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Neural responses to social threat and predictors of cognitive behavioral therapy and acceptance and commitment therapy in social anxiety disorder

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ABSTRACT

Previous research has often highlighted hyperactivity in emotion regions to simple, static social threat cues in social anxiety disorder (SAD). Investigation of the neurobiology of SAD using more naturalistic paradigms can further reveal underlying mechanisms and how these relate to clinical outcomes. We used fMRI to investigate responses to novel dynamic rejection stimuli in individuals with SAD (N=70) and healthy controls (HC; N=17), and whether these responses predicted treatment outcomes following cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT). Both HC and SAD groups reported greater distress to rejection compared to neutral social stimuli. At the neural level, HCs exhibited greater activations in social pain/rejection regions, including dorsal anterior cingulate cortex and anterior insula, to rejection stimuli. The SAD group evidenced a different pattern, with no differences in these rejection regions and relatively greater activations in the amygdala and other regions to neutral stimuli. Greater responses in anterior cingulate cortex and the amygdala to rejection vs. neutral stimuli predicted better CBT outcomes. In contrast, enhanced activity in sensory-focused posterior insula predicted ACT responses.

1. Introduction

Social anxiety disorder (SAD) is one of the most common anxiety disorders, with 12-month and lifetime prevalence rates estimated at 8% and 13%, respectively (Kessler et al., 2012; Ruscio et al., 2008). SAD is characterized by persistent and excessive fear of scrutiny or humiliation in performance-related or social-interactional situations. As such, afflicted individuals will frequently avoid social situations and/or endure them with anxiety and distress, which can have significant adverse consequences on quality of life, and social, academic, and occupational functioning (Mendlowicz and Stein, 2000).

The past several decades of research have identified multiple maladaptive biases in SAD involving hyperreactivity to threatening or potentially-threatening social information as well as excessively negative interpretations of such information that contribute to the development and maintenance of SAD (Clark and Wells, 1995; Craske et al., 2009; Rapee and Heimberg, 1997). Neuroimaging research has begun to provide valuable insights into the neurobiological substrates that mediate the maladaptive processing of social information in SAD. One of the most intensely studied neural regions in SAD is the amygdala, which is not surprising given its well-established role in fear and social processing (Adolphs, 1999; LeDoux, 1998). The amygdala is integral to fear learning and memory and has been characterized as representing a primitive threat-detection system designed to help protect the individual from harm (Amaral, 2002; LeDoux, 1998; Phelps and LeDoux, 2005). Numerous studies have found greater amygdala activity in SAD compared to healthy controls in response to socially threatening stimuli (see Brühl et al., 2014; Etkin and Wager, 2007; and Freitas-Ferrari et al., 2010 for reviews and meta-analyses), consistent with the idea that SAD is characterized by hyper-sensitivity in detecting overt and potential social threats.

The insula, a limbic region central to the integration of perceptual, emotional, and cognitive information into subjective experiences (Craig, 2011; Kurth et al., 2010), has been shown to be hyperactive in SAD relative to healthy controls in response to socially-threatening facial expressions (Amir et al., 2005; Straube et al., 2004), scenes (Boehme et al., 2014), and situations (Lorberbaum et al., 2004). Such findings are consistent with theoretical models and behavioral findings that individuals with SAD are more likely to internalize or personalize potential social threats, as well as experience them as more aversive than non-anxious individuals.

SAD has been associated with increased activity in dorsal anterior cingulate cortex (dACC) relative to healthy controls in response to socially-threatening stimuli (Amir et al., 2005; Blair et al., 2008a, 2011b). While less emphasized in SAD research than other regions, dACC would seem to represent a key target for investigation of

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maladaptive neural functioning in SAD given its role in general appraisal and monitoring of emotional information, and experiences of social pain and rejection (Eisenberger, 2012; Rotge et al., 2014), which are hallmarks of SAD. Recent work highlights a similar role in social pain and rejection for subgenual and pregenual regions of the ACC as well (Rotge et al., 2014; Wager et al., 2009).

SAD has been associated with dysfunctions in multiple regions that regulate or modulate the complex processes initiated by emotion and threat detection regions as well. Relative to healthy controls, SAD has been associated with increased activity in regions that underlie inhibition of emotion (ventrolateral prefrontal cortex; VLPFC), contextual processing (hippocampus and parahippocampal gyrus), integration of multimodal information and self-awareness (medial parietal cortex/precuneus), and perceptual and semantic processing (fusiform gyrus and other occipitotemporal regions). However, specific results vary considerably across studies (Brühl et al., 2014; Etkin and Wager, 2007).

By far the most common approach to investigating neural functioning in SAD utilizes images of emotional facial expressions as stimuli in conjunction with passive viewing or perceptual ratings or classifications of the stimuli (e.g., Birbaumer et al., 1998; Blair et al., 2008b, 2011a; Cooney et al., 2006; Evans et al., 2008; Gentili et al., 2008; Hahn et al., 2011; Klumpp et al., 2012; Phan et al., 2006, 2013a; Prater et al., 2013; Stein et al., 2002; Straube et al., 2004, 2005; Yoon et al., 2007). The widespread use of facial expressions is not surprising given that they hold particular fear-relevance for individuals who are socially anxious. They have proven to be a powerful research tool with the ability to predict important outcomes including vulnerability to developing mental disorders (e.g., Pezawas et al., 2005) and even treatment response in SAD (e.g., Doehrmann et al., 2013).

Despite the elegant simplicity of static facial expressions, there has been a growing emphasis on other types of stimuli with putatively greater ecological validity such as imagining feared social situations (Blair et al., 2010; Boehme et al., 2014; Nakao et al., 2011), anticipation of public speaking (Boehme et al., 2013; Cremers et al., 2015), performance evaluation (Giménez et al., 2012; Koric et al., 2012; Pujol et al., 2013), and exposure to social criticism (Blair et al., 2008a; Goldin et al., 2009b; Ziv et al., 2013). Such paradigms can provide valuable insights into the more complex processes that are typically encountered in SAD. Additionally, such paradigms typically evoke distress and thereby can reveal the underlying mechanisms of not only sensitivity to cues of social distress, but actual experiences of social distress and corresponding regulation attempts.

We conducted an fMRI study in which participants were scanned while being subjected to one of the most feared scenarios in SAD: criticism and rejection by others. Participants with SAD and healthy controls viewed film clips of others (i.e., actors) saying socially-rejecting statements directed at them and were instructed to imagine the situations as real (i.e., that these people were talking to them). As such, this paradigm was designed to combine the power and relevance of facial expressions with increased realism that putatively taps into the fears that lie at the core of SAD to evoke distress.

We further investigated the clinical implications of neural responses to rejection by examining whether they would predict subsequent treatment outcomes following either cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT). A handful of emerging studies have found that pre-treatment neural activity in amygdala, dACC, prefrontal, occipital, and temporal regions during simple perceptual matching tasks has predicted responses to CBT in SAD participants (Doehrmann et al., 2013; Klumpp et al., 2013, 2014). However, to our knowledge, no studies have examined how neural activity in response to an experience of rejection may relate to treatment outcomes in SAD, and no studies have examined neural patterns that may predict response to ACT, which, although generally as effective as CBT (Craske et al., 2014), involves a very different theoretical approach (Arch and Craske, 2008).

We predicted that the novel rejection stimuli used herein would engage (a) regions involved in emotional responding such as amygdala and insula, (b) regions underlying experiences of rejection including anterior insula, dACC, and ventral ACC (pre- and subgenual), (c) contextual modulation regions such as hippocampus and parahippocampal gyrus, (d) regions involved in self-awareness and theory of mind such as medial prefrontal cortex (MPFC) and precuneus given the role of perceiving others' impressions of oneself in this paradigm, (e) cognitive control regions including VLPFC and DLPFC, and (f) regions involved in processing social and linguistic information such as lateral temporal and occipital regions. We expected to see relatively greater activations in SAD individuals compared to healthy controls, particularly in amygdala, insula, and ACC, reflecting increased sensitivity to rejection and potential social threat, and that neural responses to rejection stimuli would be moderated by SAD severity, given evidence that severity of maladaptive processing of social information in SAD covaries with disorder severity (e.g., Ball et al., 2012; Brühl et al., 2011; Evans et al., 2008; Frick et al., 2013; Goldin et al., 2009a; Koric et al., 2012; Shah et al., 2009). Finally, we predicted that increased pre-treatment amygdala, ACC, prefrontal, occipital, and temporal activity would predict subsequent CBT/ACT outcomes consistent with previous related work demonstrating such a relationship (Klumpp et al., 2013, 2014; McClure et al., 2007; Siegle et al., 2006).

2. Methods

2.1. Participant recruitment and screening

Participants were recruited through the UCLA Anxiety Disorders Research Center and from the UCLA and Los Angeles community as part of a larger study evaluating two types of behavioral treatment for SAD, cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT). Participants underwent diagnostic evaluation using the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown et al., 1994), conducted by trained and reliability-certified clinicians. SAD participants met DSM-IV criteria for a current principal or co-principal diagnosis of SAD with a clinical severity rating ≥4 (on a scale of 0–8) which indicates clinically significant symptoms, distress, or impairment. Healthy control (HC) participants had no current or past psychiatric disorders.

Inclusion criteria for all participants were 18–45 years old, English-speaking, and right-handed. Exclusion criteria included standard fMRI contraindications (e.g., pregnancy; claustrophobia; non-removable metallic objects); serious medical conditions or brain damage; bipolar disorders; substance-related disorders; suicidality; psychosis; psychiatric hospitalization; and recent modifications to psychotropic medication or psychotherapy. The research protocol was approved by the UCLA Office for the Protection of Human Research Subjects and all participants provided informed consent prior to completing the ADIS-IV.

2.2. Participants

SAD Participants (N=70) and HCs (N=17) were similar on demographic variables, as shown in Table 1. Details on comorbidity and medication status are also presented in Table 1. All participants were included in baseline (pre-treatment) analyses except that 3 SAD participants with missing questionnaire data were excluded from related analyses, as described below. Analyses examining how neural activity at baseline related to treatment outcomes included only those participants who were randomized to receive an active treatment (CBT or ACT) and completed all necessary assessments (N=36), as described below.