

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 vIPFC (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/vIPFC 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)

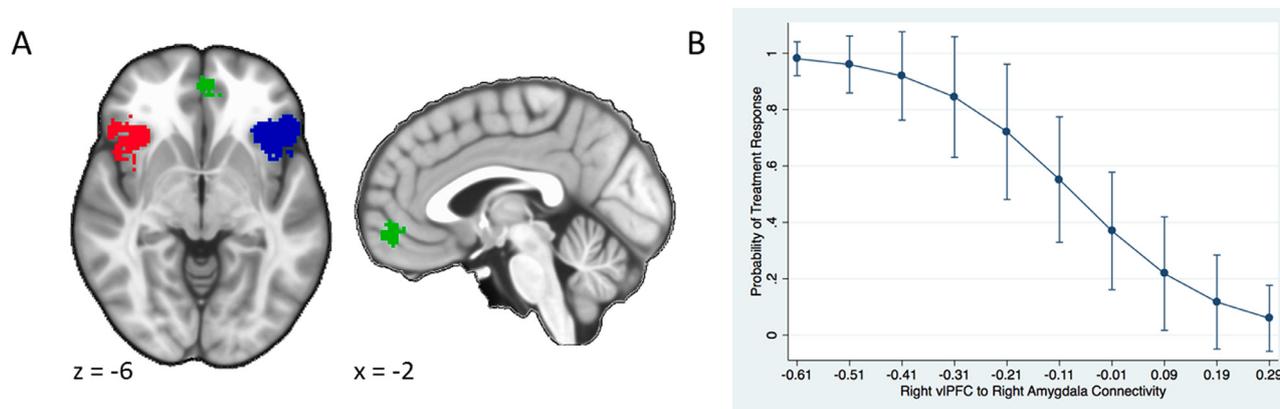


Fig. 1. (A) Prefrontal cortex regions of interest for connectivity analyses, obtained using Neurosynth displaying right and left vLPFC (red and blue) and vmPFC (green). (B) Probability of treatment response (CBT and ACT collapsed) predicted from right vLPFC-right amygdala connectivity (positive numbers indicate positive connectivity and negative numbers indicate negative connectivity). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Social Interaction Anxiety Scale, a 20-item measure of cognitive, affective and behavioral reactions to social interaction (SIAS; Mattick and Clarke, 1998); and the Social Phobia Scale, a 20-item measure describing responses to situations or themes related to being observed by others (SPS; Mattick and Clarke, 1998). A composite score was created from the LSAS, SIAS, and SPS to generate a reliable and valid index of social anxiety symptoms (consistent with the main outcome paper for this study; Craske et al., 2014). Z-scores were calculated for each measure at pre-treatment, and standardization was based on pre-treatment means and standard deviations for each subsequent assessment (see Craske et al., 2014 for details). The composite score represented averages of the three measures. In four cases where SIAS and SPS data were missing, self-report scores were based on LSAS data.

2.3. fMRI data acquisition

Participants completed an affect labeling task (a measure of implicit emotion regulation; Burklund et al., 2014b) and an explicit emotion regulation task (measuring responses during regulation of social cues; Burklund et al., 2017). See Supplemental Materials for details on MRI acquisition and preprocessing.

2.3.1. Implicit emotion regulation task

In the affect labeling task, participants viewed a series of images of emotional facial expressions and geometric shapes and were asked to complete labeling and matching tasks (affect labeling, gender labeling, affect matching and shape matching). In labeling conditions, participants responded via button press to select which of two words best match the affect or gender of the face displayed (match conditions require selection of matching images rather than matching words). The current study focused on assessment of implicit emotion regulation capacity, as indexed by the contrast of affect label versus gender label. Stimuli were presented in a blocked design, with four blocks of each condition and six trials per block (30s block, 5s per trial, order counterbalanced across participants). Each block was preceded by a 10s fixation cross and a 3s instruction cue.

2.3.2. Explicit emotion regulation task

Participants viewed blocks of video clips from actors saying rejecting, neutral, or positive phrases. They were instructed to imagine that the people in the videos were speaking directly to them. For rejecting videos, participants were asked either to passively “watch” the video, “reappraise by trying to reduce your emotional response”, or “accept by noticing how you are responding”. The current study focused on assessment of: (i) explicit ‘CBT-like’ emotion regulation

(reappraisal vs. passive viewing of rejecting videos) and (ii) explicit ‘ACT-like’ emotion regulation (acceptance vs. passive viewing of rejecting videos). Participants also viewed videos of positive statements and inanimate objects as other control conditions. Stimuli were presented in a blocked design, with two blocks of each condition type and six trials per block (30s block, 5s per trial, order counterbalanced across participants). Each block was preceded by a 5s instructional cue, followed by 11s rating period (during which participants provided ratings of perceived distress, not analyzed here) and a 10s fixation cross.

2.4. Data analysis

2.4.1. Clinically significant change index

CSCI (Loerinc et al., 2015) was calculated based on a combination of reliable change index on the SAD symptom composite (described above) and a clinical cut-off on the ADIS-IV. Treatment responders were individuals who achieved both: (i) reliable change in self-reported symptomatology on the symptom composite and (ii) movement into the non-clinical range of CSRs on the ADIS-IV (a CSR of below 4). The cutoff for reliable change was calculated as the difference between the pre-treatment and post-treatment scores across the whole sample, divided by the standard error of the difference between the two scores (Jacobson and Truax, 1991). If an individual's score exceeded the cutoff value, it was classified as a reliable change. Non-responders were defined as those who did not achieve a reliable reduction in symptom level and/or did not move below the threshold for clinically-significant CSR.

2.4.2. fMRI connectivity analyses

Psychophysiological interaction (PPI) analyses were conducted to assess task-related changes in functional connectivity of left and right amygdala seed regions (generalized PPI toolbox for SPM; McLaren et al., 2012). Amygdala seed regions were defined on the basis of anatomical masks (Automated Anatomical Labeling; AAL). Prefrontal cortical regions of interest (ROIs) were functionally-defined using an automated meta-analytic tool (Neurosynth; www.neurosynth.org; Yarkoni et al., 2011) using the search term ‘emotion regulation’. The resulting ‘forward inference’ map was parsed into prefrontal clusters: ventromedial PFC (vmPFC), right and left ventrolateral PFC (rvLPFC and lvLPFC; see Fig. 1A). Parameter estimates (β values) were extracted for each ROI using the Marsbar toolbox for SPM (Brett et al., 2002).

2.4.3. Statistical analyses

To test amygdala-PFC connectivity as moderators (i.e., CBT vs. ACT)

and predictors (i.e., CBT and ACT collapsed) of treatment response, we used logistic regression. Connectivity estimate outliers (defined as greater than 2.5 standard deviations above/below the mean) were removed from analyses ($n = 2$ for right amygdala-rvIPFC connectivity). For the moderator analysis, variables in the model were amygdala-PFC connectivity (3 PFC ROIs, 3 task conditions), treatment group, and the connectivity \times treatment group interactions. We examined the significance of the interactions. If the moderator analysis was not significant, we removed the interaction from the model and examined significance of the connectivity main effect. To estimate the predictive value of the regression model for unseen data, we used leave-one-out k -fold cross validation. This approach provides an estimate of utility of the regression model for predicting treatment response among participants whose data were not used to estimate the regression model. In leave-one-out k -fold cross validation, all participants except one are used to fit the model, then the model is used to predict the out-of-sample participant's outcome category. This is then iterated for each participant and used to predict probability of response across the full sample. Accuracy, sensitivity, and specificity can then be calculated by comparing the predicted probabilities estimated from the k -fold cross validation procedure to actual outcome (i.e. response or non-response).

3. Results

3.1. Treatment outcomes

Of the 34 participants included in the analyses, 16 achieved clinically significant change on the CSCI, 18 did not. Response rates were comparable across treatment conditions with eight participants in each group achieving responder status. Of the non-responders, none of the participants moved into the non-clinical diagnostic range on the ADIS (all retained a CSR ≥ 4), although 9 (3 CBT, 6 ACT) achieved significant reductions in self-reported symptomatology on the symptom composite measure.

3.2. Predictors of treatment outcomes

Implicit emotion regulation task: In the moderator analyses, none of the connectivity \times treatment group interactions were significant (all $p > .050$). For the predictor analysis, right vIPFC-right amygdala connectivity predicted clinically significant treatment response such that greater inverse connectivity was associated with better treatment responding regardless of treatment condition (OR = -9.01 , 95% CI = $-1.77, -46.0$, $p = .008$; see Fig. 1B). Based on the k -fold cross validation results, right vIPFC-right amygdala connectivity classified participants as treatment responders or not (using ≥ 0.5 probability as predicting treatment response and $<.5$ probability as non-response) with 69% accuracy, 67% sensitivity, and 71% specificity. No other connectivity measures were significant predictors of treatment response (all $p > .05$).

Explicit emotion regulation task: There were no significant connectivity \times treatment group interactions in moderator analyses and no significant connectivity main effects in predictor analyses on this task (all $p > .05$).

4. Discussion

Results demonstrated that stronger inverse connectivity between right amygdala and right vIPFC during implicit emotion regulation was associated with a greater likelihood of subsequent response to psychological treatment for SAD, regardless of treatment condition. In a cross-validation analysis this connectivity estimate was found to predict treatment response with 69% accuracy. None of the neural connectivity estimates assessed were significant moderators of treatment response, predicting greater likelihood of response to CBT or ACT individually.

Previous work has demonstrated regions of activation or patterns of

connectivity in response to emotional stimuli (i.e., emotional reactivity) that predict treatment response. Here we present the first findings, to our knowledge, that demonstrate how patterns of connectivity during emotion regulation predict treatment outcome. Given that current psychological treatments for SAD focus on emotion regulation skills, these analyses directly reflect how baseline capacity in treatment-relevant processes relates to treatment outcomes. Studies of emotional reactivity have highlighted the predictive value of activation in ACC, mPFC and occipital regions as well as connectivity between amygdala and ACC, caudate, putamen, central sulcus, and temporo-occipital regions (Burklund et al., 2017; Doehrmann et al., 2013; Klumpp et al., 2014; Klumpp et al., 2013; Månsson et al., 2015; Whitfield-Gabrieli et al., 2016). This implicates a broad network of regions in which reactivity might be related to treatment outcome. One previous study demonstrated prediction of CBT treatment response, defined solely by symptom reduction, at 81% accuracy using a combination of measures across diffusion MRI, resting state amygdala connectivity and multi-voxel pattern analysis (Whitfield-Gabrieli et al., 2016). Here we demonstrate prediction of clinically significant treatment response at 69% accuracy using a single, theoretically-driven index of connectivity in emotion regulation neural circuitry. This effect was specific to right amygdala-right vIPFC connectivity during implicit emotion regulation predicting response to treatment for social anxiety disorder (combining CBT and ACT).

Inverse prefrontal-amygdala connectivity has been highlighted as an index of emotion regulatory capacity whereby activation of prefrontal regions is thought to facilitate 'down-regulation' of amygdala responses (Ochsner et al., 2012). Our findings suggest that those better able to effectively engage this circuitry during implicit emotion regulation at baseline are more likely to achieve better outcomes from behavioral treatment. This effect was observed when collapsing across CBT and ACT groups and was specific to implicit emotion regulation (affect labeling). We did not observe any predictive or moderation effects of connectivity during explicit regulation (reappraisal or acceptance). While both tasks measure emotion regulation, they differ in intentionality. The goal of reappraisal or acceptance (explicit task) is to intentionally reduce emotional reactivity, while affect labeling simply involves recognizing an emotional cue, a more incidental form of regulation (Burklund et al., 2014b). We suggest that connectivity during affect labeling reflects a generalized tendency to engage regulatory circuitry when faced with emotional stimuli, whereas connectivity during explicit regulation reflects intentional engagement of this circuitry.

Alternatively, it is plausible that differences in cognitive load between the affect labeling and explicit regulation tasks impacted engagement of regulatory circuitry. In the affect labeling task, participants choose which of two words best describes the emotion in the face presented, a low cognitive load. In the explicit regulation task, participants are instructed to construct their own reappraisal or acceptance of negative statements, requiring a higher demand on cognitive capacities. A recent study demonstrated that regulatory neural connectivity (orbitofrontal cortex to amygdala functional connectivity) was modulated by the level of cognitive load (using a Stroop task; Minkova et al., 2017). Comparing individuals with SAD to healthy individuals, deficits in regulatory connectivity were observed only when cognitive load was low. There were no group differences observed in the high cognitive load condition, suggesting that regulatory capacity was impacted by attentional demands for all individuals. Therefore, the additional cognitive load of the explicit regulation task may reduce regulatory capacity among all individuals, masking individual differences in the tendency to engage regulatory circuitry. Future comparison of these possibilities would be of much interest, particularly given that the cognitive load of reappraisal and acceptance is likely reduced following treatment, where these skills are extensively practiced.

Nonetheless, our results suggest that only the extent to which emotion regulation neural circuitry is incidentally engaged (during low

cognitive load) is predictive of subsequent treatment response. In previous work, we demonstrated that enhanced inverse connectivity within this circuitry was associated with symptom reduction following treatment, collapsing across CBT and ACT groups (Young et al., 2017). Together, this would suggest a ‘building on strengths’ model (Engbreton et al., 1989; Rude and Rehm, 1991), such that individuals with greater capacity to implicitly regulate their emotions may benefit more from psychological treatment.

Given that CBT teaches reappraisal-based emotion regulation and ACT teaches acceptance-based regulation, the explicit emotion regulation task allowed direct assessment of treatment-relevant mechanisms. It might be expected that connectivity during reappraisal would predict treatment responses to CBT and connectivity during acceptance would predict treatment response to ACT. However, this moderation effect was not significant in the current analyses. It is plausible that there are treatment-specific differences in activation or connectivity outwith the primary network of emotion regulation neural circuitry investigated here. However, it should be noted that the current sample size may be too small to sufficiently assess treatment-moderator effects and that with a larger sample, neural moderators of treatment response may be observed.

5. Methodological strengths

This study has a number of methodological strengths that build upon findings from previous work. First, data were collected in the context of a high-quality randomized controlled trial using manualized treatment interventions with a high level of therapist adherence to protocol and validity in assessment methods (Craske et al., 2014). Second, the use of the CSCI as a measure of treatment responder status provides a reliable and conservative index, ensuring a clinically meaningful definition of this term. It should be noted that whereas other studies have reported higher response rates to CBT for SAD, the response rate in this study (47%) is typical when a CSCI is used (Loerinc et al., 2015).

6. Limitations

The primary limitation of this work was the sample size, although it is consistent with prior studies in this field (Doehrmann et al., 2013; Whitfield-Gabrieli et al., 2016). We had limited power to detect significant moderators of treatment response, such as baseline capacity to engage emotion regulation neural circuitry during instructed reappraisal predicting better outcomes to CBT over ACT. In addition, we used a ‘treatment completer’ analysis, rather than an ‘intent-to-treat’ analysis, which has been criticized due to the exclusion of data from individuals who did not fully comply or did not complete treatment (Gupta, 2011).

7. Future directions

Although it is not currently feasible to incorporate functional MRI assessments into standard clinical care, this evidence highlights the relevance of emotion regulation neural circuitry in individual responses to treatment conditions. Future work might consider what characteristics of the non-responder group might be better targeted in future treatment. Other methods of enhancing functional connectivity within this neural circuitry might also be investigated (e.g., transcranial direct current stimulation; Kuo et al., 2014) which may be particularly effective for individuals with low baseline connectivity. In addition, future studies should employ larger samples to permit more highly powered analyses of treatment moderators.

Contributors

DS, MDL, MGC and LB designed and oversaw the study. AN, BM and

LB were involved in data collection and management. KSY and RL proposed the current analytic strategy, KSY ran data analyses. AN, RTL and KH consulted on data analyses. KSY drafted the manuscript and all other authors provided comments and feedback.

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Conflict of interest

Authors declare no conflict of interest.

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Supplementary materials

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