

Social anxiety modulates amygdala activation during social conditioning

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Aversive social learning experiences might play a significant role in the aetiology of social anxiety disorder. Therefore, we investigated emotional learning and unlearning processes in healthy humans using a social conditioning paradigm. Forty-nine healthy subjects participated in a 2-day fMRI differential conditioning protocol. Acquisition and extinction were conducted on Day 1 and extinction recall on Day 2. BOLD responses, ratings and skin conductance responses were collected. Our data indicate successful conditioning and extinction on the neural and subjective level. As a main result, we observed a positive correlation of social anxiety and conditioning responses on the subjective level (valence and fear) as well as on the neural level with significant CS⁺/CS⁻ differentiation in the left amygdala and the left hippocampus. Further, significant CS⁺/CS⁻ differentiation in the left amygdala was found during extinction and was associated with lower scores in social anxiety. During extinction recall, we found a tendentially negative correlation of social anxiety and CS⁺/CS⁻ differentiation in the vmPFC. In sum, we were able to show that social anxiety is related to conditionability with socially threatening stimuli. This could point to an important aspect in the aetiology of social anxiety disorder.

Keywords: amygdala; fMRI; fear conditioning; social anxiety; extinction

INTRODUCTION

Social anxiety disorder—the diagnostic term for excessive fear in response to social situations (American Psychiatric Association, 2000)—is a prevalent disorder with its onset commonly during adolescence (Wittchen and Fehm, 2003; Kessler *et al.*, 2010). Considering its aetiology, negative social events (e.g. public humiliation, teasing) are discussed as important environmental factors (Erwin *et al.*, 2006; McCabe *et al.*, 2010; Carleton *et al.*, 2011). Emotional learning, e.g. fear conditioning, is thus one possible mechanism underlying the development and generalization of (pathological) social anxiety (Mineka and Zinbarg, 2006; Mineka and Oehlberg, 2008). However, the exact relationship between social anxiety and conditionability in social situations has barely been investigated.

Human neuroimaging studies on emotional learning emphasize the role of the ‘fear circuit’ comprising amongst others amygdala (Büchel *et al.*, 1998; Büchel and Dolan 2000; LeDoux, 2000; Ohman, 2005), insula (Etkin and Wager, 2007) and (dorsal) anterior cingulate gyrus (Büchel, 1998; Milad *et al.*, 2007) in the acquisition of emotional responses. In addition to fear acquisition, also the failure to extinguish conditioned fear may be important in the pathogenesis of anxiety disorders (Davis *et al.* 2006; Milad *et al.*, 2006, 2007, 2009). Like other types of learning, extinction occurs in three phases: acquisition, consolidation and recall of extinction (Quirk and Mueller, 2008; Herry *et al.*, 2010). Amygdala,

hippocampus and the medial prefrontal cortex (Quirk *et al.*, 2003; Phelps *et al.*, 2004; Bouton *et al.*, 2006; Quirk and Mueller, 2008; Lang *et al.* 2009; Herry *et al.*, 2010) are often found to be involved in the extinction process.

Differential fear conditioning paradigms are suitable for the investigation of the acquisition and the extinction of fear responses. Thereby, the paired (CS⁺) but not the unpaired (CS⁻) conditioned stimulus predicts an aversive unconditioned stimulus (UCS). Stronger responses to the CS⁺ compared with the CS⁻ indicate fear acquisition (Büchel and Dolan, 2000; DeHouwer *et al.*, 2001). Omitting the presentation of the UCS allows the investigation of extinction processes (Milad and Quirk, 2002).

Only few studies (Schneider *et al.*, 1999; Veit *et al.*, 2002; Hermann *et al.*, 2002) investigated conditioning and extinction processes in patients with social anxiety disorder. In these studies, socially irrelevant unconditioned stimuli were used and the results were inconclusive. Of specific importance are studies using socially relevant unconditioned stimuli (e.g. insults, negative evaluation) because these resemble more closely the socially aversive events discussed in relation to the aetiology of the disorder. There are only two studies investigating conditioning processes with disorder-relevant UCS (social conditioning): critical facial expressions with written verbal comments in healthy subjects (Davis *et al.*, 2010) and critical facial expressions with verbal feedback in social phobics (Lissek *et al.*, 2008). Exploring the neural correlates of social conditioning, Davis and colleagues (2010) demonstrated increased amygdala activation during the acquisition of conditioned responses. Lissek *et al.* (2008) were able to show facilitated acquisition but no reduced

Received 24 August 2011; Accepted 27 November 2011

We would like to thank Agnes Burek and Sarah Eggenwirth for help in data acquisition.

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extinction of fear responses as measured by fear potentiated startle in social phobics compared to healthy controls. To date, there are no social conditioning studies investigating the neural correlates of extinction learning and retrieval and the modulation of social conditioning by social anxiety.

Thus, we investigated the neural basis of acquisition, extinction learning and recall during social conditioning using social anxiety relevant conditioned (neutral faces) and unconditioned stimuli (film-clips with critical comments). The main goal of this functional magnetic resonance imaging (fMRI) study was to explore the relationship between social anxiety and conditionability including acquisition and extinction. We hypothesized that subjects with higher social anxiety would show greater subjective, electrodermal and neural [amygdala, insula, dorsal anterior cingulate cortex (dACC) and hippocampus] conditioned responses during acquisition. For extinction, we expected reduced extinction learning and recall associated with reduced neural activation in ventromedial prefrontal cortex, hippocampus and amygdala.

We investigated 49 healthy subjects that underwent acquisition and extinction learning and completed a questionnaire on social anxiety (Sosic *et al.*, 2008) on Day 1, followed by the recall of extinction ~24 h later.

MATERIALS AND METHODS

Subjects

Forty-nine healthy subjects (23 females, 26 males) participated in this fMRI study, which was approved by the Ethics Committee of the German Psychological Society. It was part of a larger study investigating the neural basis of emotional learning and regulation processes. Most participants were students, all of them were right-handed. Exclusion criteria were medical, neurological and psychiatric diseases, MRI contraindications, or use of psychoactive or other potentially confounding drugs or medications. All subjects gave written informed consent in accordance with the guidelines of the ethical standards of the Declaration of Helsinki. They were told that they could terminate the experiment at any time.

Eight subjects were excluded due to extensive head movements, technical problems with the stimulus presentation, early termination of the experiment, one subject fell asleep and one was excluded due to an outlier score (>2 SDs above the mean) in the social phobia inventory (SPIN; 32) (Sosic *et al.*, 2008). Thus, data of 41 subjects (19 females, 22 males) with a mean age of 23.49 (s.d. = 3.075, ranged: 19–32 years) were included in the final analysis.

Social phobia inventory

All subjects completed the German version of the SPIN (Sosic *et al.*, 2008), a self-report scale assessing three important dimensions (fear, avoidance and physiology) of social phobia. Seventeen items are rated on a scale ranging from 0 = 'not at all' to 4 = 'extremely'. The total score can range

from 0 to 68. The final sample had a mean score of $M = 14.43$ (s.d. = 7.91; range: 0–36).

Stimuli

Four pictures of neutral facial expressions from two female and two male actors served either as CS^+ or CS^- (CS types: female CS^+ , female CS^- , male CS^+ , male CS^-). Actors were similar in age, but had different hair coloring. To assess neutrality of the faces, 20 healthy students (10 females/10 males) provided ratings regarding the emotional expression in a pre-study. The unconditioned stimuli (UCS) consisted of 17 film-clips (each with a duration of 3 s) of critical comments (e.g. 'you are incompetent', 'you are boring me'). The actor in the film-clip (UCS) always corresponded with the actor in the picture shown as CS^+ immediately before.

For visual stimulation inside the scanner, an LCD projector (model EPSON EMP-7250) was used, which projected the stimuli onto a screen at the end of the scanner (visual field = 18°). Pictures and videos were viewed by means of a mirror mounted to the head coil. The sound level for stimulus presentation was adjusted individually for each subject.

Experimental procedure

Participants underwent a 2-day differential fear acquisition, extinction learning and extinction recall protocol in a 1.5-T scanner. Acquisition and extinction were conducted on Day 1, extinction recall ~24 h later. Subjects were informed in a written instruction that they would take part in a study examining the neurobiological correlates of emotion regulation. They were told that they would see pictures and film-clips of different persons and to watch attentively and imagine themselves in the situation. Subjects were not told about the contingencies or that it was a conditioning experiment until the end of the experiment on Day 2.

The acquisition phase consisted of 68 trials (17 per CS type). In every trial, one of the two CS^+ (one male and one female) or one of the two CS^- (one male and one female) was presented for 8 s. The CS^+ was always paired (100% reinforcement) with a critical comment in a 3-s film-clip (UCS), whereas the CS^- was never paired with the UCS. The UCS immediately followed the CS^+ presentation. Throughout the experiment, each CS^+ was paired with each of the 17 critical comments (UCS). Inter-trial intervals ranged from 16.25 to 18.75 s with a mean duration of 17.5 s. At the beginning of the acquisition phase, each CS was presented once (four trials); these trials were not included in the analyses. The remaining 64 trials were arranged in four blocks of 16 trials (4 × male CS^+ , 4 × male CS^- , 4 × female CS^+ , 4 × female CS^-). A pseudo-randomized stimulus order was used comprising the following restrictions: not more than three consecutive CS^+ trials (female or male actor) or three consecutive CS^- trials (female or male actor), and not more than twice the same sex (female or male actor).

Extinction learning was conducted after the acquisition phase and consisted of 13 trials of each CS (duration: 8 s; 52 trials altogether) without subsequent UCS presentation (mean trial duration: 17.5 s). Again, at the beginning of the extinction, each CS was presented once (four trials); these trials were not included in the analyses. The remaining 48 trials were arranged in three blocks of 16 trials (4 × male CS⁺, 4 × male CS⁻, 4 × female CS⁺, 4 × female CS⁻). The same restrictions for the stimulus order were applied.

The extinction recall phase (1 day later) consisted of 12 trials of each CS (duration: 8 s; 48 trials altogether). The 48 trials were arranged in three blocks of 16 trials (4 × male CS⁺, 4 × male CS⁻, 4 × female CS⁺, 4 × female CS⁻). The same restrictions for the stimulus order were applied.

All three learning phases started with a CS⁺ for half of the subjects, with a CS⁻ for the other half, and the assignment of the two female/male faces to the CS⁺ or CS⁻ was balanced across subjects.

Behavioral data

Evaluative conditioning was assessed inside and outside the scanner with ratings of the CS on three dimensions: valence and arousal with the Self Assessment Manikin (SAM; [Bradley and Lang, 1994](#)) and fear on a 9-point Likert scale. The ratings were assessed before and after acquisition, after extinction, before and after extinction recall. Ratings ranged from 1 (indicating: very unpleasant, not arousing at all, not fear inducing) to 9 (indicating: very pleasant, very arousing, very fear-inducing).

After the experiment, participants retrospectively rated the UCS on the dimensions valence, arousal and fear. Awareness of stimulus contingencies was assessed after the acquisition phase. The participants were requested to state for each CS separately how often during the experiment the picture of this person was followed by a film clip of the same person ('always', 'sometimes', 'never' or 'I don't know').

Skin conductance response

Skin conductance responses (SCRs) were collected during fMRI through AC/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte medium, placed hypothenar at the nondominant left hand. SCRs were defined in three analysis windows ([Prokasy and Ebel, 1967](#)). The maximum SCR signal between 1 and 5 s after stimulus onset was defined as the first interval response (FIR), within the time window of 5–8.5 s as the second interval response (SIR), and within the time window of 8.5–13 s as the third interval response (TIR; unconditioned response after CS⁺, respectively omission response after CS⁻). Conditioned responses were defined as larger response magnitudes in reaction to the CS⁺ than to the CS⁻ in FIR and SIR. A logarithmic transformation was conducted to ensure comparability between the subjects and to render the distribution more toward normal data of each response interval. Mean responses for

female CS and male CS were combined and then explored. Statistical analyses were performed using paired *t*-tests as implemented in PASW for Windows (Release 18.0; SPSS Inc. IL, USA). Data of 14 subjects had to be discarded because of technical problems during measurement or non-responding, leaving 27 subjects for the final analysis. Subjects were classified as non-responders, if they did not show at least three SCRs >0.05 μ s during the acquisition phase.

Magnetic resonance imaging

Brain images were acquired using a 1.5-T whole-body tomograph (Siemens Symphony with a quantum gradient system) with a standard head coil. A total of 1245 volumes was registered (acquisition: 498 volumes, extinction: 387 volumes, extinction recall: 360 volumes) using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 25 slices covering the whole brain (slice thickness = 5 mm; 1 mm gap; descending slice order; TA = 100 ms; TE = 55 ms; TR = 2.5 s; flip angle = 90°; field of view = 192 × 192 mm; matrix size = 64 × 64). Due to an incomplete steady state of magnetization, the first three volumes were discarded. The orientation of the axial slices was parallel to the OFC tissue–bone transition. Before each functional run, an anatomical scan was conducted to get highly resolved structural information for the normalization procedure. A gradient echo field map sequence was measured to get information for unwarping B_0 distortions. Data analysis was carried out with Statistical Parametric Mapping software (SPM5, Wellcome Department of Cognitive Neurology, London, UK; 2005) implemented in MatLab R2007b (Mathworks Inc., Sherborn, MA, USA). After unwarping and realignment (b-spline interpolation), slice time correction and normalization to the standard space of the Montreal Neurological Institute brain (MNI brain) was conducted. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full-width at half maximum (FWHM) of 9 mm.

All phases of the conditioning procedure were implemented in the first-level model (with three sessions), resulting in the following regressors: female CS⁺_{acquisition}, male CS⁺_{acquisition}, female CS⁻_{acquisition}, male CS⁻_{acquisition}, female UCS_{acquisition}, male UCS_{acquisition}, female non-UCS_{acquisition}, male non-UCS_{acquisition}, female CS⁺_{extinction}, male CS⁺_{extinction}, female CS⁻_{extinction}, male CS⁻_{extinction}, female UCS_{extinction}, male UCS_{extinction}, female non-UCS_{extinction}, male non-UCS_{extinction}, female CS⁺_{recall}, male CS⁺_{recall}, female CS⁻_{recall}, male CS⁻_{recall}, female UCS_{recall}, male UCS_{recall}, female non-UCS_{recall}, male non-UCS_{recall}. There were two further regressors for the first trial of each CS presentation during acquisition (regressor 1) and during extinction learning (regressor 2).

These 26 regressors were each modeled by a stick function convolved with a hemodynamic response function (hrf) in the general linear model, with a duration of 0 s for the CS and 3 s for the (non-)UCS. The non-UCS

(after CS⁻ presentation) was defined as the corresponding time windows of UCS presentation. The six-movement parameters of the rigid body transformation applied by the realignment procedure were introduced as covariates in the model. The voxel-based time series were filtered with a high-pass filter of 128 s. Conditioned responses (CS⁺ minus CS⁻ for each phase, averaged across both sex CS) were calculated on an individual level and analyzed in one-sample *t*-tests in second-level analyses as implemented in SPM5. ANOVA revealed no significant interactions between sex of participants and sex of stimuli, which allowed us to combine the male and female CS for further calculations. In order to evaluate the modulation of conditioned neural responses by social anxiety, simple regression analyses with the sum score of the SPIN as covariate was conducted for each phase.

ROIs for analyses were amygdala, insula, hippocampus, dACC and vmPFC. The intensity threshold was set to a value corresponding to $P=0.05$ uncorrected and the significance threshold to $\alpha=0.05$ on voxel level, corrected for multiple testing [family wise error (FWE) correction]. ROI analyses were performed using the small volume correction option of SPM5. The masks for the ROI analyses for amygdala, insula and hippocampus were maximum probability masks taken from the current 'Harvard-Oxford Cortical and Subcortical Structural Atlases' provided by the Harvard Center for Morphometric Analysis (<http://www.cma.mgh.harvard.edu/>) with the probability threshold at 0.25 included in the FSL software package (<http://www.fmrib.ox.ac.uk/fsl/>). Masks for the dACC and vmPFC were created by the MARINA software package (Walter et al., 2003).

RESULTS

Acquisition

Unconditioned responses

All subjects rated the UCS as significantly unpleasant ($M=3.54$, $s.d.=1.20$), arousing ($M=4.18$, $s.d.=1.93$) and fear inducing ($M=2.57$, $s.d.=1.96$) (one-sample *t*-tests; all $P<0.05$). Regarding SCRs, a significant unconditioned response was observed during UCS processing, indicating higher SCRs during the UCS than during its omission (paired *t*-test; $T=2.382$, $P=0.025$). On the neural level, all ROIs showed significant unconditioned responses (all $P_{\text{corr,ROI}}<0.05$). No significant correlation between unconditioned responses (subjective, electrodermal and neural) and social anxiety could be observed.

Contingency awareness

Participants were classified as contingency aware if they indicated that the two CS⁺ were 'sometimes' or 'always' followed by critical film clips and the two CS⁻ were 'never' followed by a film clip. This led to the classification of 38 out of 41 participants as contingency aware: all participants answered that the CS⁺ was 'always' (25 participants) or 'sometimes' (16 participants) followed by a film-clip. Regarding the CS⁻,

38 subjects correctly answered that the neutral picture they had seen was 'never' followed by a film clip. The remaining three participants were classified as unaware (two persons answered that they 'don't know' and one rated 'sometimes' for the CS⁻).

Evaluative conditioning and SCR

CS ratings collected before acquisition showed no significant differences between CS⁺ and CS⁻ on the dimensions valence ($T=1.448$, $P=0.156$), arousal ($T=-0.086$, $P=0.932$) and fear ($T=-0.443$, $P=0.660$). After acquisition, CS⁺ in contrast to CS⁻ was rated as significantly more unpleasant ($T=-6.554$, $P<0.001$), arousing ($T=6.311$, $P<0.001$) and fear inducing ($T=4.096$, $P<0.001$). Pre-compared to post-acquisition, the CS⁺ in contrast to the CS⁻ was rated as more unpleasant ($T=-6.972$, $P<0.001$), arousing ($T=6.363$, $P<0.001$) and fear provoking ($T=4.399$, $P<0.001$) (paired *t*-tests). So far, subjects successfully learned the predictive nature of the neutral faces. Notably, a higher degree of social anxiety was associated with a stronger increase of unpleasantness ($r=-0.446$, $P=0.003$) and fear ($r=0.338$, $P=0.031$); no significant correlation was found for the arousal ratings ($r=0.233$, $P=0.143$).

There were no conditioned electrodermal responses and no modulation of SCRs by social anxiety during acquisition.

fMRI data

Conditioned neural responses to the contrast CS⁺ minus CS⁻ were seen in the left amygdala (Table 1). In addition, increased marginally significant BOLD responses were found in the right dACC and the left hippocampus.

In order to examine the association between social anxiety and conditioned neural responses, we correlated the total score of the SPIN with the neural activation for the contrast CS⁺ minus CS⁻. We found significant positive correlations of social anxiety with BOLD responses for this contrast in the left amygdala and the left hippocampus (Table 2 and Figure 1).

Extinction learning

Evaluative conditioning and SCR

CS ratings collected after extinction learning showed significant differences between CS⁺ and CS⁻ on the dimensions valence ($T=-5.558$, $P<0.001$), arousal ($T=4.546$, $P<0.001$) and fear ($T=3.708$, $P<0.001$).

Pre-compared to post-extinction, the CS⁺ in contrast to the CS⁻ was rated as less unpleasant ($T=3.357$, $P=0.002$), less arousing ($T=-4.367$, $P<0.001$) and less fear inducing ($T=-3.070$, $P=0.004$) (paired *t*-tests). There was no significant correlation of this contrast (CS⁺ minus CS⁻, pre-compared to postextinction) with social anxiety (all $P>0.10$). Furthermore, there were no conditioned electrodermal responses and no modulation of SCRs by social anxiety.

Table 1 Localization, cluster size (k) and statistics of the peak voxels within the respective ROI resulting from the contrasts CS^+ minus CS^- in acquisition, extinction learning and extinction recall are shown (one-sample t -tests)

Contrast	Brain region	x	y	z	k	T_{\max}	P_{corr}
Acquisition CS^+ minus CS^-	L amygdala	-12	-6	-18	13	3.66	0.014
	L hippocampus	-12	-9	-18	5	3.40	0.054
	R dACC	12	15	33	140	3.61	0.054
Extinction learning CS^+ minus CS^-	L amygdala	-15	-9	-18	70	3.14	0.039
	R amygdala	33	-3	-24	47	3.00	0.053
	L hippocampus	-15	-9	-21	77	3.08	0.095
	R hippocampus	33	-9	-27	71	3.23	0.064
Extinction recall CS^+ minus CS^-	No significant activations						

The significance threshold was $P_{\text{corr.}} < 0.05$ (ROI analyses; FWE-corrected according to SPMS; small volume correction); All coordinates (x, y, z) are given in MNI space. L = left, R = right.

Table 2 Localization, cluster size (k) and statistics of the peak voxels within the respective ROI resulting from correlation analyses with social anxiety (SPIN) and BOLD responses in the contrast CS^+ minus CS^- in acquisition, extinction learning and extinction recall are shown

Contrast	Brain region	x	y	z	k	T_{\max}	P_{corr}
Positive correlation with social anxiety during acquisition CS^+ minus CS^-	L amygdala	-12	-6	-21	71	3.45	0.023
	L hippocampus	-33	-21	-15	83	3.58	0.037
Negative correlation with social anxiety during extinction learning CS^+ minus CS^-	L amygdala	-15	-9	-18	35	3.32	0.027
	R amygdala	33	-3	-24	40	2.80	0.079
	L hippocampus	-15	-12	-18	80	3.33	0.058
	R hippocampus	15	-15	-21	118	4.89	0.001
Negative correlation with social anxiety during extinction recall CS^+ minus CS^-	L vmPFC	-9	60	-3	106	3.64	0.055

The significance threshold was $p_{\text{corr.}} < 0.05$ (ROI analyses; FWE-corrected according to SPMS; small volume correction); All coordinates (x, y, z) are given in MNI space. L = left, R = right.

fMRI data

During extinction, significant differential responses (CS^+ minus CS^-) were found in the left amygdala, as well as trends in the right amygdala and the bilateral hippocampus (Table 1).

In addition, a significant negative correlation of social anxiety with BOLD responses for the contrast CS^+ minus CS^- in the left amygdala and the right hippocampus was found, indicating less activation in these regions in persons with higher levels of social anxiety (Table 2 and Figure 2). Further, tendentially significant negative correlations were found in the left hippocampus and the right amygdala.

Extinction recall

Evaluative conditioning and SCR

CS ratings collected before extinction recall showed significant differences between CS^+ and CS^- on the dimensions valence ($T = -5.458$, $P < 0.001$), arousal ($T = 4.245$, $P < 0.001$) and fear ($T = 3.632$, $P = 0.001$). Also after recall

a significant difference between CS^+ and CS^- regarding valence ($T = -4.375$, $P < 0.001$), arousal ($T = 4.467$, $P < 0.001$) and fear ($T = 2.823$, $P = 0.007$) was found.

There were no differences in valence, arousal and fear ratings after extinction learning than prior to extinction recall (CS^+ minus CS^-). Further, no rating differences were found pre to post extinction recall and no significant correlations with social anxiety (all $P > 0.10$) could be observed.

During extinction recall no conditioned skin conductance responses were observed in the FIR or SIR, and no modulation of SCRs by social anxiety.

fMRI data

For the extinction recall, we observed no significant differential BOLD responses (CS^+ minus CS^-). Correlations with social anxiety revealed that subjects with higher levels of social anxiety showed (marginally significant) decreased BOLD response in the left vmPFC (Table 2).

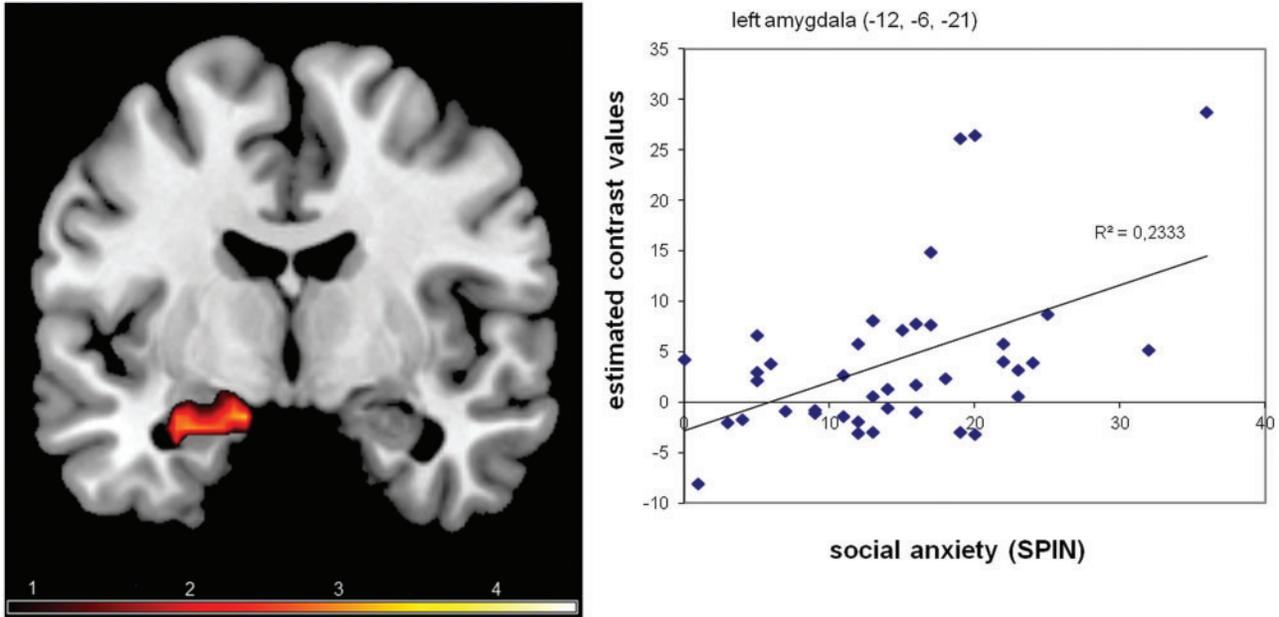


Fig. 1 Correlation of social anxiety (SPIN) with BOLD response in the left amygdala during acquisition (contrast CS^+ minus CS^-).

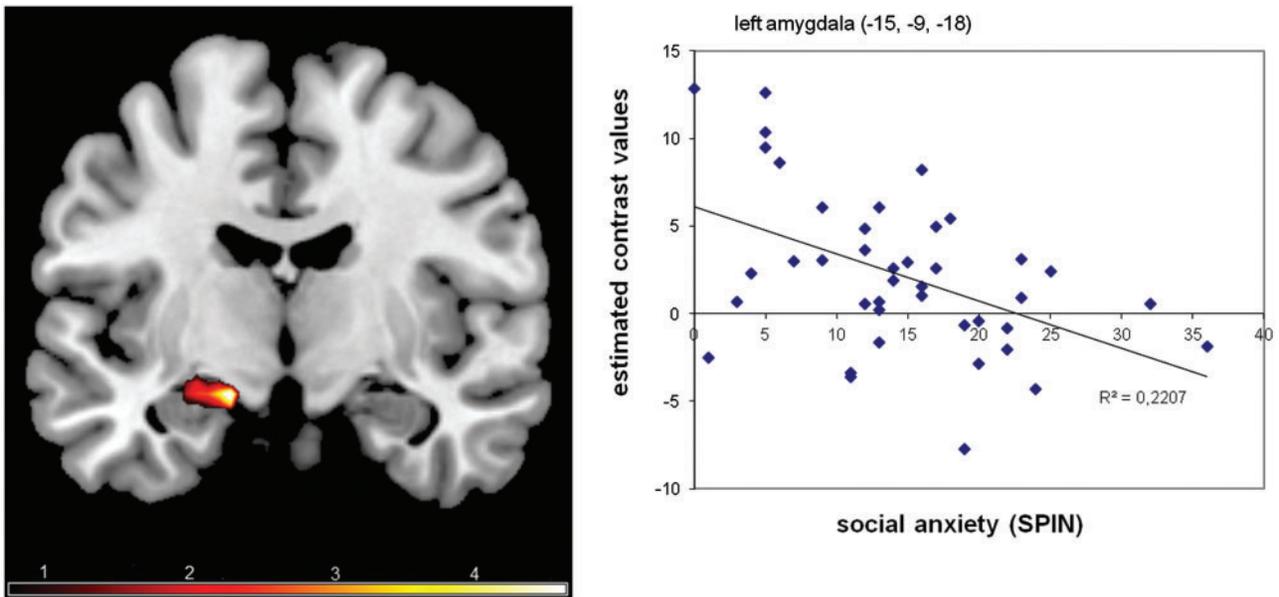


Fig. 2 Correlation of social anxiety (SPIN) with BOLD response in the left amygdala during extinction learning (contrast CS^+ minus CS^-).

DISCUSSION

Negative social learning experiences are assumed important factors in the development and maintenance of (pathological) social anxiety (Erwin *et al.*, 2006; McCabe *et al.*, 2010; Carleton *et al.*, 2011) due to altered conditioning processes. Starting from this hypothesis, we investigated the correlation between social anxiety and conditionability in an unselected sample with varying levels of social anxiety. We employed a social conditioning paradigm with acquisition,

extinction and extinction recall using socially threatening stimuli (e.g. offending statements as UCS).

Unconditioned responses

The insulting video clips led to negative ratings, increased SCRs and more neural activation in all ROIs, indicating that emotion induction was apparently successful. However, no relation with social anxiety was observed. This might at first seem surprising, if one considers that socially anxious

individuals normally respond stronger to socially threatening stimuli than less socially anxious individuals (Birbaumer *et al.*, 1998; Tillfors *et al.*, 2001, 2002; Stein *et al.*, 2002; Lorberbaum *et al.*, 2004; Straube *et al.*, 2004; Cooney *et al.*, 2006; Phan *et al.*, 2006; Evans *et al.*, 2008; Furmark, 2009). Yet, these studies mainly used stimuli and procedures inducing 'fear of negative evaluation', e.g. giving a speech (Tillfors *et al.*, 2001, 2002; Lorberbaum *et al.*, 2004), neutral faces (Birbaumer *et al.*, 1998; Cooney *et al.*, 2006), or emotional faces (Stein *et al.*, 2002; Straube *et al.*, 2004; Phan *et al.*, 2006; Evans *et al.*, 2008). Thus, these studies did not directly apply negative evaluation (this is arguable regarding emotional faces). In contrast, in the present experiment participants were insulted, which means that 'explicit negative evaluation' and not merely 'fear of negative evaluation' occurred. Therefore, our results imply that 'explicit negative evaluation' seems to trigger responses on the subjective, autonomic and central level in all individuals independent of their social anxiety scores. This is in line with the findings by Lissek *et al.* (2008) using a rather similar experimental design. Besides their finding of a facilitated fear acquisition in social phobics by enhanced startle responses, they also found no influence of social anxiety scores on subjective unconditioned responses. One could hypothesize that social anxiety does not influence the immediate reaction toward socially threatening events but the further processing of these events, e.g. by retrospective rumination (Clark and Wells, 1995; Rapee and Heimberg, 1997). Future research has to further clarify this issue.

Acquisition

Regarding the acquisition phase, we observed evaluative learning. Pre-compared to post-acquisition, the CS⁺ compared to the CS⁻ was rated as more arousing, fear inducing and unpleasant. Further, the higher the level of social anxiety, the higher the ratings of fear and unpleasantness of the CS⁺ compared to the CS⁻ after the acquisition phase compared to prior acquisition.

On the neural level, we observed enhanced differential activation in the left amygdala and trends in the right dorsal ACC and the left hippocampus for the contrast CS⁺ minus CS⁻. All of these structures are part of the human fear network. It is well established that the amygdala plays an important role in the acquisition and expression of learned fear associations (Phelps and LeDoux, 2005; Furmark, 2009; Sehlmeier *et al.*, 2009). In a social learning task, this region has been shown to be sensitive to signals predicting biological relevant outcome such as evaluating individual faces based on the social outcome they predicted in the past (Davis *et al.*, 2010). Dorsal ACC activation during fear acquisition, as found in our study, is often reported in fear-conditioning studies (e.g. LaBar *et al.*, 1998; Büchel and Dolan, 2000; Knight *et al.*, 2004; Milad *et al.*, 2007) and discussed as a typical finding during the anticipation of threat (Mechias *et al.*, 2010). Through its excitatory projections to the

basolateral amygdala, this structure is thought to be involved in mediating fear expression by excitation of the amygdala (Milad *et al.*, 2007). The observed left hippocampal activation may, in addition to the amygdala activation, reflect associative processing of emotional stimuli in declarative memory (Killgore *et al.*, 2000; Knight *et al.*, 2004).

Of particular interest is the positive correlation between social anxiety and activation in left amygdala and left hippocampus for the contrast CS⁺ minus CS⁻. Hyperactivation of the amygdala in social anxiety disorder is a common finding in studies investigating the processing of emotional faces signalling social threat (Stein *et al.*, 2002; Straube *et al.*, 2004; Phan *et al.*, 2006; Evans *et al.*, 2008; Klumpp *et al.*, 2010) and fear conditioning (Schneider *et al.*, 1999). In line with previous research (Lissek *et al.*, 2008), the stronger activation in this region in higher socially anxious subjects could be interpreted as a marker for heightened conditionability towards social threat in those subjects. Furthermore, this enhanced conditionability might be an important mechanism in the aetiology and generalisation of (pathological) social anxiety. However, further prospective studies and studies investigating patients with social anxiety disorder are needed for a clearer and more detailed interpretation.

Contrary to the ratings and the neural responses, our results showed no conditioned SCRs. However, it is not uncommon that conditioning responses differ on the different response measures (Tabbert *et al.*, 2006). Further, conditioned SCRs are a typical finding in studies using electrical stimulation as UCS (i.e., Büchel and Dolan, 2000; Merz *et al.*, 2011); studies using less intrusive UCS (e.g. highly emotional pictorial stimuli) often reported no significant differential SCRs (Klucken *et al.*, 2009; Schweckendiek *et al.*, 2011).

Extinction learning

On the subjective level, the differential evaluations of the CS⁺ and the CS⁻ were reduced after extinction in contrast to after acquisition. So far, the neural mechanisms underlying fear extinction, especially in humans, are not very well understood (Quirk and Mueller, 2008; Li *et al.*, 2009). The observation that fear spontaneously recovers after extinction learning has proposed the theory that extinction does not erase the CS–UCS association but forms a new memory trace that inhibits conditioned responses (Quirk, 2002; Quirk and Mueller, 2008; Li *et al.*, 2009).

As a main result during extinction learning, we found a significant increased left amygdala and marginally significant increased right amygdala activation in response to the CS⁺ compared with the CS⁻. This is in accordance with other studies showing an increase of activation in this region (LaBar *et al.*, 1998; Knight *et al.*, 2004; Gottfried and Dolan, 2004) interpreting heightened amygdala activation as the establishment of new associations when relationships of stimuli change (Knight *et al.*, 2004). Nevertheless, other studies report contrary findings, e.g. reduced extinction

learning in the amygdala in response to the CS⁺ in contrast to the CS⁻ (Phelps et al., 2004; Sehlmeier et al., 2011). These contrary findings might be explained by use of different UCS or other methodological procedures (number of extinction trials, early vs late extinction learning). Altogether the previous results indicate that the amygdala is important not only for the acquisition of fear but also for extinction learning.

The negative correlation between the levels of social anxiety and neural activation in response to the CS⁺ compared to CS⁻ in the left amygdala and the right hippocampus during fear extinction might indicate that in subjects with higher levels of social anxiety less fear extinction occurred than in subjects with lower levels of social anxiety. However, it is important to note that this is only one possible interpretation because so far it is uncertain how to interpret, e.g. increased amygdala activation during extinction learning. Unfortunately, the non-significant SCR conditioning effects hamper a further clarification.

Similar to the amygdala, the hippocampus has also been related to learning of altered stimulus relations during extinction, reflecting more declarative aspects of the extinction memory formation process (Knight et al., 2004; Tabbert et al., 2011).

Extinction recall

Since failure to retrieve extinction memory is thought to be important for the development and maintenance of anxiety disorders (Milad et al., 2009), we tested the extinction after 1 day by means of extinction recall. Poor retrieval could be due to uncovering phenomena like spontaneous recovery, renewal or reinstatement (Quirk, 2002).

Considering the ratings, retrieval of extinction memory was successful: the ratings of the CS⁺ and the CS⁻ did not change from after extinction learning to before extinction recall. Despite no significant neural findings for the contrast CS⁺ minus CS⁻, our data showed a tendentially significant negative correlation between vmPFC activity (in response to the CS⁺ compared to CS⁻) and social anxiety, suggesting a reduced activation of this region in high socially anxious subjects during extinction recall. This is in line with previous non-human and human studies indicating the important role of the vmPFC in extinction recall (Maren and Quirk, 2004; Milad et al., 2005, 2007; Kalish et al., 2006; Rauch et al., 2006; Quirk and Beer, 2006) by regulating fear expression through inhibition of the amygdala (Gottfried and Dolan, 2004; Phelps et al., 2004; Quirk and Beer, 2006). Only few studies investigated the neural basis of conditioning and extinction processes in patients with anxiety disorders. Milad et al. (2009) found vmPFC deactivation during extinction recall in a differential conditioning paradigm contrasting an extinguished with an unextinguished CS⁺ in a PTSD group vs a trauma-exposed non-PTSD group. The authors hypothesize that this failure to activate the vmPFC and the hippocampus during extinction recall

may contribute to a deficient expression of extinction memory in PTSD patients. Hypoactivation of the vmPFC during symptom provocation, in general, is a typical finding in anxiety disorders as, for example, PTSD (Etkin and Wager, 2007) or specific phobia (Hermann et al., 2007, 2009), possibly reflecting the expression of conditioned fear memory and deficits in reflexive/automatic emotion regulation processes.

CONCLUSION AND FUTURE PERSPECTIVE

Overall, we were able to show that social anxiety is related to altered social threat learning on the subjective and the neural level. An important question for future work could be whether patients with social anxiety disorder show similar mechanisms in emotional learning using disorder specific UCS. It would be interesting to see whether these individuals show deficits in the recruitment of the vmPFC, which regulates maladaptive fear responses, and whether training (e.g. cognitive behavioral therapy with exposure training) could help to improve such emotion regulation mechanisms. Understanding the neural substrates of these mechanisms is of high clinical relevance for two reasons: First, social anxiety disorder patients often report socially traumatic events contributing to the onset and the exacerbation of the disorder (Hackmann et al., 2000; Erwin, 2006; Carleton et al., 2011). Second, exposure and fear extinction are cornerstones of the psychotherapy of social anxiety disorder (Herry et al., 2010). Therefore, a better understanding of the mechanisms underlying pathologically impaired fear extinction is necessary for the improvement of existing and the development of novel therapeutic strategies.

Conflict of Interest

None declared.

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