Progress in Neuro-Psychopharmacology & Biological Psychiatry 45 (2013) 83–91

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder

Heide Klumpp [a,*], Daniel A. Fitzgerald [a], K. Luan Phan [a,b]

[a] Mood and Anxiety Disorders Research Program, Department of Psychiatry (HK, DAF, KLP), University of Illinois at Chicago, Chicago, IL, United States
[b] Neuropsychiatric Research Program (KLP), Mental Health Service, Jesse Brown VA Medical Center, Chicago, IL, United States

ARTICLE INFO

Article history:
Received 18 March 2013
Received in revised form 24 April 2013
Accepted 3 May 2013
Available online 10 May 2013

Keywords:
Brain imaging
Emotional faces
fMRI
Generalized social anxiety
Treatment

ABSTRACT

Cognitive behavioral therapy (CBT) is "gold standard" psychotherapy for social anxiety disorder (SAD). Cognitive models posit that preferential processing of threat mediates excessive forms of anxiety, which is supported by exaggerated amygdala, insula, and cortical reactivity to threatening socio-emotional signals in SAD. However, little is known about neural predictors of CBT success or the mechanisms by which CBT exerts its therapeutic effects. Functional magnetic resonance imaging (fMRI) was conducted during responses to social signals of threat (fearful/angry faces) against positive signals (happy faces) in 14 patients with SAD before and after 12 weeks of CBT. For comparison, 14 healthy control (HC) participants also underwent two fMRI scans, 12 weeks apart. Whole-brain voxel-wise analyses showed therapeutic success was predicted by enhanced pre-treatment activation to threatening faces in higher-order visual (superior and middle temporal gyrus), cognitive, and emotion processing areas (dorsal anterior cingulate cortex, dorsomedial prefrontal cortex). Moreover, a group by time interaction was revealed in prefrontal regions (dorsomedial, medial gyrus) and insula. The interaction was driven by relatively greater activity during threat processing in SAD, which significantly reduced after CBT but did not significantly predict response to CBT. Therefore, pre-treatment cortical hyperactivity to social threat signals may serve as a prognostic indicator of CBT success in SAD. Collectively, CBT-related brain changes involved a reduction in activity in insula, prefrontal, and extrastriate regions. Results are consistent with cognitive models, which associate decreases in threat processing bias with recovery.

1. Introduction

Generalized social anxiety disorder (gSAD), also known as social phobia, is one of the most common anxiety disorders in the United States (Kessler et al., 2005). It is characterized by excessive fear and avoidance in a range of interpersonal situations that involve potential scrutiny by others (American Psychiatric Association, 2000). It begins early in life (Otto et al., 2001) and leads to severe impairment, substantially undermining educational attainment, employment, and relationship opportunities (Hambrick et al., 2003; Safren et al., 1996/1997; Schneier et al., 1994). The disorder often precedes and is co-morbid with other psychiatric illnesses such as depression, substance abuse, and additional anxiety disorders (Schneier et al., 1992).

Cognitive theories of anxiety posit preferential attention to threat-relevant signals is a core factor in the development and maintenance of gSAD and other excessive forms of anxiety (Beck and Clark, 1997; Beck et al., 2005; Eysenck, 1992; MacLeod et al., 2002; Wells and Matthews, 1994; Williams et al., 1988). Threat bias occurs throughout stages of information processing (Beck and Clark, 1997); accordingly, enhanced processing of threat cues during goal-directed attention (Pessoa et al., 2002) is an index of bias. Functional magnetic resonance imaging (fMRI) studies indicate attentional bias to threat in gSAD is subserved in part by exaggerated activation to threatening facial expressions in the amygdala and/or insula, which are key limbic/paralimbic structures involved in emotion generation and processing (Adolphs et al., 1995; Craig, 2009; Critchley, 2009; Davidson, 2000; Davis and Whalen, 2001; Jones et al., 2010). Exaggerated cortical response has also been observed in gSAD both to, and in anticipation of, threat (Etkin and Wager, 2007; Freitas-Ferrari et al., 2010). While not as consistently demonstrated as subcortical hyperactivity, exaggerated activity has also been shown in the anterior cingulate cortex (ACC) in gSAD (Amir et al., 2005; Blair et al., 2008; Goldin et al., 2009; Phan et al., 2006) a component of the anterior attention system involved in the detection of salient cues (Posner and Petersen, 1990). Other prefrontal cortex (PFC) regions serving executive functions (Bush et al., 2000; Etkin et al., 2011) have been implicated in gSAD

Abbreviations: gSAD, generalized Social Anxiety Disorder; HC, healthy controls; fMRI, functional magnetic resonance imaging; BOLD, blood-oxygen-level-dependent; CBT, cognitive behavioral therapy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision; ACC, anterior cingulate cortex; PFC, prefrontal cortex; LSAS, Liebowitz Social Anxiety Scale; BDI, Beck Depression Inventory; CGI-I, Clinical Global Impression-Improvement.

* Corresponding author at: Department of Psychiatry, University of Illinois at Chicago, Room 246, 1747 W. Roosevelt Rd, Chicago, IL 60608, United States. Tel.: +1 312 996 0416; fax: +1 312 413 1703.
E-mail address: hklumpp@psych.uic.edu (H. Klumpp).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.05.004

such as dorsomedial, dorsolateral, and medial orbitofrontal cortex (Goldin et al., 2009; Stein et al., 2002; Tillfors et al., 2002) as well as higher-level visual regions (inferior occipital, fusiform gyrus, superior temporal sulcus; Evans et al., 2008; Goldin et al., 2009; Straube et al., 2004) engaged in social cognition (Adolphs, 1999; Fusar-Poli et al., 2009). Collectively, evidence is building to show that emotional dysregulation in gSAD is mediated by exaggerated reactivity to signals of socio-emotional threat distributed among limbic/paralimbic, prefrontal, and extrastriate regions.

Despite advances in delineating the pathophysiology of gSAD, little is known about baseline neural correlates that predict treatment response or brain-based changes following cognitive–behavioral therapy (CBT), first-line psychotherapy for gSAD and other anxiety disorders (Heimberg, 2002; Hofmann and Smits, 2008). CBT aims to reduce anxiety symptoms through the modification of negative beliefs (e.g., cognitive restructuring) and behavior (e.g., exposure to fears; Beck et al., 2005). Greater response to treatment is associated with greater reductions in anxiety symptoms, negative beliefs, impairment (Brown et al., 1995; Hofmann and Smits, 2008; Hope et al., 1995), and attentional bias to threat stimuli (Mattia et al., 1993; Pishyar et al., 2008). Findings suggest that therapeutic response is associated with enhanced implicit emotion regulation, though it is not a direct target of treatment per se. Therefore, activity in regions implicated in emotional perception (e.g., evaluation of stimulus) and response to threat signals may predict recovery or change with treatment.

Successful CBT treatment in gSAD has been shown to be predicted by exaggerated pre-treatment activation to angry faces in dorsal and ventral occipitotemporal regions (Doehrmann et al., 2013), secondary visual areas involved in the decoding and processing of cues relevant to motivational state (Lang and Bradley, 2010; Sabatinelli et al., 2013). Heightened activation in these higher-level visual areas has been proposed to correspond with emotion regulation capacity, which CBT is intended to enhance. Consequently, patients with less ability to effectively regulate emotions prior to undergoing treatment may experience reduced benefit from CBT (Doehrmann et al., 2013). Other baseline biomarkers of recovery in anxiety are ACC and amygdala. In a study of post-traumatic stress disorder (Bryant et al., 2008), CBT success was predicted by reduced ACC engagement and reduced amygdala response to subliminal fearful faces (i.e., masked). Thus, less reactivity to fear-evoking stimuli in this population is a good prognostic indicator of recovery with CBT (Bryant et al., 2008).

With regard to social anxiety and treatment-related changes in brain activity, a positron emission tomography study showed responders, regardless of treatment type (CBT or medication), exhibited reduced amygdala and ACC activity during symptom provocation involving a public speaking challenge (Furmark et al., 2002). Would analogous changes in brain activity be obtained outside of symptom elicitation, specifically, when merely processing threatening social signals? To our knowledge, this has yet to be investigated with regard to CBT in gSAD. However, fMRI studies of specific phobia comprising threat-relevant images provide clues. For example, in a study by Straube et al. (2006), baseline insula and ACC hyperactivity to spider images in phobics was significantly reduced in patients who completed CBT but not in a wait-list group of patients. Pre-treatment dorsolateral prefrontal response to spider stimuli has also been shown to decrease in patients after completing CBT (Paquette et al., 2003). Though findings have not always been replicated (Schienle et al., 2007), the extant data suggest that CBT exerts an attenuating effect on limbic-prefrontal reactivity to threat stimuli.

The objective of the present study was to evaluate neural predictors of CBT response and treatment-related brain-based changes to threat-relevant stimuli in gSAD. Accordingly, we used a perceptual face processing paradigm validated to isolate brain response to signals of threat (Hariri et al., 2002, 2005) before and after 12 weeks of manualized CBT (Hope et al., 2006). For comparison and to control for the effects of re-exposure to threat stimuli with repeated scanning, we enrolled a group of healthy control (HC) volunteers who were also scanned twice, 12 weeks apart.

Based on the literature and cognitive theory, we hypothesized symptom improvement would be predicted by greater pre-treatment activity in higher-level visual areas (e.g., occipitotemporal cortex) and less ACC and amygdala activity. Regarding brain changes, we hypothesized CBT would reduce exaggerated reactivity to threat faces in limbic/paralimbic areas (i.e., amygdala and insula), visual cortex, ACC and other medial PFC areas (e.g., dorsomedial, orbitofrontal) given their role in appraisal, response expression, and regulation (Bush et al., 2000; Etkin et al., 2011).

Furthermore, we hypothesized changes in activation would match clinical response to treatment such that post- versus pre-treatment changes in brain activation would correlate with changes in gSAD symptom severity.

2. Method

2.1. Ethics statements

All participants provided written informed consent in accordance with the Declaration of Helsinki and as approved by the Institutional Review Boards of the University of Michigan Medical School.

2.2. Participants

Fourteen individuals diagnosed with gSAD, who were not in psychotherapy, were identified through local community advertisement and via referrals from an outpatient psychiatric clinic. Fourteen demographically-matched HC were recruited through community advertisements. All participants completed the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) conducted by licensed clinicians in conjunction with measures of symptoms and negative mood such as the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) and Beck Depression Inventory (BDI) (Beck et al., 1996). Regarding symptoms, an LSAS total score cut off of 55 was used to capture levels of symptom severity that ranged from the moderate to the severe (Heimberg et al., 1999). Clinical response was measured with the Clinical Global Impression-Improvement (CGI-I) scale, a clinician-based rating that takes into consideration symptom severity and changes in a patient's functioning over time. All participants were free of psychotropic medications except for two individuals with gSAD, who were on a stable dose of bupropion for at least 8 weeks before the study with no changes in medication during the study. None of the gSAD participants had a current major depressive episode, severe depression symptoms (i.e., BDI score of 30 or greater; Beck et al., 1996), recent substance abuse/dependence (within 6 months of study), or any history of major psychiatric illness (e.g., bipolar, psychotic disorder). All participants were between 18 and 55 years of age, right-handed, and free of current and past major medical or neurologic illness, as confirmed by a Board Certified physician. None of the participants tested positive for alcohol or illegal substances. Table 1 details the demographic and clinical characteristics of the participants.

Patients received 12 weeks of manualized individual CBT (Hope et al., 2006), which consisted of one 60-minute session per week, conducted by a licensed clinical psychologist under the supervision of a licensed clinical psychologist with expertise in CBT and clinical trial investigations involving CBT to ensure adherence to treatment. CBT comprised psychoeducation, cognitive restructuring, in vivo exposures, and relapse prevention (Hope et al., 2006).

2.3. fMRI task

During scanning, all participants performed a modified emotional face matching task designed to isolate key subcortical emotion processing areas (e.g., amygdala, insula) to signals of threat (i.e., angry,