Generalized social phobia (GSP), also known as social anxiety disorder, is the most common anxiety disorder in the community (Jacobi et al 2004; Kessler et al 2005b) and is associated with significant morbidity (Mendlewicz and Stein 2000; Stein and Kean 2000; Stein et al 2000). The disorder is characterized by an excessive or unreasonable fear of social interactions where the individual fears being negatively evaluated by others. The etiology of GSP remains unknown (Charnley 2004), but there is evidence for genetic and environmental underpinnings (Chartier et al 2001; Hettema et al 2005; Stein et al 1998, 2002).

Individuals with GSP have the onset of social fears during childhood or adolescence, and these usually persist into adulthood (Kessler et al 1998). The disorder has been characterized by information biases such as excessively negative interpretation of external social events, enhanced detection of negative responses from other people, an imbalance of attention between external and self-processing, and exaggerated recall of negative aspects of an event (Clark and McManus 2002; Pineles and Mineka 2005).

Neurobiological studies of GSP have implicated the dysfunction of particular brain regions: amygdala (Birbaumer et al 1998; Schneider et al 1999; Stein et al 2002), prefrontal cortex (Lorberbaum et al 2004), and striatum (Mathew et al 2001).

Neuroimaging studies that engage emotion-processing resources of GSP through anticipated public-speaking tasks (Furman et al 2000, 2005; Lorberbaum et al 2004; Tillfors et al 2002) or viewing negative emotional faces have demonstrated an increased activation of regions associated with emotion processing such as the amygdala, prefrontal cortex, and insula compared with matched control subjects (Amir et al 2005; Birbaumer et al 1998; Phan et al 2005; Stein et al 2002; Straube et al 2004, 2005). These findings of increased activity of emotion processing regions, especially the amygdala, during processing of anxiety-provoking paradigms are not specific to GSP, however. Similar findings have been noted in posttraumatic stress disorder (Armony et al 2005; Shin et al 2005; Woodward et al 2005), obsessive compulsive disorder (OCD; Mataix-Cols et al 2003; van den Heuvel et al 2004), and panic disorder (Sakai et al 2005), suggesting that the increased activity of limbic structures is likely the result of high levels of distress and anxiety. To the best of our knowledge, ours is the first functional imaging study to examine the neural correlates of GSP during a cognitive task that is not aimed at inducing anxiety or engaging emotional systems.

This study focuses on examining striatal functioning in GSP for two reasons. First, dopamine is a key neurotransmitter in striatal structures and accumulating evidence suggests dopaminergic dysfunction in GSP. Previous work has shown an increased association of GSP with Parkinson’s disease (Stein et al 1990), and treatment of Tourette’s disorder with dopamine antagonists can induce GSP symptoms (Mikkelsen et al 1981). Thus, it has been hypothesized that GSP may be associated with striatal dysfunction (Mathew et al 2001). Consistent with this notion, animal models of GSP, such as primate subordination, have also found low striatal dopamine (Grant et al 1998). Human functional neuroimaging studies using single photon emission computerized tomography (SPECT) studies have demonstrated that GSP is associated with lower striatal dopamine D2 receptor binding potential and dopamine transporter density compared with matched control subjects (Schneier et al 2000; Tiitonen et al 1997). Nevertheless, no study has directly examined task-specific changes in the functioning of striatal structures in GSP.

Second, evidence from behavioral studies suggests that people with GSP have negative biases in social situations with a failure to learn behavioral strategies that lead to adaptive outcomes (Clark and McManus 2002). Striatal structures have been shown to modulate several types of learning behavior, including...
instrumental conditioning and implicit or procedural learning (Amso et al 2005; Barnes et al 2005; Frensch and Runger 2003; Fuji and Graybiel 2005; O’Doherty et al 2004; Reiss et al 2005; Rodriguez et al 2005; Rogan et al 2005). Implicit learning is a type of skill acquisition in which the learning occurs without awareness through repeated practice (Frensch and Runger 2003). Based on previous work demonstrating implicit memory biases in GSP (Lundh and Ost 1997), it is possible GSP may be associated with altered implicit learning due to striatal and dopaminergic dysfunction.

The Serial Reaction Time (SRT) task has been commonly used to examine implicit learning (Nissen and Bullemer 1987; Willingham et al 1989). The development of a reaction time (RT) advantage to a repeated implicit sequence compared with a random sequence is used as the indicator of implicit learning. In healthy individuals, numerous studies have demonstrated striatal regions (putamen and caudate) to be activated during the processing of the SRT task (Rauch et al 1997b; Reiss et al 2005; Schendan et al 2003; Thomas et al 2004). Rauch et al (1997b) and our group (Reiss et al 2005) have employed the SRT task in combination with functional magnetic resonance imaging (fMRI) to demonstrate a significant positive relationship between the degree of implicit learning as measured by RT advantage (i.e., behavioral data) and neural activation in striatal structures (Nissen and Bullemer 1987; Rauch and Savage 1997; Willingham et al 1989). Using the SRT task or similar implicit learning tasks, a range of neuropsychiatric populations with dopaminergic dysfunctions (i.e., Huntington’s disease [Kim et al 2004]; Tourette’s disorder [Rauch et al 2001]; and schizophrenia [Kumari et al 2002; Reiss et al, in press; Scherer et al 2003]) have demonstrated deficient activation in striatal structures compared with matched control subjects with functional neuroimaging techniques (i.e., fMRI and positron emission tomography [PET]).

Previously, two groups of patients with anxiety disorders (OCD and animal phobia) have been examined with the SRT task in combination with functional imaging. PET (Rauch et al 1997a) and fMRI (Rauch et al 2001) studies have demonstrated that OCD patients fail to activate striatal structures compared with matched control subjects on the SRT task despite similar levels of behavioral performance (i.e., amount of implicit learning). In contrast, an fMRI study compared 10 animal phobia patients to 10 healthy control subjects and did not find significant differences between these groups in implicit learning or striatal activation during the SRT task (Marti et al 2004). Our fMRI study is the first to evaluate striatal function in GSP using the SRT task. Based on previous literature demonstrating dopaminergic dysfunction in GSP, we hypothesized that individuals with GSP would be deficient in activating striatal structures during the SRT task in comparison with control subjects.

Methods and Materials

Participants

We recruited 26 right-handed, physically and neurologically healthy, psychotropic medication-free volunteers (13 subjects with GSP and 13 age-, gender-, and education-matched control subjects) through newspaper advertisements. Six subjects were excluded: three GSP subjects (one had an asymptomatic subarachnoid cyst found at the time of scanning, one had no behavioral data, and one had no fMRI data) and three control subjects (one had an inadequate behavioral response rate, one had fMRI data acquisition errors, and one fell asleep). Demographic data for the GSP and control groups included in the study appear in Table 1. All procedures were conducted in accordance with requirements of the National Research Council of Canada Research Ethics Board and the Health Research Ethics Board of the University of Manitoba. Written informed consent was obtained from all subjects before participation.

All subjects were interviewed by an experienced psychiatrist (JS), who administered the MINI International Diagnostic Interview version 5.0 (Sheehan et al 1998) for DSM-IV (American Psychiatric Association 1994). Individuals with a primary diagnosis of GSP were recruited. Comorbid mood and anxiety disorders (with the exception of OCD and posttraumatic stress disorder) were permitted if they were deemed of lower clinical priority than GSP. We excluded subjects who had a lifetime comorbid diagnosis of psychotic disorder, OCD, subthreshold OCD, Tourette’s syndrome, or either alcohol or drug abuse/dependence. Among the 10 GSP subjects, 6 had no comorbid Axis I diagnosis: major depression and generalized anxiety

Table 1. Sociodemographics, Clinical Measures, and Behavioral Performance of the Sample

<table>
<thead>
<tr>
<th>Sociodemographics</th>
<th>GSP (n = 10) Mean (SD)</th>
<th>Control (n = 10) Mean (SD)</th>
<th>t(18)</th>
<th>p</th>
<th>Grand Mean (n = 20) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female/Male</td>
<td>6/4</td>
<td>6/4</td>
<td>—</td>
<td>—</td>
<td>12/8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.1 (9.1)</td>
<td>28.4 (8.6)</td>
<td>.18</td>
<td>.86</td>
<td>28.8 (8.6)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.1 (2.5)</td>
<td>14.2 (1.8)</td>
<td>.11</td>
<td>.28</td>
<td>13.6 (2.2)</td>
</tr>
<tr>
<td>Clinical Measures on Day of the Scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liebowitz Social Anxiety Scale</td>
<td>84.5 (22.9)</td>
<td>116 (15.0)</td>
<td>7.4</td>
<td>&lt;.0005</td>
<td>54.5 (41.8)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>13.9 (10.3)</td>
<td>2.0 (3.5)</td>
<td>2.9</td>
<td>.01</td>
<td>9.0 (10.0)</td>
</tr>
<tr>
<td>Spielberger State Anxiety</td>
<td>44.2 (11.9)</td>
<td>25.1 (5.8)*</td>
<td>4.1</td>
<td>.001</td>
<td>35.7 (13.6)</td>
</tr>
<tr>
<td>Serial Reaction Time Task Behavior Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time (msec)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>438.2 (82.3)</td>
<td>389.8 (71.7)</td>
<td>1.4</td>
<td>.18</td>
<td>414.0 (79.1)</td>
</tr>
<tr>
<td>Implicit Learning</td>
<td>417.2 (81.7)</td>
<td>369.7 (68.1)</td>
<td>1.4</td>
<td>.18</td>
<td>393.4 (77.2)</td>
</tr>
<tr>
<td>Reaction Time Advantage (%)b</td>
<td>4.8 (3.6)</td>
<td>5.1 (3.7)</td>
<td>-.16</td>
<td>.88</td>
<td>5.0 (3.5)</td>
</tr>
<tr>
<td>Explicit Learning Scores</td>
<td>4.4 (8.8)</td>
<td>4.2 (1.1)</td>
<td>.4</td>
<td>.66</td>
<td>4.3 (1.0)</td>
</tr>
</tbody>
</table>

GSP, generalized social phobia.

*aReaction time based on the mean of median reaction times in milliseconds with the SD in brackets.

*b% RT advantage = 100 * (baseline RT − implicit RT)/baseline RT.

n = 8.
disorder (GAD). The remaining two subjects had two comorbid Axis I diagnoses: one had GAD and panic disorder, and one had GAD and dysthymia. All healthy comparison subjects were free of any lifetime DSM-IV mental disorder diagnosis. All subjects undergoing scanning were assessed for severity of social anxiety symptoms by using the Liebowitz Social Anxiety Scale (Heimberg et al 1999).

Clinical Measures on the Day of Scan

All subjects completed the Beck Depression Inventory (Beck 1961) and the Spielberger State–Trait Anxiety Inventory—State Version (Spielberger et al 1970).

Task

We used the SRT task modified for the functional MRI setting (for details, see Martis 2004; Rauch 1997a, 1997b). MRI-compatible eye-pieces (Avotec Silent Vision goggles, Stuart, Florida) displayed an asterisk in one of four horizontally arranged boxes for 1.0 sec, followed by a 1.2-sec interval of empty boxes. Participants pressed one of four spatially corresponding keys in response to the asterisk using separate fingers. STIM software (Neuroscan, Compumedics, Brazil) was used to create and record all SRT stimuli and data. A 25-trial practice run was followed by two runs each lasting 6.25 min and consisting of 312 trials. Each run consisted of alternating blocks of random (R) and implicit learning (IL) conditions bracketed by a 1.92-sec crosshair fixation block: +/−/IL/IL/IL/IL/IL/IL/+/. In the IL condition, the stimuli followed a 12-item sequence (position: 1−2−1−4−2−3−4−1−3−2−4−3) that repeated six times for a total of 72 trials (Martis et al 2004). In the random condition, 24 stimulus locations were pseudo-randomly presented with no immediately repeated locations. No signs were given to distinguish between R and IL blocks. For each participant, a median reaction time (RT) score was calculated for each condition, R and IL, as well as an IL reaction time advantage (RTa) score by using these median reaction times [100 * (R − IL)/R]. To provide a more refined test of group differences in IL, six RTa scores per participant were calculated, one for each IL-block across the two functional runs. A repeated-measures analysis of variance (ANOVA) was used to test for group differences in RTa scores across time.

Debriefing

Immediately following the two experimental runs, the subjects were informed that a repeating sequence had been present and were asked to attempt to recall the sequence by making 15 key presses (Martis et al 2004; Rauch et al 1997b). The longest consecutive string that matched the 12-item implicit sequence estimated the degree of explicit learning. Consistent with previous fMRI studies of SRT task (Martis et al 2004), scores ≥ 7 were considered evidence that explicit learning had occurred.

MRI Individual Analyses

Image processing and analyses were performed with Analysis of Functional NeuroImages (AFNI) software (Cox 1996). The fMRI data were slice time-corrected. Images were coregistered to the image that minimized image translation and rotation relative to all other images. The first three volumes were excluded to allow for MRI saturation. Any volumes with visually detectable movements or obvious MRI abnormalities also were excluded. Run 2 was concatenated to Run 1. The block design time series was convolved to account for the hemodynamic response function. Multiple regression analysis included nine regressors: two convolved IL and R condition regressors, three head-motion covariates (i.e., roll, pitch, and yaw), two slope regressors (one per run), and two intercept (fixation crosshair blocks) regressors (one per Run). The beta coefficient for each condition (IL and R) was divided by the mean (Run 1 and Run 2) intercept fixation crosshair coefficient to estimate percent blood oxygen level-dependent (BOLD) signal change for each condition (Cohen and Dubois 1999). To account for variations in anatomic landmarks, an 8-mm full-width half-maximum Gaussian filter was applied. Data were transformed into the Talairach and Tournoux and Montreal Neurological Institute coordinates (Cox 1996).

Alpha Control Criteria

For the whole brain analyses, Monte Carlo simulations estimated that a voxelwise probability of p < .02 and a minimum cluster volume of 640 μL would maintain an overall p < .05. For the striatum (defined via the AFNI software atlas) region of interest (ROI) analyses, a more liberal criterion was used. The ROI Monte Carlo simulations estimated that a voxelwise probability of p < .04 and a minimum cluster volume of 448 μL would maintain an overall p < .05. One-tailed testing was used for the task condition effects as we expect and only are interested in those areas that show greater BOLD responses to IL versus R.

MRI Group Analyses

A two by two repeated-measures ANOVA (within-person Condition effect and between Group effect) was used to identify common IL-related neural activation (Condition effect) and group differences unique to IL-related neural activation (Group by Condition interactions). ANOVA cluster averages were imported into SPSS 11.0 (1999) for descriptive statistic and simple effect analyses. To supplement these analyses, we tested for degree of IL-related (RTa) BOLD responses within each group. All areas of activation are reported in Montreal Neurological Institute coordinates with positive values as right, anterior, and superior. For each IL-related activation cluster identified, we tested for correlations between BOLD responses and the Liebowitz Social Anxiety Scale, the Beck Depression Inventory scores, and the Spielberger (STAI) state-anxiety inventory scores.

Results

Participant Characteristics

GSP participants did not differ significantly from healthy control subjects on sociodemographic variables (see Table 1 for age, gender, and education). The GSP participants had significantly higher levels of anxiety and depression on all clinical measures. Similar to a previous MRI study by our group (Stein et al 2002), the clinical measures suggested that the GSP subjects had moderate to severe levels of generalized social phobia and had minimal to mild levels of depression.
Task Performance

There were no significant group differences in RT or percent RT advantage means (Table 1) and both groups showed significantly faster mean RT during the IL condition compared with the R condition [GSP, t(9) = 3.9, p < .004, and control subjects, t(9) = 4.6, p < .001]. To investigate subtle between group differences in behavioral performance, a repeated measures ANOVA (group × condition × block) was conducted. This analysis did not identify a significant group by block effect $F(5,90) = 1.575, p = .175$. RT estimates were based only on correct trial responses. Mean response error rates, based on commissions and omissions, were 2.3% and 3.2% for GSP and control subjects, respectively [$t(18) = .7, p > .2$]. None of the participants showed evidence of explicit learning (EL) contamination with all EL scores less than 7. The GSP and control groups did not differ in their mean EL contamination scores [$t(18) = .4, p > .2$] with means of 4.4 (SD = 0.8) and 4.2 (SD = 1.1), respectively.

Common Group BOLD Responses to the IL Versus R Contrast

In the repeated-measures ANOVA whole-brain analysis, three brain regions were associated with greater BOLD responses to the IL condition compared to the R condition in both groups (Condition effect, Figure 1) including: the right caudate tail [$F(1,18) = 23.3, p < .001$], the right superior temporal gyrus [$F(1,18) = 12.7, p < .002$], and the right postcentral gyrus [$F(1,18) = 24.1, p < .001$]. Using a striatum ROI search region and $p$ value equivalent to a one-tailed test, the right putamen also showed greater BOLD responses to the IL condition compared with the R condition for both groups [$F(1,18) = 12.9, p < .002$ (Figure 2)]. In all clusters, the IL versus R BOLD response contrast was confirmed to be significant for each group with simple effect tests (all $p < .035$ (95% confidence intervals of the mean difference scores in Figures 1 and 2)). As well, the BOLD responses for each separate task condition (R or IL) were comparable between both groups (all $p > .2$).

Group Differences in BOLD Responses to the IL Versus R Contrast

The whole-brain analysis also identified four regions (Figure 3) in which the two groups exhibited significantly different BOLD responses in the IL versus R contrast (i.e., interaction effects) including the left caudate head [$F(1,18) = 12.9, p < .002$], left insula [$F(1,18) = 14.7, p < .001$], right insula [$F(1,18) = 14.9, p < .001$], and the left inferior parietal lobe [$F(1,18) = 12.8, p < .002$]. The left caudate head, identified in the whole-brain analyses, was also identified in the ROI analyses (data not shown), and in a subsample
analysis of noncomorbid GSP subjects (six GSP subjects vs. six healthy control subjects).

Simple effect analyses show that the healthy control group exhibited significantly higher BOLD responses to the IL condition than the R condition while the GSP group exhibited lower BOLD responses to the IL condition than the R condition in these regions (all $p < .05$; 95% mean difference confidence intervals in Figure 3). The group differences were due to relative condition differences (IL vs. R), not separate mean condition (R or IL) differences in BOLD responses (all $p > .15$).

Correlation of RTa with BOLD Responses Within Each Group

In GSP subjects, RTa was correlated with greater BOLD responses in the following extrastriatal regions: 1) right middle frontal gyrus ($r = .963$, $p \leq .001$, $\mu L = 4352$), 2) right precuneus and BA 7 ($r = .931$, $p \leq .001$, $\mu L = 4288$), 3) right postcentral gyrus and BA 40 ($r = .902$, $p \leq .001$, $\mu L = 1792$), 4) left declive ($r = .912$, $p \leq .001$, $\mu L = 1472$), 5) left cingulate gyrus and BA 24 ($r = .918$, $p \leq .001$, $\mu L = 1024$), 6) middle frontal gyrus ($r = .893$, $p \leq .001$, $\mu L = 960$), 7) middle occipital gyrus ($r = .895$, $p \leq .001$, $\mu L = 768$), and 8) middle occipital gyrus ($r = .848$, $p \leq .003$, $\mu L = 704$). In healthy control subjects, RTa was not correlated with greater BOLD responses.

Correlation Between Psychological Measures and BOLD Responses

We also tested whether individual differences in BOLD responses correlated with the GSP participants’ psychological measures. None of the clinical measures—the Leibowitz Social Anxiety Scale, the Beck Depression Inventory scores, or the Spielberger (STAI) state–anxiety inventory scores—were significantly correlated with neural responses in any of the brain regions.

Discussion

To the best of our knowledge, this study is the first to directly examine striatal function in GSP using a well-established fMRI probe of striatal functioning. Consistent with our hypothesis that GSP subjects would fail to recruit striatal structures during performance on the SRT task compared with healthy control subjects, we found a significantly lower BOLD response in the left caudate nucleus of GSP subjects during performance on the SRT task than in healthy control subjects. This difference in neural response between the groups was found in the context of similar behavioral performance (i.e., reaction time and accuracy) across the two groups. Because dopamine is the key neurotransmitter in striatal structures (Mathew et al 2001), our findings of striatal dysfunction in GSP are convergent with previous clinical and neuroimaging studies in GSP showing abnormal dopaminergic functioning (Schneier et al 2000; Tiihonen et al 1997).

We consider two possible explanations of how striatal dysfunction may ultimately be related to clinical symptoms and pathophysiology of GSP. First, Argyropoulos et al (2001) suggest that a genetic predisposition to striatal dysfunction might be important in impaired social motor functions in GSP subjects (e.g., smiling, eye movements, and speech). These motor function impairments may lead to negative cognitions related to the capacity to cope with novel social situations. These negative cognitions may, in turn, lead to greater levels of anxiety and, correspondingly, to social avoidance. Future studies of children at risk for development of GSP, for example, behaviorally inhibited children (Biederman et al 2001), are required to test whether the striatal dysfunction is present before onset of social phobia symptoms. Also, examination of striatal function in GSP subjects who have responded to treatment may be useful to delineate whether striatal dysfunction is a state or trait phenomena.

Second, striatal dysfunction in GSP may be linked to the information processing biases found in GSP, which include interpreting external social events negatively, detecting and attending excessively to negative responses from other people, and selectively recalling negative aspects of social interactions (Clark and McManus 2002). Recently, an elegant study demonstrated that within the striatum there were dissociable roles of the putamen and caudate nucleus during processing of an instrumental conditioning task (O’Doherty et al 2004). The putamen was involved in prediction of future reward, whereas the left caudate nucleus was involved in maintaining of action–reward outcome information to enable better responses to be chosen more frequently. In our study, we did not find significant differences between GSP subjects and control subjects in activation of the putamen during implicit learning. This might suggest that GSP subjects have intact putamen functioning during implicit learning and deficient recruitment of caudate nucleus. We speculate that the left caudate nucleus dysfunction might be one of the mechanisms that explain the information biases in GSP. Specifically, the GSP subjects’ caudate dysfunction might impair action–reward sequencing of social behaviors and the recollection of the successful social outcomes. Future fMRI studies of GSP subjects should consider examining neural activation patterns during an instrumental conditioning paradigm to test this hypothesis formally.

The SRT task paradigm used in this study has demonstrated differential activation of striatal structures in groups of mental disorders that are clustered together in the DSM based on common symptoms of anxiety (OCD, Rauch et al 1997a; specific phobia, Martis et al 2004); our study in GSP was powered to detect similar effect size differences between patients and control subjects. Comparable to our study, animal phobia subjects had similar behavioral performance on the SRT task, but unlike our
study, animal phobia subjects did not show evidence of striatal dysfunction. Our results are similar to previous SRT task neuroimaging studies in OCD (Rauch et al 1997a) and Tourette’s syndrome (Rauch et al 2001) that have demonstrated reduced striatal activation in the context of equivalent behavioral performance. Future imaging studies are required to compare directly striatal functioning across mental disorders.

Rauch et al (1997a) have suggested that because OCD subjects have similar behavioral performance on the implicit learning task but show reduced activation in the striatum and greater activation in the medial temporal lobe, OCD subjects may be utilizing explicit memory systems to “compensate” for the striatal dysfunction (Deckersbach et al 2002; Rauch et al 1997a). There is accumulating evidence that healthy subjects without medical or psychiatric disease also utilize the hippocampus during implicit learning (Schendan et al 2003). We did not find any regions that had greater neural activation in the GSP subject compared to healthy control subjects while processing the implicit learning task. It is noteworthy that similar to our study in GSP subjects, Tourette’s syndrome study participants also did not show greater

Figure 3. Whole-brain analysis demonstrating brain regions where the implicit learning (IL) versus random (R) contrast in blood oxygen level-dependent (BOLD) responses differed significantly between the generalized social phobia (GSP) and healthy control (HC) groups (the Group by Condition interaction effect). Mean BOLD responses for the IL, R, and IL versus R conditions are presented including the 95% confidence intervals for the IL versus R contrast.
activation of temporal regions compared with healthy control subjects while processing the implicit learning task (Rauch et al 2001). Among the GSP participants, however, degree of implicit learning (IRs) was associated with greater BOLD responses in a number of extrastriatal regions. No such associations were found with the healthy control subjects. These findings suggest that GSP subjects are recruiting different neural networks compared with healthy control subjects to have similar levels of performance on the IL task.

It is important to note that although the SRT task is an excellent probe of striatal functioning, this task also activates numerous other brain regions, including motor regions, frontal lobes, insular cortex, parietal lobes, and cerebellum (Grafton et al 1995; Thomas et al 2004). The extrastriatal regions activated during the implicit learning task in GSP subjects and healthy control subjects (Table 1) have also been found to be associated with implicit learning in previous neuroimaging studies (Rauch et al 1997b; Thomas et al 1997).

The GSP subjects also demonstrated significantly reduced BOLD response during implicit sequence learning in contrast to the random condition in bilateral insula and left inferior parietal lobe. The inferior parietal lobe maintains bidirectional connections to dorsolateral prefrontal and anterior insular cortex and has been implicated in a number of cognitive processes. These include sustained, and possibly selective, attention (Coulil et al 1996), switching from task-relevant local to global targets (Fink et al 1996), voluntary attentional control (Hopfinger et al 2000), as well as the distinction between task-irrelevant and task-relevant events (Downar et al 2001). Thus, this area may be critical for the extraction and selection of task-relevant information and has been implicated in inhibitory control with a number of paradigms (Garavan et al 1999). The precise role of the inferior parietal lobe in the genesis and maintenance of social anxiety symptoms should be further explored.

Previous studies in healthy subjects have also demonstrated activation of the insular cortex during the implicit learning task (Thomas et al 2004), and our findings of bilateral insula activation differences between GSP and healthy control subjects suggest that this region may be affected in GSP. In contrast to our study, which found decreased activation of the insula in GSP subjects compared with healthy control subjects during implicit learning, previous work has found greater activity in the insula in GSP subjects compared with healthy control subjects while anticipating a public-speaking task and viewing angry human faces in contrast to neutral human faces (Lorberbaum et al 2004; Straube et al 2004). It is possible that these differences in insula activity across studies in GSP may be explained by the fact that our study of implicit sequence learning was a cognitive task that was not aimed at symptom provocation study, whereas the anticipation of public-speaking and viewing angry faces are likely to increase anxiety, or at least more strongly engage subjects emotionally. Convergent with previous literature, our findings suggest that GSP is associated with general dysfunction in the insular cortex.

Three main limitations of our study should be considered. First, the study used a modest number of subjects that may have precluded finding smaller effect size differences between GSP subjects and healthy control subjects. Although this is true, the power of the study was similar to previous neuroimaging studies with the SRT task (Martis et al 2004; Rauch et al 1997a). The modest number of subjects is likely the reason why there was no significant relationship found between the psychological measures and neural responses. Future studies should consider including a larger number of subjects to determine whether psychological measures are associated with IL-related neural response. Second, although striatal activation is believed to contribute to implicit learning, activation of this brain area in the context of the SRT task could also be related to faster response rate in the implicit learning versus the random condition. This is a general limitation of the SRT task fMRI paradigm and does not explain the group differences found in our study. Finally, GSP subjects had higher depressive symptoms compared with control subjects. It is possible that some of the neural differences found between the clinical and control groups might be due to higher depressive symptoms rather than GSP symptoms. Although this is possible, supplementary analysis of non-comorbid social phobia subjects versus healthy control subjects showed a similar pattern of results to those in the whole sample for the left caudate where the key group difference was identified. Also, epidemiologic studies have repeatedly demonstrated that approximately 80% of adults with GSP have at least one other comorbid mental disorder diagnosis (Kessler 2005a; Magee et al 1996) suggesting that the subjects in our sample who had the primary diagnosis of GSP but had some comorbidities not deemed to be clinical priority, were representative of people with GSP in the community.

In conclusion, this study is the first to examine striatal functioning in GSP using fMRI. Consistent with previous literature demonstrating altered dopaminergic function in GSP, we found evidence for striatal dysfunction using a well-established probe of striatal functioning. In particular, we hypothesize that abnormal left caudate function may contribute to the information biases observed in GSP, wherein GSP subjects are unable to maintain the information of behaviors that led to socially rewarding outcomes or the recollection of these outcomes. Further examination of the neural correlates of GSP will facilitate the understanding of pathophysiologic mechanisms associated with this disabling anxiety disorder.

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