Psychiatry Research: Neuroimaging 261 (2017) 85–90

Contents lists available at ScienceDirect

Psychiatry Research Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

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

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ARTICLE INFO

Keywords:
Extinction
Social phobia
Cognitive behavior therapy
Amygdala
Hippocampus
VmPFC

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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http://dx.doi.org/10.1016/j.pscychresns.2017.01.009
Received 25 November 2016; Received in revised form 20 January 2017; Accepted 26 January 2017
Available online 28 January 2017
0925-4927/

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, $P < 0.001$).

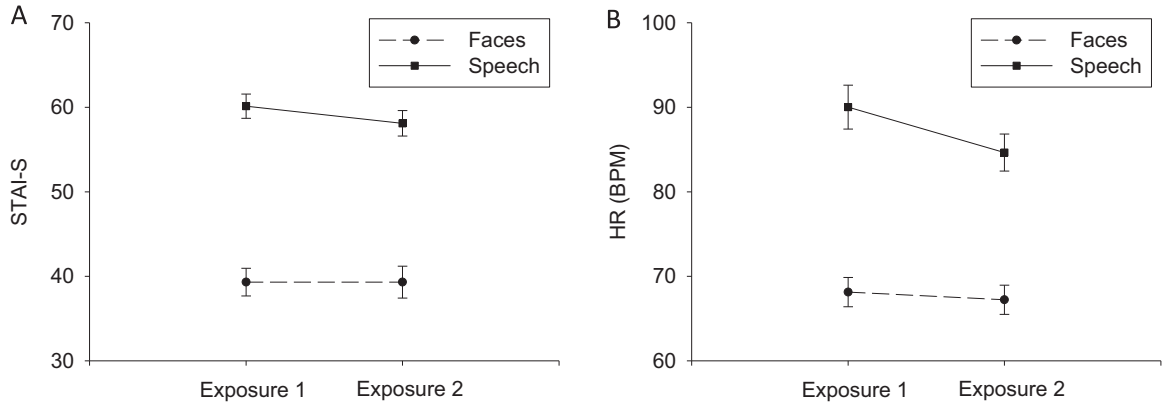

Fig. 1. Change in anxiety ratings (STAI-S) and heart rate (HR) as a function of repeated exposure to a speech stress and facial expressions (control task) respectively. (A) STAI-S decreased from the first to the second speech exposure. In contrast, STAI-S was similar during the first and second face exposure. (B) Heart rate was lower during the second relative to the first speech exposure, whereas it was similar during both face exposures.

3.2. Regional CBF changes in extinction circuitry regions

There was a bilateral decrease in rCBF as a function of speech repetition in the amygdala, while no attenuation of amygdala rCBF following repeated face presentation survived the statistical criterion. The decrease in rCBF as a function of speech repetition was significantly larger than the rCBF alterations induced by face repetition in the right amygdala (Fig. 2, Table 2). No change in rCBF from the first to the second speech was observed in the vmPFC or hippocampus.

The face-related rCBF decrease in the FFA was greater than the change induced by repeated speech performance (Left MNI-coordinates: −34,−64,−26; *Cluster size* =213 voxels; Z =4.88; $P_{FWE} < 0.001$; Right MNI-coordinates: 38,−46,−22; *Cluster size* =49 voxels; Z =4.30; P_{FWE} =0.001), indicating that the rCBF change in this region reflected repeated face exposure, but not anxiety reductions.

Interestingly, amygdala rCBF was greater during face presentations than speeches both during the first (Left MNI-coordinates: −20,2,−20; *Cluster size* =4 voxels; Z =2.72; P_{FWE} =0.04) and second exposure (Left MNI-coordinates: −24,2,−16; *Cluster size* =122 voxels; Z =3.92; P_{FWE} =0.001; Right MNI-coordinates: 28,4,−20; *Cluster size* =179 voxels; Z =4.50; $P_{FWE} < 0.001$), suggesting that the absolute rCBF level in the amygdala may be more sensitive to processing of socio-emotional stimuli than experience of social stress.

3.3. Correlations between rCBF and behavioral measures

We did not observe any correlation between the difference in amygdala rCBF from the first to the second speech and the corresponding difference in heart rate or STAI-S ratings ($Ps > 0.05$).

3.4. Exploratory whole brain analysis

No region with a greater decrease from the first to the second speech than from the first to the second face exposure, survived corrections for multiple comparisons in the whole brain analysis. Instead, we observed two clusters exhibiting a greater rCBF increase following repeated speech exposure than following repeated face exposure. One was located in the dorsal ACC (MNI-coordinates: 2,32,30; *Cluster size* =19 voxels; Z =5.19; P_{FWE} =0.008) while the other was situated in the posterior lobe of the left cerebellum (MNI-coordinates: −32,−64,−26; *Cluster size* =15 voxels; Z =5.03; P_{FWE} =0.02).

4. Discussion

We tested whether anxiety reduction following repeated exposure to a stressful speech task in SAD patients was associated with rCBF alterations in the extinction circuitry. We found partial support for the hypothesis, as amygdala rCBF was attenuated as a function of repeated speech exposure. In contrast, rCBF did not change in the hippocampus or the vmPFC. These results point to a pivotal role for the amygdala in anxiety reduction following repeated exposure to anxiety provoking situations in SAD. Activity change in this region may therefore mediate the long-term anxiolytic effect of psychological treatments involving exposure techniques as previously demonstrated (e.g. Furmark et al., 2002; Mansson et al., 2013). The findings suggest that bottom-up processes rather than top-down influences account for within-session anxiety reductions during exposure therapy in SAD.

The observed within-session reduction in amygdala rCBF is in line with previously observed between-sessions reductions in amygdala rCBF following exposure treatments extending over several weeks (Furmark et al., 2002). Our finding of a lack of change in rCBF in the hippocampus and the vmPFC are in line with the prior findings from studies that have evaluated between-session brain activity changes to symptom specific stressors in SAD following treatment (Bruhl et al., 2014). They also corroborate reports of within-session changes in brain activity in to repeated stress exposure in spider phobia (Lipka et al., 2014; Veltman et al., 2004). We speculate that one reason for the lack

Table 1
Heart rate (HR) in beats per minute (BPM) and state anxiety (STAI-S) ratings during the two speech exposures and the two face presentations.

		Exposure 1		Exposure 2		Difference		Statistics	
Stimuli	Measure	mean	SE	mean	SE	mean	SE	$F_{1,34}$	P
Speech									
	HR (BPM)	90.03	2.59	84.66	2.19	5.37	0.92	24.59	0.00002
	STAI-S	60.14	1.44	58.11	1.50	2.03	0.83	7.46	0.01
Faces									
	HR (BPM)	68.13	1.73	67.22	1.73	0.91	0.54	2.81	0.10
	STAI-S	39.31	1.64	39.31	1.89	0.00	1.09	0.00	1.00

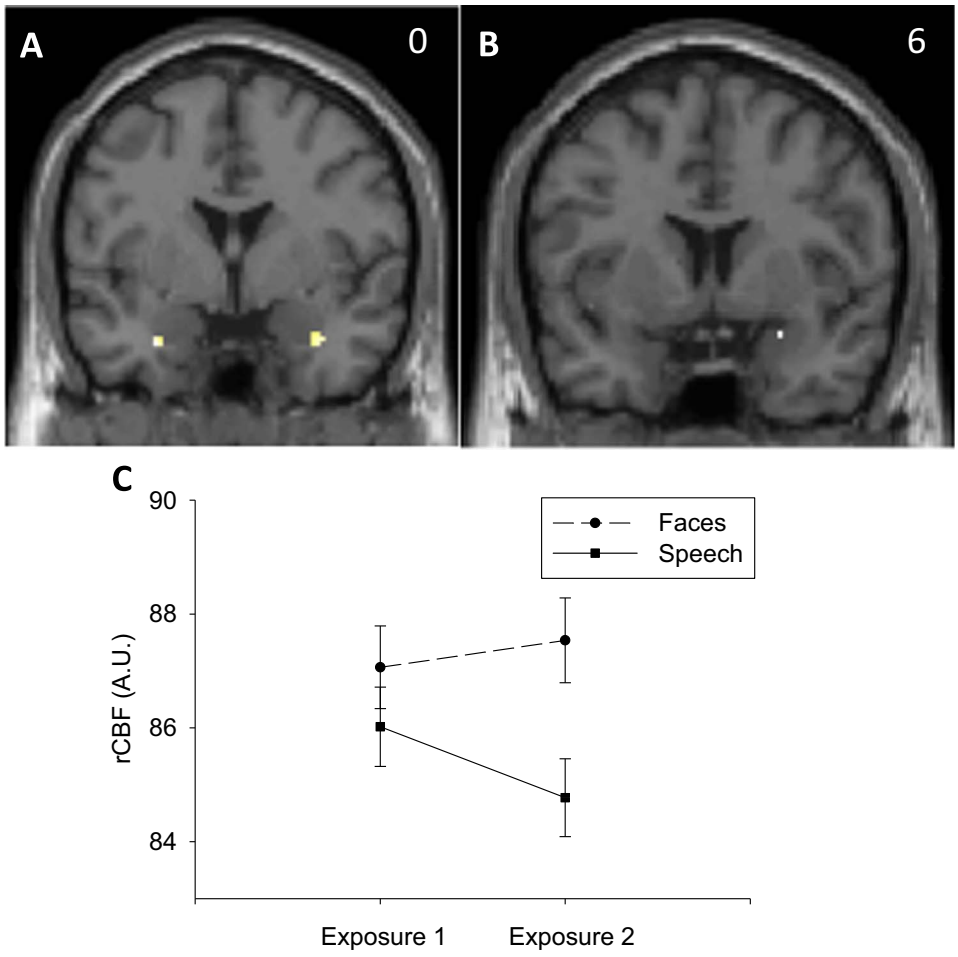

Fig. 2. Attenuation of amygdala rCBF following repeated speech as compared to face exposure. (A) Regional CBF decreased from the first to the second speech in bilateral amygdala. (B) Regional CBF decreased more in the right amygdala following repeated speech exposure than repeated face exposure. The statistical threshold was set to $p < 0.05$ using family wise error correction within the amygdala. (C) Mean rCBF for the first and second speech and face exposures in the voxel in the right amygdala displaying the maximum test statistic. Error bars represent standard error of the mean. rCBF, regional Cerebral Blood Flow.

Table 2
Differences in rCBF as a function of repeated exposure.

	MNI-coordinates			Number of voxels	*Z*	*P* (corrected)
	x	y	z			
Speech 1 > Speech 2						
L Amygdala	−30	0	−28	7	3.29	0.01
R Amygdala	36	2	−26	18	3.17	0.02
(Speech 1 > Speech 2) > (Face 1 > Face 2)						
Left Amygdala	−30	2	−22	–	1.95	0.23
Right Amygdala	26	6	−18	1	2.77	0.05

of vmPFC and hippocampus engagement could be that these regions may not be necessary for within-session anxiety reductions. Supporting this idea, a recent optogenetic study in mice show that extinction learning occurs even when the vmPFC is silenced (Do-Monte et al., 2015). An alternative explanation to the lack of vmPFC and hippocampal involvement could be that habituation, rather than extinction processes, account for exposure induced anxiety reduction. Habituation is a simpler form of learning than extinction, and proceeds without the engagement of prefrontal pathways (Leaton and Supple, 1991; Timmann et al., 1998). Either way, we propose that amygdala alterations may eventually be sufficient to account for exposure therapy.

An interesting observation unrelated to our hypotheses was that the amygdala rCBF level, but not the anxiety ratings, was greater during the face than during the speech task. Thus, between tasks, the average anxiety ratings and amygdala rCBF were negatively correlated. This observation could suggest that rCBF in the amygdala is a less than optimal anxiety read-out and warrants a discussion of whether reduction in amygdala rCBF following repeated exposure mirrors anxiety reduction (See for example Faria et al., 2012). We argue that there are reasons to believe that our finding of decreased amygdala rCBF is related to anxiety reduction. First, individuals with SAD show greater amygdala rCBF and anxiety ratings than healthy controls while performing (Tillfors et al., 2001) or anticipating (Lorberbaum et al., 2004) a speech. Second, several studies in patients with SAD have also reported positive correlations between anxiety ratings and amygdala reactivity (Evans et al., 2008; Phan et al., 2006). Third, individuals with damage to the amygdala are resilient to experience-induced anxiety disorders (Koenigs et al., 2008), suggesting that the amygdala may have a causal role in instigating anxiety. The increased amygdala rCBF to the socioemotional stimuli relative to the speech task therefore likely reflects differences in stimulus characteristics between tasks (Britton et al., 2006; Hariri et al., 2002).

The exploratory whole-brain analysis revealed increased activation of the dorsal ACC and the cerebellum following repeated exposure to the speech task. We speculate that the within-session increase in the dorsal ACC following repeated stress exposure could be related to changes in self-focus during the speech performance. A strong self-focus in performance situations is common in SAD (Clark and Wells,

1995; Spurr and Stopa, 2002) and the ACC has been shown to play a role in processing self-relevant information (Johnson et al., 2006). However, the dorsal ACC has been found to participate in a large variety of tasks such as cardiovascular control (Ahs et al., 2009; Thayer et al., 2012), fear expression (Milad and Quirk, 2012), pain processing (Peyron et al., 2000) and attention (Corbetta et al., 1991), and more studies are needed to disentangle the exact nature of our ACC finding. When considering the increased rCBF in the cerebellum following repeated stress exposure, this result is consistent with our previous observation of increased cerebellar rCBF during public speaking following CBT (Furmark et al., 2002) and may suggest a role also for the cerebellum in anxiety reduction (Schmahmann et al., 2007).

A limitation of the present study was that no healthy control group was included. Therefore, we do not know whether the reductions in the amygdala rCBF are specific to anxiety provocation in SAD or if they also occur in individuals without severe public speaking fears. Also, the inclusion of additional public speaking exposures could have informed on the dynamics of anxiety reduction as a function of repeated exposure over time. It may be that the vmPFC and hippocampus are involved in anxiety attenuation following several phobogenic exposures, and that the amygdala is involved in early anxiety reduction.

In conclusion, alterations in amygdala activity modulate short term anxiolysis following stress exposure in individuals with SAD without noticeable contribution from other nodes of the extinction circuitry. This finding may aid in understanding the working mechanisms of exposure therapy.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

This study was supported by grants from the Swedish Research Council and the Swedish Brain Foundation as well as by financial support from GlaxoSmithKlein.

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