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Research paper

Neural connectivity during affect labeling predicts treatment response to psychological therapies for social anxiety disorder

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ABSTRACT

Background: Although psychological treatments for social anxiety disorder (SAD) can be highly effective, many individuals do not respond to treatment. Identifying factors associated with improved outcomes can facilitate individualized treatment choices. We investigated whether patterns of neural connectivity predicted treatment responses and whether treatment type, cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT), moderated this effect.

Methods: Participants with SAD (n = 34) underwent fMRI prior to treatment and completed implicit and explicit emotion regulation tasks. Neural connectivity measures were estimates of amygdala-prefrontal cortex connectivity. Treatment responder status was defined using the 'clinically significant change index' (Loerinc et al., 2015).

Results: Right amygdala-right ventrolateral prefrontal cortex connectivity during implicit emotion regulation was a significant predictor of treatment response (OR = 9.01, 95% CI = 1.77, 46.0, p = .008). Stronger inverse connectivity was associated with greater likelihood of treatment response. There were no significant neural moderators of treatment response to CBT versus ACT.

Limitations: The primary limitation of this work was the small sample size which restricted the power to detect significant moderation effects, and results should be interpreted as preliminary.

Conclusions: Amygdala-vlPFC connectivity during affect labeling predicted treatment responder status following CBT or ACT for social anxiety disorder. This suggests that the functioning of neural circuitry supporting emotion regulation capacities may be a 'gateway' to receiving benefit from psychological treatments. Future work should aim to replicate this effect in a larger sample and consider methods for enhancing functional connectivity within this circuitry as a potential treatment adjunct.

1. Introduction

Although psychological treatments for social anxiety disorder (SAD) can be highly effective for some individuals, a large number of patients (as many as 55%; Loerinc et al., 2015) fail to respond to treatment, or retain residual symptoms or impairment following treatment. The ability to predict which individuals are likely to respond to which treatments not only informs individual treatment choices, but also elucidates the mechanisms of treatments themselves. Existing work in this domain has begun to identify a set of characteristics, determined by self-report, clinician assessment or task performance, that are predictive of responses to Cognitive Behavioral Therapy (CBT) for anxiety disorders (Schneider et al., 2015). Here, we extend this approach to identify neural indices that predict treatment response, an approach which can help to enhance our understanding of the effects of psychological treatment on the brain (Craske, 2014; Holmes et al., 2014).

Previous work investigating the neurobiological basis of anxiety disorders has highlighted disruptions in emotion regulation neural circuitry. The neurobiological model of emotion regulation states that reactivity to emotional stimuli in the amygdala is regulated through top-down connectivity with regions of the prefrontal cortex (PFC; Brühl et al., 2014; Goldin et al., 2009b; Ochsner and Gross, 2005; Zilverstand et al., 2016; Ziv et al., 2013). Supporting this model, previous work has demonstrated that, compared to healthy individuals, patients with SAD

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show: (i) disrupted activation in the amygdala and regions of the prefrontal cortex (for reviews, see Berkman and Lieberman, 2009; Freitas-Ferrari et al., 2010; Kim et al., 2011) and (ii) altered amygdala connectivity with vlPFC (Burklund et al., 2014a), dlPFC (Goldin et al., 2009a), vmPFC (Hahn et al., 2011; Sladky et al., 2015; Young et al., 2017) and dACC/mPFC (Demenescu et al., 2013). Emerging evidence implicates this circuitry in mechanisms of treatment response, with studies demonstrating altered connectivity following CBT between amygdala and dmPFC, mOFC and vl/dlPFC (Goldin et al., 2013, 2014; Månsson et al., 2013). In addition, we previously demonstrated that SAD symptom reduction following either CBT or Acceptance and Commitment Therapy (ACT; another form of behavioral therapy) was associated with enhanced inverse connectivity between vmPFC/vlPFC and amygdala during implicit emotion regulation (Young et al., 2017).

If, as these findings suggest, treatment for SAD works through altering connectivity within the neural circuits associated with emotion regulation, then an individual's pre-treatment connectivity may impact their likelihood of responding to treatment. No prior studies have assessed the role of emotion regulation in predicting treatment response. Most existing studies have assessed pre-treatment measures of neural activation rather than connectivity and focused on emotional reactivity, rather than regulation. These studies have demonstrated that greater symptom reduction following CBT was associated with greater pre-treatment neural responses to emotional stimuli (emotional faces or rejecting statements) within the anterior cingulate cortex (ACC), dm/vmPFC and areas of occipital and parietal lobes (Burklund et al., 2017; Doehrmann et al., 2013; Klumpp et al., 2014, 2013). The role of amygdala activation in predicting treatment response remains unclear. Symptom reduction was predicted by decreased pre-treatment amygdala reactivity in one study (Klumpp et al., 2014) and increased reactivity in another (Burklund et al., 2017).

Of the two prior studies incorporating connectivity measures, one demonstrated that long-term (1 year) outcomes following internet-delivered CBT for SAD were predicted by decreased pre-treatment amygdala-dACC connectivity during a self-referential criticism task (Månsson et al., 2015). The other, using resting state functional connectivity, found that greater symptom reduction following CBT for SAD was associated with stronger pre-treatment amygdala-ACC connectivity, stronger amygdala connectivity with caudate and putamen, and reduced amygdala connectivity with central sulcus and right temporo-occipital cluster. This study additionally found that greater inferior longitudinal fasciculus (ILF) density (the white matter tract connecting amygdala with early visual areas) prior to treatment predicted greater symptom reduction following treatment (Whitfield-Gabrieli et al., 2016). In general, these findings support a role for activation and connectivity among neural circuitry involved in emotional processing in predicting treatment response, albeit with specific directions and locations of effects varying across task design.

In the current study, we build on this work by addressing two key limitations. First, we assessed neural functional connectivity during emotion regulation, a treatment-relevant process. Both CBT and ACT focus on improving emotion regulation, 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). Measuring neural connectivity during emotion regulation allows a more direct investigation of whether treatment-relevant processes predict treatment response (Young and Craske, 2018). Second, previous studies have primarily correlated responses with self-reported symptoms following treatment, or categorized 'treatment-responders' as those showing greatest symptom reduction. A more robust measure of treatment response can be obtained through use of a 'clinically significant change index' (CSCI) (Loerinc et al., 2015). This approach requires that, in order to be classified as a 'treatment responder', an individual must: (i) demonstrate a statistically significant reduction in symptoms, and (ii) move below threshold for clinical cut-offs in an independent diagnostic evaluation.

The current study aimed to investigate whether connectivity among emotion regulation neural circuitry (amygdala-prefrontal cortex) predicts whether patients with SAD are likely to respond to treatment. A secondary aim was to investigate differential predictors for treatment responses to CBT or ACT.

2. Methods

2.1. Participant details

Full details of the randomized controlled trial for SAD comparing CBT, ACT and a wait-list control group are described elsewhere (Craske et al., 2014). Participants were recruited from flyers, internet and newspaper advertisements and referrals. Procedures were approved by the UCLA Office for the Protection of Human Research Subjects and participants provided informed consent. Participants were aged 18–45 years, English speaking, right-handed, and had a diagnosis of SAD. Exclusion criteria were: history of bipolar disorder, substance-use disorders, suicidality, psychosis or psychiatric hospitalizations; recent modifications to psychotropic medications (within past month for benzodiazepines, past 3-months for SSRIs/SNRIs and heterocyclics); current cognitive or behavioral psychotherapy for an anxiety disorder or recent modifications to other psychotherapies (within past 6 months); and standard MRI contraindications (pregnancy, claustrophobia, non-removable metal). Data analyzed here included 34 participants, 17 who subsequently received CBT and 17 who received ACT (see Supplemental Materials for Consort diagram, full details on participant inclusion and treatment overview). Table 1 presents demographic details of participants.

2.2. Assessment measures

Diagnostic evaluations were conducted using the Anxiety Disorders Interview Schedule-IV (ADIS IV; Brown et al., 1994) by trained interviewers. Included participants met DSM-IV criteria for current, principal or co-principal diagnosis of SAD, with a clinical severity rating (CSR) of 4 or higher, indicating clinically significant severity. Symptom severity was assessed using a composite of the total scores of three self-report measures: the Liebowitz Social Anxiety Scale–Self-Report Version, a 24-item measure assessing fear and avoidance of social interactions and performance situations (LSAS-SR; Fresco et al., 2001); the

Table 1
Demographic and diagnostic details of included participants (LSAS: Liebowitz Social Anxiety Scale; SIAS: Social Interaction Anxiety Scale; SPS: Social Phobia Scale).

	CBT	ACT	Full sample
N	17	17	34
Male	8	7	15
Female	9	10	19
Age: M (SD)	26.29 (6.20)	26.88 (5.07)	26.59 (5.67)
Responder Status			
Responder	8	8	16
Non-responder	9	9	18
Race/ethnicity			
White (non-Hispanic/Latino)	9	10	19
Asian/Asian-American	4	2	6
Hispanic/Latino	2	3	5
Multiracial/other race not specified	2	2	4
Baseline symptom scores			
Symptom composite: M (SD)	−0.07 (0.62)	0.00 (0.83)	−0.01 (0.73)
LSAS: M (SD)	79.94 (17.57)	85.41 (19.83)	80.33 (23.15)
SIAS: M (SD)	51.94 (11.51)	51.29 (11.65)	50.11 (14.27)
SPS: M (SD)	33.38 (10.95)	33.18 (12.40)	32.32 (12.96)