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Amygdala reactivity and connectivity during social and non-social aversive stimulation in social anxiety disorder

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ABSTRACT

Social anxiety disorder (SAD) is characterized by exaggerated amygdala reactivity in response to symptom provocation, but it is unclear if such hyper-reactivity is elicited by disorder-specific challenges only or characterizes reactions to aversive stimuli in general. Here, using functional magnetic resonance imaging in 14 patients with SAD, as compared to 12 healthy controls, we found that amygdala hyper-reactivity is confined to disorder-relevant social stimulation. SAD patients displayed increased amygdala reactivity to fearful as compared to neutral facial pictures, but not in response to generally aversive but mainly non-social stimulation when compared to neutral pictorial stimuli taken from the International Affective Picture System. The increased amygdala reactivity was not mediated by an altered prefrontal inhibition among SAD patients as compared to controls, suggesting increased bottom-up processes rather than attenuated top-down control. In conclusion, the enhanced amygdala reactivity in SAD seems specific to socially relevant stimuli rather than aversive stimuli in general.

1. Introduction

Social anxiety disorder (SAD) affects around 12% of the population in Western societies (Kessler et al., 2005), compromises quality of life (Stein and Stein, 2008), imposes high societal costs (Grant et al., 2005; Stein et al., 2005) and enhances the risk for depression (Beesdo et al., 2007). Core symptoms of SAD include excessive fear of being judged by others or scrutinized in social situations such as public speaking. The excessive concern of being negatively evaluated leads to profound anxiety in social situations or their avoidance (American Psychiatric Association, 2013).

The neurobiological underpinnings of SAD include an exaggerated amygdala response to disorder-relevant stimulation including harsh or fearful faces (Blair et al., 2008; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010; Brühl et al., 2014; Gentili et al., 2016; Stein et al., 2002) when compared to healthy controls, which is seen also during emotion processing (e.g. Klumpp et al., 2010; Phan et al., 2013). Further, studies have compared amygdala activation in response to generally aversive pictures/scenes in SAD patients vs. other anxiety disorders and healthy controls (Shah et al., 2009; Buff et al., 2016; Weidt et al., 2016) but none of these studies included comparisons of amygdala reactivity across social and non-social stimulation. The only study to date that has investigated responses to both harsh faces and aversive scenes in SAD patients reported that both categories increased amygdala reactivity, but to an equal degree as in healthy controls (Goldin et al., 2009). However, the critical three-way interaction between stimulus (faces vs. scenes), valence (negative vs. neutral) and group (SAD vs. healthy controls) was not reported. Thus, it is not clear if amygdala hyper-reactivity in SAD is generalized, characterizing exaggerated reactions to aversive stimulation at large, or if it is specific for social stimuli like faces, targeting the symptom dimensions of social anxiety.

Here, we performed a functional magnetic resonance imaging (fMRI) study in patients with SAD and healthy controls to evaluate the neural effects of social and non-social aversive stimuli. Fearful facial emotional expressions known to elicit exaggerated amygdala reactivity in SAD patients (Phan et al., 2006; Prater et al., 2013) were contrasted

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against aversive but mainly non-social scenes (Shah et al., 2009), and both types of aversive stimuli were compared to their neutral counterparts. This approach enables to test whether social and non-social stimuli affect the two groups differently, addressing if SAD patients react with heightened amygdala response to the social stimuli specifically. Moreover, because the ventromedial prefrontal cortex (vmPFC) is suggested to be critical for the regulation of amygdala activity in humans (see e.g. Motzkin et al., 2015), enhanced amygdala responsivity could mirror an intrinsically hyper-reactive amygdala complex or be a marker of attenuated prefrontal top-down inhibition. While it has been argued that anxiety disorders are characterized by a lack of modulation of the amygdala from the vmPFC (e.g. Kim et al., 2011), it is not known if this is a general mode of brain action or confined to disorder-specific stimuli discriminating between affected and non-affected individuals. Thus, we also examined if the connectivity between the amygdala and the vmPFC differs between SAD patients and healthy controls during social and non-social stimulation.

2. Methods

2.1. Participants

Fourteen patients who met the DSM-IV criteria (American Psychiatric Association, 2000) for SAD (Mean age = 32.4, SD = 8.8 years) were enrolled in the study along with 12 healthy controls (HC) (Mean age = 28.0, SD = 8.2 years). All participants were right-handed men and a subset of the data has previously been reported in Frick et al. (2013). The two groups were not statistically different in terms of their age ($t(24) = 1.28$, $p = 0.21$) or educational level ($\chi^2(1) = 0.097$, $p = 0.76$). SAD patients were recruited through newspaper advertisements and HC participants were recruited through public billboards at a local hospital. All participants underwent the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1997) administered by a master student, under supervision, at the Department of Psychology, Uppsala. Patients were initially screened with the Social Phobia Screening Questionnaire (Furmark et al., 1999) and interviewed with SCID only if they fulfilled the screening criteria for SAD. The Liebowitz Social Anxiety Scale self-report measure (LSAS-SR) (Fresco et al., 2001) was additionally administered to evaluate the self-experienced severity of social anxiety in the SAD group (Mean = 72.1, SD = 25.7). All patients met the DSM-IV criteria for SAD as primary diagnosis. Two of these patients had subthreshold obsessive-compulsive disorder and one had comorbid specific phobia. One individual received pharmacological treatment (venlafaxine).

The criteria for exclusion of the SAD group were: recently started or ongoing psychological treatment; primary diagnosis other than SAD; current drug or alcohol abuse and other psychiatric or organic disorders that could affect the results (e.g. schizophrenia). Participants from the HC group did not fulfil any of the DSM-IV axis I disorders, nor did they have a history of any psychiatric disorder.

The research was approved beforehand by the Ethical Committee at the Karolinska Institute, Stockholm. All participants provided their written informed consent before their actual participation in the research. The pre-research clinical assessments did not reveal any compromised ability to provide informed consent.

2.2. MR image acquisition

A Siemens Avanto 1.5 T whole-body MR-scanner with a 12-channel matrix head coil was employed to acquire both structural and functional images. For structural images, 176 slices were collected using a 3D magnetization-prepared rapid acquisition gradient echo sequence, repetition time 2300 ms, inversion time 1100 ms, echo time 3.93 ms, slice thickness 1 mm, field of view 256 × 256 mm, matrix 256 × 256. Functional scans were acquired using a T2*-weighted gradient echo planar imaging sequence, 30 interleaved coronal slices, repetition time 3000 ms, echo time 50 ms, slice thickness 5 mm, gap between slices 0.5 mm, field of view 220 mm, matrix 64 × 64, inplane voxel dimension 3.4 × 3.4 mm.

2.3. fMRI paradigms

All participants underwent two standard emotional paradigms – emotional faces and emotional scenes paradigms, in that order, during functional MRI. Participants viewed the stimuli in both paradigms projected on a screen through a mirror on top of the head coil.

2.3.1. Emotional face paradigm

The emotional face paradigm consisted of alternating blocks of neutral and fearful faces interspersed with blocks showing a fixation cross. Photographs of faces from the Ekman and Friesen (1976) face collection were used as stimuli. Every participant started with the neutral face block. Three neutral face blocks and three fearful face blocks were presented. Both blocks consisted of 15 faces presented for 2 s each followed by a fixation cross for 400 ms (block duration of 36 s in total). In between the face blocks, an 18-second-long rest block with white fixation cross on a black background was presented. As in other similar studies (e.g. Blair et al., 2008; Stein et al., 2002) the task also required subjects to identify the sex of the face by pressing buttons with their right index and middle fingers in order to make sure that the participants were attentive to the task during the entire paradigm. The total duration of the paradigm was 5 min and 42 s.

2.3.2. Emotional scenes paradigm

The emotional scenes paradigm consisted of alternating blocks of neutral and aversive, but mainly non-social scenes interspersed with blocks showing a black screen. Photographic stimuli for this paradigm were derived from the well standardized International Affective Picture System (IAPS) (Lang et al., 2008). Every participant started with the neutral block. Both blocks consisted of 5 scenes presented for 3.9 s, each followed by a black screen for another 3.9 s (block duration of 39 s in total). In between the blocks with scenes, a 21-second-long rest block with white fixation cross on a black background was presented. During presentation of each scene, participants responded through a button press if the scene was unpleasant (middle finger) or not (index finger). The total duration of the paradigm was 8 min and 35 s. The following IAPS slides were used: aversive- 1300, 3000, 3010, 3015, 3051, 3053, 3060, 3062, 3063, 3064, 3080, 3120, 3130, 3150, 3170, 3266, 3400, 9040, 9252, 9253, 9405, 9410, 9420, 9570, 9921; neutral- 2440, 2480, 2518, 2570, 2580, 2620, 2840, 2850, 2870, 2880, 2890, 5731, 7140, 7180, 7205, 7215, 7234, 7235, 7490, 7491, 7500, 7700, 9210, 9360, 9700.

2.4. Behavioral and demographic analyses

All behavioral and demographic data were analyzed using IBM SPSS Statistics 22 software. Data on valence, arousal, accuracy and reaction times were analyzed using between-group t-tests with the alpha level set to $p < 0.05$.

2.5. Functional magnetic resonance imaging analyses

The functional magnetic resonance imaging analyses were performed by using Statistical Parametric Mapping Software 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2017a (MathWorks, Natick, MA, USA). The first three volumes for each participant were discarded to allow for T1 equilibration effects. Standard image pre-processing steps were done: (1) realignment of functional volumes to mean volume in order to correct for motion, (2) co-registration of structural and functional images, (3) normalizing functional images to Montreal Neurological Institute (MNI) standard space and re-slicing to 3 mm isotropic voxels