



Prefrontal mediation of emotion regulation in social anxiety disorder during laughter perception



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ABSTRACT

Social anxiety disorder (SAD) is characterized by negatively biased perception of social cues and deficits in emotion regulation. While negatively biased perception is thought to maintain social anxiety, emotion regulation represents an ability necessary to overcome both biased perception and social anxiety. Here, we used laughter as a social threat in a functional magnetic resonance imaging (fMRI) study to identify cerebral mediators linking SAD with attention and interpretation biases and their modification through cognitive emotion regulation in the form of reappraisal. We found that reappraisal abolished the negative laughter interpretation bias in SAD and that this process was directly mediated through activation patterns of the left dorsolateral prefrontal cortex (DLPFC) serving as a cerebral pivot between biased social perception and its normalization through reappraisal. Connectivity analyses revealed reduced prefrontal control over threat-processing sensory cortices (here: the temporal voice area) during cognitive emotion regulation in SAD. Our results indicate a central role for the left DLPFC in SAD which might represent a valuable target for future research on interventions either aiming to directly modulate cognitive emotion regulation in SAD or to evaluate its potential as physiological marker for psychotherapeutic interventions relying on emotion regulation.

1. Introduction

“To be the laughing-stock” is a central fear in social anxiety disorder (SAD). SAD is one of the most frequently diagnosed psychiatric disorders with a 12-month prevalence of 6.8% in the US (Kessler et al., 2005). SAD is characterized by an intense fear of the scrutiny of others in social and performance situations often accompanied by symptoms of the autonomic nervous system like heart racing, sweating, trembling, nausea, difficulty in breathing or blushing. This leads many individuals with SAD to avoid social situations. As in most psychiatric disorders, genetic and environmental factors contribute to the development of SAD, which has an estimated heritability of 56% (Isomura et al., 2014) and often manifests already in early adolescence. Both, genetic factors indicating foremost serotonergic but also monoaminergic dysfunction (Stein and Stein, 2008) as well as maladaptive learning mechanisms building on a temperamental trait termed behavioral inhibition (Haller et al., 2015) appear to be implicated in the pathogenesis of SAD. Interestingly, the prevalence and expression of SAD is culturally dependent. The prevalence of SAD ranges from low rates (0.2 – 0.8%) in Eastern and African cultures to rates an order of

magnitude larger in US and Brazilian samples (6.8 – 9.1%; Hofmann et al., 2010). SAD is associated with a loss in the quality of life (Mendlowicz and Stein, 2000) and high economic burden (Lipsitz and Schneier, 2000). From the therapeutic perspective, cognitive behavioral therapy and treatment with selective serotonin (and norepinephrin) reuptake inhibitors represent the best evaluated state-of-the-art treatments (for a comprehensive review on SAD see Stein and Stein, 2008).

At the perceptual level, individuals with SAD exhibit cognitive biases indicating increased sensitivity to signals of social threat. Two of these are negative interpretation biases (Machado-de-Sousa et al., 2010; Quadflieg et al., 2007), characterized by negative interpretations of ambiguous social signals, and attention biases (Gilboa-Schechtman et al., 1999; Mogg and Bradley, 2002), which manifest as faster responses to social threat signals. Such biases are assumed to be causally linked to the maintenance of SAD symptoms (Clark and Wells, 1995; Rapee and Heimberg, 1997). Cognitive behavioral therapy (CBT), the gold standard psychotherapy for anxiety disorders (Hofmann and Smits, 2008) reduces SAD symptoms as well as attention and interpretation biases (Calamaras et al., 2012). Interestingly, self-efficacy in cognitive reappraisal, an emotion regula-

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tion technique applied during CBT, mediates the psychotherapeutic effects in SAD (Goldin et al., 2012) along with perceived responsibility for change (Delsignore et al., 2008). The exact relationships between SAD, biased social perception and emotion regulation, however, remain to be clarified both at the behavioral as well as the cerebral level.

While neuroimaging studies in SAD have mostly indicated increased activation to social threat in the limbic system, secondary visual cortices as well as mediofrontal and orbitofrontal cortices (Brühl et al., 2014; Miskovic and Schmidt, 2012), the processing of an attention bias towards signals of social threat has been linked to lateral and medial aspects of the prefrontal cortex in healthy participants (Browning et al., 2010) as well as several anxiety and stress-related disorders (Dresler et al., 2012; Fani et al., 2012; Monk et al., 2006; Price et al., 2011) with the delineation of decreased prefrontal activation to attended signals of social threat (Browning et al., 2010).

In previous studies using laughter recordings as a symptom-provoking tool, we confirmed negative interpretation and attention biases for laughter perception in SAD (Kreifelts et al., 2014; Ritter et al., 2015) based on the phobogenic properties of laughter in social anxiety (Edwards et al., 2010). In a functional magnetic resonance imaging (fMRI) study, we demonstrated the mediation of the attention bias through activation in the left dorsolateral prefrontal cortex (DLPFC; Kreifelts et al., 2014).

Beyond the mediation of cognitive biases, the DLPFC¹ has been implicated in emotion regulation (Buhle et al., 2014; Kohn et al., 2014). Current models and meta-analyses of emotion regulation (Kohn et al., 2014; Ochsner et al., 2012) posit the DLPFC in a feed forward loop between the ventrolateral prefrontal cortex where the appraisal of emotional events is initiated and the need to regulate the emotion is signaled, and mediofrontal as well as semantic and sensory processing areas which together with the amygdala and basal ganglia in turn participate in the generation of a regulated emotional state. The DLPFC itself processes the regulation in the form of cognitive control processes which entail the coordination of thoughts and actions in accordance with internally represented goals (Ahmed et al., 2015). Functional characterization of the part of the DLPFC involved in emotion regulation shows that it subserves selective attention, working memory, reasoning and social cognition processes, suggesting that it has a more general role in cognitive control (Kohn et al., 2014). This appears to be consistent with the notion of the DLPFC as neural interface between cognition and emotion (Ochsner and Gross, 2005).

In individuals with SAD an altered dorsal prefrontal activation during cognitive emotion regulation has been observed (Brühl et al., 2013; Goldin et al., 2009a, 2009b; Ziv et al., 2013). Critically, however, in these studies (Goldin et al., 2009a, 2009b; Ziv et al., 2013) patients with SAD did not differ from healthy participants with regard to the behavioral correlates of cognitive emotion regulation (i.e., both groups exhibited comparable behavior during emotion regulation) or no direct quantitative behavioral correlate of emotion regulation was recorded (Brühl et al., 2013). Furthermore, those previous studies did not explicitly test the relationship between emotion regulation-associated brain responses and behavior.

The aim of the present study was to investigate SAD-related behavioral and cerebral correlates of cognitive emotion regulation on biased social perception. To this end, individuals with SAD and healthy participants were confronted with various types of laughter (i.e., joyful,

ticking and taunting laughter) during fMRI to identify mediators (here: cerebral activation and functional connectivity) linking SAD with associated cognitive biases and their modification through reappraisal via mediation analysis.

We hypothesized negative interpretation and attention biases during laughter perception in SAD and the reduction of both biases through cognitive emotion regulation (Mobini et al., 2014). Second, we hypothesized a positive correlation between the reduction of SAD-associated interpretation and attention biases and increases in prefrontal activation. The main aim of our study, however, was the evaluation of the link between behavioral changes, cerebral responses and individual psychopathology using mediation analysis.

2. Methods

2.1. Participants

Participants ranging in social anxiety severity from minimal social anxiety to severe SAD were included. Twenty-six individuals (13 female, mean age 24.4, SD 2.9 years) were recruited through public announcements inviting volunteers to participate who perceived themselves as either outgoing or as suffering from social anxiety. All participants were right-handed as assessed with the Edinburgh Inventory (Oldfield, 1971) and native German speakers. None of them had taken regular medication for at least six months, or had a history of impaired hearing, substance abuse, or neurological illness. Vision was normal or corrected to normal. All participants were examined using the Structured Clinical Interview for DSM-IV (SCID; Wittchen et al., 1997). The LSAS (self-report; Stangier and Heidenreich, 2003) was used to assess severity of social anxiety. According to the results of the SCID examination, twelve participants were diagnosed with SAD by a fully trained psychiatrist (B.K.) while the remaining participants did not suffer from any psychiatric disorder (= healthy controls, HC). The severity distribution of social anxiety (LSAS scores) among individuals with SAD and HC is given in the [Supplementary material](#). Three of the participants with SAD had a history of major depression but had been in remission for at least one year. General anxiety and depressive symptoms were assessed using the State-Trait-Anxiety-Inventory (STAI; Laux et al., 1981) and the Beck Depression Inventory (BDI-II; Hautzinger et al., 2009). The “Mehrfachwahl-Wortschatz-Intelligenz-Test” (MWT-B; Lehrl, 2005) was applied to measure premorbid intelligence. The socio-demographic and psychometric data are given in [Table 1](#). The study was carried out in accordance with the recommendations of the University of Tübingen ethical review board and in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, as revised in 2013). The study protocol was approved by the University of Tübingen ethical review board. All participants gave written informed consent prior to inclusion in the study.

2.2. Stimulus material and experimental design

Sixty videos (1.5 s) of laughing faces were used as stimulus material comprising three types of laughter (joyful/friendly [JOY], ticking [TIC] and taunting/unfriendly [TAU] laughter) balanced for laughter type. For further details on validation see [Supplementary material](#). The experiment consisted of two runs. During each run all stimuli were presented within an event-related design. The onsets of the stimuli were jittered relative to the scan onsets in steps of 1/4 of the repetition time (TR=1700 ms) to reduce effects of stimulus expectancy. The average inter-stimulus interval was 10.5 s (range: 8.8–12.2 s). Additionally, null events with durations of 10.5 s were randomly inserted in the trial sequence with the frequency of one null event per 10 trials leading to a maximum interstimulus interval of 23 s. In one run, the participants were asked to imagine they were directly addressed by the laughter (NO REAPPRAISAL) while in the other run

¹ Please note that the term „dorsolateral prefrontal cortex” (DLPFC) corresponds to the definition of the DLPFC as that part of the prefrontal cortex comprising the Brodmann areas (BA) 8, 9, 10 and 46 (e.g., Petrides and Pandya, 1999). Based on a recent parcellation study of the dorsal frontal cortex (Sallet et al., 2013) the DLPFC-ROI of the present study most strongly overlaps with the more posterior situated BA8a. This definition of the term DLPFC also converges with recent meta-analyses on emotion regulation (Buhle et al., 2014; Kohn et al., 2014) where the cerebral correlates of emotion regulation described in the DLPFC strongly overlapped with BA8.

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