Psychiatry Research: Neuroimaging 212 (2013) 108–115

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

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

General emotion processing in social anxiety disorder: Neural issues of cognitive control

Annette Beatrix Brühl [a,*], Uwe Herwig [a,b], Aba Delsignore [c], Lutz Jäncke [d], Michael Rufer [c]

[a] Clinic for General and Social Psychiatry, University Hospital of Psychiatry, Zürich, Switzerland
[b] Department of Psychiatry und Psychotherapy III, University of Ulm, Ulm, Germany
[c] Department of Psychiatry and Psychotherapy, University Hospital Zürich, Zürich, Switzerland
[d] Division Neuropsychology, Institute of Psychology, University of Zürich, Zürich, Switzerland

ARTICLE INFO

Article history:
Received in revised form
7 May 2012
Accepted 18 May 2012

Keywords:
Emotion regulation
Reappraisal
Anticipation
Medial prefrontal cortex (MPFC)
Amygdala
Functional magnetic resonance imaging (fMRI)

ABSTRACT

Anxiety disorders are characterized by deficient emotion regulation prior to and in anxiety-evoking situations. Patients with social anxiety disorder (SAD) have increased brain activation also during the anticipation and perception of non-specific emotional stimuli pointing to biased general emotion processing. In the current study we addressed the neural correlates of emotion regulation by cognitive control during the anticipation and perception of non-specific emotional stimuli in patients with SAD. Thirty-two patients with SAD underwent functional magnetic resonance imaging during the announced anticipation and perception of emotional stimuli. Half of them were trained and instructed to apply reality-checking as a control strategy, the others anticipated and perceived the stimuli. Reality checking significantly ($p < 0.01$) reduced activity in insular, amygdalar and medial thalamic areas during the anticipation and perception of negative emotional stimuli. The medial prefrontal cortex was comparably active in both groups ($p > 0.50$). The results suggest that cognitive control in patients with SAD influences emotion processing structures, supporting the usefulness of emotion regulation training in the psychotherapy of SAD. In contrast to studies in healthy subjects, cognitive control was not associated with increased activation of prefrontal regions in SAD. This points to possibly disturbed general emotion regulating circuits in SAD.

1. Introduction

Anxiety disorders are the most frequent mental disorders, with a lifetime prevalence of 29% (Kessler et al., 2005) and a 1-year prevalence of 14% corresponding to more than 60 million affected persons in the European Union (Wittchen et al., 2011). The most common subtype of anxiety disorders is social anxiety disorder (SAD, Jefferys, 1997; Kessler et al., 2005). Even with sufficient treatment, regardless of the type of treatment and even with a combination of psychotherapy and pharmacological treatment, a relevant number of patients cannot reach remission (e.g., Stangier et al., 2011; Heldt et al., 2006; Baldwin et al., 2011). Investigating the neural basis of anxiety disorders and of treatment aspects could improve the efficacy of therapy in anxiety disorders.

Anxious states and anxiety disorders are characterized by emotional hyperreactivity and cognitive biases in attention and interpretation of possibly threatening stimuli (Bishop, 2008; Bogels and Mansell, 2004; Mogg et al., 2008; Yoon and Zinbarg, 2008; Hirsch et al., 2006; Goldin et al., 2009b), which is most pronounced in the period preceding an event, thus in anticipation of events.

Psychotherapy, particularly cognitive behavioral therapy (CBT), aims at reducing and correcting these cognitive biases (Clark and Beck, 2010). One important CBT strategy is to check the reality and to (re)appraise a situation in a realistic, non-threatening way, which is a method to cognitively control emotions (Gross, 2002; Gross and Thompson, 2007). In empirical studies, CBT has been shown to change information processing biases, particularly in anxiety disorders (review: Clark and Beck, 2010) and amongst these in SAD (Schneier, 2006) with a proven efficacy in a number of randomized controlled trials (meta-analyses: Ponniah and Hollon, 2008; Acarturk et al., 2009). Most studies on psychological mechanisms and therapeutic interventions in specific anxiety disorders focus on that content and those situations which are most and specifically feared.

Studies addressing the neural circuit of emotion processing in SAD showed increased activities in certain brain regions (meta-analyses: Etkin and Wager, 2007; Freitas-Ferrari et al., 2010), particularly when processing social stimuli. Affected structures in SAD are the bilateral amygdaloid regions, the bilateral insular cortex, cingulate cortex and prefrontal cortical structures (Etkin and Wager, 2007). Additionally, two studies detected similarly increased activations in this circuit in SAD when processing non-social stimuli (Brühl et al., 2011; Shah et al., 2009), suggesting disturbed *general* emotion processing and regulation.

* Corresponding author. Tel.: +41 44 384 23 57; fax: +41 44 384 25 06.
E-mail address: annette.bruehl@puk.zh.ch (A.B. Brühl).

0925-4927/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pscychresns.2012.05.006

In the current neurobiological model of emotion regulation, as investigated by many functional neuroimaging studies in healthy subjects, medial, dorso- and ventro-lateral prefrontal cortex (MPFC, DLPFC, VLPFC) as well as the anterior cingulate cortex (ACC) mediate top-down-appraisal, whereas the amygdalar region, ventral striatum and insular cortex are supposed to encode, from the bottom-up, the affective properties of stimuli (recent reviews: Ochsner and Gross, 2007; Etkin et al., 2011; Bishop, 2007; Hartley and Phelps, 2010). During the anticipation of emotional stimuli, emotion regulation by reappraisal in healthy subjects reduced activity in amygdalar and insular regions by activation of regions involved in top-down appraisal (MPFC, DLPFC, VLPFC, ACC) in healthy subjects (Herwig et al., 2007a).

Social anxiety in SAD correlates with the tendency to suppress emotional expressions (Kashdan and Steger, 2006), which is another emotion regulation strategy, and patients with SAD use reappraisal less frequently and less efficiently than healthy subjects (Goldin et al., 2009a). Until today, only two studies have investigated the neural correlates of cognitive control in SAD in comparison to healthy subjects, both during the confrontation with negative social stimuli (harsh faces, Goldin et al., 2009b) and negative self-beliefs (Goldin et al., 2009a). Both studies resulted in SAD in reduced activation of top-down-regulatory brain regions and less reduction of negative affect on the behavioral level, suggestive of regulatory deficits in response to the specific relevant stimuli.

This study addresses the neural correlates of emotion regulation in SAD in the field of general emotion processing during the anticipation and perception of emotional stimuli, as has been done before by our group in healthy subjects (Herwig et al., 2007a). We investigated the neural correlates of cognitive control by reappraisal in SAD during the anticipation and perception of general emotional, but not social stimuli. Therefore, we compared a group of patients with SAD exerting cognitive control with another group of patients with SAD not using a specific cognitive control strategy, in parallel to the study in healthy subjects.

2. Methods

2.1. Subjects

Thirty-two right-handed outpatients with the current diagnosis of generalized SAD participated in this study. Written informed consent was obtained after a thorough explanation of the study to the participants. The study was approved by the local ethics committee. Patients were recruited from the outpatient clinic at the Department of Psychiatry and Psychotherapy of the University Hospital Zurich prior to a cognitive-behavioral group therapy for SAD. Patients had no experience with specific cognitive behavioral therapy. Diagnosis of SAD and comorbid Axis-I diagnosis were established using the Mini-International Neuropsychiatric Interview for DSM-IV (M.I.N.I., Sheehan et al., 1998) and an additional semi-structured clinical interview. Diagnosis of generalized SAD was defined according to DSM-IV (American Psychiatric Association, 2000) as fear in most social situations. For demographic data and the results of the psychometric

Table 1
Demographic, psychometric and behavioral data of the included subjects.

Mean/SD (range)	BAS	COG	Statistics
N	14	14	
Age	33.4/12.0 (20–53)	35.2/9.3 (21–49)	n.s. ($t=0.44$, $F=2.02$, $p=0.66$)
Gender	7 f/7 m	6 f/8 m	n.s. (chi2=0.14, $p=0.70$)
Years of education			
Medication	5 (a)	4 (b)	n.s. (chi2=0.16, $p=0.68$)
STAI 1	42.5/12.9 (25–66)	44.1/10.9 (28–62)	n.s. ($t=0.32$, $F=0.18$, $p=0.75$)
STAI 2	53.6/12.4 (33–74)	52.8/8.2 (32–62)	n.s. ($t=0.18$, $F=2.69$, $p=0.86$)
SDS	55.1/13 (32–77)	54.3/7.4 (36–62)	n.s. ($t=0.19$, $F=3.54$, $p=0.85$)
ERQ (Rea)	3.2/1.7 (1–6)	3.2/1.8 (1–7)	n.s. ($t=0.07$, $F=0.0$, $p=0.95$)
ERQ (Supp)	4.3/0.9 (3–5.3)	3.8/1.2 (1.8–5.8)	n.s. ($t=1.10$, $F=0.35$, $p=0.28$)
LSAS	69.7/16.2 (47–103)	71.1/22.2 (26–103)	n.s. ($t=0.18$, $F=1.57$, $p=0.86$)
SPS	30.2/14.4 (10–60)	32.7/17.4 (10–64)	n.s. ($t=0.39$, $F=1.43$, $p=0.69$)
SIAS	34.2/9.6 (20–50)	44.6/9.6 (19–57)	sign. ($t=2.77$, $F=0.35$, $p=0.01$)
BDI	19.7/10.5 (3–41)	15.8/8.0 (0–30)	n.s. ($t=1.0$, $F=0.48$, $p=0.33$)
Rating negative pictures	2.7/0.6, a: 0.882	2.7/0.5, a: 0.824	n.s. ($t=0.09$, $p=0.929$)
Rating positive pictures	7.4/0.8, a: 0.950	7.8/0.6, a: 0.922	n.s. ($t=1.483$, $p=0.150$)
Rating neutral pictures	5.1/0.4, a: 0.845	5.1/0.1, a: 0.645	n.s. ($t=0.026$, $p=0.979$)

(a) 2, citalopram; 2, sertraline; 1, venlafaxine/mirtazapine. (b) 2, sertraline; 1, venlafaxine; 1, escitalopram/mirtazapine. Given are mean/SD (range) of the respective scores. Abbreviations: STAI, State-Trait Anxiety Inventory, STAI 1, state version, STAI 2, trait version; SDS, Self-rating Depression Scale; ERQ, Emotion Regulation Questionnaire; Rea, reappraisal-subscore; Supp, suppression subscore; LSAS, Liebowitz Social Anxiety Scale; SPS, Social Phobia Scale; SIAS, Social Interaction Anxiety Scale; BDI, Beck Depression Index. n.s., notsignificant. a: Cronbach's alpha.

Table 2
Brain regions influenced by cognitive control during the *anticipation* of negative emotional pictures.

Anatomic regions	BA	Peak Tal: *x*, *y*, *z*	Cluster size (mm^3)	*t* max	*p* max
MidFG/DLPFC *L*	8	−24, 17, 34	802	−4.025	0.0004
SFG/SMA/DLPFC *L*	6	−12, −19, 52	2186	−3.822	0.0007
*Mid Cingulate/Medial FG *L*	24	−12, −4, 37	146	−3.231	0.0033
Precuneus *L*	7	−3, −58, 37	801	−3.340	0.0025
Mid insula/claustrum *L*	13/	−30, −4, 7	1115	−3.547	0.0015
Supramarginal gyrus/STG *L*	40	−48, −22, 22	5521	−4.193	0.0003
Intraparietal sulcus *R*	7/40	48, −31, 34	1062	−3.356	0.0024
Extended amygdalar complex *L*		−24, −4, −2	576	−3.520	0.0016

Random effects group comparison. Significance level: voxelwise $p<0.01$, clusterwise $p<0.05$ corrected. Clusters fitting merely the voxel-based level $p<0.01$ are marked with an asterisk. Given are t max/p max voxel-based. Abbreviations: BA, Brodmann area; Tal, Talairach coordinate; R, right; L, left; MPFC, medial prefrontal cortex; MFG, medial frontal gyrus; MidFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; mid, middle.

scores, refer to Table 1,2. The first 16 patients participated in the trial without cognitive control ("basic group"), which has been reported before (Brühl et al., 2011). Sixteen other patients were included in the group performing cognitive control ("cognitive control group"). Of each group, two participants were excluded due to excessive head movements (>3 mm in one direction) and reported drowsiness and inability to concentrate in the scanner. The final dataset included 28 patients (13 f, 15 m) due to reasons of compliance and quality of the functional data in two subjects. Matching of the groups was sufficient (Table 1). One patient fulfilled criteria for current depressive episode; however, SAD was the primary diagnosis. All other patients had no Axis-I comorbidities and no history of psychiatric disorder, neurological disorders or head trauma. Further exclusion criteria were pregnancy and other contraindications against functional magnetic resonance imaging (fMRI). In total, nine of the included patients were taking antidepressant medication due to reactive depressive symptoms (Table 1, all dosages stable for more than 1 month).

2.2. Questionnaires and picture ratings

Social anxiety was assessed with the Liebowitz Social Anxiety Scale (LSAS, Liebowitz, 1987), the Social Phobia Scale and the Social Interaction Anxiety Scale (SPS and SIAS, Mattick and Clarke, 1998); trait emotion regulation strategies were evaluated using the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003). Depressive symptoms were assessed with the Beck Depression Inventory (BDI, Beck et al., 1961). Results of these psychometric assessments are given in Table 1. Immediately after scanning, subjects rated the emotional valence of the pictures (printouts) on a visual analog scale (very negative=1, very positive=9). These ratings were analyzed first with regard to reliability by computing Cronbach's alpha. Thereafter, in each subject an individual mean score of valence rating in each condition (positive, negative, neutral) was computed. Group comparison of these scores was performed using Student's t-tests (two-tailed, $p<0.05$). In order to assess attention and performance (sleepiness, anxiety during scanning, performance of cognitive control instruction), subjects were after scanning questioned within a semi-structured interview about their experiences during the task. All but one subject of each group reported no significant sleepiness or drowsiness, nor any significant anxiety during scanning. All subjects of the cognitive control group stated explicitly that they were able to perform the "reality check" as instructed. None of the basic group reported anything comparable to a cognitive control strategy when asked about their experiences during the task. Statistical analyses were performed using SPSS18.0.

2.3. Experimental task

During fMRI, participants performed a task (programmed with Presentation™, Neurobehavioral Systems, USA) consisting of 56 trials involving the expectation and perception of emotional pictures (Fig. 1). The task has been described in detail previously (Herwig et al., 2007b; Brühl et al., 2011). In summary, emotional pictures from the International Affective Pictures System (Lang et al., 2005) were announced according to their valence and presented. Besides the clear announcement of negative (*ng*), positive (*ps*) and neutral (*nt*) pictures, a fourth "unknown" announcement condition was followed by either a positive or a negative picture (50% each). Anticipation and picture presentation periods lasted 7920 ms each (corresponding to 4 times of repetition of the fMRI scans (TR)). The fixation period (fixation screen) lasted 15840 ms (8 TR), allowing the blood oxygen level dependent (BOLD) signal to wear off. Before scanning, all participants performed a training session during which they were presented a shorter version of the task with similar pictures. To avoid memory effects, the training pictures did not appear during the main task. The participants thus knew timing, cues, and range of content of the pictures.

2.3.1. Task instruction

In the "basic group", subjects were instructed to expect the emotional stimuli following the cue, to be aware of the indicated emotional valence, and to look at the upcoming emotional picture.

Subjects in the "cognitive control group" were instructed to perform "reality checking" derived as a standard intervention from cognitive–behavioral therapy (Hand, 2000; Otto et al., 2004) during the unpleasant and unknown expectation conditions, not during the pleasant and neutral expectation conditions, in order to reduce anticipatory emotional arousal after cue presentation.

Specifically, the instructions (see Herwig et al. 2007a) were as follows: *If you see the cue announcing either a definitely negative or an unknown, i.e., either positive or negative, picture, you are supposed to focus your attention to the realistic evaluation of the current situation. For example, "the cue means that the upcoming picture can be either positive or negative, as was explained to me before. I do not know now, what will come up. This is an experiment. I will expect the upcoming picture. I am lying on my back in the scanner….". During the presentation of a negative picture I am supposed to be an observer, perceiving the complete reality. Exemplary thoughts are "I am lying in the scanner, the pictures are shown via video goggles. I am watching a picture of a snake with the mouth wide open. The snake is of gray color. It is a photograph. The picture is presented to me within the frame of an experiment, as was explained to me before…. In case of a positive or neutral announcement and the respective picture, I just observe it."*

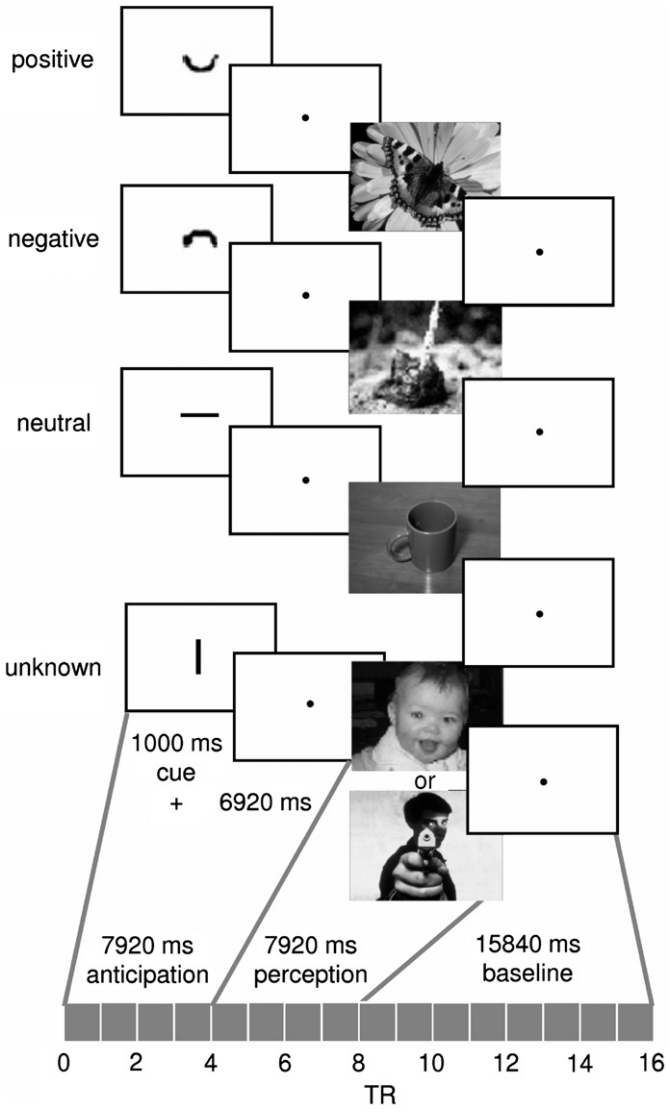

Fig. 1. Schematic summary of the paradigm for anticipation and perception of emotional stimuli (cues are enlarged for reasons of presentation, $1TR=1980$ ms).

After scanning, both groups were asked in an unstructured non-quantitative interview about their experience with the task and how they were able to perform the task. The "cognitive control group" was further asked explicitly about the subjective ability to perform the reality checking.

2.4. Functional magnetic resonance imaging (fMRI)

2.4.1. Image acquisition

Imaging was performed with a 3.0 T GE Signa HD Scanner (GE Medical Systems, Milwaukee, WI, USA, 8-channel head-coil). Echo-planar imaging was performed for functional MR imaging (repetition time (TR)/echo time (TE) 1980/32 ms, 22 sequential axial slices, whole brain, basic group and 3 subjects of the control group: slice thickness/gap 5/0.5 mm, voxel size $3.4\times3.4\times5$ mm, field of view 220 mm, due to technical reasons changed parameters in 11 subjects of the control group: slice thickness/gap 3.5/1.0 mm, voxel size $3.125\times3.125\times4.5$ mm, field of view 200 mm). Altogether 908 volumes were obtained, 16 per run. High-resolution 3-D T1 weighted anatomical volumes were acquired (TR/TE 9.9/2.9 ms; voxel size $1\times1\times1$ mm, axial orientation) for coregistration with the functional data. Furthermore, T2-weighted images in parallel to the EPI sequence were acquired to exclude possible T2-sensitive abnormalities. Stimuli were presented via digital goggles (Resonance Technologies, USA).

2.4.2. FMRI analysis and statistics

FMRI data were analyzed using BrainVoyagerQX 2.0.7 (Brain Innovation, Maastricht, NL). Preprocessing of the functional data included motion correction, slice-scan-time correction, high-frequency temporal filtering, linear detrending, transformation

into Talairach space (Talairach and Tournoux, 1988), and spatial smoothing (8 mm full-width at half-maximum Gaussian kernel, resulting voxel size $3 \times 3 \times 3$ mm). Eight predictors (anticipation (expectation, exp) and perception (perc) of each negative, positive, neutral, unknown valence) built the design matrix. Expectation and perception period were each modeled as an epoch using a two-gamma hemodynamic response function provided by BrainVoyager adapted to the applied period duration. Three-dimensional statistical parametric maps were calculated with separate subject predictors using a general linear model. The results of the contrasts "exp ng > exp nt" and "perc ng > perc nt" in each the "basic" and the "cognitive control group" are presented in the supplementary material (supplementary Tables 1–4). Furthermore, a comparison of the mean beta-weights of the conditions "exp ng > exp nt" and "perc ng > perc nt" in an anatomically defined cubic ROI derived from the meta-analysis by Kalisch (2009) in the MPFC (converted to Talairach space with GingerALE 2.1.1 (Eickhoff et al., 2009): $x, y, z = -3, 9, 49$; volume $10 \times 10 \times 10$ mm^3) between the groups was computed.

The main target of cognitive control strategies is the regulation of the amygdalar complex (e.g., Ochsner et al., 2004; Herwig et al., 2007a; Quirk et al., 2003; Goldin et al., 2009a; Goldin et al., 2008), which is a central structure in anxiety-related processes (Shin and Liberzon, 2009). Our previous study (Brühl et al., 2011) had resulted in amygdalar activation in the contrast of the negative versus neutral expectation period. Therefore, we focused on this contrast in the current analysis.

Random effects group comparison between the basic and the cognitive control group were computed in the frame of a general linear model (GLM) on the contrast "exp ng > exp nt" and the respective contrast during the perception of the announced pictures ("perc ng > perc nt"). A Monte-Carlo simulation was used to correct for multiple comparisons: in the expectation condition, maps with a voxel-wise threshold of $p < 0.01$ were submitted to a Monte-Carlo simulation to estimate cluster level false positive rates, yielding after 1000 iterations a minimum cluster-size threshold of 9 voxels at $3 \times 3 \times 3$ mm (243 mm^3), corresponding to a corrected cluster level of $p < 0.05$ (Goebel et al., 2006). One cluster resulting from the group comparison did not survive the correction for multiple comparisons. However, we present this cluster marked with an asterisk as we consider it functionally interesting and relevant. Due to stronger general activations in the perception period, we applied in the perception contrast a voxel-wise threshold of $p < 0.005$ and a minimum cluster size threshold of 6 voxels [1] at $3 \times 3 \times 3$ mm (162 mm^3) resulting in a corrected cluster level of $p < 0.05$.

3. Results

3.1. Questionnaires and picture ratings

The two groups did not differ with respect to age, gender, medication, depression, anxiety and other clinical measures (Table 1). There was only one significant difference in the SIAS with a higher mean score in the cognitive control group. However, because of the similarity of the groups in the other measures, we do not consider this difference to be relevant. Cognitive control had no influence on the rating of the valence of the pictures after scanning (Table 1).

3.2. Effect of cognitive control during the anticipation of negative pictures in SAD: Group comparison

Comparing patients with SAD exerting cognitive control by reappraisal during the anticipation of negative emotional stimuli

Table 3
Brain regions influenced by cognitive control during the *perception* of negative pictures.

Anatomic regions	BA	Peak Tal *x*, *y*, *z*	Cluster size (mm^3)	*t* max	*p* max
MidFG *L*	6	−30, 11, 52	223	−4.103	0.00036
DLPFC/Middle/superior frontal gyrus *L*	6	−18, −4, 67	454	−3.727	0.0009
IPS/superior parietal lobe *R*	7	33, −49, 46	1458	−4.156	0.0003
Superior/Inferior parietal lobe/IPS *L*	7	−24, −46, 31	3688	−4.514	0.0002
STG *R*	13/22	45, −19, 7	2496	−3.877	0.0006
STG/Transverse TG *L*	42	−66, −16, 13	341	−4.439	0.0001
Middle temporal/occipital gyrus *R*	37/19	33, −58, 1	6519	−4.945	0.00004
MTG *L*	21	−67, −37, -5	623	−4.661	0.00008
Precuneus *L*	7	−9, −76, 43	1521	−3.849	0.0007
Dorsal thalamus/Pulvinar *L*		−15, −31, 10	658	−3.601	0.0013
PHG/ext. amygdala *L*		−24, −16, −8	753	−4.676	0.00008
Cerebellum		12, −67, −35	6906	−4.711	0.00007

Random effects group comparison. Significance level: voxelwise $p < 0.005$, clusterwise $p < 0.05$ corrected. Given are *t* max/*p* max (voxel-based).; Abbreviations: BA, Brodmann area; Tal, Talairach coordinate; R, right; L, left; MidFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; IPS, intraparietal sulcus; STG, superior temporal gyrus; TG, temporal gyrus; MTG, middle temporal gyrus; PHG, parahippocampalgyrus.

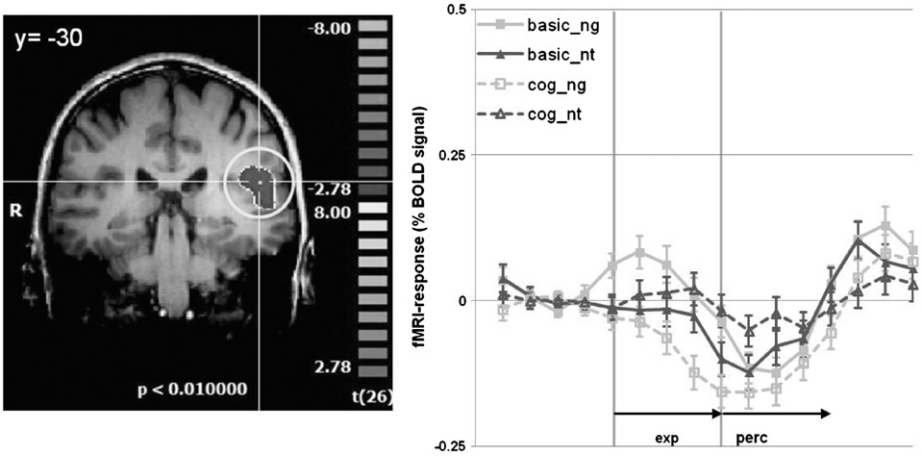

Fig. 2. Reduced brain activity in the left parietotemporal cortex during the anticipation of negative versus neutral pictures in patients applying cognitive control compared to the basic group (random effects group comparison, $p < 0.01$ voxelwise, clusterwise $p < 0.05$ corrected for multiple comparisons, color bars representing *t*-values). In the time course, the anticipation period (exp) is depicted between the grey bars, followed by the perception (perc) of the respective picture (also consider the delay of the hemodynamic response function. Abbreviations: *R*—right, *y*—Talairach coordinate indicating the position of the coronal section, basic-time course of the basic group, cog-time-course of the group applying cognitive control, ng— negative, nt—neutral.

with patients with SAD not exerting cognitive control resulted in no brain regions with increased activity at the statistical level of $p < 0.05$ corrected (Table 3). However, activity in the left amygdalar complex, the left middle insular cortex, the left DLPFC and the bilateral parietotemporal regions (Fig. 2) was reduced in the cognitive control group.

3.3. *Effect of cognitive control during the perception of negative pictures in SAD: Group comparison*

Cognitive control exerted by patients with SAD during the perception of negative versus neutral pictures resulted in decreased activity in left prefrontal, bilateral temporal and parietal areas (Fig. 3) compared to patients in the basic group (Table 4). Furthermore, activity in left thalamic and parahippocampal-amygdalar areas (Fig. 4) was reduced due to cognitive control by reappraisal. There were no regions with increased activity due to cognitive control.

3.4. *Effect of cognitive control in the MPFC in SAD*

The MPFC was activated in both groups in the expectation and perception contrasts exp ng > exp nt and perc ng > perc nt in the anatomically defined ROI (Table 4, Fig. 5). However, we found no significant difference between the two groups on the two contrasts exp ng > exp nt ($p > 0.52$, $t = 0.649$) and perc ng > perc nt ($p > 0.59$, $t = 0.545$).

4. Discussion

The main aim of this study was the investigation of neural mechanisms of cognitive control strategies in SAD during the expectation and perception of negative and ambiguously cued emotional stimuli without social content. We found reduced activity in dorsolateral prefrontal and cingulate cortex, left amygdala and left insula as well as in bilateral parietotemporal regions in patients with SAD applying reappraisal as cognitive control strategy compared to patients with SAD not using cognitive control. There were no regions with increased brain activity associated with reappraisal. The MPFC, which was activated in previous studies investigating emotion regulation (meta-analyses: Kalisch, 2009; Diekhof et al., 2011), was also active in the basic group (Brühl et al., 2011), and was, compared to that, not further increased in the cognitive control group, as was found in healthy subjects applying cognitive control in the same task (Herwig et al., 2007a).

The reduction of brain activation in emotion processing due to cognitive control points to regulatory effects similar to those in healthy subjects (Ochsner and Gross, 2007; Etkin et al., 2011; Bishop, 2007; Hartley and Phelps, 2010). The amygdala and the insula are brain regions typically activated in states of fear and anxiety (recent reviews: Canteras et al., 2010; Etkin, 2010). In our paradigm, the anticipation of negative emotional stimuli is a model eliciting general mild fear, defined as evoked by an imminently upcoming negative event (Barlow, 2000). In this way, our paradigm is suited to test general emotion processing, not the specific anxiety and reactions evoked by the confrontation with the specific 'feared' class of stimuli in a specific anxiety disorder. Our results indicate that patients with SAD are able to reduce amygdalar and insular activity using cognitive control techniques in general emotional situations lacking the specific social content of SAD.

However, the lack of increased recruitment of MPFC activity due to cognitive control points to differing mechanisms of emotion regulation in SAD when compared to findings in healthy subjects (Herwig et al., 2007a). Our results are in line with the findings of previous studies using social stimuli and negative self-beliefs during emotion regulation (Goldin et al., 2009b; Goldin et al., 2009a; Blair et al., 2011).

In summary, patients suffering from SAD can exert some influence on the activity of their amygdala when reappraising anticipated negative events. However, the neural circuit seems to differ from that in healthy subjects by a here indicated lack of additional MPFC activation or recruitment. One explanation for

Table 4
Effect of cognitive control in the medial prefrontal cortex (anatomically defined cubic ROI, $x, y, z = 1, 16, 51$; $10 \times 10 \times 10$ mm^3).

Beta weights mean (SD)	BAS	COG	Statistics
exp ng > exp nt	0.269 (0.257)	0.351 (0.393)	n.s. ($t = 0.649$, $p = 0.522$)
perc ng > perc nt	0.299 (0.428)	0.369 (0.209)	n.s. ($t = 0.545$, $p = 0.590$)

Group comparison (t-test).; Abbreviations: exp expectation, perc perception, ng negative, nt neutral, BAS basic group, COG cognitive control group.

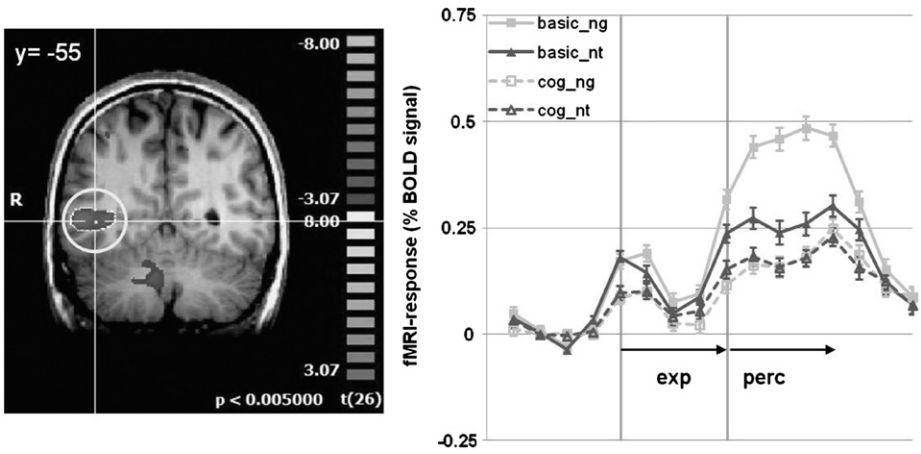

Fig. 3. Reduced brain activity in the right temporo-occipital cortex during the perception of negative versus neutral pictures in patients applying cognitive control compared to the basic group (random effects group comparison, $p < 0.005$ voxelwise, clusterwise $p < 0.05$ corrected for multiple comparisons, color bars representing t-values). In the time course, the anticipation period (exp) is depicted between the grey bars, followed by the perception (perc) of the respective picture (also consider the delay of the hemodynamic response function. *R*—right, *y*—Talairach coordinate indicating the position of the coronal section, basic-time course of the basic group, cog-time-course of the group applying cognitive control, ng—negative, nt—neutral.

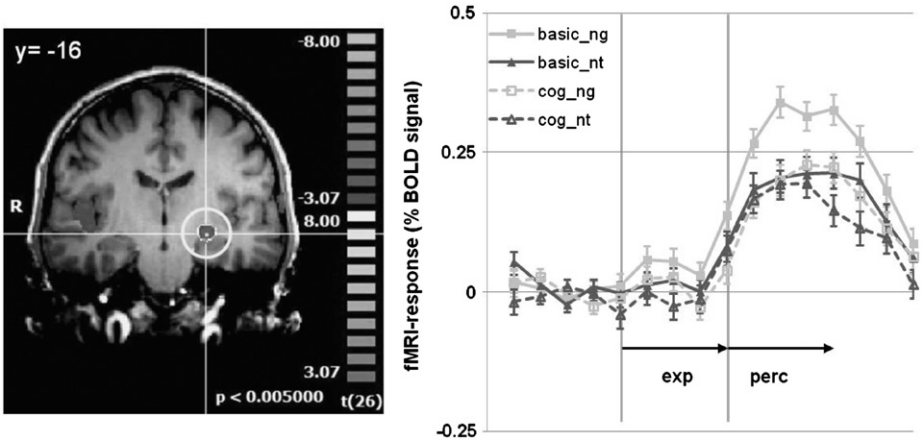

Fig. 4. Reduced brain activity in the left parahippocampal gyrus/amygdalar region during the perception of negative versus neutral pictures in patients applying cognitive control compared to the basic group (random effects group comparison, $p < 0.005$ voxelwise, clusterwise $p < 0.05$ corrected for multiple comparisons, color bars representing t-values). In the time course, the anticipation period (exp) is depicted between the grey bars, followed by the perception (perc) of the respective picture (also consider the delay of the hemodynamic response function. Abbreviations: R – right, y – Talairach coordinate indicating the position of the coronal section, basic – time course of the basic group, cog – time-course of the group applying cognitive control, ng negative, nt neutral.

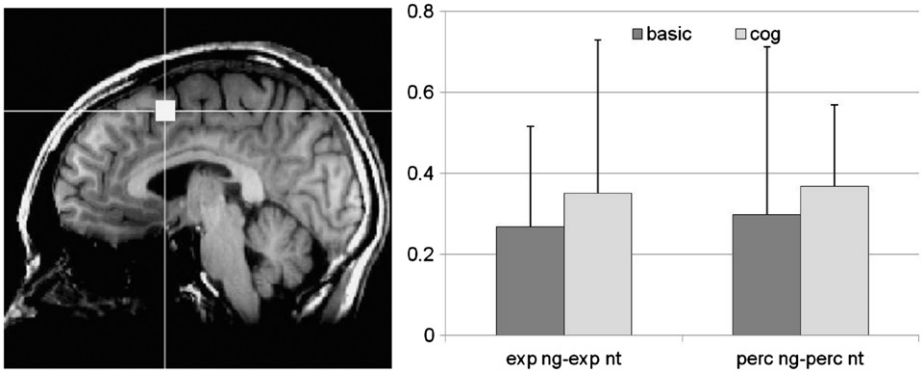

Fig. 5. Effect of cognitive control during the anticipation (exp) and perception (perc) in an anatomically defined cubic region of interest in the medial prefrontal cortex (indicated by the bright dot, Talairach coordinates derived from the meta-analysis of Kalisch (2009), $x, y, z = -3, 9, 49$, converted from MNI-space with GingerALE2.1.1; volume $10 \times 10 \times 10\ mm^3$). The MPFC was activated in both groups, however without significant difference (exp ng > exp nt ($p > 0.52$, $t = 0.649$) and perc ng > perc nt ($p > 0.59$, $t = 0.545$). Error bars indicate standard deviation (SD). Abbreviations: basic – basic group, cog – group applying cognitive control, ng—negative, nt—neutral.

this could be the increased activation of the MPFC when comparing SAD with healthy subjects in this task (Brühl et al., 2011), possibly corresponding to a ceiling effect.

This lack of additional recruitment of MPFC and DLPFC could be the neural correlate of emotion regulation difficulties and deficits in SAD (Kashdan and Steger, 2006). The current study confirms the findings on deficient regulatory circuits in previous studies on emotion regulation in SAD (Goldin et al., 2009a; Goldin et al., 2009b) and adds evidence for deficits in the regulation of not only stimuli specific to the social anxiety, but also during the processing and regulation of general emotional stimuli.

This could be clinically relevant and support training of emotion regulation when dealing with everyday situations without any social content in the psychotherapy of SAD.

Regarding possible limitations of our study, the effects of antidepressant medication in nine subjects should be discussed. It is important to note that there was no meaningful difference between the two groups regarding medication. Therefore, the medication should not account for the between-group effects observed in our study. Furthermore, possible medication effects would rather be expected to diminish emotional reactivity and thus reduce the observed effects. A further limitation is the higher level of social anxiety in the cognitive control group measured with the SIAS. However, this group difference was not present in the other psychometric measures, particularly not in the other measures of social anxiety, and is not significant any more when applying correction for multiple comparisons (in total 9 comparisons, requiring $p < 0.006$ to reach significance). We additionally computed a group comparison controlling for the SIAS, revealing no qualitative difference compared to the presented analysis (data not shown). Furthermore, we examined in the current study general emotion processing and regulation, not specific social anxiety-related stimuli. Besides this limitation, we did not match the included subjects for *IQ* or other cognitive measures. At least regular scholar education was an inclusion criterion as well as a lack of cognitive impairments. Nearly all subjects were currently employed. To our best knowledge, there are no data in the literature that patients suffering from SAD have specific intellectual impairments (Pubmed search). Another issue of our task is that we intentionally decided not to use any behavioral control measures. The preparation and execution of an answer would in any form have been a distractor and could have interfered with the brain activities and processes under investigation due to evaluation and reaction preparation, thereby increasing cognitive

demands and reducing emotional reactions (Pessoa, 2008). Therefore, we opted for a 'pure' emotional anticipation task. Participants confirmed their attention and ability to perform the task in the interview after scanning. We verified general attention and performance by controlling for individual brain activation in primary visual brain regions. At last, the previous study in healthy subjects (Herwig et al., 2007a) was conducted some years before. Due to methodological issues (e.g., change of the scanner in the meantime) we computed no direct comparisons with this previous study. However, various studies have examined the neural correlates of emotion regulation in healthy subjects (meta-analyses: Kalisch, 2009; Diekhof et al., 2011), and the findings converge to suggest a emotion-regulating brain regions, such that a qualitative comparison between healthy subjects and SAD seemed reasonable.

In conclusion, the results of the current study suggest that emotion regulation by reappraisal may be, from a neurobiological point of view, successful in SAD patients, supporting the usefulness of training in reappraisal as an emotion-regulation strategy in the psychotherapy of SAD. However, the neural circuit of emotion regulation seems to differ from that in healthy subjects when dealing with non-social emotional stimuli. This points to disturbances in general emotion processing and regulation in SAD.

Acknowledgement

The study was funded by the Swiss National Science Foundation (SNSF).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.05.006.

References

Acarturk, C., Cuijpers, P., van Straten, A., de Graaf, R., 2009. Psychological treatment of social anxiety disorder: a meta-analysis. Psychological Medicine 39, 241–254.
American Psychiatric Association, 2000. Diagnostic and Statistic Manual of Mental Disorders. American Psychiatric Association, Washington, DC.
Baldwin, D., Woods, R., Lawson, R., Taylor, D., 2011. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. British Medical Journal, 342.
Barlow, D.H., 2000. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. American Psychologist 55, 1247–1263.
Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of General Psychiatry 4, 561–571.
Bishop, S.J., 2007. Neurocognitive mechanisms of anxiety: an integrative account. Trends in Cognitive Sciences 11, 307–316.
Bishop, S.J., 2008. Neural mechanisms underlying selective attention to threat. Annals of the New York Academy of Sciences 1129, 141–152.
Blair, K.S., Geraci, M., Otero, M., Majestic, C., Odenheimer, S., Jacobs, M., Blair, R.J.R., Pine, D.S., 2011. Atypical modulation of medial prefrontal cortex to self-referential comments in generalized social phobia. Psychiatry Research: Neuroimaging 193, 38–45.
Bogels, S.M., Mansell, W., 2004. Attention processes in the maintenance and treatment of social phobia: hypervigilance, avoidance and self-focused attention. Clinical Psychology Review 24, 827–856.
Brühl, A.B., Rufer, M., Delsignore, A., Kaffenberger, T., Jäncke, L., Herwig, U., 2011. Neural correlates of altered general emotion processing in social anxiety disorder. Brain Research 1378, 72–83.
Canteras, N.S., Resstel, L.B., Bertoglio, L.J., Carobrez Ade, P., Guimaraes, F.S., 2010. Neuroanatomy of anxiety. Current Topics in Behavioral Neurosciences 2, 77–96.
Clark, D.A., Beck, A.T., 2010. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. Trends in Cognitive Sciences 14, 418–424.
Diekhof, E.K., Geier, K., Falkai, P., Gruber, O., 2011. Fear is only as deep as the mind allows: a coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. NeuroImage 58, 275–285.
Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Human Brain Mapping 30, 2907–2926.
Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD. social anxiety disorder, and specific phobia. American Journal of Psychiatry 164, 1476–1488.
Etkin, A., 2010. Functional neuroanatomy of anxiety: a neural circuit perspective. Current Topics in Behavioral Neurosciences 2, 251–277.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences 15, 85–93.
Freitas-Ferrari, M.C., Hallak, J.E.C., Trzesniak, C., Filho, A.S., Machado-de-Sousa, J.P., Chagas, M.H.N., Nardi, A.E., Crippa, J.A.S., 2010. Neuroimaging in social anxiety disorder: a systematic review of the literature. Progress in Neuro-Psychopharmacology and Biological Psychiatry 34, 565–580.
Goebel, R., Esposito, F., Formisano, E., 2006. Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. Human Brain Mapping 27, 392–401.
Goldin, P.R., McRae, K., Ramel, W., Gross, J.J., 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biological Psychiatry 63, 577–586.
Goldin, P.R., Manber-Ball, T., Werner, K., Heimberg, R., Gross, J.J., 2009a. Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. Biological Psychiatry 66, 1091–1099.
Goldin, P.R., Manber, T., Hakimi, S., Canli, T., Gross, J.J., 2009b. Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. Archives of General Psychiatry 66, 170–180.
Gross, J.J., 2002. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 39, 281–291.
Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of Personality and Social Psychology 85, 348–362.
Gross, J.J., Thompson, R.A., 2007. Emotion regulation—conceptual foundations In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. Guilford Press, New York, pp. 3–24.
Hand, I., 2000. Group exposure in vivo for agoraphobics (1974): a multifaceted pilot study and its impact on subsequent agoraphobia research. Behavioural and Cognitive Psychotherapy 28, 335–351.
Hartley, C.A., Phelps, E.A., 2010. Changing fear: the neurocircuitry of emotion regulation. Neuropsychopharmacology 35, 136–146.
Heldt, E., Gus Manfro, G., Kipper, L., Blaya, C., Isolan, L., Otto, M.W., 2006. One-year follow-up of pharmacotherapy-resistant patients with panic disorder treated with cognitive-behavior therapy: outcome and predictors of remission. Behaviour Research and Therapy 44, 657–665.
Herwig, U., Baumgartner, T., Kaffenberger, T., Brühl, A., Kottlow, M., Schreiter-Gasser, U., Abler, B., Jäncke, L., Rufer, M., 2007a. Modulation of anticipatory emotion and perception processing by cognitive control. NeuroImage 37, 652–662.
Herwig, U., Kaffenberger, T., Baumgartner, T., Jäncke, L., 2007b. Neural correlates of a 'pessimistic' attitude when anticipating events of unknown emotional valence. NeuroImage 34, 848–858.
Hirsch, C.R., Clark, D.M., Mathews, A., 2006. Imagery and Interpretations in social phobia: support for the combined cognitive biases hypothesis. Behavior Therapy 37, 223–236.
Jefferys, D., 1997. Social phobia. The most common anxiety disorder. Australian Family Physician 26 (1061), 1064–1067.
Kalisch, R., 2009. The functional neuroanatomy of reappraisal: time matters. Neuroscience and Biobehavioral Reviews 33, 1215–1226.
Kashdan, T.B., Steger, M.F., 2006. Expanding the topography of social anxiety. An experience-sampling assessment of positive emotions, positive events, and emotion suppression. Psychological Science 17, 120–128.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry 62, 593–602.
Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-6. Center for Research in Psychophysiology, University of Florida, Gainesville, FL.
Liebowitz, M.R., 1987. Social phobia. Modern Problems of Pharmacopsychiatry 22, 141–173.
Mattick, R.P., Clarke, J.C., 1998. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behaviour Research and Therapy 36, 455–470.
Mogg, K., Holmes, A., Garner, M., Bradley, B.P., 2008. Effects of threat cues on attentional shifting, disengagement and response slowing in anxious individuals. Behaviour Research and Therapy 46, 656–667.
Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D.E., Gross, J.J., 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23, 483–499.

Ochsner, K.N., Gross, J.J., 2007. The neural architecture of emotion regulation In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. Guilford Press, New York, pp. 87–109.
Otto, M.W., Smits, J.A., Reese, H.E., 2004. Cognitive-behavioral therapy for the treatment of anxiety disorders. Journal of Clinical Psychiatry 65 (Suppl 5), 34–41.
Pessoa, L., 2008. On the relationship between emotion and cognition. Nature Reviews Neuroscience 9, 148–158.
Ponniah, K., Hollon, S.D., 2008. Empirically supported psychological interventions for social phobia in adults: a qualitative review of randomized controlled trials. Psychological Medicine 38, 3–14.
Quirk, G.J., Likhtik, E., Pelletier, J.G., Pare, D., 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. Journal of Neuroscience 23, 8800–8807.
Schneier, F.R., 2006. Social anxiety disorder. New England Journal of Medicine 355, 1029–1036.
Shah, S.G., Klumpp, H., Angstadt, M., Nathan, P.J., Phan, K.L., 2009. Amygdala and insula response to emotional images in patients with generalized social anxiety disorder. Journal of Psychiatry and Neuroscience 34, 296–302.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, G.C., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry 59, 22–33.
Shin, L.M., Liberzon, I., 2009. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 35, 169–191.
Stangier, U., Schramm, E., Heidenreich, T., Berger, M., Clark, D.M., 2011. Cognitive therapy vs interpersonal psychotherapy in social anxiety disorder: a randomized controlled trial. Archives of General Psychiatry 68, 692–700.
Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: Three-dimensional Proportional System. Thieme Medical, New York.
Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology 21, 655–679.
Yoon, K.L., Zinbarg, R.E., 2008. Interpreting neutral faces as threatening is a default mode for socially anxious individuals. Journal of Abnormal Psychology 117, 680–685.