Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder

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Social anxiety disorder patients suffer from excessive anxious responses in social interaction leading to avoidance behavior and social impairment. Although the amygdala has a central role in perception and processing of threatening cues, little is known about the involved networks and corresponding dysfunctions in social anxiety. Therefore, this study aims to investigate the functional connectivity network of the amygdala in patients with social anxiety disorder and to identify regions that might influence amygdalar reactivity via modulatory pathways.

Ten patients with anxiety disorders (social and/or panic) and 27 healthy controls underwent a facial emotion processing task as well as 6-min functional MRI at resting state. Individual voxel-wise functional connectivity maps were calculated using the amygdala as seed region. Group comparisons were done by random-effects analysis in SPM.

Patients exhibited an amygdala hyperactivation during the emotional task and decreased functional coupling of the left amygdala with the medial orbitofrontal cortex and the posterior cingulate cortex/precuneus. The strength of this functional connectivity showed a negative association with the severity of state anxiety. In addition, an exploratory analysis revealed further reduced functional connectivity and a marked functional separation between the medial orbitofrontal and anterior cingulate cortices in the patient group.

Our results suggest alterations within the amygdalar functional connectivity network in social anxiety disorder. Combined with the amygdalar hyperactivation our findings corroborate the proposed dysfunction of the fronto-amygdalar inhibition in anxiety disorders and indicate a modulatory influence of the anterior and posterior cingulate cortices on threat perception and processing.

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Introduction

Social anxiety disorder (SAD), classified as “social phobia” in DSM-IV, is characterized by an excessive physiological and emotional arousal (Milad and Rauch, 2007) in response to social interaction, unfamiliar faces and performance situations like public speaking (Milad and Rauch, 2007; Tillfors et al., 2001). The repeated experience of anxiety in relatively harmless situations (Rauch et al., 2003) leads to pronounced avoidance behavior and consecutively interferes with daily life, occupational performance and relationships of SAD patients.

The subcortical brain region most often associated with the neural processing of anxiety and threat is the amygdala. It is essential for initial processing of emotional memory and arousal (Cahill et al., 1996), fast evaluation of novel stimuli ( Larson et al., 2006) and threat perception (Cannistraro and Rauch, 2003). Electrical stimulation of the amygdala has been shown to elicit fear, anxiety and social withdrawal and to increase the stress response via cortisol release (Drevets et al., 2008; Lanteaume et al., 2007). Lesions within the amygdala compromise face processing (Young et al., 1995) and judgment of trustworthiness in social context (Adolphs et al., 1998), impair the recognition of fear (Broks et al., 1998) and increase social anxiety (Peather et al., 2001). Accordingly, functional amygdalar hyperactivation in response to aversive and potentially threatening social stimuli (Etkin and Wager, 2007; Phelps et al., 2001; Rauch et al., 2003; Tillfors et al., 2001) and during face perception ( Hariri et al., 2002; Phan et al., 2006; Stein et al., 2002) is consistently observed in SAD patients.

Less known, however, is the way how this important relay station of social performance and emotion perception interacts with other regions of the anxiety network (Cannistraro and Rauch, 2003). Receiving input from higher-order sensory cortices, the amygdala
appears to have a centre or gate function in a hub of connections associated with the perception, evaluation and response to threatening and socially relevant stimuli (Ghashghaei and Barbas, 2002; Stein et al., 2007a). With respect to the amygdala hyperreactivity, inverse activation patterns have been identified in several other areas of the anxiety network in functional magnetic resonance imaging (fMRI) studies examining the reaction to and suppression of negative affect (Phan et al., 2005). This suggests a disturbed interplay between these regions in anxiety-prone subjects (Stein et al., 2007b) and challenged SAD patients (Lorberbaum et al., 2004; Phan et al., 2006; Stein et al., 2002; Tillfors et al., 2001).

Resting-state functional connectivity MRI (rs-fMRI) has become a valuable tool for the investigation of network function, allowing for a paradigm-free analysis of connectivity in functional MRI without a priori assumptions about neural activation (Biswal et al., 1995; Greicius et al., 2003). Investigating the spatial distribution of correlations in the spontaneous activity of the brain not only resembles the activation patterns found within task-specific fMRI, but also reflects structural connections between these regions (Fox et al., 2005; Greicius et al., 2008). Alterations of resting-state connectivity were shown in attention deficit hyperactivity disorder (Castellanos et al., 2008), Alzheimer's disease (Greicius et al., 2004), obsessive compulsive disorder (Harrison et al., 2008), depression (Anand et al., 2005), bipolar disorder (Wang et al., 2008) and schizophrenia (Salvador et al., 2010). Functional connectivity analysis furthermore revealed a discorrelation of task-related networks in patients with generalized anxiety disorder (Etkin et al., 2009; Monk et al., 2008), social anxiety disorder in adolescents (Guye et al., 2008) and adults (Zhao et al., 2007) as well as specific phobia (Ahs et al., 2009), pointing to a dysregulation of the fronto-amygdalar interplay.

Although alterations of some resting-state networks in social anxiety disorder patients were suggested (Liao et al.), the role of primary emotional processing structures such as the amygdala in resting-state networks is still unknown. We hypothesized that dysfunctions in the fronto-amygdalar network of SAD patients are reflected by an altered functional connectivity of the amygdala as assessed with rs-fMRI. Hence, this study investigated spontaneous blood oxygen level dependent (BOLD) activity patterns in patients with social anxiety and/or panic disorder compared to healthy controls. Primary data analysis focused on the amygdala due to its crucial role in threat assessment. In addition, an exploratory connectivity analysis was performed targeting alterations in indirect modulatory pathways by using areas with disrupted amygdalar connectivity as secondary seed regions. Finally, borders between functionally distinct regions were evaluated based on the variability of individual connectivity maps (Biswal et al., 2010), since putative functional boundaries between areas were suggested to provide supplementary insight into the functional organization of brain networks (Cohen et al., 2008).

Methods

Participants

Fifteen unmedicated patients with anxiety disorders and 30 healthy controls were recruited from the local community via media advertisements. Patients had to fulfill criteria for social anxiety disorder and/or panic disorder (SAD/PD) according to the Structured Clinical Interview for DSM-IV Diagnoses (SCID) and no other DSM-IV diagnosis except for agoraphobia. Healthy controls were required to have no history of or current psychiatric DSM-IV diagnosis. Five patients and 3 healthy volunteers had to be excluded because they were non-compliant with the study protocol. Thus, 10 patients (9 males) with anxiety disorder (7 SAD only, 2 SAD + PD, 1 PD only) and 27 healthy volunteers (11 males) were included in the final analysis. Mean age ± SD of the subjects included was 27.7 ± 7.2 years for healthy controls and 28.6 ± 4.3 years for patients. Within the patient group onset of disease occurred during childhood in 3 cases, at adolescence in 4 patients and 3 subjects experienced first episodes in adulthood with an overall age range for disease onset of 6 to 31 years.

At the screening visit, each participant underwent a medical examination including general physical and neurological screening, electrocardiogram, routine laboratory tests and medical history assessment. Psychopathology was evaluated by means of psychiatric consultation and the German version of the SCID. Inclusion criteria for all participants were physical health, signed written informed consent and age of 18 to 60 years. Exclusion criteria were any abnormalities in physical and neurological examination at screening visit, current or past substance abuse, any intake of psychotropic medication within 3 months prior to inclusion, any implant or stainless steel graft, pregnancy (tested at the screening visit and before the fMRI scan using an urine HCG pregnancy test) and intake of oral contraceptives or other hormonal treatment. All participants completed the Spielberger State and Trait Anxiety Inventory (STAI) questionnaire (Spielberger et al., 1970). The study was approved by the Ethics Committee of the Medical University of Vienna and all subjects received reimbursement for participation.

fMRI measurements

The subjects were measured in a 3 Tesla Medspec S300 MR Scanner (Bruker Biospin, Germany). The participants performed a facial expression discrimination task (FEDT) as well as a resting-state scan. During FEDT, a previously established fMRI protocol was applied to obtain an optimized representation of amygdala BOLD signal changes (Robinson et al., 2004; Windischberger et al., 2010). Briefly, single-shot gradient-recalled echo planar imaging (GR-EPI) sequences were employed (TE = 31 ms, TR = 1000 ms, matrix size = 128 × 91) resulting in a total slab width of 34.5 mm with 10 axial slices of 3 mm thickness aligned to the AC-PC line (0.5 mm slice gap). Functional connectivity MRI measurements in resting state (rs-fMRI) were carried out as described previously (Weissenbacher et al., 2009). Participants were instructed to relax in the scanner, stay awake with eyes open without fixation (at low-level illumination) and “allow thoughts to come and go freely.” The resting-state scan lasted 360 s. Data were acquired using single-shot GR-EPI (TE = 40 ms, TR = 1000 ms, matrix size = 96 × 64) resulting in 14 axial slices of 6 mm thickness aligned to the AC-PC line (1 mm slice gap).

Facial expression discrimination task

Since hyperactivation of the amygdala in response to facial expressions is one of the most reproduced findings in patients with social anxiety disorder (Phan et al., 2006; Stein et al., 2002), we wanted to ensure that our patient sample represents the same neurobiological characteristics as commonly reported. To examine amygdala reactivity to faces of different emotional expressions, subjects completed a modified version of a facial expression discrimination task introduced by Hariri et al. (2002). The paradigm design is depicted in Fig. 1a and has been described earlier by our group (Windischberger et al., 2010). Briefly, a facial expression discrimination task (FEDT) alternated with a shape discrimination task for sensorimotor control (SDT) in a conventional block design with an in-between fixation cross baseline condition. The participants were presented either a triplet of facial stimuli showing one of seven emotions (happiness, anger, fear, sadness, surprise, disgust and calm/neutral) or a triplet of geometric shapes with different colors (Fig. 1a). By pressing the left or right button, subjects had to match a facial expression (or shape of two figures) displayed at the bottom of each slide to the facial expression (or shape) at the top. Five 20 s FEDT blocks were alternated with five 20 s SDT blocks, with 20 s baseline periods in-between. Individual stimuli were taken from a set of 100
different FEDT slides and 50 SDT slides in true randomized order, hence, the total run time was 420 s. Facial stimuli were created from the NimStim Set of Facial Expressions (MacArthur Foundation Research Network on Early Experience and Brain Development, http://www.macbrain.org/resources.htm). Each of the participants completed a practice trial of the paradigm before the respective fMRI scan using stimuli not shown in the scanning session. The task was presented using the Presentation software package (Neurobehavioral Systems Inc., Albany, CA) via a transparent screen at the scanner’s bore.

Evaluation of facial expression discrimination task

Standard preprocessing was carried out in SPM (http://www.fil.ion.ucl.ac.uk/spm/) for both the FEDT task and the resting-state scans. It included correction for slice-timing differences, realignment, normalization to MNI space and spatial smoothing with a Gaussian kernel of 9 mm FWHM. First-level analysis was carried out using the general linear model framework implemented in SPM. Individual task-specific activation maps were calculated by contrasting BOLD signal changes of the FEDT task against the SDT control task.

Functional connectivity analysis

In addition to standard preprocessing, resting-state data were corrected as proposed in a previous study (Weissenbacher et al., 2009). In short, linear regression was used to correct for changes in ventricular, white matter and global signal. Data were band-pass filtered with a 12-term finite impulse response (FIR) filter (0.007<f<0.08 Hz) implemented in IDL (RSI, USA). Functional connectivity analysis was carried out by applying a seed-region approach (Biswal et al., 1995) using the left and right amygdala as defined in the automated anatomical labeling-atlas (AAL (Tzourio-Mazoyer et al., 2002)) included in the MRicron software package (http://www.sph.sc.edu/comd/orden/mricron.html). BOLD signal time courses were averaged within the left and right amygdala, respectively, and correlated voxel-wise with the entire brain. Finally, correlation maps were converted to z-values using Fisher’s r-to-z transformation to enable group comparisons.

Statistical assessment

Voxel-wise group comparisons between patients and healthy controls were carried out in SPM by one-way ANOVA (p<0.001 uncorrected voxel level, p<0.05 corrected cluster level), controlling for age. An additional extent threshold of k=0.4 cm³ (=50 voxels) was applied to reduce false positives. To evaluate differences in amygdala reactivity induced by FEDT the task reaction time and error rate were also included as covariates. Due to the inhomogeneous gender distribution within the patients and healthy controls, group differences were additionally calculated between male SAD patients (n=7) and male healthy subjects (n=11). Also, we tested for sex differences within the healthy control group. Considering the reduced statistical power, these subgroups were also evaluated exploratively at lower thresholds.

Furthermore, fMRI data were correlated with STAI scores using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA). Here, individual task specific activation from the FEDT as well as z-values from functional connectivity analysis were extracted from clusters showing significant group differences. All tests were carried out two-tailed.

Subsequent network analysis

Complementary to our primary investigation of the amygdala network, two further exploratory connectivity analyses were carried out. First, to assess potential alterations of indirect modulatory pathways, additional seed regions were defined based on functional clusters showing significant differences in amygdala connectivity between patients and healthy controls (p<0.001, k=0.4 cm³, p<0.05 corrected cluster level). Connectivity analysis was done as within the main analysis (cross-correlation between average seed time course, z-transformation, ANOVA).

Second, borders between functionally distinct regions were evaluated based on the variability of individual connectivity maps. A recent study demonstrated the applicability to delineate functionally segregated areas within a single subject (Cohen et al., 2008), hence, the variability of such boundaries can be computed across individuals. Borders were defined as proposed earlier (Biswal et al., 2010), with respect to the amygdala network. Voxel-wise coefficients of variation (= SD/mean) across subjects were calculated from z-transformed correlation maps of the amygdala network (i.e., where the amygdala served as seed region) for patients and healthy controls separately. Coefficients of variation were rank-ordered and given as relative degree of variation (i.e., percentile). Due to lack of comparable patient data, evaluation of functional boundaries was focused on clusters identified in the preceding analysis of this study.

Results

Facial expression discrimination task

The comparison of patients to healthy controls revealed a hyperactivation of the left amygdala in response to faces showing emotional expressions (t = 4.91, p<0.0001, Table 1, Fig. 1b). At lower thresholds, this was also found for the right amygdala (t = 3.34, p<0.005), and the hyperreactivity was still present when comparing only male SAD patients with male healthy subjects (t = 3.33 and t = 3.07, p<0.005 for left and right amygdala, respectively). No
differences in amygdala reactivity were found between healthy male and female subjects.

**Functional connectivity analysis**

Anxiety disorder patients had a significantly lower functional connectivity between the left amygdala and left medial orbitofrontal cortex (mOFC, t = −4.83, p < 0.001, p < 0.05 cluster-level-corrected) as well as the left posterior cingulate cortex/precuneus (PCC/precuneus, t = −4.35, p < 0.001, Table 1, Fig. 2). Regions were identified by means of the AAL-Atlas (Tzourio-Mazoyer et al., 2002), but it is important to note that the mOFC cluster (“superior frontal gyrus, medial orbital” (Tzourio-Mazoyer et al., 2002)) also includes parts of the ventromedial frontal cortex (Herrmann et al., 2007). The second herein revealed cluster corresponds to the precuneus region within the AAL-atlas (Tzourio-Mazoyer et al., 2002). However, the region is equivalent to the posterior part of the task-negative network identified in previous rs-fMRI network studies (Fox et al., 2005), and therefore covers the posterior cingulate cortex as well.

Within the analysis including only male subjects and SAD patients still reduced functional connectivity was found between patients and controls within the left mOFC (t = −4.29, p < 0.001) and the left PCC/precuneus (t = −3.93, p < 0.001). Moreover, this subgroup exhibited attenuated left amygdalar functional connectivity with the right pallidum and left inferior occipital cortex (p < 0.001, Table 1). At lower thresholds, further deficiencies were found within the bilateral ventral striatum, left hippocampus and left medial frontal cortex (p < 0.005).

No deficits were found for the right amygdala. However, patients had higher functional connectivity between right amygdala and the right middle occipital cortex/angular gyrus (t = 4.49, p < 0.0001, Table 1). Testing for sex differences in left or right amygdala functional connectivity within the healthy controls showed no significant sex effects in the amygdala, OFC, PCC/precuneus or ventral striatum.

**Spielberger state and trait anxiety scores (STAI)**

The average STAI state anxiety scores were 42.1 ± 9.0 (mean ± SD) for patients and 30.3 ± 5.1 for healthy controls (p < 0.0001). Similarly, the mean STAI trait anxiety scores were 41.6 ± 11.5 for patients and 29.0 ± 7.0 for healthy subjects (p < 0.01). Within our healthy control group, males and females did not significantly differ in STAI state or trait scores.

For the FEDT, no significant associations were found between left or right amygdala reactivity and STAI state or trait anxiety scores. However, within the functional connectivity analysis STAI state anxiety scores showed a negative association with z-values of clusters in the mOFC (r = −0.38, p < 0.05) as well as the PCC/precuneus (r = −0.46, p < 0.005) for the entire study population. For trait scores, the z-values of the PCC/precuneus cluster nearly reached statistical significance (r = −0.32, p = 0.053).

**Subsequent network analysis**

Proceeding from the left medial orbitofrontal cluster (Fig. 2d), patients exhibited further decreased functional connectivity with the anterior cingulate cortex (ACC, t = −4.94 and t = −4.17, p < 0.001, Table 1, Fig. 3a). These two ACC clusters also showed a negative association with state anxiety scores (r = −0.36, p < 0.05 and r = −0.44, p < 0.01, respectively). In addition and consistent with previous results from a large database (Biswal et al., 2010), our exploratory analysis revealed sharp boundaries between functional areas of the amygdala network. In particular, voxel-wise maps containing the coefficient of variation (=SD/mean) of amygdalar connectivity showed a marked separation between the mOFC and ACC clusters identified within the functional connectivity analysis in patients but not within healthy controls (Fig. 3b–c).

**Discussion**

We observed a reduced resting-state functional connectivity between left amygdala and medial orbitofrontal cortex as well as posterior cingulate cortex/precuneus in patients with social anxiety disorder as compared to healthy controls. The patient sample exhibited the typical amygdala hyperactivation to emotionally-laden facial expressions. Our findings therefore substantiate the proposed fronto-amygdalar network disruption in anxiety disorders (Etkin and Wager, 2007; Phelps et al., 2004). Also, we found decreased functional connectivity between the medial orbitofrontal and anterior cingulate cortices in patients, suggesting an indirect modulation of the amygdala network via the orbitofrontal cortex.
Orbitofrontal cortex

The OFC has a crucial role in the modulation of fear via the amygdala (Quirk et al., 2003; Rosenkranz and Grace, 2002). Humans suffering from anxiety disorders, including the patients examined here, consistently show increased amygdala reactivity during the processing of emotional stimuli (Hariri et al., 2002; Monk et al., 2008; Stein et al., 2002; Stein et al., 2007b). This amygdalar hyperactivation has been frequently reported to be inversely associated with orbitofrontal reactivity during the suppression of negative emotions (Phan et al., 2005) and presence of threatening stimuli (Garcia et al., 1999), in generalized anxiety disorder (Monk et al., 2008) and posttraumatic stress disorder (Shin et al., 2005; Williams et al., 2006). Our data are in support of a disturbed inhibitory regulation of the OFC onto the amygdala in social anxiety disorder patients. However, alterations within the OFC might not be specific to anxiety disorders when taking into account similar findings in depression (Drevets et al., 2008; Frodl et al., 2010) and bipolar disorder (Versace et al., 2010).

The OFC is involved in the engagement of interpersonal relationships, moral behavior and social aggression (Blair et al., 1999; Greene et al., 2001). Lesions within the medial orbitofrontal cortex enhance the response to stressors or fear conditions stimuli (Morgan and LeDoux, 1995; Sullivan et al., 1999) resulting in severe impairments in

Fig. 2. Functional connectivity analysis. Comparing healthy controls (b) with anxiety disorder patients (c) showed reduced functionally connectivity between the left amygdala (= seed region shown in a) and medial orbitofrontal as well posterior cingulate cortices (d). Crosshair at MNI-coordinates x/y/z: −8/42/−14 mm (top and middle row) and −10/−56/48 mm (bottom row). Left is right.

Fig. 3. Subsequent network analysis. Proceeding from the main analysis, the medial orbitofrontal cortex was functionally defined as additional seed region (shown in Fig. 2d and here in Fig. 3 indicated by green dot). This reveals further decreased functional coupling with the anterior cingulate cortex in patients (a). Voxel-wise computation of the coefficient of variation (Biswal et al., 2010) delineates putative functional boundaries (yellow lines in b and c), showing a marked separation between the medial orbitofrontal and anterior cingulate cortices in patients (c) but not in healthy controls (b). Crosshair at MNI-coordinates x/y/z: −6/36/−4 mm.
social behavior (Damasio et al., 1985; Hornak et al., 2003; Rolls et al., 1994) and difficulties in identifying social signals from facial and voice expressions (Hornak et al., 2003; Hornak et al., 1996). In addition, reduced orbitofrontal activation was observed in patients with SAD during public speaking (Lorberbaum et al., 2004; Tillfors et al., 2001) and anxiety-provoking tasks (Mayberg et al., 1999; Simpson et al., 2001) as well as in patients suffering from specific phobia (Hermann et al., 2007). Hence, a hypoactive medial OFC has been associated with a failure of fear and anxiety inhibition, while a hyperactive lateral OFC seems to be relevant in anxiety-laden cognitions (Guyer et al., 2008; Milad and Rauch, 2007).

The circuit between the amygdala and orbitofrontal cortex is involved in recognition and perception of emotional response (Barbas et al., 2003; Gusnard et al., 2003), fear extinction (Pessoa et al., 2005) and together with the thalamus is responsible for the assessment of threat-related information (Cannistraro and Rauch, 2003). It was shown that early developmental disruption of the amygdala-prefrontal circuit indicates an attentional bias toward threats and leads to the development of pathological anxiety (Amaral, 2003; Milad and Rauch, 2007). Also, reduced functional coupling within the network between OFC and amygdala was reported in anxiety-prone subjects (Stein et al., 2007b) and corresponding white matter deficits of the OFC–amygdala connection were shown in patients with social anxiety disorder (Phan et al., 2009). Accordingly, our results demonstrating a reduced connectivity between the OFC and the amygdala substantiate the hypothesis of a disturbed fronto-amygdalar connection on a functional level.

Posterior cingulate cortex

The social anxiety disorder patients in our sample exhibited decreased amygdalar functional connectivity with the posterior cingulate cortex/precuneus. This “default prefrontal network” (or “default mode network,” comprising among others the posterior cingulate and medial prefrontal cortices (Fox et al., 2005; Greicius et al., 2003)), relates to self-referential functions including mood and emotion as well as reactions to such stimuli (Pessoa et al., 2005; Saleem et al., 2008) and has been implicated in pathological anxiety (Simpson et al., 2001). The investigation of effective connectivity of the amygdala region in healthy subjects revealed a strong influence of the posterior cingulate (Stein et al., 2007a), which is supported by structural findings of white matter tracts in animals (Köter, 2004; Stein et al., 2007a). Moreover, a possible role for the PCC/precuneus in amygdalar network were missed through our analysis. Hence, we would expect a similar functional connectivity pattern in panic disorder with possibly additional deficiencies in the hippocampus or insula (Cannistraro and Rauch, 2003; Rauch et al., 2004). Considering the limited number of patients with panic disorder included here, the specifics of network dysfunctions in panic disorder still need to be investigated.

The small sample size of this study might be a reason why only the orbitofrontal cluster withstood the correction for multiple comparisons. While type I errors are hardly caused by limited statistical power, it is still possible that less pronounced deficits within the amygdalar network were missed through our analysis. Hence, further studies seem reasonable to evaluate additional deficiencies in social anxiety disorders, e.g., the direct amygdala–ACC pathway (Etkin et al., 2010).

Also, this study was not able to assess sex differences within SAD patients due to an unbalanced gender distribution. However, attenuated amygdalar functional connectivity was still present when comparing only male subjects. Also, in the relevant regions, no sex differences were found within our healthy controls. Moreover, a meta-analysis investigating functional response to emotional tasks showed equal activations in males and females (Wager et al., 2003). Still, this remains an interesting issue for future studies, considering the higher prevalence of anxiety disorders in female patients (Ohyan and Schatzberg, 2010).

Recently, two studies in healthy controls (Roy et al., 2007) and patients with generalized anxiety disorder (Etkin et al., 2009) demonstrated distinct functional connectivity patterns for the amygdala when choosing amygdalar subregions like the basolateral and centromedial amygdala as seed. However, this approach has a major limitation as the amygdala is particularly susceptible to image distortion, normalization failure and draining vein effects (Robinson et al., 2004) and accurate delineation in the human brain is still under debate (Amunts et al., 2005). Therefore, and since most of the human literature is based on functional results of the whole amygdala region...
we chose a more conservative approach using the AAL template for investigation of the amygdalar network.

The lateralization of the human amygdala has been reported abundantly in the literature, possibly explaining our finding of an altered connectivity only within the left hemisphere. While direct electrical stimulation of the right human amygdala induces only negative emotions, left amygdala stimulation causes fear, anxiety and sadness as well as happiness (Lanteaume et al., 2007). In addition, only left amygdala hyperactivation to fearful and happy faces is associated with increasing fearfulness and decreasing happiness ratings (Morris et al., 1996). Our results are in line with a meta-analysis of functional neuroimaging studies showing an overall lateralization of amygdala activations to the left hemisphere (Baas et al., 2004), particularly for negative emotions (Wager et al., 2003).

Finally, within a recent study in bipolar patients, connectivity analysis during the perception of facial stimuli suggested a lateralization of OFC–amygdala functional connectivity by demonstrating associations of right and left amygdalar connectivity with trait and state markers of depression, respectively (Verse et al., 2010).

Conclusions

Our data suggest a severe disorganization between major parts of the functional amygdala network already in resting state in patients with social anxiety, extending orbitofrontal de

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Broks, P., Young, A.W., Maratos, E.J., Coffey, P.J., Calder, A.J., Alger, I., Mayes, A.R., 2005; Stein et al., 2007b) and provide a possible biological rationale for the pathophysiology of social anxiety disorder.

Conflict of interest statement

Without any relevance to this work, S. Kasper declares that he has received grant/research support from Eli Lilly, H. Lundbeck A/S, Bristol-Myers Squibb, Servier, Sepracor, GlaxoSmithKline, Organon, and has served as a consultant or on advisory boards for AstraZeneca, Austrian Sick Fund, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, H. Lundbeck A/S, Pfizer, Organon, Sepracor, Jansen, and Novartis, and has served on speakers' bureaus for AstraZeneca, Eli Lilly, H. Lundbeck A/S, Servier, Sepracor and Jansen. R. Lanzenberger received travel grants and conference speaker honoraria from AstraZeneca, H. Lundbeck A/S, Servier. A. Hahn received a travel grant from Pfizer. P. Stein and C. Spindelegger received a travel grant from H. Lundbeck A/S. C. Windschberger, E. Moser, and A. Weissenbacher declare no conflict of interest.

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