



Treatment for social anxiety disorder alters functional connectivity in emotion regulation neural circuitry

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ABSTRACT

Social anxiety disorder (SAD) is characterized at a neurobiological level by disrupted activity in emotion regulation neural circuitry. Previous work has demonstrated amygdala hyperreactivity and disrupted prefrontal responses to social cues in individuals with SAD (Kim et al., 2011). While exposure-based psychological treatments effectively reduce SAD symptoms, not all individuals respond to treatment. Better understanding of the neural mechanisms involved offers the potential to improve treatment efficacy. In this study, we investigated functional connectivity in emotion regulation neural circuitry in a randomized controlled treatment trial for SAD. Participants with SAD underwent fMRI scanning while performing an implicit emotion regulation task prior to treatment (n=62). Following 12 weeks of cognitive behavioral therapy, acceptance and commitment therapy, or wait-list, participants completed a second scan (n=42). Psychophysiological interaction analyses using amygdala seed regions demonstrated differences between SAD and healthy control participants (HC; n=16) in right amygdala-vmPFC connectivity. SAD participants demonstrated more negative amygdala-to-vmPFC connectivity, compared to HC participants, an effect that was correlated with SAD symptom severity. Post-treatment symptom reduction was correlated with altered amygdala-to-vm/vlPFC connectivity, independent of treatment type. Greater symptom reduction was associated with more negative amygdala-to-vm/vlPFC connectivity. These findings suggest that effective psychological treatment for SAD enhances amygdala-prefrontal functional connectivity.

1. Introduction

Social anxiety disorder (SAD) is characterized by a fear of being judged or scrutinized by others in social situations (Kessler et al., 2009). While psychological treatments, including cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT), have been shown to be efficacious for SAD in randomized controlled trials (Craske et al., 2014; Rodebaugh et al., 2004), many individuals do not respond, or retain residual symptoms and impairment after treatment. Better understanding of the mechanisms of efficacious treatment change, such as associated changes in neural activity, may ultimately aid the development of more targeted interventions.

1.1. SAD and emotion regulation

The prevailing neurobiological model of anxiety disorders posits that amygdala hyperreactivity to fearful or threatening stimuli is

associated with heightened emotional *reactivity*, while disrupted processing in prefrontal regions is linked to impairments in emotional *regulation* (Berkman and Lieberman, 2009; Freitas-Ferrari et al., 2010; Kim et al., 2011). Neuroscientific investigation of SAD has repeatedly shown heightened amygdala reactivity to social or emotional cues (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Phan et al., 2006; Stein et al., 2002), the extent of which has been shown to correlate with symptom severity (Cooney et al., 2006; Goldin et al., 2009b; Phan et al., 2006; Shah and Angstadt, 2009).

Compared to the body of work investigating emotional reactivity in SAD, few studies have assessed disruptions in emotion regulation. Across these studies, there is a general trend for disrupted (increased or decreased) levels of activity in prefrontal regions (dorsolateral and ventrolateral prefrontal cortex, dl/vlPFC, dorsal anterior cingulate cortex, dACC) among individuals with SAD, relative to healthy control participants when explicitly instructed to engage in a regulatory strategy (for recent meta-analyses, see Brühl et al., 2014; Zilverstand

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et al., 2016). However, findings are not entirely consistent, with two recent studies demonstrated no significant differences in prefrontal activity during regulation between groups of SAD and healthy control participants (Burklund et al., 2015; Gaebler et al., 2014).

Data from one of these studies (Burklund et al., 2015; upon which the analyses in the current paper are also based) was acquired using an implicit, rather than an explicit, emotion regulation strategy (affect labeling). Affect labeling, the act of putting feelings into words, is considered an ‘incidental’ or ‘implicit’ form of emotion regulation and has been shown to be an effective regulatory strategy, diminishing the intensity of emotional reactions to labeled stimuli (Kircanski et al., 2012; Lieberman et al., 2011; Niles et al., 2015; Tabibnia et al., 2008). It is commonly used in the laboratory to investigate emotional regulation as it provides a way to measure activation in emotion regulation circuitry independent of the effort or intentionality that is typically required to engage in voluntary regulation (Creswell et al., 2007; Lieberman et al., 2007; Payer et al., 2012). Both explicit and incidental forms of emotion regulation have been shown to increase PFC and decrease amygdala activity in healthy participants (Burklund et al., 2014; Delgado et al., 2008; Hariri et al., 2000; Lieberman et al., 2007; Ochsner et al., 2002). It is notable, therefore, that when task demands are minimal, amygdala reactivity was found to be heightened in individuals with SAD, relative to healthy individuals, but there was no significant difference in right vLPFC activity during implicit emotion regulation (Burklund et al., 2015). One explanation for this effect is that dysregulated amygdala activity in SAD during implicit emotion regulation may be attributable to disrupted communication, or functional connectivity, between amygdala and prefrontal cortex, rather than a failure to activate prefrontal regions per se.

Previous functional connectivity studies have shown that while viewing face stimuli, greater SAD symptom severity was associated with greater amygdala to fusiform gyrus and amygdala to superior temporal sulcus connectivity in one study (Frick et al., 2013), or amygdala to dACC/dorsal medial PFC connectivity in another (Demenescu et al., 2013). Functional connectivity studies of emotion regulation found that while reappraising negative self-beliefs, participants with SAD demonstrated altered amygdala-prefrontal connectivity relative to HC participants. Greater prefrontal activity (in both dlPFC and right vLPFC) was associated with reduced amygdala activity, indicative of an inverse connection, to a greater extent in healthy control than SAD participants (Goldin et al., 2009a). A similar effect was demonstrated in resting state functional connectivity analyses, showing reduced correlation in amygdala and vmPFC activity in patients with SAD, compared to healthy adults (Hahn et al., 2011). Finally, one study of effective connectivity within this circuitry (using dynamic causal modeling) demonstrated impairments in bidirectional connectivity from vmPFC to amygdala in patients with SAD while perceiving emotional cues (Sladky et al., 2015a).

1.2. Treatment studies

Psychological treatments for SAD aim to alter emotion regulation capacities, albeit through different approaches. CBT teaches ‘reappraisal’, the intentional re-framing of negative or unpleasant thoughts or experiences (Craske, 2010). ACT promotes ‘acceptance’, the acknowledgement that emotional experiences are fleeting and can be viewed with a sense of perspective (Hayes et al., 1999). Existing studies assessing the neural correlates of CBT for SAD have investigated differences in emotional reactivity and explicit reappraisal. In a study of internet-delivered CBT (iCBT) for SAD, treatment-related reductions in amygdala reactivity to affective faces were associated with i) increases in mOFC activity (i.e., inverse connectivity) and ii) decreases in ventral and dorsal lateral PFC activity (i.e., positive connectivity) (Månsson et al., 2013). Two studies comparing CBT to wait-list groups of SAD patients demonstrated treatment-related increases in i) inverse connectivity between the dmPFC and left amygdala while reappraising

Table 1
Participant demographic information.

	Pre-treatment assessment				Post-treatment assessment		
	HC	SAD			SAD		
	–	CBT	ACT	WL	CBT	ACT	WL
N	16	20	24	18	13	16	13
Age mean years (SD)	27.47 (6.59)	27.80 (7.30)	27.46 (5.93)	26.54 (6.52)	26.77 (6.85)	26.93 (5.10)	27.11 (6.26)
Gender (M/F)	7/9	12/8	11/13	10/8	7/6	9/7	8/5
Mean LSAS Score (SD)	17.76 (6.21)	79.86 (15.55)	87.69 (19.17)	74.77 (20.13)	55.99 (22.80)	58.91 (22.07)	71.65 (16.91)

negative self-beliefs (Goldin et al., 2013), and ii) positive connectivity among prefrontal regions including medial PFC, dmPFC, left dACC, left dlPFC and left vLPFC when reappraising social criticism (Goldin et al., 2014). These studies have all focused on explicit emotion regulation, requiring intentional engagement with a regulatory strategy. It is unknown whether treatment for SAD impacts functioning within amygdala-prefrontal neural circuitry during incidental emotion regulation, when task demands are reduced, and how such connectivity might be affected by different treatment strategies.

1.3. Aims and hypotheses

In the current study, we aimed to investigate the effects of psychological therapy for SAD on neural functional connectivity during incidental emotion regulation. We also assessed differences in functional connectivity across two treatments conditions (CBT and ACT) compared to a wait-list (WL) control group. Data in this study was obtained as part of a larger RCT for SAD (Craske et al., 2014). It was hypothesized that individuals who experienced reduction of SAD symptoms following psychological treatment (CBT or ACT) would demonstrate improved prefrontal ‘down-regulation’ of amygdala reactivity as evidenced by greater inverse functional connectivity.

2. Methods

Data were collected as part of a RCT of CBT and ACT for social anxiety disorder. Full details of methods and outcomes for the RCT are reported elsewhere (Craske et al., 2014). Below is a brief description of methodology relevant to the current study.

2.1. Participant recruitment and screening

Participants were recruited through the University of California, Los Angeles (UCLA) Anxiety and Depression Research Center, flyers posted throughout the UCLA community, newspaper and internet advertisements. Participants provided informed consent prior to assessment and the research protocol was approved by the UCLA Office for the Protection of Human Research Subjects. Participants were aged 18–45 years old, English speaking and right-handed (see Table 1 for demographic details by group). Exclusion criteria were: standard MRI exclusions (pregnancy, claustrophobia, non-removable metal, serious medical conditions or brain damage); history of bipolar disorder, substance-use disorders, suicidality, psychosis or psychiatric hospitalizations; modifications to psychotropic medication (past month for benzodiazepines, past 3 months for SSRIs/SNRIs and heterocyclics); current cognitive or behavioral psychotherapy for anxiety disorder or modifications to other psychotherapies in the past 6 months.

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