Research report

Differential modulation of neural activity throughout the distributed neural system for face perception in patients with Social Phobia and healthy subjects

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Abstract

Social Phobia (SP) is a marked and persistent fear of social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Faces of others are perceived as threatening by social phobic patients (SPP). To investigate how face processing is altered in the distributed neural system for face perception in Social Phobia, we designed an event-related fMRI study in which Healthy Controls (HC) and SPP were presented with angry, fearful, disgusted, happy and neutral faces and scrambled pictures (visual baseline). As compared to HC, SPP showed increased neural activity not only in regions involved in emotional processing including left amygdala and insula, as expected from previous reports, but also in the bilateral superior temporal sulcus (STS), a part of the core system for face perception that is involved in the evaluation of expression and personal traits. In addition SPP showed a significantly weaker activation in the left fusiform gyrus, left dorsolateral prefrontal cortex, and bilateral intraparietal sulcus as compared to HC. These effects were found not only in response to emotional faces but also to neutral faces as compared to scrambled pictures. Thus, SPP showed enhanced activity in brain areas related to processing of information about emotional expression and personality traits. In contrast, brain activity was decreased in areas for attention and for processing other information from the face, perhaps as a result of a feeling of wariness.

These results indicate a differential modulation of neural activity throughout the different parts of the distributed neural system for face perception in SPP as compared to HC.

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1. Introduction

Faces are perhaps the most prominent social cue [30,31]. Social Phobia patients (SPP) process faces differently from healthy control (HC) subjects. According to the Diagnostic and Statistic Manual of Psychiatric Disorders-IV TR [4], Social Phobia (SP) is ‘a marked and persistent fear of social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others’. A significant behavioral effect in SPP while processing social relevant stimuli, and in particular toward face processing, has been previously demonstrated. Specifically, behavioral studies have reported that SPP tend to judge neutral faces as negative [56], to remember critical faces better than accepting ones [39], and to scan faces with a different pattern of eye movements than that used by HC [32]. These results suggest that SPP view still images of faces with a negative or wary attitude.

Actually, several functional studies have investigated face perception in SPP. Birbaumer et al. [10] described an increased response in the amygdala in SPP while processing neutral human faces. A study by Stein et al. [48] showed stronger activation of left allocortex (including the amygdala and uncus) in SPP as compared to HC while watching angry and contemptuous faces as compared to happy faces. Other studies have shown that the degree of amygdala activation during the perception of faces with negative
expressions is directly correlated with the severity of symptoms in SPP [43], and even with the degree of normal social anxiety in healthy subjects [33,49]. Finally, a differential temporal dynamic pattern of activity was found in SPP as compared to HC in the amygdala bilaterally but not in the fusiform gyrus while subjects viewed faces with different emotional expressions (happy, fearful, or angry) [13]. Other studies examined other areas of the limbic system and showed, for example, a higher activation of the anterior cingulate cortex in SPP in response to disgust faces as compared to neutral faces [6]. One event-related study compared angry vs. neutral faces and showed hyperactivation of the insula in SPP as compared to HC [50].

Altogether, these studies suggest that the insula, the amygdala, and other limbic structures play a fundamental role in how SPP process faces differently as compared to controls. Studies in healthy volunteers indicate that the amygdala is involved in the recognition of face expression – particularly fear – in evaluating personality traits, in particular trustworthiness, and in maintaining a vigilant or wary state [1,9,12,23,30,41,52,55]. The insula is recruited during the perception of disgust and in strong emotions – both negative, such as feeling cheated [46], and positive emotions, such as romantic [7] and maternal [36] love – perhaps related to its role in representing visceral sensation [17].

Because the amygdala, insula, and other limbic structures play a role in the emotional response to faces, these brain regions are considered to be a component of the ‘extended system’ for face perception, which includes non-visual areas extracting information from faces [25,30,31]. Previous studies of face processing in SPP have focused their attention on this part of the distributed neural system for face perception. Along with the ‘extended system’ for extracting additional face information, including emotions, the neural system for face perception includes also a ‘core system’ for visual face processing. The core system can be further divided into components that are primarily involved in the recognition of identity (fusiform gyrus), or in the perception of changeable aspects of faces, such as eye gaze and emotional expression. Judgments of personality traits, such as trustworthiness [54], appear to involve more the component for perception of changeable aspects, namely the superior temporal sulcus (STS), perhaps because of its role in evaluating expression [22] and intention [3,26].

Previous fMRI studies of Social Phobia that used face stimuli were not intended to investigate abnormalities in face perception but, rather, because they are effective stimuli for evoking social threat.

Therefore, we decided to investigate the neural basis of altered face processing in SPP in the broader context of the distributed neural system for face perception by adopting a fast event-related experiment in which subjects viewed faces with different emotional expressions, including a neutral expression, and scrambled pictures for a low-level visual baseline.

Results revealed a redistributed activity in different parts of the face perception system in SPP. Patients with SPP showed stronger activity in components of the system that are involved more in the evaluation of expression and the formation of inferences about personal traits, in addition to stronger activity in areas associated with emotional response, and weaker activity in other components associated with attention to faces and recognition of identity.

2. Materials and methods

2.1. Subjects

2.1.1. Social Phobic patients

Eight right-handed subjects (4M/4F) (mean age 39 ± 7 years) with a diagnosis of Social Phobia according to the DSM-IV-TR [4] criteria were recruited. SPP were without psychiatric comorbidity and other medical conditions. No patient was receiving any pharmacological or psychotherapeutic treatment at the time of the fMRI session and at the time of the fMRI session.

2.1.2. Healthy controls

Seven right-handed healthy control subjects (4M/3F) (mean age 30 ± 7 years) were recruited as well. HC subjects did not have any psychiatric or medical disorders and were not taking any medications at the time of recruitment or at the time of the fMRI session.

After the study procedure and risk involved have been explained, all subjects gave their written informed consent under a protocol approved by the Ethical Committee of the University of Pisa.

All subjects received medical, neurological, and psychiatric examinations, and a structural MRI to exclude any disorders that could affect brain function (other than Social Phobia). During the psychiatric interview, a trained physician administered the Leibowitz Scale for Social Phobia (LSSP) [37]. Furthermore, subjects completed the Interaction Anxiety Scale (IAS) [35] and the Anxiety Sensitivity Scale (ASS) [34] to assess the degree of social anxiety in both healthy subjects and social phobic patients. Before and after the fMRI session, each subject completed the State-Trait-Anxiety-Scale (STAI-x1) [47] to assess state anxiety.

2.2. Stimuli

Stimuli were faces and nonsense pictures. Faces with emotional expressions belonging to 10 different subjects were taken from Ekman and Friesen’s standardised set [21]. Nonsense (scrambled) pictures were phase-scrambled images of these faces and, consequently, matched the faces in terms of spatial frequencies, luminance, and contrast. We selected faces with angry, fearful, disgust, and happy expressions as well as faces with neutral expression.

2.3. Task

During the fMRI sessions the participants performed a one-back repetition detection task based on face identity. For scrambled pictures, a one-back repetition detection task was performed as well in order to control for sensorimotor activations. During the one-back repetition detection task for faces subjects indicated whether each face image was of same person in the immediately preceding face image by pressing a button in the right (yes) or left (no) hand. For scrambled pictures subjects indicated whether successive pictures were identical or not. Subjects were instructed to respond during the interstimulus interval. We used a fast event-related design in which each stimulus was presented for 2000 ms with an interstimulus interval of 1500 ms. Faces and scrambled pictures were presented in a pseudo-randomized order: each face with an emotional expression was presented after two to four faces with a neutral one.

2.4. Imaging

Responses to different faces and scrambled pictures were measured using blood oxygen level dependent (BOLD) contrast fMRI with the acquisition of T2*-weighted gradient echo-planar images in a 1.5T GE scanner (General Electric, Milwaukee, WI). In each time series, the whole brain volume was acquired 188 times, each volume consisting of 26 contiguous 5-mm-thick axial slices (TR = 2000 ms, TE = 40 ms, flip angle 90°, FOV = 24 cm, resolution = 64 × 64 pixels).

Eight time series were obtained in each fMRI session. Each time series began with 30 s of rest before the presentation of the stimuli. In each time series, two blocks of 38 face stimuli were presented. The two face blocks were separated by an interval of 15 s of rest, a block of eight scrambled pictures, and another 15 s interval of rest.

High-resolution T1-weighted spoiled gradient recall images (1.2-mm-thick axial slices, TR = 12.1 ms, TE = 5.22 ms, flip angle = 20°, FOV = 24 cm, resolution = 256 × 256 pixels) were obtained for each subject to provide detailed brain anatomy.

2.5. Statistics

We used AFNI (Analysis of Functional NeuroImages, http://afni.nimh.nih.gov/) [16] for data analysis. After spatial registration and slice time correction, we normalized the time series for each voxel to the mean, and smoothed the data spatially (Gaussian kernel 8 mm half-width). Image data were then analyzed with multiple regressions. Six regressors of interest were used to model the hemodynamic response for each face expression (including neutral faces) and for the scrambled pictures. We also used 6 regressors of no-interest to factor out the effect of head movements and 16 regressors of no-interest for the linear and quadratic trends in each time series. The β-weight for each of regressor of interest was used as an index of the magnitude of response to the corresponding stimulus relative to the baseline. An omnibus test of the combined significance of all regressors for responses to faces was calculated to identify voxels that were face-responsive.

A group analysis was performed to test the significance of the interaction between the contrast for faces vs. scrambled pictures and group (SPP and HC) using
r-tests. To perform the group analysis, the maps of response magnitudes for the comparisons for faces vs. scrambled were converted to Talairach space [51]. r-Tests are random effects tests in which each subject accounts for a single degree of freedom. Significant clusters were defined as contiguous voxels with \( p < 0.01 \) (uncorrected) and a volume >250 \( \mu l \).

We also performed a region of interest analysis to assess differences in activations in the two groups in the fusiform gyrus and superior temporal sulcus. The temporal fusiform gyrus was defined on the high-resolution anatomical image merged across subjects bounded laterally by the occipito-temporal sulcus and medially by the collateral sulcus, and bounded anteriorly by the plane 2 cm posterior to the anterior commissure and posteriorly by the plane 7 cm posterior to the anterior commissure. The STS was defined as the full length of that sulcus on the same high-resolution anatomical image merged across subjects. The functional ROI within the fusiform gyrus was defined as those voxels that showed a significant response to faces, relative to the no stimulus baseline, in both SPP and HC (\( p < 0.01 \), volume >250 \( \mu l \)). The functional ROI in the superior temporal sulcus was defined as those voxels that showed a significant difference between the response to emotional and neutral faces in both SPP and HC (\( p < 0.01 \), volume >250 \( \mu l \)).

3. Results

3.1. Clinical scale results

SPP as compared to HC had significantly higher levels of social anxiety, as assessed with the IAS (mean \( \pm \) S.E.: 49.3 \( \pm \) 1.42 vs. 33.7 \( \pm \) 0.71, \( p < 0.01 \)), the AAS (mean \( \pm \) S.E.: 40.7 \( \pm \) 1.41 vs. 23.5 \( \pm \) 2.20, \( p < 0.01 \)), and the LSSP (mean \( \pm \) S.E.: 69.6 \( \pm \) 1.01 vs. 24.7 \( \pm \) 1.25, \( p < 0.01 \)). No differences were found in state anxiety, as assessed by STAI-x1, between pre- and post-scan sessions, and between the two groups of subjects (mean \( \pm \) S.E.: HC-pre 36.3 \( \pm \) 0.9; HC-post 38.4 \( \pm \) 1.3; SPP-pre 35.6 \( \pm \) 1.2; SPP-post 38.7 \( \pm \) 1.0; HC-pre vs. HC-post, \( p = 0.20 \); SPP-pre vs. SPP-post, \( p = 0.06 \); HC-pre vs. SPP-pre, \( p = 0.67 \); HC-post vs. SPP-post, \( p = 0.84 \)). Although the SPP had higher scores than the HC on measures of social anxiety, as expected, the lack of differences for indices of state anxiety in the two groups, suggests that the measured differences in brain response were not due to non-specific differences in arousal.

3.2. Behavioral results

No significant differences between the two groups were found in reaction time or accuracy in the one-back recognition detection task on faces (reaction time (mean \( \pm \) S.E.): SPP = 1120 \( \pm \) 110 ms; HC = 1031 \( \pm \) 112 ms, \( p = 0.08 \); accuracy (mean \( \pm \) S.E.): SPP = 92.37 \( \pm \) 0.50%; HC = 93.53 \( \pm \) 0.58%, \( p = 0.15 \)). As the task is quite simple, performance was at ceiling levels in both groups. The lack of differences on accuracy and response times for the one-back repetition detection task in the two groups suggests that the differences in brain response are not due to differences in behavioral performance.

3.3. fMRI results

The two groups showed a similar pattern of activation for faces as compared to scrambled pictures involving areas of the core system for face perception, such as the fusiform gyrus and the superior temporal sulcus, as well as of the extended system, such as the insula, the intraparietal sulcus, and the prefrontal cortex (Fig. 1).

The between-group analysis showed a stronger response for faces than to scrambled pictures in SPP as compared to HC in the left amygdala, left insula, bilateral STS, as well as loci in right parietal and left medial occipital cortex. A stronger response in HC than in SPP was found in the intraparietal sulcus bilaterally, the left prefrontal cortex, the left medial frontal gyrus, and the left fusiform gyrus (Table 1 and Fig. 2).

3.4. ROI analysis results

3.4.1. Fusiform gyrus

In the right fusiform gyrus (Talairach coordinates: 38, –59, –10; volume: 1077 \( \mu l \)), as expected, we found increased activation for faces as compared to scrambled pictures in both HC and SPP. Moreover, emotional faces activated the right fusiform gyrus more than neutral ones. A similar pattern was also found in the left fusiform gyrus (–42, –56, –7.5; 2805 \( \mu l \)) in HC. In SPP the responses to emotional faces in the left fusiform area was stronger than the responses to neutral faces and scrambled images but the responses to neutral faces and scrambled images did not differ from each other (Fig. 3). No differences were found between the groups for the patterns of differential responses to stimuli in these regions.

3.4.2. STS

The locations of these ROIs in the STS (Talairach coordinates: 47, –52, 16; volume: 123 \( \mu l \); and –52, –35, 5; volume: 621 \( \mu l \)) were similar to regions identified in previous studies as showing a stronger response for faces with emotional expressions [22,54]. The pattern of differential responses to emotional faces, neutral faces,
Table 1
Areas with a significant contrast between the differential responses to faces and scrambled pictures in SPP and HC subjects (p < 0.01; cluster volume >250 μl)

<table>
<thead>
<tr>
<th>Location</th>
<th>Brodmann area</th>
<th>Hemisphere</th>
<th>Talairach coordinates (x, y, z)</th>
<th>Volume</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPP &gt; HC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuneus</td>
<td>17</td>
<td>L</td>
<td>-1, -84, 10</td>
<td>577</td>
<td>3.193</td>
</tr>
<tr>
<td>Parietal</td>
<td>31</td>
<td>R</td>
<td>-24, -42, 29</td>
<td>526</td>
<td>3.835</td>
</tr>
<tr>
<td>Superior temporal sulcus</td>
<td>41</td>
<td>R</td>
<td>-34, -44, 10</td>
<td>286</td>
<td>2.977</td>
</tr>
<tr>
<td>Amygdala</td>
<td>41</td>
<td>L</td>
<td>-41, -34, 9</td>
<td>1579</td>
<td>4.06</td>
</tr>
<tr>
<td>Insula/inferior frontal gyrus</td>
<td>13</td>
<td>L</td>
<td>-26, -5, -14</td>
<td>335</td>
<td>3.644</td>
</tr>
<tr>
<td><strong>HC &gt; SPP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraparietal sulcus</td>
<td>7</td>
<td>R</td>
<td>35, -53, 47</td>
<td>1003</td>
<td>3.129</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>7</td>
<td>L</td>
<td>-35, -56, 44</td>
<td>401</td>
<td>2.966</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>37</td>
<td>L</td>
<td>-37, -41, -9</td>
<td>557</td>
<td>3.286</td>
</tr>
</tbody>
</table>

The Z-score is reported for the maximum in each cluster.

Fig. 2. Sagittal and coronal images from group analysis for the interaction between the contrast for faces vs. scrambled pictures and group (HC vs. SPP) are shown. The yellow lines in the sagittal images correspond to the locations of the coronal slices and, similarly, the yellow line in the coronal slice indicates the location of the sagittal section. Significant clusters were defined as contiguous voxels with p < 0.01 (t-test uncorrected) and cluster volume >250 μl. 1: superior temporal sulcus; 2: dorsolateral prefrontal cortex; 3: fusiform gyrus; 4-7: intraparietal sulcus; 5: amygdala; 6: insula.

and scrambled images did not differ significantly for SPP and HC subjects. In these regions, we did not find any differential patterns of response between the two groups for each type of stimulus.

4. Discussion

The results showed a differential response to faces throughout the distributed neural system for face perception [25,30,31] in SPP, as compared to HC. Specifically, the response to faces in SPP was stronger as compared to HC in bilaterally STS, the core system perceptual area that has been associated with perception of expression [22,54], the evaluation of the intentions and personality traits of others [26,55], and more generally with social evaluation of others [3]. Activation was also stronger in areas that are associated with emotional responses, namely the left insula and left amygdala. By contrast, the response to faces in SPP was weaker than HC in the left fusiform gyrus, the core system perceptual area associated with perception of identity, the intraparietal sulcus bilaterally, and the left prefrontal cortex. These effects were not limited to emotional expressions, but were also seen for the responses to faces with neutral expressions. These results suggest a specific pattern of activity in different parts of the distributed neural system for face perception in Social Phobia. In fact, SPP showed enhanced processing of information about emotional expression and personality traits, that supports the hypothesis of a hypervigilant and possibly wary coping with socially relevant stimuli in SPP, as suggested by previous behavioral [5,32,39,56] and functional studies [38,50]. On the contrary, the response in areas for attention and processing...
other information from the face was weaker in SPP, likely due to an avoidant response associated with increased wariness also consistent with previous behavioral studies [32].

The location of the STS region that responded more strongly to faces in SPP is consistent with loci that have been reported for perception of facial expression [22,54]. Stronger activation of the STS in SPP than in HC was also found in a study by Straube et al. [50] comparing angry vs. neutral faces in an implicit task. STS is also activated during explicit judgment of the trustworthiness of faces [55]. More generally, this region of the STS is associated with the perception of biological motion and the evaluation of intentions associated with others’ actions [8,11,14,26,28,40]. Augmented processing in this region, therefore, may reflect increased social evaluation of the face.

Increased response in the amygdala and insula in SPP has also been reported in earlier studies using different experimental designs [10,15,38,43,48,50]. HC who are anxiety-prone also show stronger responses to faces in these regions than do less anxious HC [33,49]. Amygdala plays a central role in several emotional processes [2,11,44,57]. In particular, it is associated with fear processing and response to potentially threatening stimuli that may require enhanced vigilance [2,12,20,27,44,52]. The amygdala shows a stronger response to the faces of strangers than to personally familiar faces, suggesting that it plays a role in the normal, guarded reaction to unfamiliar others [19,24,27]. Finally, a recent contribution by Benuzzi et al. [9] suggested that the amygdala is involved in orienting attention to process socially relevant facial parts. The insula is also associated with strong emotional responses, such as disgust [45,53] as well as the representation of visceral sensation [17] and might play a role in several anxiety disorders [42]. These results suggest that the response to faces in SPP is associated with negative emotions and a guarded or wary attitude.

In parallel with increased activity in areas associated with social evaluation, negative emotions, and a guarded or wary attitude, face perception in SPP lead to a decreased activity in areas associated with attention and other aspects of face processing. In a study of anticipatory anxiety for public speaking in SPP, Lorberbaum et al. [38] also found decreased activity in areas associated with attention, namely left dorsolateral prefrontal cortex, the left anterior cingulate and left medial prefrontal cortex. In our study, face perception in SPP was associated with decreased activity in parietal and frontal areas, as well as in the part of left fusiform cortex.

Previous studies of face perception in SPP did not report a decreased response in fusiform cortex and attention-related areas. This difference may be due to our use of a low-level baseline specifically viewing scrambled pictures. Previous studies compared responses to faces with different expressions to each other (e.g. Stein et al. [48] and Amir et al. [6]), rather than the response to faces as compared to a baseline with no faces. We found, however, that even neutral faces evoked the same pattern of altered responses in SPP, which we would not have detected if we had use faces for control baseline instead of the scrambled pictures low-level baseline. Indeed others have also shown that neutral faces evoke more amygdala activity in SPP than in HC [15]. The decreased activity in SPP in the fusiform gyrus, intraparietal sulcus, and dorsolateral prefrontal cortex, therefore, was not evident in the difference between
activity evoked by expressive and neutral faces. We also used a rapid event-related experimental design with jittered presentation rates that might have minimized adaptation effects.

Patients with Social Phobia scan faces with different patterns of eye movements as compared to those found in HC [32]. The decreased response to faces in fusiform cortex, therefore, may also be due in part to differences in scanning patterns. Autistic patients, for example, have a reduced response to faces in the fusiform gyrus that may be attributable to reduced fixation of the eye region [18,29]. In this fMRI study, we did not monitor eye movements while subjects viewed our stimuli and, therefore, we cannot rule out this account. However, the SPP did not differ from the HC on accuracy on the one-back repetition task, suggesting that they examined faces long enough to assess correctly their identity.

In conclusion, our results show that altered face processing in SPP is associated with both enhanced activity in some parts of the distributed system for face perception, reflecting increased vigilance and social evaluation with negative emotion, and decreased activity in other parts, reflecting an avoidance response. Thus, the abnormal processing is not restricted to an altered emotional response but also involves alterations of perception, cognition, and attention, suggesting that clinical evaluation and therapeutic approaches for SPP should focus on more than just the emotional aspects.

Conflict of interest

None.

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References