First publ. in: Biological Psychiatry 56 (2004), pp. 921-930

Effect of Task Conditions on Brain Responses to Threatening Faces in Social Phobics: An Event-Related Functional Magnetic Resonance Imaging Study

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Background: *The aim of this study was to identify brain activation to socially threatening stimuli in social phobic subjects during different experimental conditions.*

Methods: *With event-related functional magnetic resonance imaging, brain activation to photographs and schematic pictures depicting angry or neutral facial expressions was measured in social phobic subjects and healthy control subjects, while subjects assessed either emotional expression (angry vs. neutral; explicit task) or picture type (photographic vs. schematic; implicit task).*

Results: *Compared with control subjects, phobics showed greater responses to angry than to neutral photographic faces in the insula regardless of task, whereas amygdala, parahippocampal gyrus, and extrastriate visual cortex were more strongly activated only during the implicit task. Phobics, in contrast to control subjects, showed similar activation patterns during both tasks. For schematic angry versus neutral faces, activation of insula and extrastriate visual cortex was found in phobics, but not in control subjects, during both tasks.*

Conclusions: *Differences between social phobics and control subjects in brain responses to socially threatening faces are most pronounced when facial expression is task-irrelevant. Phobics intensively process angry (photographic as well as schematic) facial expressions, regardless of whether this is required. The insula plays a unique role in the processing of threat signals by social phobics.*

Key Words: Social phobia, fMRI, insula, emotion, task conditions

Social phobia is characterized by fear of social interactions and includes a hypersensitivity to signals of social threat, such as angry facial expressions (e.g., Lundh and Öst 1996; Mogg and Bradley 2002; for reviews see Bell et al 1999; Heinrichs and Hofmann 2001; Li et al 2001). In the search for neuronal correlates of this disorder, several functional imaging studies have demonstrated anomalies in responses of the amygdala in social phobics. By means of positron emission tomography (PET), increased amygdalar cerebral blood flow during real or anticipated public speaking was shown in social phobics compared with healthy control subjects (Furmark et al 2002; Tillfors et al 2001, 2002). With functional magnetic resonance imaging (fMRI), increased activation of the amygdala was found in social phobics in response to pictures depicting angry and contemptuous (Stein et al 2002) or neutral facial expressions (Birbaumer et al 1998; Veit et al 2002) and during classical conditioning (Schneider et al 1999). These results support the widely recognized role of the amygdala in the processing of threat-relevant stimuli (Büchel and Dolan 2000; LeDoux 1998; Öhman and Mineka 2001).

In contrast to the results for the amygdala, the involvement of further brain areas in the processing of socially threatening stimuli is less clear. Recently, a block design fMRI study with social phobics found increased activation of medial temporal lobe areas, including the amygdala and parahippocampal gyrus and dorsomedial prefrontal cortex (DMPFC), specifically to angry and contemptuous faces (Stein et al 2002). The enhanced responsiveness of these areas was interpreted to reflect increased emotional processing of threatening faces. Remarkably, there was no evidence of increased activation in other brain areas that are supposed to be important for the processing of threatening visual stimuli and the mediation of fear, such as the insula or extrastriate visual cortex (for reviews see Critchley 2003; Haxby et al 2002; Phan et al 2002). For example, in a recent event-related fMRI study, we found a significant response of the insula to phobia-relevant pictures in animal phobics (Dilger et al 2003). Rauch et al (1997) demonstrated insula activation during symptom provocation across different anxiety disorders (obsessive-compulsive disorder, simple phobia, posttraumatic stress disorder). Current theories propose a special role of the insula for emotional experiences, especially in relation to sensed dangers (Critchley 2003; Damasio et al 2000).

Furthermore, studies with healthy subjects showed a strong influence of the emotional valence of visual stimuli, such as facial expressions, on activation of extrastriate visual cortex. Most consistently, enhanced responses to unpleasant versus neutral faces were described in the fusiform gyrus (e.g., Keightley et al 2003; Vuilleumier et al 2001; Winston et al 2003) and superior temporal sulcus (STS) (e.g., LaBar et al 2003; Narumoto et al 2001; Winston et al 2002, 2003). The posterior fusiform gyrus is strongly involved in face detection and recognition (e.g., Joseph 2001; Kanwisher et al 1997; Vuilleumier et al 2003), and the posterior STS is implicated in the evaluation of the social relevance of stimuli (for reviews, see Allison et al 2000; Haxby et al 2002). The specific involvement of these areas in the processing of social threat signals in social phobics remains to be elucidated.

The present study aimed at a detailed examination of brain activation to angry versus neutral facial expressions in social phobics by using 1) an event-related fMRI design; 2) a priori–defined brain regions of interest (ROIs); 3) different kinds of facial pictures; and 4) different task instructions.

Event-related designs permit the presentation of stimuli in random order and, therefore, a reduction of anticipation effects. Furthermore, they represent adequate experimental designs for

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Received June 15, 2004; revised September 17, 2004; accepted September 22, 2004.

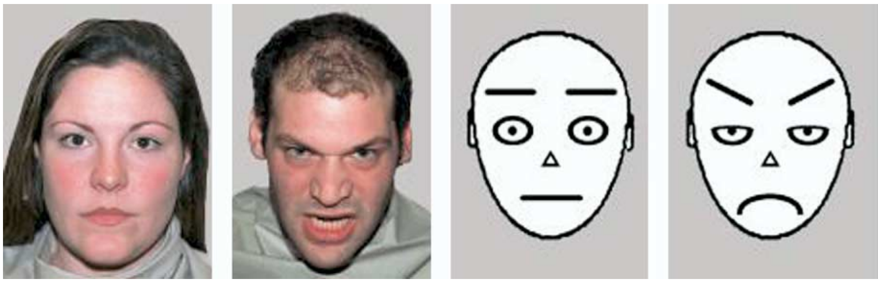

Figure 1. Examples of stimuli. From left to right: neutral photographic, angry photographic, neutral schematic, angry schematic.

the investigation of specific tasks, such as the discrimination of emotional expression. Besides these advantages, event-related designs, however, show a decreased sensitivity in the detection of functional activation compared with block designs (Liu and Frank 2004).

The ROIs were selected a priori to increase the chance of detecting significant responses in brain areas that have been shown to be involved in the processing of threatening visual information in healthy control subjects or phobic subjects, such as DMPFC, insula, amygdala, parahippocampal gyrus, fusiform gyrus, and STS (e.g., Critchley et al 2002; Dilger et al 2003; Keightley et al 2003; Paquette et al 2003; Stein et al 2002; Vuilleumeir et al 2001; Winston et al 2003).

Besides photographs of faces, we presented schematic facial pictures. The schematic faces used were prototypic line drawings of facial expressions, which provide enough information for the recognition of emotional expression (Öhman et al 2001). We examined whether such simplified stimuli elicit differential brain responses in social phobics relative to healthy control subjects and whether potential effects, such as specific activations in amygdala, insula, or extrastriate areas, correspond to results found for photographic faces.

Most importantly, we varied the task condition. In healthy subjects, task conditions have been demonstrated to affect brain activation to emotional stimuli (e.g., Critchley et al 2000; Keightley et al 2003; Lange et al 2003). Gur et al (2002) showed that task instructions that focused attention either to the emotional expression or to nonemotional aspects (gender) of faces led to task-specific anomalies in brain activation of schizophrenic patients compared with healthy control subjects (hypoactivation in limbic areas in patients during the emotional task). Accordingly, we used two task conditions to modify the focus of attention. In the first condition, subjects had to attend explicitly to the emotional expression of faces (explicit task), whereas the second condition, which required identifying whether the stimulus was photographic or schematic, did not refer to the emotional content of stimuli (implicit task). Thus, we were able to examine the influence of the distinction between task-relevant and task-irrelevant threat stimuli on brain activation to these stimuli in social phobics compared with healthy control subjects.

Methods and Materials

Subjects

Ten subjects with social phobia (six female, four male; mean [SD] age 25.0 [3.3] years) and 10 healthy control subjects (six female, four male; aged 23.2 [3.9] years), all right-handed, provided written informed consent to volunteer in the study. All experimental procedures were approved by the ethics committee of the University of Jena. The participants were recruited by newspaper advertisement and by public announcements to the university student population. Subjects received 6 Euro per hour for participation. In addition, social phobics were offered a 10-session group training to improve their social competence (Hinsch and Pfingsten 2002). Fifty-four potential social phobic subjects were screened by means of a personal interview. According to the outcomes of a structured clinical interview (Wittchen et al 1997), 10 participants met the criteria of DSM-IV for social phobia but had no history of other Axis I or II disorders. Furthermore, accepted subjects had never received psychotropic medication, were not in therapy, and did not have any other major medical disorder. Their average score on the Social Phobia and Anxiety Inventory (SPAI; Turner et al 1989; German version, Fydrich 2002) was 89.7 (5.95). Control subjects, who were matched for age, gender, and level of education, had no current diagnosis or previous history of major disorders according to DSM-IV criteria. Their average score on the SPAI was 28.47 (12.83). Scores on the Beck Depression Inventory (German version, Hautzinger et al 1995) were higher in phobics than in control subjects (10.3 [6.5] vs. 3.9 [3.75]; $t = 2.6$; $p < .05$) but far below scores of clinical relevance.

Stimuli and Tasks

In the magnetic resonance scanner, subjects were exposed to pictures of photographic and schematic faces with either an angry or a neutral expression. The photographic faces comprised nine male and nine female faces, all Caucasian, and were taken from a standardized battery of facial expression stimuli (MacBrain Face Stimulus Set [see http://www.macbrain.org/faces/#faces]; see Figure 1 for examples). The set contained two pictures of each individual, one depicting an angry and one a neutral facial expression. The computer-generated schematic pictures of an angry and a neutral face (see Figure 1) were similar to those used by Öhman et al (2001). For each task condition, all photographic face stimuli were used twice, and each of the schematic faces was used 36 times, resulting in 36 faces for each category of facial expression (neutral photographic, angry photographic, neutral schematic, angry schematic). All faces were presented against the same grey background. Pictures were shown in random order with a back-projection screen on an overhead mirror for 1 sec each, with a stimulus onset asynchrony of 3.45 sec. Additionally, 36 null events (a fixation cross indistinguishable from the fixation cross seen during the interstimulus intervals; see Josephs and Henson 1999) were randomly intermixed into the run. Pictures were presented under two task conditions. In condition one, subjects were asked to determine whether a photographic or a schematic face was shown. In condition two, subjects had to decide which emotional expression (angry or neutral) was depicted in the picture. For judgment, subjects pressed one of two buttons of an optic fiber response box with either the first or the middle finger of the right hand. Accuracy of judgment was measured with Experimental Runtime System software (version 3.29; BeriSoft Corporation, Frankfurt/Main, Germany). Order of tasks, the two randomization schemes

Table 1. Task Performance: Descriptive Data

Condition	Phobics		Control Subjects	
	Implicit	Explicit	Implicit	Explicit
Correct Responses (%)				
Photographic angry	96.2 (3.6)	88.5 (9.7)	97.9 (2.4)	83.3 (10.4)
Photographic neutral	97.2 (3.0)	83.7 (12.9)	96.5 (3.5)	80.9 (13.4)
Schematic angry	96.5 (2.0)	87.8 (11.2)	97.6 (1.7)	83.3 (7.6)
Schematic neutral	98.6 (2.6)	93.4 (10.8)	97.5 (3.1)	90.6 (6.8)
Reaction Times (msec)				
Photographic angry	752.9 (58.6)	833.9 (48.9)	748.0 (54.7)	862.1 (59.4)
Photographic neutral	738.8 (55.8)	863.4 (53.3)	745.1 (54.3)	889.8 (39.8)
Schematic angry	727.9 (44.0)	826.2 (58.7)	736.3 (70.7)	856.8 (39.6)
Schematic neutral	721.4 (48.3)	796.6 (48.0)	743.4 (68.0)	827.4 (61.0)

Data are given as mean (SD)

of stimuli, and the assignment of response buttons to the relevant stimulus attributes were counterbalanced across subjects. After the fMRI session, participants rated all pictures according to a Likert scale, with nine choices to assess valence (1 = very unpleasant to 9 = very pleasant) and arousal (1 = not arousing to 9 = very arousing).

Reaction times, accuracy of task performance, and ratings were analyzed by repeated-measures analysis of variance (ANOVA) with SPSS software (version 10; SPSS, Chicago, Illinois). A probability level of $p < .05$ was considered statistically significant. All data presented in the text are expressed as means ± SEM. For analysis of reaction times and accuracy, two subjects of each group had to be excluded due to technical problems during registration of button presses.

fMRI Data Acquisition and Analysis

Scanning was performed in a 1.5-T magnetic resonance scanner ("Vision Plus"; Siemens Medical Systems, Erlangen, Germany). After acquisition of a high-resolution T1-weighted anatomical volume (192 slices, echo time [TE] = 6 msec, matrix = 256 × 256, voxel size = 1 × 1 × 1 mm), two runs (one per task) of T2*-weighted echo-planar images (EPIs) were measured (TE = 60 msec, flip angle = 90°, matrix = 64 × 64, field of view = 192 mm, repetition time = 2.3 sec). Each run comprised 275 volumes of 20 axial slices (thickness = 4 mm, gap = 1 mm, in-plane resolution = 3 × 3 mm). The volumes were acquired parallel to the lateral sulcus and covered the a priori–defined ROIs. Before imaging, a shimming procedure to improve field homogeneity was performed. Visual inspection of the EPI data revealed signal loss due to susceptibility artefacts in the inferior parts of the frontal cortex as well as in the anterior parts of the medial temporal lobe. These regions were not included in data analysis. The first four volumes of each run were discarded from analysis to ensure that steady-state tissue magnetization was reached.

Preprocessing and analysis of the functional data was performed with Brain Voyager 2000 software (version 4.9; Brain Innovation, Maastricht, The Netherlands). The volumes were realigned to the first volume to minimize the effects of head movements on data analysis. Further data preprocessing comprised a correction for slice time errors and spatial (8-mm full-width half-maximum isotropic Gaussian kernel) as well as temporal (high pass filter: 5 cycles per run) smoothing. Anatomical and functional images were coregistered and normalized to the Talairach space (Talairach and Tournoux 1988). Statistical analysis was performed by multiple linear regression of the signal time course at each voxel. The expected blood oxygen level–dependent (BOLD) signal change for each event type (= predictor) was modeled by a canonical hemodynamic response function (modified γ function; $\delta = 2.5$, $\tau = 1.25$). Within- and between-group statistical comparisons were conducted with a mixed-effect analysis, which considers intersubject variance and permits population-level inferences. In the first step, voxelwise statistical maps were generated, and the relevant, planned contrasts of predictor estimates (β weights) were computed for each individual. In the second step, group analysis of these individual contrasts was performed with *t* tests. The results of the analysis were considered statistically significant for *t* values with $p < .005$ within the a priori–defined ROIs. A cluster threshold of 50 contiguously activated voxels (interpolated, isotropic 1 mm) was used to minimize false-positive results. The following ROIs were defined a priori: DMPFC, insula, amygdala, parahippocampal gyrus, posterior fusiform gyrus (from y = −30), and STS. The ROIs were defined with Talairach daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html), except for the amygdala and the STS. The amygdala was defined according to our previous study with phobic subjects (sphere of 9 mm; see Dilger et al 2003) and the posterior STS according to the suggestions by Winston et al (2003) (sphere of 12 mm).

Results

Behavioral Data

Photographic Faces. Task performance (accuracy, reaction time; see Table 1 for numeric data) did not differ between phobics and control subjects when testing main and interaction effects with a 2 × 2 × 2 (group × expression × task) repeated-measures ANOVA. For accuracy, only a main effect of task was found. There were 97.0% ± .7% correct answers for the implicit task, compared with 84.1% ± 2.6% correct answers during the explicit task [$F(1,14) = 24.1$, $p < .0001$]. Reaction times showed an effect of task [$F(1,14) = 132.8$, $p < .0001$] and an interaction of task × expression [$F(1,14) = 11.4$, $p < .01$]. Thus, subjects were faster in the implicit task (746.2 ± 13.8 msec) compared with the explicit task (862.3 ± 11.6 msec). The interaction was based on faster reaction times to angry versus neutral faces in the explicit task (angry: 848 ± 13.7 msec; neutral: 876.6 ± 11.8 msec; $p < .01$), whereas no significant differences were found for the implicit task (angry: 750.4 ± 14.2 msec; neutral: 742.0 ± 13.8 msec).

Postscanning arousal ratings of the photographic faces showed a main effect of expression [$F(1,18) = 42.5$, $p < .0001$] and an interaction of group × expression [$F(1,18) = 10.4$, $p < .01$], indicating that both groups rated the angry faces as more arousing than the neutral faces. In addition, social phobics rated

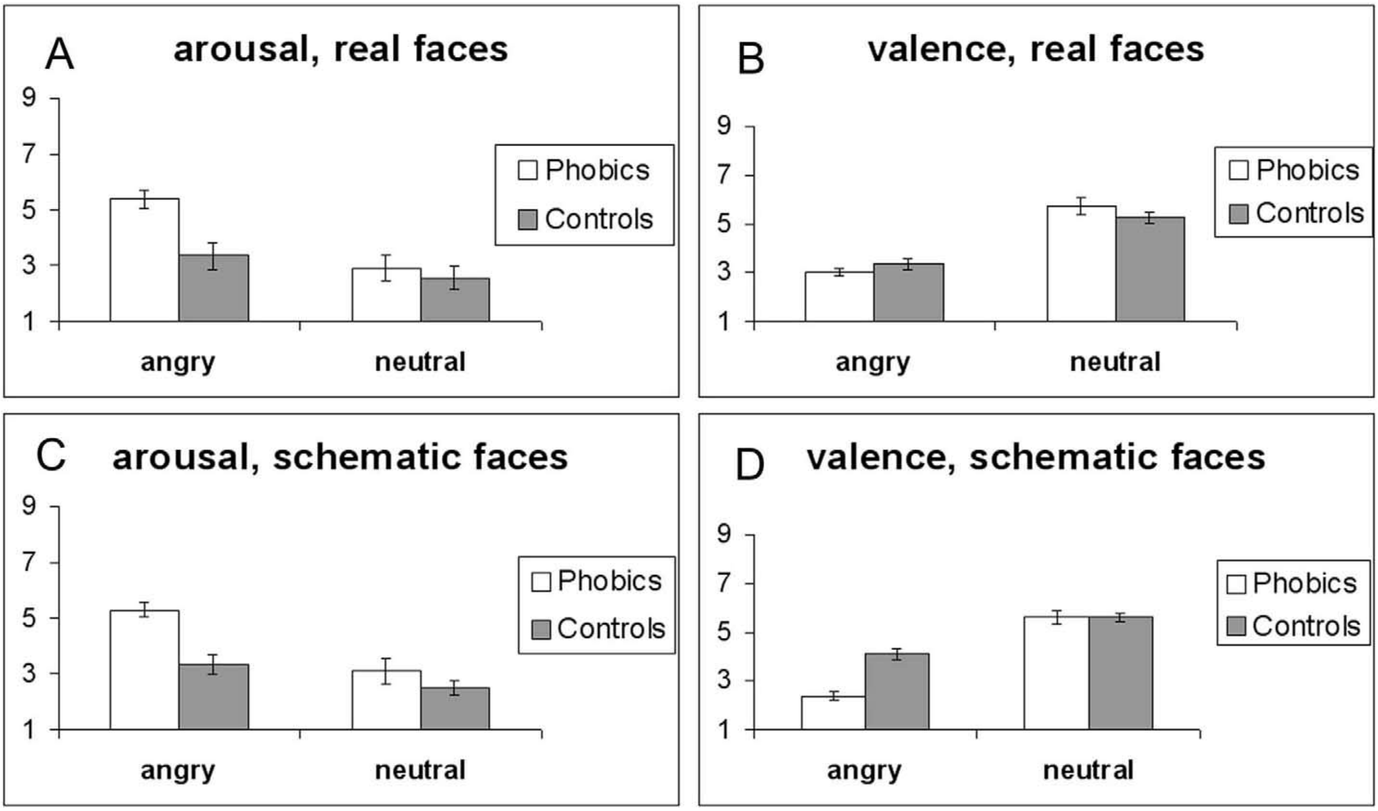

Figure 2. Ratings of arousal (1 = not arousing to 9 = very arousing) and valence (1 = very unpleasant to 9 = very pleasant) of stimuli. Arousal ratings were significantly increased in phobics compared with control subjects for photographic angry **(A)** and schematic angry faces. **(C)** Photographic angry faces were similarly rated as unpleasent by phobics and control subjects. **(B)** Schematic angry faces were rated as significantly more unpleasant by phobics. **(D)** There were no significant differences between phobics and control subjects in the ratings of neutral faces.

photographic angry faces as more arousing than did control subjects (5.4 ± .3 vs. 3.4 ± .5; $t = 3.3$, $p < .005$; Figure 2A), whereas no group effect was found for the neutral faces (2.9 ± .5 vs. 2.6 ± .4; Figure 2A). For valence ratings of photographic faces, there was a main effect of expression [$F(1,18) = 117.3$, $p < .0001$]. All subjects rated angry faces as more unpleasant (3.0 ± .2 in phobics; 3.4 ± .4 in control subjects; Figure 2B) than neutral faces (5.7 ± .5; 5.3 ± .3; Figure 2B).

Schematic Faces. Task performance (accuracy, reaction time; see Table 1 for numeric data) did not differ between phobics and control subjects when testing main and interaction effects with a 2 × 2 × 2 (group × expression × task) repeated-measures ANOVA. Accuracy was dependent on task condition. The ratio was 97.6% ± .5% (implicit task) to 88.9% ± 2.1% (explicit task) correct answers [$F(1,14) = 17.2$, $p < .01$]. Reaction times showed an effect of task [$F(1,14) = 61.9$, $p < .0001$]. Thus, subjects were faster in the implicit task (732.2 ± 14.6 msec) compared with the explicit task (826.8 ± 11.8 msec).

A main effect of expression and an interaction of group × expression for arousal [$F(1,18) = 23.0$, $p < .0001$ and $F(1,18) =$

Table 2. Significant Activation to Angry Versus Neutral Photographic Faces During the Implicit Task

		Phobics				Control Subjects				Phobics > Control Subjects			
Region of Interest	Side	x	y	z	t	x	y	z	t	x	y	z	t
Insula	R	37	−15	−4	5.50					40	−6	−1	3.44
	L	−38	−6	14	8.65					−41	−9	11	6.88
Amygdala	R	26	−8	−22	5.23					22	−6	−23	3.54
	L	−29	−1	−16	3.97								
Parahippocampal Gyrus	R	28	−12	−25	7.18	25	−45	−11	4.89	28	−15	−25	3.56
	L	−32	−42	−7	6.47					−35	−33	−22	3.59
Fusiform Gyrus	R	43	−51	−13	7.20	31	−49	−13	4.23	37	−45	−19	3.99
	L	−32	−42	−16	10.08					−38	−75	−13	4.42
STS	R	55	−51	11	4.80					52	−48	14	3.56
	L	−59	−45	2	3.67	−53	−40	−7	3.60	−65	−39	8	3.77

x, y, z, Talairach coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected, cluster ≥ 50 mm^3); STS, superior temporal sulcus; L, left; R, right.

5.0, $p < .05$] as well as for valence [$F(1,18) = 82.5$, $p < .0001$ and $F(1,18) = 10.8$, $p < .005$] was found. These results indicate that subjects rated the schematic angry face as more arousing and as more unpleasant than the neutral schematic face. In addition, phobics, compared with control subjects, rated the schematic angry face as significantly more arousing (5.3 ± .6 vs. 3.6 ± .6; $t = 2.1$, $p < .05$; Figure 2C) and unpleasant (2.4 ± .3 vs. 4.1 ± .3; $t = 3.9$, $p < .01$; Figure 2D). No significant group differences were found for the neutral face (arousal: 3.4 ± .7 vs. 2.4 ± .4; valence: 5.6 ± .3 vs. 5.6 ± .2; Figure 2C and D).

fMRI Data

Photographic Faces. For the implicit task, the contrast angry versus neutral faces revealed pronounced differences between phobics and control subjects (see Table 1). Several brain regions were activated in phobics but not control subjects. These areas comprised left and right insula, left and right amygdala, left fusiform gyrus, left parahippocampal gyrus, and right STS (Table 2; see Figure 3 for insula activation). Right fusiform gyrus, right parahippocampal gyrus, and left STS were activated in both phobics and control subjects (Table 2). Between-group comparisons revealed greater brain responses in phobics relative to control subjects in all ROIs, except in the DMPFC and the left amygdala (Table 2; see Figure 4 for responses in fusiform gyrus and STS).

During the explicit task, activation to angry versus neutral faces was found in both phobics and control subjects in all ROIs (Table 3). Between-group comparisons for this task revealed that phobics showed stronger BOLD responses in the left and right insula than control subjects (Table 3). Therefore, the insula was the only region where phobics had significantly greater responses than control subjects, regardless of task condition (Tables 2 and 3; Figure 3). For neither of the tasks was there any ROI indicating stronger activation in control subjects compared with phobics.

Furthermore, we performed within-group comparisons that explored intertask differences in activation to angry versus neutral faces. In control subjects, these contrasts revealed stronger activation in nearly all ROIs in the explicit relative to the implicit task. In phobics, this effect was restricted to the right parahippocampal gyrus (Table 4), indicating that phobics showed similarly strong activations regardless of task condition. For neither of the groups was there any ROI indicating increased activation in the implicit compared with the explicit task.

Schematic Faces. For the implicit task, no differential activation to angry versus neutral faces was found in control subjects in any ROI (Table 5). In contrast, phobics demonstrated activation of the right insula and left STS (Table 5; Figures 5 and 6). Activation in the left STS was significantly greater in phobics compared with control subjects (Table 5).

Under the explicit condition, control subjects showed activation to angry versus neutral faces in the left DMPFC (Table 5). In phobics, activations were found in the right DMPFC, left insula, and left fusiform gyrus (Table 5; see Figures 5 and 6 for responses in the insula and fusiform gyrus). Compared with control subjects, activation in the right DMPFC and left fusiform gyrus was significantly greater (Table 5).

Within-group comparisons regarding intertask differences revealed that control subjects had stronger activations in left DMPFC under the explicit compared with the implicit condition (Table 5).

There was no amygdalar activation to schematic faces in phobics. Additional analysis revealed that schematic faces led to strong habituation effects. Examination of the time course of activation in the right amygdala during the implicit task (under this condition, there was the most pronounced effect for photographic faces; see Table 2) showed significant differences of parameter estimates (angry vs. neutral) for the first half of the run (2.9 ± 1.0; $p < .01$) but not for the second half (.2 ± .6; $p > .5$).

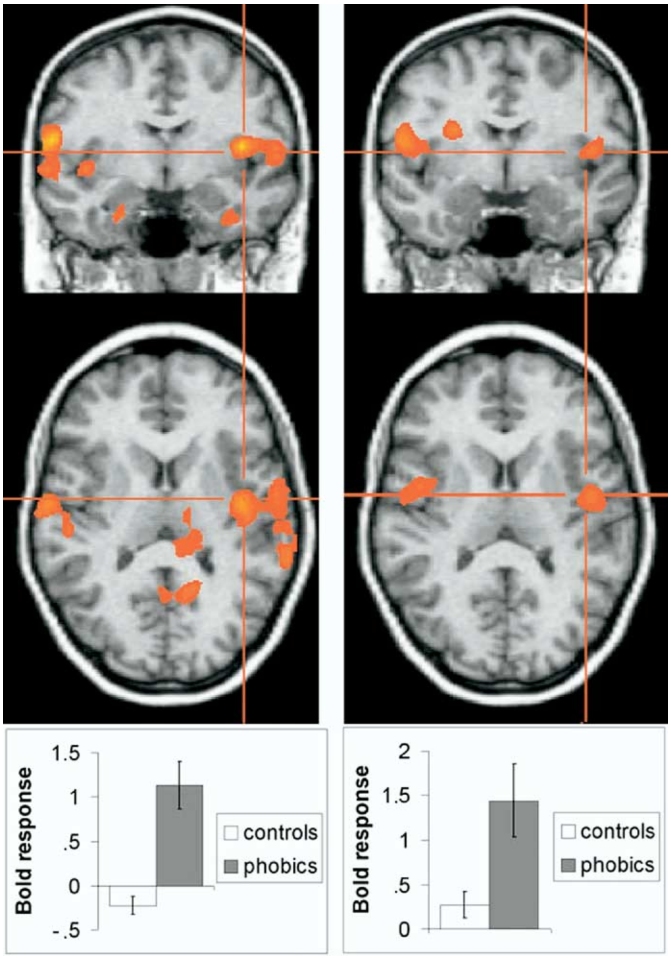

Figure 3. Insula activation to photographic angry versus neutral faces is increased in social phobics relative to control subjects regardless of task. Left: implicit task (y = −6; z = 10). Right: explicit task (y = −4; z = 10). Statistical parametric maps are overlaid on a T1 scan (radiologic convention: left = right). The plots show the contrasts of parameter estimates (angry vs. neutral; mean ± SEM for maximally activated voxel in the left insula). Bold, blood oxygen level–dependent.

Discussion

We found in phobics relative to control subjects greater responses to photographic angry versus neutral faces in the insula regardless of task, whereas the amygdala, parahippocampal gyrus, fusiform gyrus, and STS showed increased activation only during the implicit task. Furthermore, under both task conditions, phobics exhibited similarly strong brain responses, suggesting that angry facial expressions were intensively processed even when this was not required.

Phobic subjects also responded sensitively to schematic faces and showed, in contrast to control subjects, significant activation in the insula and extrastriate cortex during both tasks. Although only responses in extrastriate cortex were significantly increased in phobics compared with control subjects, it remains remark-

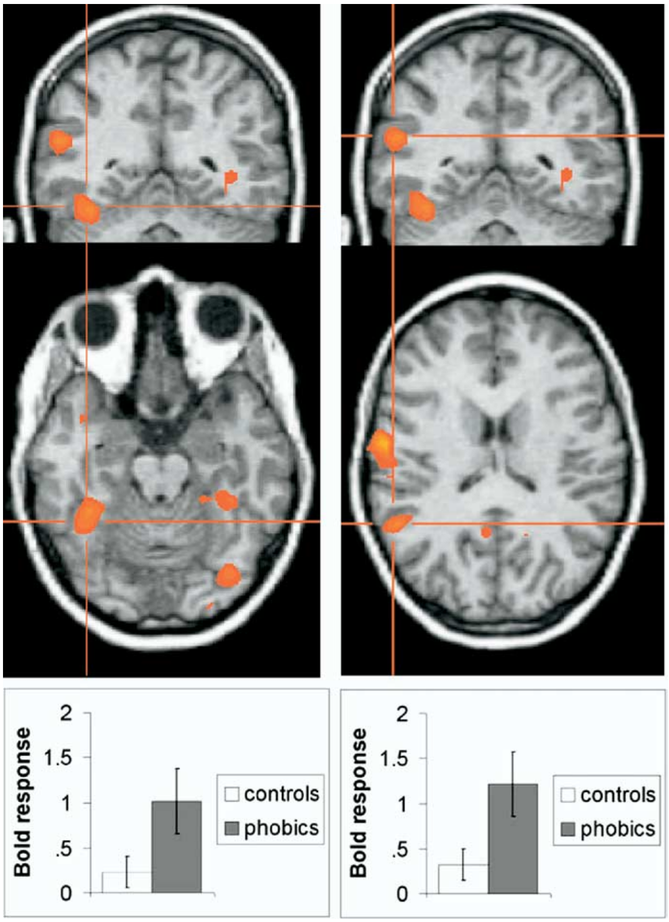

Figure 4. Extrastriate activation to photographic angry versus neutral faces is increased in social phobics relative to control subjects during the implicit task. Left: right fusiform gyrus (y = −47; z = −17). Right: right superior temporal sulcus (y = −47; z = 17). Statistical parametric maps are overlaid on a T1 scan (radiologic convention: left = right). The plots show the contrasts of parameter estimates (angry vs. neutral; mean ± SEM for maximally activated voxel in the ROI). Bold, blood oxygen level– dependent.

able that differential brain activation to the stereotypically presented schematic faces was found in social phobics at all.

The arousal ratings of faces confirmed the behavioral relevance of the photographic as well as the schematic angry faces for social phobics. In addition, valence of the schematic angry face was rated as significantly more unpleasant by phobics than by control subjects, suggesting a specific emotional significance; however, behavioral and fMRI data for schematic faces are only partially comparable. In contrast to the repeated presentation during the scanning session (leading to strong habituation effects), schematic faces were shown only once during the ratings.

The consistent results for the insula suggest a crucial role of this brain area in the processing of socially threatening signals in social phobics. The insular cortex has been shown to be generally involved in the recognition and experience of aversive states, such as disgust, fear, or pain (e.g., Dilger et al 2003; Peyron et al 2002; Phillips et al 1997). Critchley et al (2001, 2002; see for review Critchley 2003) provided strong evidence that the insula might support the interaction of perceived threat signals and bodily states of arousal leading to emotional experiences. This is consistent with the currently influential hypothesis that the insula is involved in monitoring the emotion-relevant physiological state of the individual (Damasio et al 2000). In line with such an evaluative function of the insula, recent studies with healthy subjects demonstrated enhanced insula activation to threatening faces when subjects were explicitly instructed to process the facial expressions (e.g., Anderson et al 2003; Gorno-Tempini et al 2001; Winston et al 2003; but see Lange et al 2003). In the present study, the same phenomenon was observed for control subjects, whereas phobics seemed intensively to evaluate the threat relevance of angry faces regardless of task condition.

Previous functional imaging studies with phobic patients show inconsistent findings concerning insula activation. Significantly increased activation of the insula associated with provocation of anxiety symptoms was reported by Rauch et al (1997), who used pooled data across different anxiety disorders (obsessive-compulsive disorder, simple phobia, posttraumatic stress disorder). A specific involvement of the insula has also been described in spider phobics in response to spider pictures (Dilger et al 2003) and fearful faces (Wright et al 2003). In contrast to these findings, other recent fMRI studies did not report insula activation to spider videos in spider phobics (Paquette et al 2003) or to angry faces in social phobics (Stein et al 2002). Furthermore, a PET study by Furmark et al (2002) even found reduced insula activity in social phobics during public speaking. Such discrepancies between studies with phobic subjects require further

Table 3. Significant Activation to Angry Versus Neutral Photographic Faces During the Explicit Task

		Phobics				Control Subjects				Phobics > Control Subjects			
Region of Interest	Side	x	y	z	t	x	y	z	t	x	y	z	t
DMPFC	R	13	42	26	3.76	2	48	33	4.18				
	L					−8	47	28	5.30				
Insula	R	37	0	11	6.64	31	−12	14	3.74	40	0	11	3.26
	L	−35	18	5	8.49	−48	−2	−1	4.54	−40	−6	8	3.05
Amygdala	R					29	−8	−16	4.45				
	L	−30	−6	−16	4.66								
Parahippocampal Gyrus	R	34	−42	−4	5.52	32	−12	−16	4.00				
	L	−37	−15	−16	7.80	−38	−46	−7	4.02				
Fusiform Gyrus	R	34	−44	−8	4.29	37	−42	−19	5.03				
	L	−37	−59	−12	6.13	−23	−69	−10	5.72				
STS	R	49	−54	2	6.20	52	−51	2	5.15				
	L	−56	−51	5	4.42	−68	−42	0	4.70				

x, y, z, Talairach coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected, cluster ≥ 50 mm^3); DMPFC, dorsomedial prefrontal cortex; L, left; R, right; STS, superior temporal sulcus.

Table 4. Significant Intertask Differences in Activation to Angry Versus Neutral Photographic Faces

Region of Interest	Side	Explicit > Implicit			
		x	y	z	*t*
Phobics					
Parahippocampal gyrus	R	31	−37	−7	4.15
Control Subjects					
DMPFC	R	4	48	33	4.16
DMPFC	L	−8	45	28	4.19
Insula	R	40	−3	2	3.69
	L	−38	19	−1	4.24
Parahippocampal gyrus	L	−8	−42	4	4.74
Fusiform gyrus	R	28	−79	−15	4.45
STS	R	58	−34	5	5.91
	L	−68	−42	0	4.20

x, y, z, Talairach coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected, cluster ≥ 50 mm^3); DMPFC, dorsomedial prefrontal cortex; L, left; R, right; STS, superior temporal sulcus.

investigation. An important variable, which should be investigated, is the influence of the amount of subjects' distraction while threatening stimuli or situations are present. High processing demand by cognitive tasks or by active behavior (e.g., in the study by Furmark et al 2002) could attenuate or even suppress insula activation (e.g., Critchley et al 2002).

In contrast to the results for the insula, the increased amygdalar activation to angry faces in social phobics compared with control subjects was restricted to the implicit task and to the right amygdala. The amygdala has been shown to be involved in the detection of threat signals and in the rapid mediation of fear responses (for review see Büchel and Dolan 2000; LeDoux 1998; Öhman and Mineka 2001), although there is also evidence for a more general role of the amygdala in the processing of emotionally arousing stimuli (e.g., Kilpatrick and Cahill 2003; Winston et al 2003). In healthy subjects, especially fearful relative to neutral faces have been found to activate the amygdala (for review see Phan et al 2002). Angry faces seem to be less effective in evoking increased amygdalar responses (Blair et al 1999; Whalen et al 2001). Here, control subjects showed amygdalar activation to angry versus neutral photographic faces in the explicit condition, whereas phobics showed amygdalar activation in both tasks. We did not observe amygdalar activation to schematic faces, which led to strong effects of habituation (see also Breiter et al 1996; Phelps et al 2000; Rauch et al 2000; but see Wright et al 2002).

Elevated reactivity of the amygdala to phobia-relevant experimental conditions has been previously described in animal phobics (Dilger et al 2003, but see Paquette et al 2003) as well as in social phobics (Birbaumer et al 1998; Furmark et al 2002; Stein et al 2002; Tillfors et al 2001, 2002; Veit et al 2002). The present findings extend the results of Stein et al (2002), who reported amygdalar activation in social phobics to threatening versus happy faces in a gender decision task. There is evidence for stronger amygdalar responses to clearly fear-relevant stimuli during implicitly compared with explicitly emotional tasks (e.g., Critchley et al 2000; Keightley et al 2003; Lange et al 2002; but see Anderson et al 2003; Gur et al 2002). A similar effect was present in our study. Amygdalar activation was bilateral during the implicit task but restricted to the left hemisphere during the explicit task. Attenuation of amygdalar responses in phobics during the explicit task, which might be due to cognitive modulation of subcortical activity (e.g., Keightley et al 2003), might also explain the absence of group differences in amygdalar activation during the explicit task.

The other ROI within the medial temporal lobe, the parahippocampal gyrus, was also more strongly activated in phobics than in control subjects during the implicit task. This increased response is in accordance with previous studies with phobic patients. Stein et al (2002) found greater left parahippocampal activation to angry faces in social phobics than in control subjects during a gender decision task. Paquette et al (2003) reported activation in the left and in the right parahippocampal gyrus when spider phobics were exposed to film excerpts depicting spiders. The parahippocampal gyrus has been strongly associated with memory functions (Brewer et al 1998; Wagner et al

Table 5. Significant Activation to Angry Versus Neutral Schematic Faces

Region of Interest	Side	Phobics				Control Subjects				Phobics > Control Subjects			
		x	y	z	*t*	x	y	z	*t*	x	y	z	*t*
Implicit Task													
Insula	R	40	−21	5	4.08								
STS	L	−56	−51	8	5.01					−56	−42	11	4.08
Explicit Task													
DMPFC	R	10	51	20	3.77					10	54	11	4.98
DMPFC	L					−8	36	32	5.91[a]				
Insula	L	−40	−12	19	4.22								
Fusiform gyrus	L	−35	−72	−13	4.54					−35	−72	−13	3.36

x, y, z, Talairach coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected, cluster ≥ 50 mm^3); STS, superior temporal sulcus; DMPFC, dorsomedial prefrontal cortex; L, left; R, right.

[a]Significantly greater than in the implicit task.

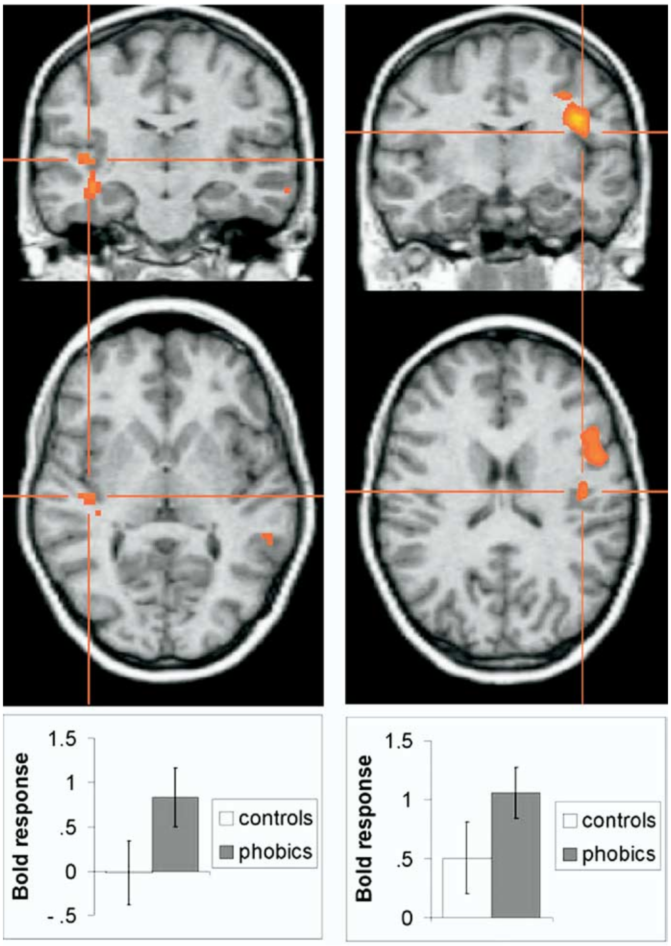

Figure 5. Insula activation to schematic angry versus neutral faces in social phobics. Left: activation of right insula during the implicit task (y = −17; z = 4). Right: activation of left insula during the explicit task (y = −11; z = 18). Statistical parametric maps are overlaid on a T1 scan (radiologic convention: left = right). The plots show the contrasts of parameter estimates (angry vs. neutral; mean ± SEM for maximally activated voxel in the ROI). Bold, blood oxygen level–dependent.

1998). Thus, the functional role of the parahippocampal activity in phobics might be found in the strength of encoding processes (see also Kilpatrick and Cahill 2003). The parahippocampal response might also reflect a stronger automatic activation of information related to threat signals in phobics relative to control subjects (see also Paquette et al 2003), especially under the implicit condition.

In the ROIs of extrastriate cortex (fusiform gyrus and STS), phobics showed similarly strong responses to photographic faces during both tasks, whereas control subjects exhibited significantly less activation during the implicit task. For schematic faces, phobics showed increased visual processing as well, although activation was task-specific (STS in the implicit and fusiform gyrus in the explicit task). Several studies with healthy subjects demonstrated that activation in the fusiform gyrus is modulated by the emotional importance of facial expressions and the attention focus during picture processing (e.g., Keightley et al 2003; Pessoa et al 2002; Vuilleumier et al 2001). The posterior STS is supposed to play a crucial role for the evaluation of the social relevance of stimuli (for reviews see Allison et al 2000; Haxby et al 2002). For example, activity of STS neurons in monkeys is specifically evoked by pictures depicting expressions relevant for the interaction with conspecifics (e.g., Brothers and Ring 1993; Hasselmo et al 1989). Several fMRI studies showed activation of the STS when subjects were requested to evaluate the social content of pictures (e.g., LaBar et al 2003; Narumoto et al 2001; Winston et al 2002, 2003). The pattern of results of the present study, especially for photographic faces, suggests that visual processing and evaluation of photographic angry faces is increased in phobics as compared with control subjects in situations in which attending to facial expression is task-irrelevant. It seems that social phobics' attention is strongly captured by angry facial expressions, whereas for control subjects angry faces are less salient (see also Heinrichs and Hofmann 2001).

Phobics and control subjects showed a similar activation pattern in the DMPFC. Activation was only observed in the explicit task, regardless of picture type (photographic or schematic). This is in line with evidence that the DMPFC is especially activated during explicit emotional decisions (Gusnard et al 2001; Lane et al 1997); however, there was a lack of significant differences in the direct comparisons between phobics and control subjects. This result and the absence of significant activation under the implicit condition do not seem to support the hypothesis of a specific role of the DMPFC in the processing

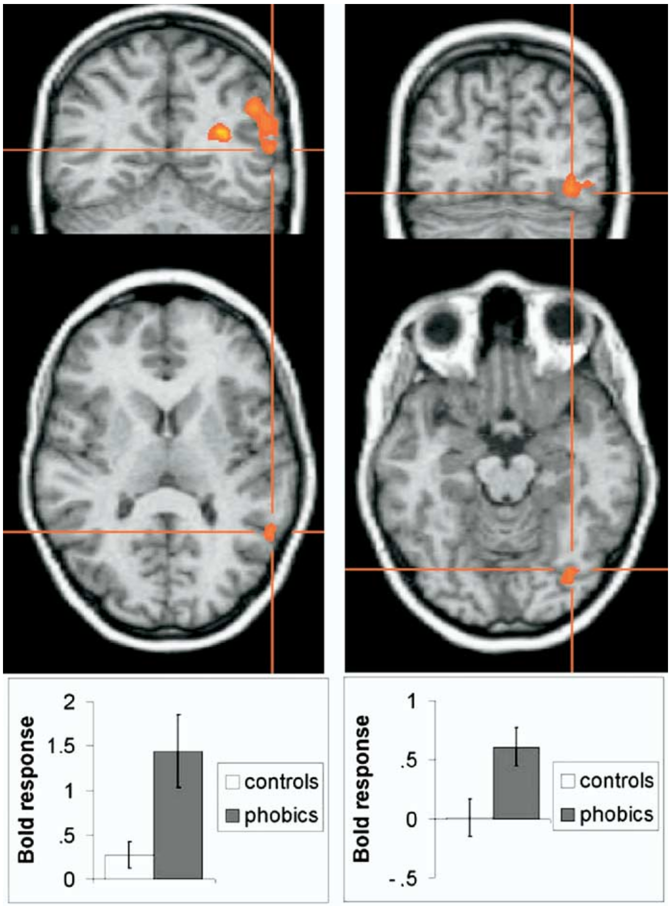

Figure 6. Extrastriate activation to schematic angry versus neutral faces in social phobics. Left: activation of left superior temporal sulcus during the implicit task (y = −52; z = 8). Right: activation of left fusiform gyrus during the explicit task (y = −71; z = −14). Statistical parametric maps are overlaid on a T1 scan (radiologic convention: left = right). The plots show the contrasts of parameter estimates (angry vs. neutral; mean ± SEM for maximally activated voxel in the ROI). Bold, blood oxygen level–dependent.

of social phobia–relevant stimuli. In contrast to our findings, Stein et al (2002) reported increased activation to threatening faces in the DMPFC in social phobics relative to control subjects when subjects attended to the gender of faces. The results of this study were based on the specific contrast used for analysis (threatening vs. happy faces) and on a blocked picture presentation and are therefore not directly comparable to our findings. Future functional imaging studies should directly compare event-related and blocked designs concerning their effects on medial prefrontal activation. It might be that activation in DMPFC is detected during sustained periods of threat-relevant stimulation rather than during short-lasting events.

In conclusion, our results highlight the importance of varying experimental conditions for the detailed investigation of brain activation to threat signals in social phobic subjects. The consistently increased activation of the insula across experimental conditions suggests a significant role of this brain region in the processing of threat-relevant stimuli. Furthermore, the results indicate that social phobics, in contrast to control subjects, intensively process angry facial expressions regardless of whether focussed processing is required or not. A limitation of this study is the small sample size, which might have restricted the detection of further significant differences. Furthermore, the relatively liberal, uncorrected significance level used for the ROI analysis might have resulted in false-positive results. The present fMRI study shows preliminary findings regarding task-dependent brain responses to threat signals in phobic subjects, and further work is strongly needed.

The study was supported by the Deutsche-Forschungs-Gemeinschaft (DFG project number: Mi 265/5-1/2). Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set.

We are very grateful to Ms. I. Krummbein for her expert technical assistance.

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