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Emotion regulation related neural predictors of cognitive behavioral therapy response in social anxiety disorder

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ABSTRACT

Social anxiety disorder (SAD) is characterized by aberrant prefrontal activity during reappraisal, an adaptive cognitive approach aimed at downregulating the automatic response evoked by a negative event. Cognitive behavioral therapy (CBT) is first-line psychotherapy for SAD, however, many remain symptomatic after treatment indicating baseline individual differences in neurofunctional activity may factor into CBT outcome. An emotion regulation strategy practiced in CBT is cognitive restructuring, a proxy for reappraisal. Therefore, neural response during reappraisal may serve as a brain-based predictor of CBT success. Prior to 12 weeks of individual CBT, 34 patients with SAD completed a validated emotion regulation task during fMRI. Task instructions included 'Reappraise,' that is, use a cognitive approach to reduce affective state to a negative image, which was contrasted with looking at a negative image ('Look'). Regression results for Reappraise (vs. Look) revealed greater reduction in symptom severity was predicted by less pre-CBT activation in the dorsolateral prefrontal cortex (DLPFC). Regarding predictive validity, DLPFC significantly classified responder status. Post-hoc analysis revealed DLPFC activity, but not demographic data, baseline clinical measures, or reappraisal-related affective state during fMRI, significantly accounted for the variance in symptom reduction. Findings indicate patients with SAD are more likely to benefit from CBT if there is less pre-treatment DLPFC recruitment, a region strongly implicated in emotion regulation. Patients with reduced baseline frontal activation when reappraising negative stimuli may be especially helped by explicit cognitive interventions. Further research is necessary to establish DLPFC as a stable brain-based marker of treatment outcome.

1. Introduction

Social anxiety disorder (SAD) is a common psychiatric illness characterized by pervasive fears of potential scrutiny by others (Kessler et al., 2005). Inappropriate, excessive fears in SAD are due in part to emotion dysregulation as indicated by an overreliance on expressive suppression, a generally maladaptive avoidance regulation strategy to cope with emotion (Heimberg et al., 2014; Spokas et al., 2009). Suppression in SAD is mediated by social concerns, for example, the belief that inhibiting expressions reduces the likelihood of negative evaluation (Spokas et al., 2009). In addition to suppression, socially anxious individuals report low levels of self-efficacy when implementing emotion regulation strategies including cognitive reappraisal (Werner et al., 2011). Reappraisal is an antecedent form of regulation directed at cognitively changing a situation to alter its emotional significance; it is considered an adaptive, explicit regulation approach known to engender social support and psychological well-being (Gross and John, 2003).

Cognitive behavioral therapy (CBT) is a first-line psychotherapy for SAD and other anxiety disorders (Hofmann and Smits, 2008) that aims to reduce symptoms by increasing adaptive emotion regulation (O'Toole et al., 2015), and indeed, reappraisal is utilized more frequently in SAD patients who participated in CBT (Moscovitch et al., 2012). Although CBT is the "gold standard" psychotherapy for SAD, response rate varies considerably ranging from 4% to 80% (Loerinc et al., 2015). Thus, many patients remain symptomatic after completing treatment. Increasingly, the utility of brain-based predictors is being realized as they are frequently superior in foretelling who is likely to achieve clinically-meaningful response to CBT relative to demographic and/or baseline clinical information alone (Ball et al., 2014; Doehrmann et al., 2013; Thompson et al., 2015). Evidence brain-based markers may be

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more sensitive in predicting treatment outcome than non-imaging measures are in line with the conceptualization psychiatric illnesses are brain illnesses (Downar et al., 2016). In other words, it stands to reason that individual differences in brain pathophysiology will interact with mechanisms of treatment.

In neuroimaging studies, reappraisal includes interpreting (e.g., "reframing") an aversive stimulus to decrease the negative affect evoked by it (Webb et al., 2012), an approach that generally echoes cognitive strategies employed in CBT, for example, generating alternative appraisals to negate negative beliefs (Hofmann, 2004; Hope et al., 2006). Cognitive reappraisal has been widely studied with functional magnetic resonance imaging (fMRI) and converging data in healthy individuals show reappraisal engages regions central in higher-order processes (e.g., attention, inhibition, working memory) such as dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), as well as ventromedial prefrontal cortex (VMPFC) and ventrolateral prefrontal cortex (VLPFC), though ventral areas have been less consistently observed (Buhle et al., 2014; Messina et al., 2015). Together, these regions form a cognitive control network which underlies the ability to deliberately modulate reactions to emotional stimuli.

Consistent with behavioral observations of emotion dysregulation in SAD, Goldin et al. (2009a) observed less DLPFC and less dorsal ACC (dACC) recruitment in SAD when reappraising negative faces compared to healthy controls. Moreover, SAD participants failed to exhibit more reappraise-related activity in any regions relative to controls. In a separate study, there was evidence of delayed engagement of DLPFC, dACC, VLPFC, MPFC, and dorsomedial PFC (DMPFC) when reappraising negative beliefs compared to controls (Goldin et al., 2009b). Findings suggest patients with SAD were able to eventually recruit regions that support regulation but may have required additional time to override the initial emotional reactivity to negative stimuli (Goldin et al., 2009b). Patterns of prefrontal hypo-activity or delayed reappraise-related recruitment in SAD relative to healthy controls has also been shown in other tasks involving negative socio-emotional stimuli (Ziv et al., 2013). Altogether, these data are consonant with reports of reduced activation in dorsal and ventral lateral regions during reappraisal in other anxiety disorders (e.g., panic disorder, generalized anxiety disorder) and major depressive disorder suggesting impairment in cognitive reappraisal capacity is a transdiagnostic factor in internalizing psychopathologies (Zilverstand et al., 2016).

The clinical implication is that pre-CBT variation in frontal activity during reappraise may interact with CBT outcome as this cognitive approach is a proxy to the interventions practiced in CBT (e.g., cognitive restructuring) (Arch and Craske, 2009). While this has yet to be examined in SAD, *less* baseline DLPFC activation in reappraise, relative to looking at aversive images, has been shown to predict CBT success in panic disorder (Reinecke et al., 2014), which has shared neurobiological features with SAD (Demenescu et al., 2013). These data suggest CBT may be most beneficial to those who have greater regulation deficiency when using a cognitive approach to downregulate emotional reactivity.

Results also indicate the DLPFC or other areas involved in emotion regulation may be a mechanistic target of CBT. In support, SAD patients who completed CBT relative to a waitlist control group exhibited increased DLPFC and DMPFC activity when reappraising negative social situations suggesting a generalization of the techniques learned in CBT (Goldin et al., 2013). There is also evidence of greater pre-to-post CBT reappraisal-related activation (compared to waitlist control) in the superior/middle frontal gyrus and middle occipital gyrus as well as less activity in posterior superior temporal gyrus, which collectively predicted 24% of the variance in symptom severity reduction. Yet, neural changes in other conditions (i.e., react praise, react criticism) did not significantly account for the decrease in social anxiety symptoms nor did self-reported pre-to-post-CBT decreases in negative emotion. Findings signify neural correlates of emotion regulation were a target of CBT. These data indicate reappraise-related disturbances in SAD interact with CBT and that alterations in brain response during reappraise contribute to a reduction in symptoms. However, it is not clear if frontal regions key to reappraisal predict CBT outcome in SAD.

The goal of the present study was to test whether pre-CBT brain activity using cognitive reappraisal to reduce negative affective state evoked by aversive images predicted clinical improvement in patients with SAD. To this end we employed an emotion regulation task (ERT) based on paradigms previously used to examine cognitive reappraisal mechanisms in other labs (Ochsner et al., 2002) and in our lab in healthy participants (Phan et al., 2005) and patient cohorts (MacNamara et al., 2016; Rabinak et al., 2014). We hypothesized larger decreases in symptom severity would be predicted by less pre-CBT activation in cognitive control areas when reappraising negative images compared to naturally reacting to negative images (i.e., "Look Negative"). We also hypothesized brain activity, but not demographic data, clinical measures, or on-line reappraisal ability, would significantly account for the pre-to-post change in symptom severity after completing CBT. Lastly, we explored whether baseline symptom severity correlated with less neurofunctional activity in reappraise relative to "Look Negative."

2. Methods

2.1. Participants

All participants provided written informed consent as approved by the local Institutional Review Board at the University of Illinois at Chicago (UIC) and all procedures complied with the Helsinki Declaration. Diagnosis was based on the Structured Clinical Interview for DSM-IV ("SCID-IV"; First et al., 1995) and the clinician-administered Liebowitz Social Anxiety Scale total score ("LSAS"; Liebowitz, 1987) determined symptom severity. Depression level was evaluated with the clinician-administered Hamilton Depression Rating Scale ("HAM-D"; Hamilton, 1960). Regarding self-reported symptoms, the Beck Depression Inventory (BDI; Beck et al., 1996) and the Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) assessed depression and general trait anxiety level, respectively. A master's-level clinician trained in the SCID-IV and clinician-administered measures performed assessments. The Emotion Regulation Questionnaire ("ERQ"; Gross and John, 2003) was used to evaluate subjective habitual use of reappraisal and expressive suppression. Participants were compensated for their time.

Participants were between 18 and 55 years of age, free of major medical or neurologic illness as confirmed by a Board Certified physician. SAD was required to be the primary diagnosis and participants with comorbidity were not excluded. All participants were free of psychotropic medications and none were receiving concurrent psychotherapy. None of the participants tested positive for drugs.

Exclusion criteria included contraindications to magnetic resonance imaging (e.g., pregnancy, claustrophobia, non-removable ferrous objects), current substance abuse or dependence (within 6 months of study), or history of major psychiatric illness (e.g., bipolar disorder, psychotic disorder, pervasive developmental disorder).

2.2. Treatment

Within a week of the fMRI scan, patients began once-weekly sessions of manualized individual CBT for 12 weeks, which comprised psycho-education, cognitive restructuring, in vivo exposures to fears, and relapse prevention (Hope et al., 2006). A CBT-trained licensed clinical psychologist or post-doctoral clinical psychologist conducted treatment. The clinicians were supervised by a licensed clinical psychologist with expertise in CBT and clinical trials. Response to CBT was defined as a 50% (or more) reduction in symptom severity as indexed with the LSAS total score (Jakubovski and Bloch, 2014; Roy-Byrne et al., 2010; van Vliet et al., 1994). Symptom severity was assessed by a non-treating clinician.