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Within-session effect of repeated stress exposure on extinction circuitry function in social anxiety disorder

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ABSTRACT

Anxiety reduction following repeated exposure to stressful experiences is generally held to depend on neural processes involved in extinction of conditioned fear. We predicted that repeated exposure to stressful experiences would change activity throughout the circuitry serving extinction, including ventromedial prefrontal cortex (vmPFC), the hippocampus and the amygdala. To test this prediction, 36 participants diagnosed with SAD performed two successive speeches in front of an observing audience while regional cerebral blood flow (rCBF) was recorded using positron emission tomography. To control for non-anxiolytic effects of repeated exposure, rCBF was also measured during repeated presentations of neutral and angry facial expressions. Results showed that anxiety ratings and heart rate decreased from the first to the second speech, indicating an anxiolytic effect of repeated exposure. Exposure attenuated rCBF in the amygdala whereas no change in rCBF was observed in the vmPFC or hippocampus. The rCBF-reductions in the amygdala were greater following repetition of the speech task than repetition of face exposure indicating that they were specific to anxiety attenuation and not due to a reduced novelty. Our findings suggest that amygdala-related attenuation processes are key to understanding the working mechanisms of exposure therapy.

1. Introduction

A key ingredient in effective psychotherapy for anxiety disorders is exposure to anxiety inducing situations (Craske et al., 2008), as repeated exposure to feared situations reduce anxiety. The experimental analogue to exposure therapy is generally assumed to be extinction of conditioned fear (Bouton, 1988; Craske and Mystkowski, 2006). During extinction, a cue previously paired with an aversive event, such as an electric shock, is repeatedly presented without the shock occurrence resulting in diminished cued fear. In animals, this well established experimental model has been used to acquire knowledge about the neural circuitry underlying the anxiolytic effect of exposure therapy (Maren et al., 2013) and show that the amygdala, the hippocampus and the ventromedial prefrontal cortex (vmPFC) form an extinction circuitry involved in inhibiting learned fear responses to conditioned fear cues (Ahs et al., 2015; Kalisch et al., 2006; Milad and Quirk, 2002; Milad et al., 2007). Specifically, the hippocampus and the vmPFC are thought to inhibit learned fear memories in the amygdala (Maren, 2011). These seminal findings in non-human animals translate to fear extinction studies in humans, as evident from a large body of neuroimaging studies (for reviews, see Diekhof et al., 2011; Vanelzakker et al., 2014).

It could be argued that if extinction of fear is a valid experimental model for exposure therapy, repeated exposure should induce changes in the extinction circuitry. However, when considering neuroimaging studies in SAD that have compared symptom provocation before and after cognitive behavior therapy (CBT), where exposure to feared situations is a critical ingredient, changes do not seem to occur in all components of the circuitry. Instead, alterations are restricted predominantly to the amygdala, whereas activity in the hippocampus and the vmPFC seems relatively unaffected (Bruhl et al., 2014; Furmark et al., 2002; Mansson et al., 2013). However, studies that have compared treatment-related changes in brain responses during symptom provocation typically rely on one scanning session before, and one after treatment. This design does not capture within-session changes to repeated exposure, which may still be driven by the extinction circuitry. To examine if short term extinction mechanisms serve as an experimental model for anxiety relief as a function of repeated exposures to stressful situations, it therefore seems important to characterize within-session alterations in the circuitry supporting extinction. Such

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studies of within-session changes to repeated stress exposure exist in participants with spider phobia, where reduced activity has been noted in the amygdala, whereas no changes were observed in the hippocampus or the vmPFC (Lipka et al., 2014; Veltman et al., 2004). Another study in patients with dental phobia found decreased activity in the vmPFC to repeated stress exposure without any reported change in the amygdala or the hippocampus (Hermann et al., 2013). These findings may call into question whether alterations throughout the whole extinction circuitry are necessary for anxiety relief following exposure therapy, which motivates translational research in other diagnoses than specific phobia.

We here measured within-session changes in regional cerebral blood flow (rCBF) between two consecutive public speaking exposures in patients with SAD and evaluated changes within the hippocampus, vmPFC and amygdala. As a non-anxiogenic control task, patients viewed repeated presentations of neutral or angry facial expressions. For the control task, we expected repeated face presentation to reduce amygdala responses, but to a lesser degree than repeated stress exposure. We also hypothesized that the repeated face presentations would attenuate fusiform face area (FFA) responses.

2. Methods

2.1. Subjects

Thirty-six subjects (20 women, 16 men; age 21–50 years (mean 37.6, SD 8.6)) fulfilling the DSM-IV criteria for SAD, and currently not on medication, were recruited through newspaper advertisements. Structured clinical diagnostic interviews for DSM-IV (SCID) (First et al., 1996) were administered by a clinical psychologist. Subjects also underwent the Swedish version of Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and a medical examination. Main criteria for exclusion were: treatment of social anxiety in the past six months, current serious or dominant psychiatric disorder other than social phobia, chronic use of prescribed medication, abuse of alcohol/narcotics, pregnancy, menopause, left handedness, previous PET-examination, and somatic/neurological disorder that could be expected to influence the outcome of the study. The methods have been described in more detail elsewhere (Furmark et al., 2008, 2005, 2009). Written informed consent was obtained from all subjects. The study was approved by the regional ethic and radio-isotope committees respectively.

2.2. Procedure

2.2.1. Speech task

Participants performed a 2.5 min speech in front of 6–8 silently observing people while being scanned. Heart rate was monitored continuously and the state version of the State-Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970) was administered immediately after the speech. The procedure was repeated after about 30 min of rest. The same speech was performed on both occasions.

2.2.2. Face task

Participants viewed two 2.5 min blocks of faces displaying either neutral or angry emotional expressions. Thirty facial stimuli were displayed within each block. Each face was presented for 3 s with an inter-trial interval of 2 s. Face stimuli were taken from the Ekman series (Ekman and Friesen, 1976). The order of face blocks was counterbalanced between participants so half of them viewed neutral faces first, while the other half viewed angry faces first. This way, responses to the different types of emotional facial expressions were averaged for each exposure. However, the two face tasks always followed the two speech tasks to reduce the influence of anticipatory anxiety during the face task.

2.3. PET assessments

The scanner used was a 32-ring ECAT EXACT HR+(Siemens/CTI, Knoxville, Tennessee) that enables acquisition of 63 contiguous planes of data with a distance of 2.46 mm. This results in a total axial field of view of 155 mm. A 10 min transmission scan was performed using three retractable germanium (68Ge) rotation line sources. As PET tracer, ^{15}O-water was used and approximately 10 MBq/kg of body weight was administered intravenously. The emission scan started automatically when the tracer bolus reached the brain and consisted of three 30-second frames for each speech. It was reconstructed with a filter back projection using an 8-mm Hanning filter, resulting in a spatial resolution of about 5 mm in the field of view that were represented in a matrix of 128*128 pixels. Data were then corrected for photon attenuation, decay, scattered radiation, and random coincidences. To obtain a better statistical power a summation image of the three frames was made. The summation image was realigned to the Montreal neurological institute (MNI) stereotactic template (ICBM 152), using the SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) and images were smoothed using a 12 mm Gaussian kernel.

2.4. State anxiety and psychophysiology

The state version of the State-Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970) was administered immediately after each speech and face task. Heart rate was monitored continuously throughout the PET scanning with Psylab (Contact Precision Instruments Inc., London, UK) using a standard electrocardiography (ECG) lead I and standard collars. Heart rate was calculated from the R-R interval in the ECG and averaged over each 150 s block of the speech and face tasks.

2.5. Statistical analysis

Statistical parametrical maps were computed in the SPM8 (Wellcome Department of Cognitive Neurology, London, UK) software. Bilateral amygdala and hippocampus regions of interest (ROI) were defined as in the Automated Anatomical Labeling (AAL) library in the WFU PickAtlas software (Maldjian et al., 2003). The vmPFC was defined as BA 25 dilated by 2 mm to include all voxels that were circumscribed by this region as defined in the TD library. This region corresponds to cluster 1 in the parcellation by Beckmann et al. (2009), and is the region of the medial PFC with the strongest white matter connectivity to the amygdala. The definition of the FFA was based on a previous study of face processing (Gschwind et al., 2012), that we have previously applied (Ahs et al., 2014). We used family-wise error (FWE) correction for multiple comparisons within each ROI with the statistical level of significance set to $p < 0.05$. Brain locations are described in Montreal Neurological Institute (MNI) coordinates (xyz).

Heart rate and STAI-S changes were evaluated with repeated measures ANOVA performed in SPSS (Version 14.0, SPSS inc., Chicago, Illinois).

3. Results

3.1. State anxiety and heart rate

Heart rate and STAI-S ratings decreased significantly from the first to the second speech, indicating that task repetition was anxiolytic, while the changes in heart rate and STAI-S ratings from the first to the second face-presentation in the control task were non-significant (Fig. 1, Table 1). As predicted, STAI-S ratings and heart rate were higher during speech than face tasks indicating that the speech task successfully induced anxiety (see Table 1 for means; STAI-S: $F_{1,34}$ =106.24, $P < 0.001$; Heart rate: $F_{1,34}$ =68.81, $P < 0.001$).