



Brain activation to task-irrelevant disorder-related threat in social anxiety disorder: The impact of symptom severity



Carina Yvonne Heitmann^{a,*}, Katharina Feldker^a, Paula Neumeister^a, Leonie Brinkmann^a, Elisabeth Schrammen^a, Pienie Zwitserlood^b, Thomas Straube^a

^aInstitute of Medical Psychology and Systems Neuroscience, University of Muenster, Germany

^bInstitute of Psychology, University of Muenster, Germany

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ABSTRACT

Unintentional and uncontrollable processing of threat has been suggested to contribute to the pathology of social anxiety disorder (SAD). The present study investigated the neural correlates of processing task-irrelevant, highly ecologically valid, disorder-related stimuli as a function of symptom severity in SAD. Twenty-four SAD patients and 24 healthy controls (HC) performed a feature-based comparison task during functional magnetic resonance imaging, while task-irrelevant, disorder-related or neutral scenes were presented simultaneously at a different spatial position. SAD patients showed greater activity than HC in response to disorder-related versus neutral scenes in brain regions associated with self-referential processing (e.g. insula, precuneus, dorsomedial prefrontal cortex) and emotion regulation (e.g. dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus). Symptom severity was positively associated with amygdala activity, and negatively with activation in dorsal anterior cingulate cortex and dlPFC in SAD patients. Additional correlation analysis revealed that amygdala-prefrontal coupling was positively associated with symptom severity. A network of brain regions is thus involved in SAD patients' processing of task-irrelevant, complex, ecologically valid, disorder-related scenes. Furthermore, increasing symptom severity in SAD patients seems to reflect a growing imbalance between neural mechanisms related to stimulus-driven bottom-up and regulatory top-down processes resulting in dysfunctional regulation strategies.

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1. Introduction

Social anxiety disorder (SAD) describes the pathological fear of negative evaluation by other people. Patients suffering from SAD are characterized by anxiety in social interactions (e.g. small talk on parties, discussions) and performance situations (e.g. giving a speech, job interview) (American Psychiatric Association, 2013). With a prevalence rate of 7–13% in Western countries (Furmark, 2002) and 12.1% in the USA (Kessler et al., 2005), SAD is one of the most frequent anxiety disorders.

Automatic threat processing, that is, the attentional capture by, and the detection and processing of, threat stimuli that are outside the current attentional focus and/or task-irrelevant (Carretié, 2014; Moors and De Houwer, 2006), is considered a critical factor for the development and maintenance of SAD and other anxiety disorders (Bar-Haim et al., 2007; Morrison and Heimberg, 2013; Öhman and Mineka, 2001). Automatic processing as defined here is often operationalized by engaging participants in a main task with neutral stimuli, while threat stimuli

are presented simultaneously, but remain task-irrelevant (Carretié, 2014). According to biased-competition models, the extent to which task-irrelevant stimuli are processed is strongly mediated by both top-down control and stimulus-driven bottom-up mechanisms (Beck and Kastner, 2009). Thus, unintentional processing of task-irrelevant threat stimuli may be caused by their strong exogenous influence on attention and enhanced sensory processing (bottom-up), which seems to be associated with increased amygdala activity in anxiety. Additionally, attentional control (top-down) may be reduced, due to altered prefrontal functioning (Bishop, 2008; Connor et al., 2004; Eysenck and Derakshan, 2011; Ochsner and Gross, 2005; Öhman, 2005). This imbalance may well be aggravated with increasing anxiety (Bishop, 2009; Bishop et al., 2004b; Cisler and Koster, 2010; Eysenck and Derakshan, 2011), rendering the processing of threat more unintentional and uncontrollable, which represent two important indicators of automatic information processing (Bargh, 1994; Teachman et al., 2012).

Most functional imaging studies on brain responses during automatic processing of task-irrelevant threat stimuli in SAD presented emotional faces, which were judged with respect to emotion-irrelevant aspects such as gender discrimination (Blair, Shaywitz, et al., 2008; Campbell et al., 2007; Gentili et al., 2008; Stein et al., 2002; Straube et al., 2004). Other studies either used gender judgment on stimuli with

* Corresponding author at: Institute of Medical Psychology and Systems Neuroscience, University of Muenster, Von-Esmarch-Straße 52, D-48149 Muenster, Germany.

E-mail address: carina.heitmann@uni-muenster.de (C.Y. Heitmann).

emotional prosody (Quadflieg et al., 2008), disorder-related words in grammatical decision (Schmidt et al., 2010) or in an emotional Stroop task (Boehme et al., 2015). These studies particularly reported amygdala hyperactivation and less consistent hyperactivations in the insula, prefrontal regions (e.g. orbitofrontal cortex, dorsolateral prefrontal cortex (dlPFC)), anterior cingulate cortex (ACC), and superior temporal sulcus (STS) in SAD patients, suggesting emotional encoding even when the task does not focus on stimulus valence. These findings are in large parts compatible to those obtained when attention is not focused elsewhere (e.g. Heitmann et al., 2016; Klumpp et al., 2012; Straube et al., 2005). These studies without attentional restrictions present a neural network including amygdala, thalamus, insula, globus pallidus, ACC, mid-cingulate cortex (MCC), posterior cingulate cortex (PCC), precuneus, STS, cuneus, medial prefrontal cortex (mPFC), and lateral prefrontal cortex (lPFC), associated with increased threat detection, abnormal self-referential processing and interoception in SAD patients (Brühl et al., 2014; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010; Miskovic and Schmidt, 2012).

However, previous studies on automatic processing in SAD did not use a visually separated feature-based attention task with emotionally neutral stimuli (in the presence of task-irrelevant emotional distractor stimuli), or used emotional stimuli that were only partially relevant for SAD, such as faces (Schulz et al., 2013) or words, which are limited in their ecological validity. Thus, the question arises how patients with SAD process highly ecologically valid disorder-related stimuli, when these are task-irrelevant and presented spatially separate from the task stimuli. This situation, often encountered in real life outside the laboratory, is implemented in concurrent but distinct target-distractor (CDTD) tasks (Carretié, 2014). Previous studies in healthy participants (HC) could show that processing of task-irrelevant stimuli, although presented at a central position, is significantly affected by a spatially non-overlapping main task (e.g. Mocaiber et al., 2010; Nordström and Wiens, 2012; Sand and Wiens, 2011; Wiens et al., 2012; Wiens et al., 2011). This task configuration allows to investigate to which degree task-irrelevant emotional stimuli capture attention, and are processed even at task-irrelevant locations (Wiens et al., 2012).

The present study investigated neural correlates of such automatic, disorder-related scene processing in SAD patients and HC. We used visually complex, disorder-related scenes that depict situations SAD patients are afraid of (and neutral control scenes). We used such scenes as task-irrelevant stimuli in an attention-demanding CDTD task. The task-irrelevant scenes were presented at the center of the screen and the emotionally neutral task-stimuli above and below the scene.

Additionally, the influence of symptom severity was examined with correlation analysis. We expected increased automatic threat processing in SAD patients, reflected by hyperactivation in the regions related to affective processing in SAD (amygdala, insula, thalamus, globus pallidus, cingulate cortex, precuneus, STS and prefrontal cortex) (Brühl et al., 2014; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010; Miskovic and Schmidt, 2012), relative to HC (interaction of Scene Type by Group: SAD patients > HC, disorder-related scenes > neutral scenes). Furthermore, we expected hyperactivations in SAD patients to increase with increasing symptom severity. Finally, based on biased-competition models suggesting diminished attentional control depending on inter-individual differences in anxiety vulnerability (Bishop, 2008), we expected increasing symptom severity in SAD patients to be accompanied by reduced activation in prefrontal regions.

2. Materials and methods

2.1. Subjects

SAD patients were recruited via public notices, local paper ads and from a collaborating outpatient clinic. HC were selected from a volunteer database of the Collaborative Research Center "Fear, Anxiety, Anxiety Disorders" (TRR SFB 58; <http://sftrr58.uni-muenster.de/>) or were

recruited by means of flyers and newspaper ads. All participants had normal or corrected-to-normal vision, were right-handed (Oldfield, 1971), met the general MRI-requirements, had no history of neurological diseases or psychotic disorders, did not currently take psychotropic medication, and were screened by a psychologist using the standardized clinical interview (SCID; Wittchen et al., 1997). SAD patients fulfilled the criteria for current generalized social anxiety disorder according to DSM-IV as main diagnosis. HC were free of any diagnosis. All participants completed the clinician-administered Liebowitz-Social-Anxiety-Scale (LSAS; Stangier and Heidenreich, 2005), Social Phobia Scale (SPS; Stangier et al., 1999b), Social Interaction Anxiety Scale (SIAS; Stangier et al., 1999a), Fragebogen zur Selbstbeschreibung in sozialen Situationen (FSSS; Kolbeck, 2008), Social Phobia Anxiety Inventory (SPAI; Fydrich, 2003), and Fear of Negative Evaluation Scale (FNE; Vormbrock and Neuser, 1983). To address depressive symptomatology all participants filled in the Beck Depression Inventory (BDI; Hautzinger et al., 1995).

Out of 33 SAD patients, nine were excluded from statistical analysis due to a BDI score > 30 ($n = 2$), missing behavioral responses or technical problems ($n = 2$), misunderstanding of the behavioral task ($n = 1$), or <90% correct answers in the behavioral task ($n = 4$). Matched to the 24 SAD patients (17 female), a control group consisting of 24 HC (16 female), who had $\geq 90\%$ correct answers in the behavioral task, was chosen. Patients and HC groups did not differ in gender, mean age, and educational attainment (see Table 1 for sample details).

Comorbid diagnoses in SAD patients ($n = 9$, multiple entries possible) were current Major Depression Episode ($n = 2$), specific phobia ($n = 7$), Obsessive Compulsive Disorder ($n = 1$), and General Anxiety Disorder ($n = 1$). As expected, SAD patients scored higher than HC in all social anxiety-sensitive questionnaires (Table 1). BDI scores were also significantly increased in SAD patients, but remained under the clinical significance level, and were comparable to scores from other studies (e.g. Straube et al., 2004).

The study conforms to the Declaration of Helsinki and was approved by the ethics committee of the University of Muenster, Germany. Written informed consent was obtained from each participant prior to the experiment. Participants received monetary compensation for participation.

2.2. Experimental design

Fifty disorder-related scenes and 50 matched neutral scenes from the Social Anxiety Picture Set Muenster (SAPS-M; see Heitmann et al. (2016) for a detailed description of the properties of the stimulus set

Table 1

Mean age, mean educational attainment (years), and mean scores (\pm standard deviation) for social anxiety-related questionnaires (LSAS, SPS, SIAS, FSSS, SPAI, FNE) and Beck Depression Inventory (BDI) for patients suffering from social anxiety disorder (SAD) and healthy controls (HC).

	SAD ($M \pm SD$)	HC ($M \pm SD$)	t-value	P-value (2-tailed)
Age	27.29 \pm 7.69	27.38 \pm 5.77	-0.042	0.966
Education	12.88 \pm 1.30	13.38 \pm 1.14	-1.422	0.162
LSAS	64.13 \pm 16.32	9.67 \pm 6.93	15.050	≤ 0.001
SPS	31.38 \pm 9.90	2.17 \pm 2.94	13.850	≤ 0.001
SIAS	45.88 \pm 14.03	10.13 \pm 6.77	11.243	≤ 0.001
FSSS	1.80 \pm 0.39	0.37 \pm 0.27	14.841	≤ 0.001
SPAI	3.72 \pm 0.76	0.58 \pm 0.57	16.200	≤ 0.001
FNE	62.00 \pm 8.72	31.83 \pm 6.47	13.617	≤ 0.001
BDI	10.54 \pm 7.32	1.50 \pm 2.99	5.602	≤ 0.001

Note: M = Mean; SD = standard deviation; LSAS = Liebowitz Social Anxiety Scale; SPS = Social Phobia Scale; SIAS = Social Interaction Anxiety Scale; FSSS = Fragebogen zur Selbstbeschreibung in sozialen Situationen; SPAI = Social Phobia and Anxiety Inventory; FNE = Fear of Negative Evaluation Scale; BDI = Beck Depression Inventory.

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