



Task-dependent modulation of amygdala connectivity in social anxiety disorder



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ABSTRACT

Increased amygdala activation is consistently found in patients suffering from social anxiety disorder (SAD), a psychiatric condition characterized by an intense fear of social situations and scrutiny. Disruptions in the amygdalar-frontal network in SAD may explain the inability of frontal regions to appropriately down-regulate amygdalar hyper-activation.

In this study, we measured 15 SAD patients and 15 healthy controls during an affective counting Stroop task with emotional faces to assess the interaction of affective stimuli with a cognitive task in SAD, as well as to investigate the causal interactions between the amygdala and the medial orbitofrontal cortex (OFC) using dynamic causal modeling (DCM).

Here we show for the first time that differences in OFC-amygdala effective connectivity between SAD patients and healthy controls are influenced by cognitive load during task processing. In SAD patients relative to controls dysfunctional amygdala regulation was observed during passive viewing of harsh faces. This could be linked to ongoing self-initiated cognitive processes (such as rumination and anticipation of negative events) that hinder successful amygdala regulation. However, between-group differences diminished during cognitive processing, suggesting that attentional load interfered with emotional processing in both patients and controls.

1. Introduction

Social anxiety disorder (SAD) is a psychiatric condition in which people suffer from intense dread of social situations and of other people's scrutiny. Studies focusing on its neural correlates have confirmed the central role of the amygdala (Davis and Whalen, 2001; Phelps and LeDoux, 2005), which is hyperactive in SAD patients compared to healthy controls (HC) during the perception of emotional facial expressions (Ball et al., 2012; Fitzgerald et al., 2006; Klumpp et al., 2012; Phan et al., 2006; Stein et al., 2002). Other studies have observed similar results using different types of stimuli that can be considered to be anxiety-inducing for SAD patients, such as reading negative comments referring to oneself (Blair et al., 2011), perception of social situations illustrated in images (Nakao et al., 2011), speech anticipation (Tillfors et al., 2001), direct eye gaze (Schneier et al., 2011, 2009), and situations involving uncertainty (Krain et al., 2008).

In addition to amygdalar hyperactivity, SAD has also been asso-

ciated with aberrant activations of regions within the prefrontal cortex implicated in voluntary and automatic emotion regulation during anxiety-inducing stimuli (Hariri et al., 2003; Labuschagne et al., 2012; McClure et al., 2007; Monk et al., 2008; Phillips et al., 2008; Sladky et al., 2012). Disruptions of the amygdalar-prefrontal network in SAD have also been confirmed by resting-state functional connectivity studies (Hahn et al., 2011; Liao et al., 2010; Qiu et al., 2011).

While there is general agreement that SAD is characterized by dysfunctional amygdalar-prefrontal circuitry (for a review, see Bishop, 2007), little is known about the underlying SAD-specific temporal and causal dependencies within the network. Recently, we provided evidence for the inability of the medial orbitofrontal cortex (OFC) to down-regulate amygdalar hyperactivity in SAD patients relative to controls during exposure to emotional faces (Sladky et al., 2013b). Here, we aim to expand our previous findings by investigating the interaction between affective stimuli and a cognitive task in the clinical context of SAD. Based on previous work that has demonstrated the

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importance of attentional load and the availability of perceptual resources on emotion processing and regulation (Blair et al., 2007; Pessoa et al., 2005; Silvert et al., 2007; Schultz and Heimberg, 2008), we aim to investigate how simultaneous processing of a cognitive task during emotional face perception affects the effective connectivity between OFC and amygdala. For this purpose, the affective counting Stroop task proposed by Blair et al. (Blair et al., 2007) was used, in which emotional faces served as distractors during a goal-directed processing task with a varying attentional load.

Specifically, we used dynamic causal modeling (Friston et al., 2003) to assess the effective connectivity between the amygdala and OFC, which has been implicated as an important neuronal regulator (Phillips et al., 2008; Ray and Zald, 2012). During passive viewing we hypothesize that OFC would successfully inhibit the amygdalar activation during emotional processing in healthy controls, which down-regulation would be dysfunctional in patients. If cognitive load interferes with emotional processing, we expect to observe increased amygdalar activation in SAD, relative to HC, in the absence of cognitive demand, which should become attenuated during the cognitive task with increasing attentional load. On the other hand, if emotional processing of harsh distractors interferes with cognitive processing in SAD, we expect to see longer reaction times during the cognitive task in patients compared to controls, as suggested by previous findings (Blair et al., 2007).

2. Methods and materials

2.1. Study population

Fifteen SAD patients (7 males and 8 females, mean age \pm SD: 26.6 \pm 8.6 years) and 15 matched healthy control (HC) participants (8 males and 7 females, mean age \pm SD: 25.4 \pm 3.4 years) took part in the study. All participants provided written informed consent prior to the study and were financially reimbursed for their participation. The study was approved by the institutional advisory board of the Medical University of Vienna in accordance with the Declaration of Helsinki and national laws.

Both SAD patients and HC underwent clinical assessment by the psychiatrists of the Department of Psychiatry and Psychotherapy of the General Hospital in Vienna. None of the participants had any history of neurological or psychiatric disorders, with the exception of SAD in the patient group. Additional exclusion criteria included pregnancy, current or prior history of substance abuse, or any psychotropic medication within the last three months. On the day of the experiment, a compulsory drug screening was conducted using ToxiQUICK PAN-10 test panels (ACON Laboratories, San Diego, USA), which were negative for all participants.

All participants were tested with the German version of the Structured Clinical Interview for DSM-IV (SCID) (Eysenck, 1997). Additionally, they completed the State-Trait Anxiety Inventory, State (STAI-S) and Trait (STAI-T) versions (Spielberger et al., 1983), as well as the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) and the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). Based on the psychometric scores, SAD patients reported greater levels of social anxiety on the LSAS, HAM-A, and STAI (Table 1).

2.2. MRI Acquisition parameters and fMRI paradigm

Participants were scanned in a 3 T TIM TRIO MR scanner (Siemens Medical, Erlangen, Germany) using a high-sensitivity 32-channel head coil. 485 whole-brain volumes oriented along the AC–PC line with a matrix size of 128 \times 128 \times 20 voxels were acquired at a repetition time of TR=1.8 s, using a GE single-shot echo planar imaging (EPI) sequence (TE=40 ms, FOV=190 \times 190 mm², voxel size=1.5 \times 1.5 \times 3 mm³, interslice gap=2.1 mm, and bandwidth=1446 Hz/px). The purpose of the high spatial resolution was to minimize MRI signal losses in the ventral

Table 1.

Psychometric data. All subjects were evaluated using Liebowitz Social Anxiety Scale (LSAS), State-Trait Anxiety Inventory (STAI-S/T), and Hamilton Anxiety Rating Scale (HAM-A). Table shows mean \pm SD, two-tailed two-sample *t*-test used for group comparison.

Group	HC	SAD	<i>t</i> -test
Gender	7 f/8 m	8 f/7 m	
Age [years]	25.4 \pm 3.4	26.6 \pm 8.6	<i>t</i> ₂₈ =0.50, <i>p</i> > 0.6
LSAS	5.3 \pm 7.3	75.6 \pm 22.7	<i>t</i> ₂₈ =11.42, <i>p</i> < 0.001
HAM-A	0.5 \pm 0.6	16.9 \pm 5.0	<i>t</i> ₂₈ =12.61, <i>p</i> < 0.001
STAI-S	25.6 \pm 3.3	42.1 \pm 12.8	<i>t</i> ₂₈ =4.83, <i>p</i> < 0.001
STAI-T	27.0 \pm 4.8	52.2 \pm 11.2	<i>t</i> ₂₈ =8.01, <i>p</i> < 0.001

brain regions due to the local field inhomogeneity leading to intra-voxel dephasing effects (Robinson et al., 2004).

The Affective counting Stroop task (Blair et al., 2007) was adapted for the current study. In this task, participants were sequentially presented with two numerical displays in the form of a 3-by-3 matrix consisting of numbers and asterisks. Between the presentations of the numerical displays, we displayed distractors in the form of harsh faces (disgusted or angry) or scrambled, unrecognizable neutral faces, which were obtained from the NimStim facial stimulus set (Tottenham et al., 2009). An example of the presentation stimuli can be seen in Fig. 1. Participants had to decide whether the first or the second matrix displayed contained the greater quantity of digits, irrespective of the value of the displayed numbers. The task contained three different Stroop conditions: congruent (the number of digits corresponded to the value), incongruent (the number of digits differed from the value), and a passive viewing condition, in which asterisks were shown instead of numbers and no response from the participant was required. The conditions were presented in a randomized order. A crosshair was shown with jittered presentation duration (3400–7700 ms, uniform distribution) between the task events.

2.3. Preprocessing and general linear model (GLM) analysis of fMRI data

Data were preprocessed and analyzed using SPM12b (FIL Methods Group, Wellcome Trust Center for Neuroimaging, University College London, <http://www.fil.ion.ucl.ac.uk>). We performed slice-timing correction (Sladky et al., 2011), realignment to compensate for movement, normalization to standard MNI space using an additionally acquired T₁-weighted MPR anatomical scan for each participant, and spatial smoothing (8 mm FWHM) to reduce inter-subject variability and increase signal-to-noise ratios.

Single-subject GLM analysis included regressors for Stroop task complexity (passive viewing, congruent and incongruent) and distractor valence (harsh faces, neutral) using boxcar functions aligned to stimulus presentation onsets, convolved with SPM's canonical HRF, and the six realignment parameter vectors taken from the realignment procedure. Thus, a separate block of trials was modeled for each of the following conditions: congruent harsh, congruent neutral, incongruent harsh, incongruent neutral, passive viewing harsh and passive viewing neutral. A second-level group analysis of the harsh-neutral contrast (irrespective of the cognitive load) was performed using one-sample *t*-tests across all participants to localize the bilateral amygdalae and OFC, comprising the emotion processing circuitry (Sabatinelli et al., 2011). Significance threshold for the statistical parametric map was set to *p* < 0.001 (uncorrected) with a minimum cluster extent of *k*=10 voxels (Lieberman and Cunningham, 2009). To verify the validity of this approach in the context of our study, we used an independent method to perform a cluster-level correction. An anatomically defined mask was created in SPM's Anatomy toolbox (Eickhoff et al., 2007, 2006, 2005), including our a priori regions of interests (*k*=940 vx). The modified version of AFNI's 3dClustSim, was used for statistical thresh-

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