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

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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.

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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.