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Predicting cognitive behavioral therapy response in social anxiety disorder with anterior cingulate cortex and amygdala during emotion regulation

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A B S T R A C T

Background: Cognitive Behavioral Therapy (CBT) for social anxiety disorder (SAD) and other internalizing conditions attempts to improve emotion regulation. Accumulating data indicate anterior cingulate cortex (ACC), and to a lesser extent amygdala, activation in various tasks predicts treatment outcome. However, little is known about ACC and amygdala activation to emotion regulation in predicting clinical improvement following CBT in SAD.

Methods: Before treatment, 38 SAD patients completed implicit and explicit emotion regulation paradigms during fMRI. Implicit regulation involved attentional control over negative distractors. Explicit regulation comprised cognitive reappraisal to negative images. Pre-CBT brain activity was circumscribed to anatomical-based ACC sub-regions (rostral, dorsal) and amygdala masks, which were submitted to ROC curves to examine predictive validity as well as correlational analysis to evaluate prognostic change in symptom severity.

Results: More rostral (rACC) activity in implicit regulation and less rACC activity during explicit regulation distinguished responders (34%) from non-responders. Greater amygdala response in implicit regulation also foretold responder status. Baseline rACC and amygdala activity during attentional control correlated with pre-to-post CBT change in symptom severity such that more activation was related to greater decline in symptoms. No significant correlations were observed for explicit regulation.

Conclusions: Across forms of regulation, rACC activity predicted responder status whereas amygdala as a neuromarker was limited to implicit regulation. While the direction of effects (enhanced vs. reduced) in rACC activity was task-dependent, results suggest SAD patients with deficient regulation benefited more from CBT. Findings support previous studies involving patients with depression and suggest the rACC may be a viable marker of clinical improvement in SAD.

1. Introduction

Social anxiety disorder (SAD) is a common, disabling, and costly mental illness in the U.S. (Aderka et al., 2012; Greenberg et al., 1999; Moitra et al., 2011). The disorder is highly comorbid with major depressive disorder, other anxiety disorders (Kessler et al., 2005), and is associated with functional impairment in major life domains (Aderka et al., 2012; Stein and Kean, 2000). Adding burden to the individual and society, the course of SAD tends to be protracted unless effectively treated (Stein and Stein, 2008). Cognitive Behavioral Therapy (CBT) is empirically-supported psychotherapy for SAD and other internalizing conditions (Hofmann and Smits, 2008; Hofmann et al., 2012). In CBT patients are taught adaptive ways to manage negative events; therefore, improvement in regulating emotions is a treatment target (Arch and Craske, 2009). Though CBT is broadly efficacious, clinical outcome varies considerably, for example, in real-world settings recovery following CBT ranges from 14% to 48% (Parker and Waller, 2015).

Identifying which patient is likely to benefit from treatment has been an intensive area of research as it has the potential to contribute to precision medicine by guiding treatment selection and developing novel interventions. Accruing data indicate brain-based predictors are frequently better in foretelling who is likely to improve following CBT relative to demographic or baseline clinical information alone (Ball et al., 2014; Klumpp et al., 2017; Thompson et al., 2015; Doehrmann et al., 2013). These reports suggest that baseline variance in brain activity interacts with CBT. Less clear is the extent to which a

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neuromarker is both prognostic of clinical outcome and relevant to the active components of CBT.

More specifically, the majority of research in neuromarkers over the past decade has been in patients with depression treated with pharmacotherapy and to a lesser extent CBT (Fu et al., 2008; Pizzagalli, 2011; Siegle et al., 2012; Siegle et al., 2006; Godlewska et al., 2016; Salvadore et al., 2009; Carl et al., 2016; Arns et al., 2015; Hunter et al., 2013; Konarski et al., 2009; Korb et al., 2009; Mayberg et al., 1997; Mulert et al., 2007; Pizzagalli et al., 2001; Rentzsch et al., 2014). Neuroimaging studies with fMRI or PET that have identified neuromarkers predominately involved simple, affective tasks (e.g., viewing negative words or images) (Siegle et al., 2012; Siegle et al., 2006; Godlewska et al., 2016; Salvadore et al., 2009); (though see Carl and colleagues (Carl et al., 2016) concerning reward processing), or resting state (Arns et al., 2015; Hunter et al., 2013; Konarski et al., 2009; Korb et al., 2009; Mayberg et al., 1997; Mulert et al., 2007; Pizzagalli et al., 2001; Rentzsch et al., 2014), a probe of self-referential processes (Andrews-Hanna et al., 2010; Greicius et al., 2003; Long et al., 2008; McKiernan et al., 2003). Across these studies, treatment response has generally been predicted by baseline rostral anterior cingulate cortex (ACC) activity (Siegle et al., 2012; Siegle et al., 2006; Salvadore et al., 2009; Arns et al., 2015; Hunter et al., 2013; Konarski et al., 2009; Korb et al., 2009; Mayberg et al., 1997; Mulert et al., 2007; Pizzagalli et al., 2001; Rentzsch et al., 2014); however, joint rostral and dorsal ACC (Carl et al., 2016; Rentzsch et al., 2014) and activity in dorsal ACC singly (Godlewska et al., 2016) have also functioned as neuromarkers. Collectively, the ACC, particularly rostral ACC, appears to be a reproducible predictor of treatment outcome in depression, which shares neurobiological features with SAD (Hamilton et al., 2015). Yet, little is known about rostral or dorsal ACC (rACC, dACC) regions predicting CBT outcome as it relates to tasks that probe emotion regulation even though skills practiced in CBT are intended to enhance regulation (Hofmann and Smits, 2008; Hofmann et al., 2012).

Regulation includes reappraisal, a cognitive approach (e.g., reframing stimulus content) intended to dampen or alter the trajectory of an emotional response to a negative event (Gross and John, 2003). Evidence of emotion dysregulation in SAD are positive associations between SAD and maladaptive regulation strategies along with low confidence when implementing reappraisal in daily life (Werner et al., 2011). Cognitive interventions in CBT encompass strategies akin to reappraisal (e.g., cognitive restructuring) (Arch and Craske, 2009) and reappraisal is utilized more frequently in SAD patients who participated in CBT (Moscovitch et al., 2012). Thus, reappraisal, an adaptive explicit form of regulation (Gross and John, 2003), is a proxy to techniques practiced in CBT. In contrast to an explicit approach, implicit emotion regulation is automatic in nature and encompasses attentional control, for example, the ability to effectively execute goal-directed behavior in the face of salient, sensory-driven distractors. SAD is associated with deficient attentional control as evinced by recurrent reports of attentional bias to threat-relevant stimuli (Bögels and Mansell, 2004). Although CBT does not directly focus on remediating attentional bias to threat per se, clinical improvement in SAD is associated with increased attentional control (Lundh and Öst, 2001; Mattia et al., 1993; Pishyar et al., 2008) suggesting implicit regulation is benefited by CBT techniques.

Brain regions that underlie emotion regulation include the ACC, which is part of a cortico-limbic system and serves as central hub for cognitive and emotional networks. Broadly, the affective, rACC is implicated in implicit regulation (Egner et al., 2008; Etkin et al., 2006; Ochsner et al., 2009) and evaluative functions (e.g., assessing salience of stimuli) (Bush et al., 2000; Etkin et al., 2011). The rACC has interconnections with the amygdala, a key region in detecting salient stimuli and generating emotional reactions (Barrett et al., 2007; Hariri and Whalen, 2011; Lindquist et al., 2012; Wager et al., 2008; Whalen, 1998). The rACC also receives input from the dorsal 'cognitive' division of the ACC. Relative to rACC, the dorsal ACC (dACC) is more closely involved with conflict-related processes (e.g., conflict monitoring, error detection) and adaptive response to motivationally-relevant information (Bush et al., 2000; Etkin et al., 2011; Banich et al., 2009; Botvinick et al., 2001; Carter et al., 1998; Liu et al., 2006; MacDonald et al., 2000).

Indices of successful reappraisal include self-reported reduction in negative affective state and a negative relationship between frontal regions and amygdala reactivity (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012). The dACC may be especially pertinent in reappraisal as indicated by meta-analytic studies showing its recruitment in healthy individuals along with reduced amygdala reactivity (Buhle et al., 2014; Messina et al., 2015). In SAD, delayed dACC engagement, among other frontal regions, has been observed when reappraising negative beliefs compared to controls (Goldin et al., 2009). Findings further support the role dACC plays in reappraisal in addition to evidence of emotion dysregulation in SAD.

Conversely, rACC engagement is frequently demonstrated during attentional control in the context of salient distractors, attesting to its function in effectively managing competing streams of information (Bush et al., 2000; Etkin et al., 2011; Kanske and Kotz, 2011; Pessoa et al., 2002). In keeping with a top-down model of effective regulation, rACC activity in implicit regulation has been shown to reduce amygdala reactivity (Etkin et al., 2006). In SAD, there are reports of reduced rACC activation, relative to healthy participants, in the face of emotional distractors (Wheaton et al., 2014; Klumpp et al., 2013a) suggesting attentional bias to salient distractors is due in part to deficient rACC activity, a key region in resolving such emotional interference (Etkin et al., 2011; Kanske and Kotz, 2011).

Altogether, successful regulation is indicated by an inverse relationship between dACC or rACC engagement and amygdala activity (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012). Accordingly, demonstrations of delayed or hypoactive ACC activity in SAD suggest inefficient or diminished regulation facility.

With regard to ACC as a predictor of CBT response in SAD, a machine-learning approach by Månsson and colleagues (Månsson et al., 2015) revealed dACC-related information to negative stimuli in SAD was highly predictive in classifying CBT responders a year after completing treatment whereas limbic/paralimbic (amygdala, hippocampus, insula) and prefrontal regions (dorsolateral prefrontal cortex [DLPFC], ventromedial prefrontal cortex [VMPFC]) were less predictive. In further support, our correlational findings based on conventional whole-brain thresholds revealed pre-CBT rACC and dACC response to emotional stimuli, or during resting-state, corresponded with decreases in social anxiety symptoms ($\Delta_{PreTx\ -\ PostTx}$) (Klumpp et al., 2013a; Klumpp et al., 2014a). Concerning implicit regulation, we observed clinical improvement was predicted by less dACC-DLPFC functional coupling, along with insula engagement, to threat distractors. Findings suggest that less baseline regulation capability at the neural level was prognostic of better CBT outcome (Klumpp et al., 2016).

For explicit emotion regulation, limited research in SAD has failed to show a link between ACC activity and CBT outcome thus far. Specifically, when using cognitive reappraisal to reduce negative affective state that would otherwise result from viewing negative stimuli, pre-to-post CBT alterations in prefrontal activity, posterior superior temporal gyrus, and middle occipital gyrus significantly accounted for the reduction in social anxiety symptoms (Goldin et al., 2014). However, it is possible that brain regions related to neurofunctional change over the course of CBT may not serve as neuromarkers. In a separate study, we explored baseline neural predictors using a conservative threshold (i.e., correction for multiple comparisons) and whole-brain findings demonstrated clinical improvement following CBT was predicted by less reappraisal-related activity in the DLPFC but not ACC (Klumpp et al., 2017).

Although a conservative approach may have reduced our ability to detect ACC effects, results are in line with implicit regulation findings

as patients with deficient regulation prior to starting CBT benefited more from treatment. Nonetheless, the issue of what constitutes significant neural activity is important as determination of significance in fMRI research is on-going (Eklund, 2016; Woo et al., 2014) and in lieu of a gold standard criterion, attempts to protect against Type I error may be overly conservative (Lieberman and Cunningham, 2009). Consequently, reliance on stringent criteria may impede the detection of reproducible neuromarkers, particularly when shifting from the discovery phase to the generalization phase of neural treatment predictors (Gabrieli et al., 2015). In other words, a neuromarker may be statistically robust yet not stable or generalizable, which are essential biomarker characteristics. Alternatively, a neuromarker may be significant and meaningful, but given cost constraints and resulting low power, not survive correction and result in Type II error.

In general, 'CBT neuromarker' studies of SAD indicate baseline activation in frontal regions (e.g., ACC) and/or subcortical regions (e.g., amygdala) during emotion processing, emotion regulation, or resting state predict symptom improvement (Klumpp et al., 2017; Doehrmann et al., 2013; Månsson et al., 2015; Klumpp et al., 2016; Goldin et al., 2014; Klumpp et al., 2014b; Klumpp et al., 2013b). However, results have been inconsistent, which may relate to methodological differences across studies. That is, the direction of neuromarker effects (enhanced vs. reduced activation) is sensitive to the neurocognitive probe of interest (e.g., type of task), location within a region (e.g., dorsal versus rostral ACC) (Lueken and Hahn, 2016), and criteria used to define 'significance' of brain activity as noted above.

In the current study, we extend the literature by drawing on our previous investigations, which revealed implicit regulation-related dACC activity predicted CBT outcome (Klumpp et al., 2016) whereas explicit regulation failed to yield an ACC neuromarker (Klumpp et al., 2017). Notably, in contrast to these studies, hypotheses were tested with anatomy-based masks independent of a brain map. By taking a completely a priori approach, significant results would strengthen the proposal that the ACC is a promising marker of CBT response in SAD and contribute to methodological considerations when testing theoretically-relevant, propitious treatment predictors. Anatomical based, a priori prediction is a more stringent test of the hypothesis, as anatomical boundaries will be less specific than neurofunctional boundaries, including many likely null voxels along with the key voxels of interest.

Based on literature and theory, we hypothesized ACC activity, but not clinical or demographic data, would significantly portend CBT 'responders' as a neuromarker. We also expected greater baseline rACC activity during implicit regulation would foretell clinical improvement. We hypothesized dACC in explicit regulation would predict responder status, however, no supposition was made as to the direction of activation (i.e., less or more) due to lack of data in the literature. Given strong anatomical connections between the ACC and amygdala (Ghashghaei et al., 2007), the predictive validity of amygdala was explored in addition to ACC-amygdala relationships as an index of emotion regulation success before starting CBT. In accordance with a top-down framework of regulation (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012) and evidence of inefficient or impoverished ACC recruitment during explicit or implicit regulation in SAD (Goldin et al., 2009; Wheaton et al., 2014; Klumpp et al., 2013a), a positive ACC-amygdala association would suggest deficient regulation and an inverse relationship, effective emotion regulation. A secondary aim was to evaluate relationships between pre-to-post change in symptom severity and ACC and amygdala activity.

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); 50% of participants were reported in a previous implicit regulation study (Klumpp et al., 2016) and 76% were reported in an explicit regulation study (Klumpp et al., 2017). Treatment-seeking patients with generalized SAD were recruited through the Mood and Anxiety Disorders Program at UIC by means of flyers posted throughout the communities, newspaper, and internet advertisement. Interested participants completed a phone screen followed by a psychiatric evaluation during which time participants reviewed the consent form. After attaining consent, participants met with a clinician trained in the Structured Clinical Interview for DSM-IV (SCID-IV; (First et al., 1995)) and clinician-administered measures. The participant's medical history was reviewed by a Board Certified physician and during the evaluation participants completed self-report measures.

Diagnosis was based on the SCID-IV and the clinician-administered Liebowitz Social Anxiety Scale (LSAS; (Liebowitz, 1987)) was used to assess symptom severity. Depression level was examined with the clinician-administered Hamilton Depression Rating Scale (HAM-D; (Hamilton, 1960)). A non-treating clinician administered the LSAS and HAM-D before and immediately after CBT was completed. Self-reported attentional control was evaluated with the Attentional Control Scale where higher scores signify more control (ACS; (Derryberry and Reed, 2002)). Subjective emotion regulation was assessed with the Emotion Regulation Questionnaire (ERQ; (Gross and John, 2003)). Higher scores indicate greater habitual use of reappraisal and expressive suppression (Gross and John, 2003). Treating clinicians completed the Clinical Global Impression Rating Scale (CGI; (Busner and Targum, 2007)) which encompasses the Clinical Improvement Scale (CGI-I) measuring global improvement with scores ranging from 1 (very much improved) through 7 (very much worse).

All measures were collected within a week of study entry and baseline fMRI scan. Participants were required to test negative on a urine toxicology screen before the scan. All participants were compensated for their time and all procedures complied with the Helsinki Declaration.

2.2. Inclusion/exclusion criteria

Participants were between 18 and 65 years of age, free of major medical or neurologic illness as confirmed by a Board Certified physician. All but two participants were free of psychotropic medications (i.e., sertraline) and none were receiving concurrent psychotherapy.

Exclusion criteria included contraindications to magnetic resonance imaging (e.g., pregnancy, non-removable ferrous objects), current substance dependence (within 6 months of study), history of other major psychiatric illness (e.g., bipolar disorder, psychotic disorders), or current cognitive dysfunction (e.g., traumatic brain injury, pervasive developmental disorder, dementia).

2.3. Treatment

Within a week of the fMRI scan, patients began once-weekly sessions of manualized individual CBT for 12 weeks, which included psycho-education, cognitive techniques to reduce negative beliefs (e.g., cognitive restructuring), in vivo exposure 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.

Patients were considered to be 'Responders' if their CGI score was 1 or 2 and if they met the criterion value based on a reliable change index (RCI) (Loerinc et al., 2015). The LSAS total score was used to calculate the RCI where an absolute value > 1.96 indicates change is statistically significant (Jacobson and Truax, 1991).

2.4. fMRI tasks

The order of implicit and explicit emotion regulation tasks were counterbalanced across participants. In the Emotional Faces Interference Task (EFIT), participants viewed a string of six letters superimposed on a task-irrelevant face distractor and instructed to identify target letters (N or X). In low perceptual load trials, the string was comprised entirely of target letters whereas under high perceptual load, the string included a single target letter and five non-target letters (H, K, M, W, Z) in randomized order. Distractor faces were from a standardized set of photographs and consisted of fearful, angry, and neutral expressions from 8 different individuals (Eckman and Friesen, 1976). The experiment involved two image acquisition runs, each comprising 12 blocks of 5 trials. A mixed block/event-related design was employed whereby perceptual load (low vs. high) varied across blocks and facial expression (fearful, angry, neutral) varied within blocks on a trial-by-trial basis. Images were presented for 200 ms followed by a fixation cross presented for 1800 ms; responses were made via button press. Within blocks, trials were separated by a jittered inter-stimulus interval lasting 2–6 s; trials between blocks were separated by 4–8 s.

The Emotion Regulation Task (ERT) comprised 64 unpleasant and 32 neutral International Affective Picture System images (Lang et al., 2008). Eight 20-s blocks of each condition (four images presented for 5 s each) were interspersed with 20-s baseline blocks (comprising a fixation cross). At the beginning of each block, participants were instructed to: 1) use a cognitive strategy to reduce negative affect evoked by an aversive image ("Reappraise"); 2) attend to, be aware of, and "feel what you naturally feel" when looking at an aversive image ("Maintain"); or 3) view neutral images ("Look"). Immediately following each task block, participants were asked to rate "How negative do you feel?" on a 5-point scale (1 = not at all, 5 = extremely) via button response. The order of blocks was pseudo-randomized over 4 separate runs of 5 min each. Consistent with prior studies involving healthy participants (Ochsner et al., 2002; Gorka et al., 2016) and anxious individuals who did not receive CBT (Phan et al., 2005; Fitzgerald et al., 2017; MacNamara et al., 2015; Rabinak et al., 2014), all conditions were practiced with images not used in the experiment prior to the scan to ensure understanding of task instructions.

2.5. fMRI data acquisition and preprocessing

Scanning was conducted on a 3.0 Tesla MR 750 scanner (General Electric Healthcare; Waukesha, WI) using a standard radiofrequency coil. Blood oxygen-level dependent (BOLD)-functional images were acquired using a gradient-echo echo-planar imaging sequence with the following parameters: TR = 2 s, TE = 25 ms, flip angle = 90^0, field of view = 22 × 22 cm (Greenberg et al., 1999), acquisition matrix 64 × 64; 44 axial, 3-mm-thick slices with no gap. For anatomical localization, a high-resolution, T1-weighted volumetric anatomical scan was acquired.

Data from all participants met criteria for quality with minimal motion correction (movements were < 3 mm and < 3 degrees rotation in any one direction) and the first 4 volumes from each run were discarded to allow for T1 equilibration effects. Conventional preprocessing steps were used in Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London www.fil.ion.ucl.ac.uk/spm). Briefly, images were temporally corrected to account for differences in slice time collection, spatially realigned to the first image of the first run, normalized to a Montreal Neurological Institute (MNI) template, resampled to 2 × 2 × 2 mm voxels, and smoothed with an 8 mm isotropic Gaussian kernel.

2.6. fMRI analyses

A general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Nuisance regressors comprising 6 motion parameters were included to correct for motion artifacts. In EFIT, blocks of low and high perceptual load were modeled separately based on task-irrelevant face type (fearful, angry, neutral) resulting in six regressors (fearful low, fearful high, angry low, angry high, neutral low, neutral high). To maximize threat distractor signal, we collapsed across angry and fear. Threat (fearful, angry) Low vs. Threat (fearful, angry) High load was the contrast of interest as both conditions comprised negative distractors. A Neutral Low vs. Neutral High contrast was also analyzed to determine whether significant effects were driven by task-irrelevant threat as opposed to task-irrelevant neutral distractors.

In ERT, blocks of Reappraise, Maintain, and Look trials were modeled separately in relation to an implicit baseline (i.e., fixation cross), the effects of which were estimated for each voxel. Reappraise vs. Maintain was the contrast of interest as both conditions comprised negative stimuli. Although the design did not involve the reappraisal of neutral images, as is conventional (Ochsner et al., 2002; Gorka et al., 2016; Phan et al., 2005; Fitzgerald et al., 2017; MacNamara et al., 2015; Rabinak et al., 2014), the contrast Look vs. Fixation was also analyzed to assess whether activity related to neutral images predicted CBT response.

To test hypothesis, the Automatic Anatomical Labeling (AAL) system (Tzourio-Mazoyer et al., 2002) was used to generate masks. Rostral ACC (rACC) comprised anterior cingulum encompassing primarily BA24 (search volume = 21,704 mm). AAL median cingulate anterior to y = 0 delineated dorsal ACC (dACC) primarily incorporating BA32 (search volume = 9416 mm) (Fig. 1). AAL bilateral amygdala had a search volume of 3744 mm (Fig. 1). Activation (β weights, arbitrary units [a.u.]) derived from these regions of interest (ROIs) were submitted to tests in the Statistical Package for the Social Sciences (Chicago, IL version 22).

Two-tailed Pearson's correlations were used to assess associations among rACC, dACC, and amygdala activity during implicit and explicit regulation. ROC curves were used to examine whether these ROIs and non-fMRI continuous measures (e.g., social anxiety symptoms) classified responder status (yes/no). To evaluate stability, significant predictors based on ROC analysis were submitted to binomial logistic regression and bootstrap confidence intervals (10,000 samples) estimated prediction error. To assess relationships between activation and change in symptom severity as indexed with LSAS ($\Delta_{PreTx\ -\ PostTx}$), ROIs were submitted to two-tailed partial correlations with alpha level at 0.05 controlling for baseline symptom severity.

3. Results

3.1. Participants

Thirty-eight patients with SAD (63% female) had a mean age of 25.2 ± 5.9 years and education level of 15.7 ± 2.6 years. Average symptom severity (LSAS total score) was 77.8 ± 15.8, which is consistent with the generalized SAD subtype (Mennin et al., 2002). The HAM-D total score indicated patients were mildly symptomatic (average 8.0 ± 5.2) (Zimmerman et al., 2013).

With regard to comorbidity, 12 patients had generalized anxiety disorder; 9, major depressive disorder; 7, dysthymia; 3, specific phobia; 3, panic disorder; 2, posttraumatic stress disorder; 1, adjustment disorder; 1, alcohol abuse; and 1, an eating disorder. Twelve patients had two or more comorbid diagnoses. Concerning race/ethnicity 53% self-identified as Caucasian, 18% as Asian, 8% as African American, 3% as American Indian or Alaskan Native, 18% as more than one race, and 42% self-identified as Hispanic or Latino.

3.2. Treatment effects

After completing 12 sessions of CBT, all patients showed significant

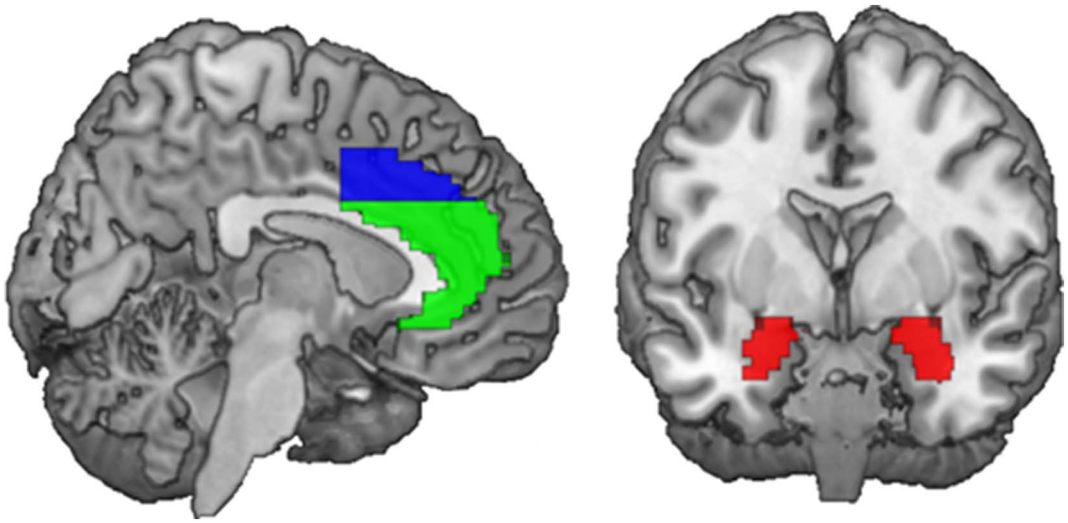

Fig. 1. Blue depicts dorsal anterior cingulate cortex mask and green illustrates rostral anterior cingulate cortex mask (left panel). Red represents bilateral amygdala mask (right panel). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Descriptive statistics (M, mean; SD, standard deviation) for clinical and emotion regulation measures.

	Pre-CBT *M (SD)*	Post-CBT *M (SD)*	*p*	Cohen's *d*
LSAS	77.8 (15.8)	49.2 (25.5)	< 0.001	1.6
HAM-D	8.0 (5.2)	3.5 (3.6)	< 0.001	1.0
ACS	46.5 (8.5)	52.0 (9.2)	< 0.001	-0.7
ERQ-R	23.4 (5.8)	29.6 (5.2)	< 0.001	-1.1
ERQ-S	17.3 (5.9)	15.4 (6.0)	0.036	0.6

LSAS = Liebowitz Social Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; ACS = Attention Control Scale; ERQ-R = Emotion Regulation Questionnaire, Reappraisal Subscale; ERQ-S = Emotion Regulation Questionnaire, Suppression Subscale.

pre-to-post treatment reductions in social anxiety symptoms (LSAS [(37) $t = 8.78$, $p < 0.001$]) and depression level (HAM-D [t(37) $= 5.67$, $p < 0.001$]). Self-report revealed a pre-to-post CBT increase in attentional control (ACS [t(37) = 4.46, $p < 0.001$]). Regarding emotion regulation tendencies, post-CBT data was missing for one subject. Nevertheless, ERQ results showed a pre-to-post increase in the habitual use of reappraisal (ERQ [t(36) = 6.65, $p < 0.001$]) and a decrease in the less adaptive regulation strategy, suppression (Gross and John, 2003) (ERQ [t(36) = 2.18, $p < 0.036$]). See Table 1 for descriptive statistics.

As determined with CGI and RCI comprising LSAS, 34.2% (13/38) were considered CBT Responders and 65.8% (25/38) were Non-Responders. Responders and Non-Responders were equivalent in pre-CBT symptom severity (LSAS [t(36) = 1.34, $p = 0.19$]), depression level (HAM-D [t(36) = 1.39, $p = 0.17$]), attentional control (ACS [t (36) = 0.05, $p = 0.96$]), use of reappraisal [t (Werner et al., 2011) $= 0.19$, $p = 0.85$] and suppression [t (Werner et al., 2011) $= 1.01$, $p = 0.32$] (ERQ), age [t (Werner et al., 2011) $= 1.62$, $p = 0.12$], education level in years [t (Werner et al., 2011) $= 0.76$, $p = 0.45$], and race/ethnicity [χ^2 *(Kessler et al., 2005)* $= 5.85$, $p = 0.21$].

3.3. Implicit emotion regulation behavioral performance

To assess the effectiveness of task conditions, accuracy and reaction time (RT) for accurate trials were submitted to a 2 (Distractor type: threat, neutral) × 2 (Perceptual Load: low, high) ANOVA with repeated measures on the last factor. Results for accuracy revealed a main effect of Load [F (Aderka et al., 2012; Moscovitch et al., 2012) = 323.40, $p < 0.001$] but not Distractor type [F (Aderka et al., 2012; Moscovitch et al., 2012) = 2.19, $p = 0.15$]; there was no Load × Distractor interaction [F (Aderka et al., 2012; Moscovitch et al., 2012) = 0.59, $p = 0.45$]. Follow-up paired *t*-tests showed all participants were more accurate on average in identifying targets in the low (95% ± 7%) relative to high load (63% ± 11%) condition [t (Moscovitch et al., 2012) = 18.09, $p < 0.001$]. RT findings were similar as there was a main effect of Load [F (Aderka et al., 2012; Moscovitch et al., 2012) $= 358.53$, $p < 0.001$] but not Distractor [F (Aderka et al., 2012; Moscovitch et al., 2012) = 0.79, $p = 0.79$] and there was no interaction [F (Aderka et al., 2012; Moscovitch et al., 2012) = 0.51, $p = 0.48$]. Follow-up paired *t*-tests showed all participants were faster on average in identifying targets in the low (817.27 ms ± 121.70 ms) compared to high load (1172.31 ms ± 182.11 ms) condition [t (Moscovitch et al., 2012) = 18.94, $p < 0.001$].

3.4. Explicit emotion regulation behavioral performance

As a manipulation check, a repeated measures ANOVA for Reappraise, Maintain, and Look revealed a main effect of condition [F (Greenberg et al., 1999; Lieberman and Cunningham, 2009) = 128.04, $p < 0.001$]. Follow-up paired *t*-tests demonstrated patients reported feeling less negative during Reappraise (2.53 ± 0.80) than Maintain (2.98 ± 0.58) (t(37) = 4.21, $p < 0.001$). As expected, negative affective state was higher in Maintain relative to Look (1.34 ± 0.51) (t (37) = 16.67, $p < 0.001$) and Reappraise relative to Look (t(37) $= 10.64$, $p < 0.001$).

3.5. Predictors of responder status

ROC curve analysis indicated clinically-meaningful change was not predicted by baseline symptom severity (i.e., LSAS, HAM-D), demographic characteristics (age, education level), self-reported attentional control (ACS), emotion regulation tendencies (ERQ), or race/ethnicity (as tested with chi square); lowest $p = 0.08$.

3.5.1. Implicit regulation

To assess regulatory facility at the neural level, Pearson's correlations for threat distractors in the Low (> High) load condition were conducted. Results showed amygdala activity positively correlated with rACC ($r = 0.44$, $p < 0.01$) and dACC ($r = 0.46$, $p < 0.04$). To evaluate the predictive ability of ROIs, ROC curve analysis was performed. Findings revealed responder status was predicted by greater baseline EFIT activity (larger result indicates more positive test) in the rACC for threat distractors in Low (> High) load condition

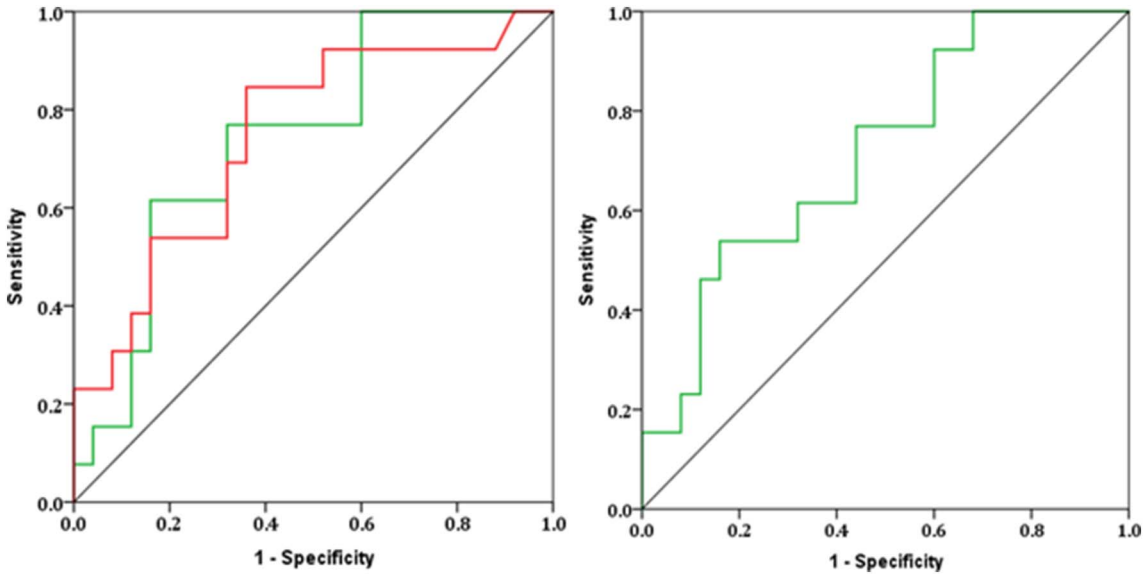

Fig. 2. ROC curves for implicit regulation; green depicts rostral anterior cingulate cortex and red illustrates amygdala (left panel). ROC curve regarding explicit regulation; green represents rostral anterior cingulate cortex (right panel). ROC, Receiver operating characteristic.

(Area = 0.74, $p < 0.02$) as well as amygdala (Area = 0.75, $p < 0.01$) (Fig. 2). Results were not significant for dACC (Area = 0.64, $p = 0.17$). To estimate prediction error, rACC and amygdala were each submitted to separate binomial linear regression analysis where predictor criterion (yes/no based on CGI and RCI for LSAS) was the dependent variable. Bootstrap results for rACC was B = 0.33, SE = 0.20 (CI 95%: 0.10 to 0.83) and for amygdala, B = 0.47, SE = 0.25 (CI 95%: 0.17 to 1.14).

Concerning neutral distractors in Low (> High) perceptual load, Pearson's correlations showed amygdala activity was negatively associated with dACC ($r = -0.32$, $p < 0.05$) but not rACC ($r = -0.24$, $p = 0.15$). ROC curve results were not significant for rACC, dACC, or amygdala (lowest $p = 0.16$).

3.5.2. Explicit regulation

In Reappraise (> Maintain), amygdala positively correlated with rACC ($r = 0.50$, $p < 0.001$) and dACC ($r = 0.53$, $p < 0.001$). ROC curve analysis revealed less (smaller result indicates more positive test) baseline rACC activation in Reappraise (> vs. Maintain) differentiated responders from non-responders (Area = 0.72, $p < 0.03$) (Fig. 2). Findings were not significant for dACC (Area = 0.57, $p = 0.51$) or amygdala activity (Area = 0.60, $p = 0.30$). Bootstrap results for rACC was B = −1.74, SE = 0.84 (CI 95%: -3.9 to −0.68). Regarding Look (> fixation cross) amygdala activity did not correlate with rACC ($r = -0.20$, $p = 0.22$) or dACC ($r = -0.19$, $p = 0.23$). ROC analysis for Look (> fixation cross) did not reveal significant effects for any region (lowest $p = 0.57$).

3.6. Neurofunctional activity and symptom change

Implicit regulation: Partial correlations controlling for baseline symptom severity indexed with LSAS revealed positive relationships between symptom change ($\Delta_{PreTx - PostTx}$) and pre-treatment activity to threat distractors in Low (> High) perceptual load in rACC ($r = 0.35$, $p < 0.033$) and amygdala ($r = 0.48$, $p < 0.003$) ROIs (Fig. 3).

No significant relationship between dACC activity and symptom change was observed ($r = 0.29$, $p = 0.08$). Correlations were not significant for neutral distractors in Low (> High) perceptual load for any region (lowest $p = 0.55$).

Explicit regulation: No relationships emerged between symptom change ($\Delta_{PreTx - PostTx}$) and activity in Reappraise (> Maintain) for rACC ($r = -0.29$, $p = 0.08$), dACC ($r = -0.18$, $p = 0.28$), or amygdala ($r = -0.11$, $p = 0.53$) ROIs when controlling for baseline symptom severity. Correlational analysis for Look (> fixation cross) were not significant for any region (lowest $p = 0.24$).

4. Discussion

The primary objective of the current study was to test the hypothesis that clinically-meaningful change immediately following CBT would be predicted by baseline anterior cingulate cortex (ACC) activity during emotion regulation in patients with social anxiety disorder (SAD). Amygdala as a CBT neuromarker was an exploratory aim. Behavioral data confirmed patients followed task instructions. For implicit regulation, accuracy was higher and response times faster for threat and neutral distractors in the low, relative to high, perceptual load condition. Moreover, negative affective state was reported as diminished during cognitive reappraisal of negative images compared to experiencing naturally the emotions incurred by such images (i.e., 'Maintain' condition). Yet, despite behavioral evidence of successful implicit and explicit regulation, ACC and amygdala activity, in the presence of negative stimuli, were positively correlated.

Building on models of effective emotion regulation wherein frontal engagement downregulates emotional reactivity (e.g., attenuates amygdala reactivity) (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012) along with reports of inefficient or impoverished ACC activity during regulation in SAD (Goldin et al., 2009; Wheaton et al., 2014; Klumpp et al., 2013b), the absence of pre-CBT inverse ACC-amygdala relationships to threat signals during regulation suggests patients were not effectual or efficient in modulating amygdala response. Even so, our study did not comprise a healthy control comparison group or direct fear processing condition, therefore, we cannot rule out the possibility that the ACC-amygdala relationship constituted emotional reactivity, as opposed to aberrant regulation, as SAD is also associated with exaggerated rACC and dACC response to negative stimuli (Brühl et al., 2014).

With regard to treatment outcome, results revealed social anxiety symptoms significantly decreased after CBT (LSAS $\Delta_{PreTx - PostTx}$); however, many remained symptomatic according to LSAS cut-offs (Mennin et al., 2002). Clinically-meaningful change was observed in approximately 34% of patients, which is consistent with the literature (Parker and Waller, 2015). As hypothesized brain activity, but not clinical or demographic measures, significantly classified responder status. Findings are in keeping with accumulating reports that neural

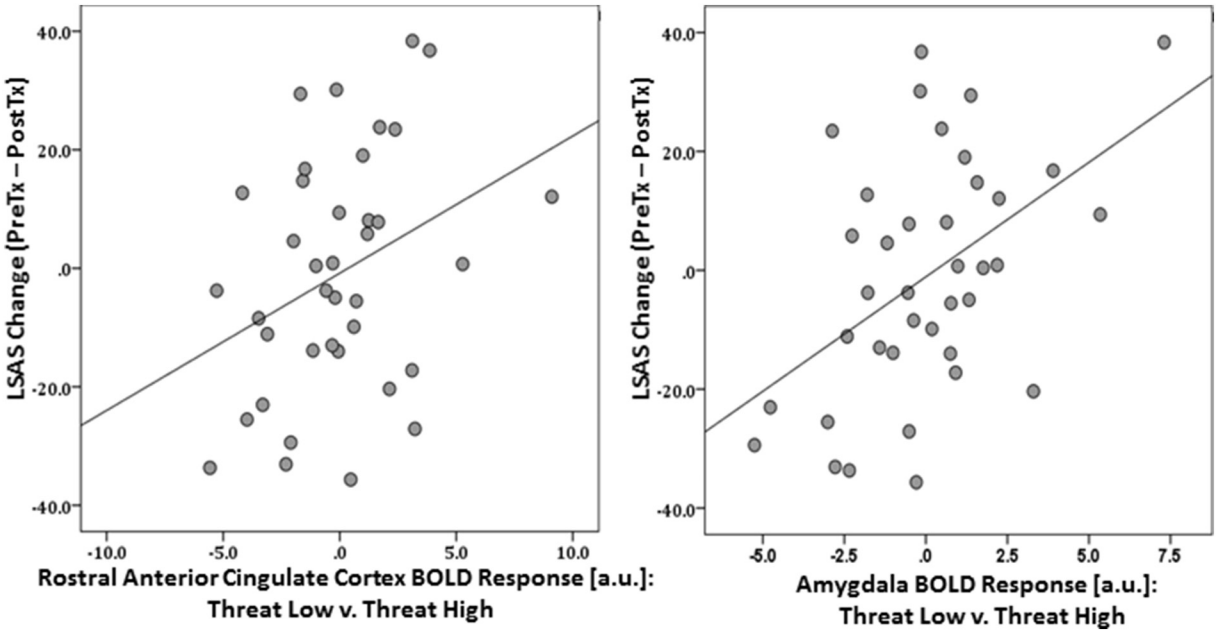

Fig. 3. Controlling for baseline symptom severity, scatterplots illustrating relationship between pre-to-post CBT change in symptom severity as indexed with LSAS (Liebowitz Social Anxiety Scale) and rostral anterior cingulate activity (left panel) and amygdala activity (right panel) during implicit regulation. Implicit regulation refers to threat distractors under low perceptual load (> threat distractors under high perceptual load).

predictors are frequently better than clinical or demographic characteristics in determining who is likely to benefit from CBT (Ball et al., 2014; Klumpp et al., 2017; Thompson et al., 2015; Doehrmann et al., 2013).

Regarding predictor effects, ROC results concerning implicit regulation revealed clinically-meaningful change was foretold by more pre-CBT activity in the rostral ACC (rACC) and amygdala to threat distractors. Findings suggest CBT may be especially helpful for those SAD patients who have relatively less implicit emotion regulation capability at the neural level. Notably, rACC and amygdala engagement were modulated by load on attentional resources such that baseline activation was greater under low (> high) perceptual load. We propose the rACC and amygdala activity reflected reactivity to task-irrelevant threat signals as demands on cognitive resources were minimal under low load and thus available (i.e., 'left over') to process salient, task-irrelevant stimuli (Lavie, 1995; Lavie et al., 2004). In other words, activation reflected biased attention to motivationally-relevant signals. Alternatively, rACC and amygdala activity served a preparatory function in resolving emotional conflict (Kanske and Kotz, 2011). Emotion has been shown to expedite conflict resolution, therefore, rACC and amygdala activity may pertain to early engagement of a system to effectively carry out an action (Kanske and Kotz, 2011; Gray, 2004). However, since the cognitive goal was non-affective in nature (i.e., decide whether an X or N was present) and attentional bias to threat stimuli is frequently reported in SAD (Bögels and Mansell, 2004), rACC and amygdala results suggest relatively poorer regulation facility predicted CBT response.

Concerning explicit regulation, ROC results demonstrated less baseline rACC activity during reappraisal (vs. viewing negative images) significantly predicted responder status yet amygdala did not portend CBT response. Despite the difference in the direction of rACC activation, findings are similar to that of implicit regulation as patients with more deficient regulation did better in CBT. Based on meta-analytic studies involving healthy individuals we expected dACC, not rACC, to correspond with clinical improvement given consistent reports of dACC recruitment in reappraisal (Buhle et al., 2014; Messina et al., 2015). Potentially, CBT neuromarkers are not necessarily linked to functional activity in regions associated with optimal functioning as observed in healthy individuals. Alternatively, our rACC finding maps on to indications rACC is involved in mediating dorsal medial and lateral prefrontal areas associated with reappraisal. For example, in a study that demarcated mediators of reappraisal with a pathway-mapping approach, rACC was shown to be part of a large-scale network that predicted reappraisal success in healthy participants (Wager et al., 2008).

Implicit and explicit regulation results partially replicate our earlier studies where better CBT outcome in SAD was predicted by less regulation facility in the presence of negative stimuli (Klumpp et al., 2017; Klumpp et al., 2016). However, in these studies neither rACC nor amygdala served as 'CBT neuromarkers.' The inconsistency may be explained by taking a conventional whole-brain approach in previous studies to identify potential neuromarkers rather than the a priori approach employed here such that results are independent of a brain map. In the current study, findings suggest rACC, but not dACC, as a CBT neuromarker pertains to both implicit/automatic and explicit/deliberate forms of regulation in SAD. Findings contribute to early (Mayberg et al., 1997) and continued reports of rACC as a biomarker of treatment outcome. That is, neuroimaging and neurophysiological studies comprising tasks that probe affective circuitry, executive functions, or self-referential processes (e.g., resting state) demonstrate elevated baseline rACC activity frequently classifies responder status or corresponds with change in depression severity following various interventions (e.g., pharmacotherapy, neurostimulation, CBT) (Pizzagalli, 2011; Siegle et al., 2012; Siegle et al., 2006; Hunter et al., 2013). These data along with evidence of reduced rACC volume in major depressive disorder, SAD, and other anxiety disorders relative to healthy individuals (van Tol and van der Wee, 2010) suggests rACC plays a role in the neurobiology of internalizing disorders and may serve as a transdiagnostic marker of clinical outcome.

While the direction of baseline rACC activity (less vs. more) as a predictor was task dependent, results indicate CBT may be particularly helpful to patients who have greater regulation deficiency or inefficiency when using a cognitive approach to downregulate emotional reactivity or when carrying out a cognitive goal in the face of negative distractors. CBT constitutes an amalgam of techniques aimed at decreasing maladaptive thoughts and behaviors while increasing adaptive ones. For example, the reappraise condition is similar to cognitive approaches practiced in CBT (e.g., cognitive restructuring) and commonly used to make social situations less fearful (Hope et al.,

2006).

With regard to attentional control, self-report results revealed a significant increase after completing CBT in SAD. The finding is consistent with evidence CBT success in SAD is associated with enhanced attentional control (Lundh and Öst, 2001; Mattia et al., 1993; Pishyar et al., 2008). Since CBT does not directly target implicit regulation, the improvement may be due to contingency learning over the course of treatment, which is fostered by activation of a fear structure (Foa and Kozak, 1986). For example, CBT strategies are practiced in the context of anxiety-evoking events (negative thoughts, in vivo exposures), thus, patients with less attentional control at the start of CBT and, therefore, greater attentional bias to threat stimuli, may be more proficient in learning new contingencies that result from facing fears (i.e., associating a threat signal with a benign outcome). In support, a dot-probe study demonstrated improvement in social anxiety was predicted by attentional bias (i.e., 'vigilance') to threatening faces prior to CBT but not attentional avoidance (Price et al., 2011).

Findings also have implications for interventions that more directly target regulation processes. For example, attention bias modification, aimed at directing attention away from threat stimuli, has been shown to reduce attentional bias and anxiety symptoms (Amir et al., 2009; Clarke et al., 2014). Similarly, there is evidence cognitive bias modification, which is intended to reduce negative appraisals, decreases threat interpretation bias and anxiety symptoms (Beard and Amir, 2008; Beard et al., 2011). Accordingly, patients with neuromarkers indicative of deficient regulation may benefit more from such targeted treatments alone or as an adjunct to CBT.

A secondary aim of the current study was to evaluate relationships between pre-CBT neurofunctional activity and pre-to-post change in symptom severity (LSAS $\Delta_{PreTx\ -\ PostTx}$). Partial correlations controlling for baseline symptom severity revealed rACC and amygdala activation to threat distractors in Low (> High) perceptual load positively corresponded with change in symptom severity. For explicit regulation, neither the ACC nor amygdala correlated with pre-to-post change in social anxiety symptoms. These data suggest variance related to emotional interference contributed more to individual differences in clinical improvement than explicit regulation insofar as ACC and amygdala are concerned. It is possible that providing instructions on cognitive regulation strategies along with the practice of reappraisal to ensure understanding of instructions before the experiment may have reduced individual differences at the neural level.

This study is not without important limitations. First and foremost, there was no treatment control or waitlist control group, therefore, neural and clinical findings cannot be causally attributed to CBT and could be due to factors not related to treatment such as differential regression to the mean, response biases, Hawthorne effect, other non-specific factors, or natural recovery in patients. Second, our sample size was relatively modest and not adequately powered to evaluate the stability of neural predictors beyond bootstrapping. Third, regions of interest (ROIs) were based on an atlas and, therefore, may not be as accurate as manually-traced ROIs. Fourth, we used a recommended approach to define responder status (Loerinc et al., 2015), which may be considered overly conservative. Fifth, implicit emotion regulation comprised threatening face distractors and explicit regulation consisted of generally negative images. Therefore, the potential influence of stimuli on results cannot be ruled out and findings may not generalize to other types of negative content (e.g., ideographic stimuli). Sixth, the objective of the study was to test a priori regions of interest as predictors outside a brain map; consequently, no conclusions can be made with regard to its significance at the whole-brain level. Lastly, CBT encompasses an amalgam of techniques; therefore, we cannot conclude neural predictors are limited to any one particular cognitive or behavioral strategy.

In summary, the ACC has consistently been implicated as a neuromarker in treatment response albeit in depression. The ACC is theoretically-relevant to CBT due to the role it plays in emotion regulation, which CBT aims to improve. The predictive validity of amygdala was also evaluated due to its strong connectivity with ACC (Ghashghaei et al., 2007). In SAD patients, results revealed greater baseline rostral ACC and amygdala reactivity during implicit regulation was predictive of clinically-meaningful improvement. Additionally, activation in these regions were associated with reductions in social anxiety symptoms. For explicit regulation, improvement corresponded with less baseline rostral ACC activity in cognitive reappraisal. However, neither ACC nor amygdala activity in the context of reappraisal corresponded with change in symptom severity. Together, these preliminary data are in line with early observations that rostral ACC recurrently interacts with treatment outcome. Further study with larger samples are needed to test the stability and generalizability of rostral ACC as a predictor in CBT response.

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References

Aderka, I.M., et al., 2012. Functional impairment in social anxiety disorder. J. Anxiety Disord. 26, 393–400.
Greenberg, P.E., et al., 1999. The economic burden of anxiety disorders in the 1990s. J. Clin. Psychiatry 60, 427–435.
Moitra, E., Beard, C., Weisberg, R.B., Keller, M.B., 2011. Occupational impairment and social anxiety disorder in a sample of primary care patients. J. Affect. Disord. 130, 209–212.
Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62, 617–627.
Stein, M.B., Kean, Y.M., 2000. Disability and quality of life in social phobia: epidemiologic findings. Am. J. Psychiatry 157, 1606–1613.
Stein, M.B., Stein, D.J., 2008. Social anxiety disorder. Lancet 371, 1115–1125.
Hofmann, S.G., Smits, J.A.J., 2008. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatry 69, 621–632.
Hofmann, S.G., Asnaani, A., Vonk, I.J.J., Sawyer, A.T., Fang, A., 2012. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn. Ther. Res. 36, 427–440.
Arch, J.J., Craske, M.G., 2009. First-line treatment: a critical appraisal of cognitive behavioral therapy developments and alternatives. Psychiatr. Clin. North Am. 32, 525–547.
Parker, Z.J., Waller, G., 2015. Factors related to psychotherapists' self-assessment when treating anxiety and other disorders. Behav. Res. Ther. 66, 1–7.
Ball, T.M., Stein, M.B., Ramsawh, H.J., Campbell-Sills, L., Paulus, M.P., 2014. Single-subject anxiety treatment outcome prediction using functional neuroimaging. Neuropsychopharmacology 39, 1254–1261.
Klumpp, H., et al., 2017. Emotion regulation related neural predictors of cognitive behavioral therapy response in social anxiety disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 75, 106–112.
Thompson, D.G., et al., 2015. FMRI activation during executive function predicts response to cognitive behavioral therapy in older, depressed adults. Am. J. Geriatr. Psychiatry 23, 13–22.
Doehrmann, O., Ghosh, S.S., Polli, F.E., Reynolds, G.O., Horn, F., Keshavan, A., Triantafyllou, C., Saygin, Z.M., Whitfield-Gabrieli, S., Hofmann, S.G., et al., 2013. Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. JAMA Psychiatry 70, 87–97.
Fu, C.H.Y., et al., 2008. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol. Psychiatry 64, 505–512.
Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36, 183–206.
Siegle, G.J., et al., 2012. Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Arch. Gen. Psychiatry 69, 913–924.
Siegle, G.J., Carter, C.S., Thase, M.E., 2006. Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am. J. Psychiatry 163, 735–738.
Godlewska, B.R., Browning, M., Norbury, R., Cowen, P.J., Harmer, C.J., 2016. Early changes in emotional processing as a marker of clinical response to SSRI treatment in

depression. Transl. Psychiatry 6 e957.
Salvadore, G., et al., 2009. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol. Psychiatry 65, 289–295.
Carl, H., et al., 2016. Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder. J. Affect. Disord. 203, 204–212.
Arns, M., et al., 2015. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? Eur. Neuropsychopharmacol. 25, 1190–1200.
Hunter, A.M., Korb, A.S., Cook, I.A., Leuchter, A.F., 2013. Rostral anterior cingulate activity in major depressive disorder: state or trait marker of responsiveness to medication? J. Neuropsychiatr. Clin. Neurosci. 25, 126–133.
Konarski, J.Z., et al., 2009. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. J. Psychiatry Neurosci. 34, 175–180.
Korb, A.S., Hunter, A.M., Cook, I.A., Leuchter, A.F., 2009. Rostral anterior cingulate cortex theta current density and response to antidepressants and placebo in major depression. Clin. Neurophysiol. 120, 1313–1319.
Mayberg, H.S., et al., 1997. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8, 1057–1061.
Mulert, C., et al., 2007. Rostral anterior cingulate cortex activity in the theta band predicts response to antidepressive medication. Clin. EEG Neurosci. 38, 78–81.
Pizzagalli, D., et al., 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am. J. Psychiatry 158, 405–415.
Rentzsch, J., Adli, M., Wiethoff, K., Gómez-Carrillo de Castro, A., Gallinat, J., 2014. Pretreatment anterior cingulate activity predicts antidepressant treatment response in major depressive episodes. Eur. Arch. Psychiatry Clin. Neurosci. 264, 213–223.
Andrews-Hanna, J.R., Reidler, J.S., Huang, C., Buckner, R.L., 2010. Evidence for the default network's role in spontaneous cognition. J. Neurophysiol. 104, 322–335.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. 100, 253–258.
Long, X.-Y., et al., 2008. Default mode network as revealed with multiple methods for resting-state functional MRI analysis. J. Neurosci. Methods 171, 349–355.
McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., Binder, J.R., 2003. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. J. Cogn. Neurosci. 15, 394–408.
Hamilton, J.P., Chen, M.C., Waugh, C.E., Joormann, J., Gotlib, I.H., 2015. Distinctive and common neural underpinnings of major depression, social anxiety, and their comorbidity. Soc. Cogn. Affect. Neurosci. 10, 552–560.
Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85, 348–362.
Werner, K.H., Goldin, P.R., Ball, T.M., Heimberg, R.G., Gross, J.J., 2011. Assessing emotion regulation in social anxiety disorder: the Emotion Regulation Interview. J. Psychopathol. Behav. Assess. 33, 346–354.
Moscovitch, D.A., et al., 2012. Changes in judgment biases and use of emotion regulation strategies during cognitive-behavioral therapy for social anxiety disorder: distinguishing treatment responders from nonresponders. Cogn. Ther. Res. 36, 261–271.
Bögels, S.M., Mansell, W., 2004. Attention processes in the maintenance and treatment of social phobia: hypervigilance, avoidance and self-focused attention. Clin. Psychol. Rev. 24, 827–856.
Lundh, L.G., Öst, L.G., 2001. Attentional bias, self-consciousness and perfectionism in social phobia before and after cognitive-behaviour therapy. Scand. J. Behav. Ther. 30, 4–16.
Mattia, J.I., Heimberg, R.G., Hope, D.A., 1993. The revised Stroop color-naming task in social phobics. Behav. Res. Ther. 31, 305–313.
Pishyar, R., Harris, L.M., Menzies, R.G., 2008. Responsiveness of measures of attentional bias to clinical change in social phobia. Cognit. Emot. 22, 1209–1227.
Egner, T., Etkin, A., Gale, S., Hirsch, J., 2008. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cereb. Cortex 18, 1475–1484.
Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51, 871–882.
Ochsner, K.N., Hughes, B., Robertson, E.R., Cooper, J.C., Gabrieli, J.D.E., 2009. Neural systems supporting the control of affective and cognitive conflicts. J. Cogn. Neurosci. 21, 1842–1855.
Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15, 85–93.
Barrett, L.F., Mesquita, B., Ochsner, K.N., Gross, J.J., 2007. The experience of emotion. Annu. Rev. Psychol. 58, 373–403.
Hariri, A.R., Whalen, P.J., 2011. The amygdala: inside and out. F1000 Biol. Rep. 3 (2).
Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2012. The brain basis of emotion: a meta-analytic review. Behav. Brain Sci. 35, 121–143.
Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M.A., Ochsner, K.N., 2008. Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways. Neuron 59, 1037–1050.
Whalen, P.J., 1998. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. Curr. Dir. Psychol. Sci. 7, 177–188.
Banich, M.T., et al., 2009. Cognitive control mechanisms, emotion & memory: a neural perspective with implications for psychopathology. Neurosci. Biobehav. Rev. 33, 613–630.
Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol. Rev. 108, 624–652.
Carter, C.S., et al., 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 280, 747–749.
Liu, X., Banich, M.T., Jacobson, B.L., Tanabe, J.L., 2006. Functional dissociation of attentional selection within PFC: response and non-response related aspects of attentional selection as ascertained by fMRI. Cereb. Cortex 16, 827–834.
MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.
Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala-frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. 2, 303–312.
Eippert, F., et al., 2007. Regulation of emotional responses elicited by threat-related stimuli. Hum. Brain Mapp. 28, 409–423.
Frank, D.W., et al., 2014. Emotion regulation: quantitative meta-analysis of functional activation and deactivation. Neurosci. Biobehav. Rev. 45, 202–211.
Ochsner, K.N., Silvers, J.A., Buhle, J.T., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann. N. Y. Acad. Sci. 1251, E1–24.
Buhle, J.T., et al., 2014. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb. Cortex 24, 2981–2990.
Messina, I., Bianco, S., Sambin, M., Viviani, R., 2015. Executive and semantic processes in reappraisal of negative stimuli: insights from a meta-analysis of neuroimaging studies. Front. Psychol. 6.
Goldin, P.R., Manber-Ball, T., Werner, K., Heimberg, R., Gross, J.J., 2009. Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. Biol. Psychiatry 66, 1091–1099.
Kanske, P., Kotz, S.A., 2011. Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? Cereb. Cortex 21, 911–919.
Pessoa, L., Kastner, S., Ungerleider, L.G., 2002. Attentional control of the processing of neutral and emotional stimuli. Cogn. Brain Res. 15, 31–45.
Wheaton, M.G., Fitzgerald, D.A., Phan, K.L., Klumpp, H., 2014. Perceptual load modulates anterior cingulate cortex response to threat distractors in generalized social anxiety disorder. Biol. Psychol. 101, 13–17.
Klumpp, H., Fitzgerald, D.A., Phan, K.L., 2013a. Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 45, 83–91.
Månsson, K.N.T., et al., 2015. Predicting long-term outcome of Internet-delivered cognitive behavior therapy for social anxiety disorder using fMRI and support vector machine learning. Transl. Psychiatry 5 e530.
Klumpp, H., Fitzgerald, D.A., Angstadt, M., Post, D., Phan, K.L., 2014a. Neural response during attentional control and emotion processing predicts improvement after cognitive behavioral therapy in generalized social anxiety disorder. Psychol. Med. 44, 3109–3121.
Klumpp, H., et al., 2016. Prefrontal control and predictors of cognitive behavioral therapy response in social anxiety disorder. Soc. Cogn. Affect. Neurosci. 11, 630–640.
Goldin, P.R., et al., 2014. Impact of cognitive-behavioral therapy for social anxiety disorder on the neural bases of emotional reactivity to and regulation of social evaluation. Behav. Res. Ther. 62, 97–106.
Eklund, 2016. Correction for Eklund et al., Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. 113, E4929.
Woo, C.-W., Krishnan, A., Wager, T.D., 2014. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. NeuroImage 91, 412–419.
Lieberman, M.D., Cunningham, W.A., 2009. Type I and type II error concerns in fMRI research: re-balancing the scale. Soc. Cogn. Affect. Neurosci. 4, 423–428.
Gabrieli, J.D.E., Ghosh, S.S., Whitfield-Gabrieli, S., 2015. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. Neuron 85, 11–26.
Klumpp, H., Keutmann, M.K., Fitzgerald, D.A., Shankman, S.A., Phan, K.L., 2014b. Resting state amygdala-prefrontal connectivity predicts symptom change after cognitive behavioral therapy in generalized social anxiety disorder. Biol. Mood Anxiety Disord. 4, 14.
Klumpp, H., Post, D., Angstadt, M., Fitzgerald, D.A., Phan, K.L., 2013b. Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. Biol. Mood Anxiety Disord. 3, 7.
Lueken, U., Hahn, T., 2016. Functional neuroimaging of psychotherapeutic processes in anxiety and depression: from mechanisms to predictions. Curr. Opin. Psychiatry 29, 25–31.
Ghashghaei, H.T., Hilgetag, C.C., Barbas, H., 2007. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. NeuroImage 34, 905–923.
First, M., Spitzer, R., Gibbon, M. & Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), version 2. (Biometrics Research, 1995).
Liebowitz, M.R., 1987. Social phobia. Mod. Probl. Pharmacopsychiatry 22, 141–173.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Derryberry, D., Reed, M.A., 2002. Anxiety-related attentional biases and their regulation by attentional control. J. Abnorm. Psychol. 111, 225–236.
Busner, J., Targum, S.D., 2007. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry Edgmont Pa Townsh. 4, 28–37.
Hope, D.A., Heimberg, R.G., Turk, C.L., 2006. Managing Social Anxiety: A Cognitive-behavioral Therapy Approach. Oxford University Press, USA.
Loerinc, A.G., et al., 2015. Response rates for CBT for anxiety disorders: need for standardized criteria. Clin. Psychol. Rev. 42, 72–82.
Jacobson, N.S., Truax, P., 1991. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J. Consult. Clin. Psychol. 59, 12–19.

Eckman, P., Friesen, W., 1976. Pictures of Facial Affect. Consulting Psychologists Press.
Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. University of Florida.
Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D.E., 2002. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. J. Cogn. Neurosci. 14, 1215–1229.
Gorka, S.M., et al., 2016. Cannabinoid modulation of frontolimbic activation and connectivity during volitional regulation of negative affect. Neuropsychopharmacology 41, 1888–1896.
Phan, K.L., et al., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol. Psychiatry 57, 210–219.
Fitzgerald, J.M., et al., 2017. Individual differences in cognitive reappraisal use and emotion regulatory brain function in combat-exposed veterans with and without PTSD. Depress. Anxiety 34, 79–88.
MacNamara, A., et al., 2015. Emotion regulatory brain function and SSRI treatment in PTSD: neural correlates and predictors of change. Neuropsychopharmacology 41, 611–618. http://dx.doi.org/10.1038/npp.2015.190.
Rabinak, C.A., et al., 2014. Focal and aberrant prefrontal engagement during emotion regulation in veterans with posttraumatic stress disorder. Depress. Anxiety 31, 851–861.
Tzourio-Mazoyer, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.
Mennin, D.S., et al., 2002. Screening for social anxiety disorder in the clinical setting: using the Liebowitz Social Anxiety Scale. J. Anxiety Disord. 16, 661–673.
Zimmerman, M., Martinez, J.H., Young, D., Chelminski, I., Dalrymple, K., 2013. Severity classification on the Hamilton depression rating scale. J. Affect. Disord. 150, 384–388.
Brühl, A.B., Delsignore, A., Komossa, K., Weidt, S., 2014. Neuroimaging in social anxiety disorder—a meta-analytic review resulting in a new neurofunctional model. Neurosci. Biobehav. Rev. 47, 260–280.
Lavie, N., 1995. Perceptual load as a necessary condition for selective attention. J. Exp. Psychol. Hum. Percept. Perform. 21, 451–468.
Lavie, N., Hirst, A., De Fockert, J.W., Viding, E., 2004. Load theory of selective attention and cognitive control. J. Exp. Psychol. Gen. 133, 339–354.
Gray, J.R., 2004. Integration of emotion and cognitive control. Curr. Dir. Psychol. Sci. 13, 46–48.
van Tol, M.J., van der Wee, N.A., 2010. Regional brain volume in depression and anxiety disorders. Arch. Gen. Psychiatry 67, 1002–1011.
Foa, E.B., Kozak, M.J., 1986. Emotional processing of fear: exposure to corrective information. Psychol. Bull. 99, 20–35.
Price, R.B., Eldreth, D.A., Mohlman, J., 2011. Deficient prefrontal attentional control in late-life generalized anxiety disorder: an fMRI investigation. Transl. Psychiatry 1, e46.
Amir, N., et al., 2009. Attention training in individuals with generalized social phobia: a randomized controlled trial. J. Consult. Clin. Psychol. 77, 961–973.
Clarke, P.J., Notebaert, L., MacLeod, C., 2014. Absence of evidence or evidence of absence: reflecting on therapeutic implementations of attentional bias modification. BMC Psychiatry 14.
Beard, C., Amir, N., 2008. A multi-session interpretation modification program: changes in interpretation and social anxiety symptoms. Behav. Res. Ther. 46, 1135–1141.
Beard, C., Weisberg, R.B., Amir, N., 2011. Combined cognitive bias modification treatment for social anxiety disorder: a pilot trial. Depress. Anxiety 28, 981–988.