefrontal cortex) of the human brain fear system.16,19,24 Given the reciprocity of these distributed neural systems for fear recognition and response, multiple parts of the circuitry may be implicated. These hypotheses await confirmation in future studies that include groups of subjects with a variety of anxiety disorders (and those not yet disordered but “anxiety-prone,” perhaps on the basis of high levels of trait anxiety or neuroticism, or on the basis of family history), all challenged with stimuli that are salient to each. There is preliminary evidence to suggest that, in depressed patients,30 successful treatment of social phobia may be associated with a reduction in amygdala hyperreactivity.67 These observations remain to be replicated in future fMRI studies of patients with GSP, where treatment effects can be evaluated in conjunction with possible genetic influences (eg, serotonin transporter polymorphisms) on amygdala responsivity to threatening stimuli.68

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