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Neural responses to social threat and predictors of cognitive behavioral therapy and acceptance and commitment therapy in social anxiety disorder

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Abstract

Previous research has often highlighted hyperactivity in emotion regions to simple, static social threat cues in social anxiety disorder (SAD). Investigation of the neurobiology of SAD using more naturalistic paradigms can further reveal underlying mechanisms and how these relate to clinical outcomes. We used fMRI to investigate responses to novel dynamic rejection stimuli in individuals with SAD (N=70) and healthy controls (HC; N=17), and whether these responses predicted treatment outcomes following cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT). Both HC and SAD groups reported greater distress to rejection compared to neutral social stimuli. At the neural level, HCs exhibited greater activations in social pain/rejection regions, including dorsal anterior cingulate cortex and anterior insula, to rejection stimuli. The SAD group evidenced a different pattern, with no differences in these rejection regions and relatively greater activations in the amygdala and other regions to neutral stimuli. Greater responses in anterior cingulate cortex and the amygdala to rejection vs. neutral stimuli predicted better CBT outcomes. In contrast, enhanced activity in sensory-focused posterior insula predicted ACT responses.

Keywords

fMRI; rejection; treatment prediction; anterior cingulate cortex; amygdala

1. Introduction

Social anxiety disorder (SAD) is one of the most common anxiety disorders, with 12-month and lifetime prevalence rates estimated at 8% and 13%, respectively (Kessler et al., 2012; Ruscio et al., 2008). SAD is characterized by persistent and excessive fear of scrutiny or humiliation in performance-related or social-interactional situations. As such, afflicted

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individuals will frequently avoid social situations and/or endure them with anxiety and distress, which can have significant adverse consequences on quality of life, and social, academic, and occupational functioning (Mendlowicz & Stein, 2000).

The past several decades of research have identified multiple maladaptive biases in SAD involving hyperreactivity to threatening or potentially-threatening social information as well as excessively negative interpretations of such information that contribute to the development and maintenance of SAD (Clark & Wells, 1995; Craske et al., 2009; Rapee & Heimberg, 1997). Neuroimaging research has begun to provide valuable insights into the neurobiological substrates that mediate the maladaptive processing of social information in SAD. One of the most intensely studied neural regions in SAD is the amygdala, which is not surprising given its well-established role in fear and social processing (Adolphs, 1999; Ledoux, 1998). The amygdala is integral to fear learning and memory and has been characterized as representing a primitive threat-detection system designed to help protect the individual from harm (Amaral, 2002; LeDoux, 1998; Phelps & LeDoux, 2005). Numerous studies have found greater amygdala activity in SAD compared to healthy controls in response to socially threatening stimuli (see Brühl et al., 2014; Etkin & Wager, 2007; and Freitas-Ferrari et al., 2010 for reviews and meta-analyses), consistent with the idea that SAD is characterized by hyper-sensitivity in detecting overt and potential social threats.

The insula, a limbic region central to the integration of perceptual, emotional, and cognitive information into subjective experiences (Craig, 2011; Kurth et al., 2010), has been shown to be hyperactive in SAD relative to healthy controls in response to socially-threatening facial expressions (Amir et al., 2005; Straube et al., 2004), scenes (Boehme et al., 2014), and situations (Lorberbaum et al., 2004). Such findings are consistent with theoretical models and behavioral findings that individuals with SAD are more likely to internalize or personalize potential social threats, as well as experience them as more aversive than non-anxious individuals.

SAD has been associated with increased activity in dorsal anterior cingulate cortex (dACC) relative to healthy controls in response to socially-threatening stimuli (Amir et al., 2005; Blair et al., 2008a; 2011b). While less emphasized in SAD research than other regions, dACC would seem to represent a key target for investigation of maladaptive neural functioning in SAD given its role in general appraisal and monitoring of emotional information, and experiences of social pain and rejection (Eisenberger, 2012; Rotge et al., 2014), which are hallmarks of SAD. Recent work highlights a similar role in social pain and rejection for subgenual and pregenual regions of the ACC as well (Rotge et al., 2014; Wager et al., 2009).

SAD has been associated with dysfunctions in multiple regions that regulate or modulate the complex processes initiated by emotion and threat detection regions as well. Relative to healthy controls, SAD has been associated with increased activity in regions that underlie inhibition of emotion (ventrolateral prefrontal cortex; VLPFC), contextual processing (hippocampus and parahippocampal gyrus), integration of multimodal information and self-awareness (medial parietal cortex/precuneus), and perceptual and semantic processing

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(fusiform gyrus and other occipitotemporal regions). However, specific results vary considerably across studies (Brühl et al., 2014; Etkin & Wager, 2007).

By far the most common approach to investigating neural functioning in SAD utilizes images of emotional facial expressions as stimuli in conjunction with passive viewing or perceptual ratings or classifications of the stimuli (e.g., Birbaumer et al., 1998; Blair et al., 2008b, 2011a; Cooney et al., 2006; Evans et al., 2008; Gentili et al., 2008; Hahn et al., 2011; Klumpp et al., 2012; Phan et al., 2006, 2013; Prater et al., 2013; Stein et al., 2002; Straube et al., 2004, 2005; Yoon et al. 2007). The widespread use of facial expressions is not surprising given that they hold particular fear-relevance for individuals who are socially anxious. They have proven to be a powerful research tool with the ability to predict important outcomes including vulnerability to developing mental disorders (e.g., Pezawas et al., 2005) and even treatment response in SAD (e.g., Doehrmann et al., 2013).

Despite the elegant simplicity of static facial expressions, there has been a growing emphasis on other types of stimuli with putatively greater ecological validity such as imagining feared social situations (Blair et al., 2010; Boehme et al., 2014; Nakao et al., 2011), anticipation of public speaking (Boehme et al., 2013; Cremers et al., 2015), performance evaluation (Gimenez et al., 2012; Koric et al., 2012; Pujol et al., 2013), and exposure to social criticism (Blair et al., 2008a; Goldin et al., 2009, 2011b; Ziv et al., 2013a). Such paradigms can provide valuable insights into the more complex processes that are typically encountered in SAD. Additionally, such paradigms typically evoke distress and thereby can reveal the underlying mechanisms of not only sensitivity to cues of social distress, but actual experiences of social distress and corresponding regulation attempts.

We conducted an fMRI study in which participants were scanned while being subjected to one of the most feared scenarios in SAD: criticism and rejection by others. Participants with SAD and healthy controls viewed film clips of others (i.e., actors) saying socially-rejecting statements directed at them and were instructed to imagine the situations as real (i.e., that these people were talking to them). As such, this paradigm was designed to combine the power and relevance of facial expressions with increased realism that putatively taps into the fears that lie at the core of SAD to evoke distress.

We further investigated the clinical implications of neural responses to rejection by examining whether they would predict subsequent treatment outcomes following either cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT). A handful of emerging studies have found that pre-treatment neural activity in amygdala, dACC, prefrontal, occipital, and temporal regions during simple perceptual matching tasks has predicted responses to CBT in SAD participants (Doehrmann et al., 2013; Klumpp et al., 2013, 2014). However, to our knowledge, no studies have examined how neural activity in response to an experience of rejection may relate to treatment outcomes in SAD, and no studies have examined neural patterns that may predict response to ACT, which, although generally as effective as CBT (Craske et al., 2014), involves a very different theoretical approach (Arch & Craske, 2008).

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We predicted that the novel rejection stimuli used herein would engage (a) regions involved in emotional responding such as amygdala and insula, (b) regions underlying experiences of rejection including anterior insula, dACC, and ventral ACC (pre- and subgenual), (c) contextual modulation regions such as hippocampus and parahippocampal gyrus, (d) regions involved in self-awareness and theory of mind such as medial prefrontal cortex (MPFC) and precuneus given the role of perceiving others' impressions of oneself in this paradigm, (e) cognitive control regions including VLPFC and DLPFC, and (f) regions involved in processing social and linguistic information such as lateral temporal and occipital regions. We expected to see relatively greater activations in SAD individuals compared to healthy controls, particularly in amygdala, insula, and ACC, reflecting increased sensitivity to rejection and potential social threat, and that neural responses to rejection stimuli would be moderated by SAD severity, given evidence that severity of maladaptive processing of social information in SAD covaries with disorder severity (e.g., Ball et al., 2012; Brühl et al., 2011; Evans et al., 2008; Frick et al., 2013b; Goldin et al., 2009; Koric et al., 2012; Shah et al., 2009). Finally, we predicted that increased pre-treatment amygdala, ACC, prefrontal, occipital, and temporal activity would predict subsequent CBT/ACT outcomes consistent with previous related work demonstrating such a relationship (Klumpp et al., 2014; McClure et al., 2007; Siegle et al., 2006).

2. Methods

2.1. Participant recruitment and screening

Participants were recruited through the UCLA Anxiety Disorders Research Center and from the UCLA and Los Angeles community as part of a larger study evaluating two types of behavioral treatment for SAD, cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT). Participants underwent diagnostic evaluation using the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown et al., 1994), conducted by trained and reliability-certified clinicians. SAD participants met DSM-IV criteria for a current principal or co-principal diagnosis of SAD with a clinical severity rating ≥4 (on a scale of 0-8) which indicates clinically significant symptoms, distress, or impairment. Healthy control (HC) participants had no current or past psychiatric disorders.

Inclusion criteria for all participants were 18-45 years old, English-speaking, and right-handed. Exclusion criteria included standard fMRI contraindications (e.g., pregnancy; claustrophobia; non-removable metallic objects); serious medical conditions or brain damage; bipolar disorders; substance-related disorders; suicidality; psychosis; psychiatric hospitalization; and recent modifications to psychotropic medication or psychotherapy. The research protocol was approved by the UCLA Office for the Protection of Human Research Subjects and all participants provided informed consent prior to completing the ADIS-IV.

2.2. Participants

SAD Participants (N=70) and HCs (N=17) were similar on demographic variables, as shown in Table 1. Details on comorbidity and medication status are also presented in Table 1. All participants were included in baseline (pre-treatment) analyses except that 3 SAD participants with missing questionnaire data were excluded from related analyses, as

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described below. Analyses examining how neural activity at baseline related to treatment outcomes included only those participants who were randomized to receive an active treatment (CBT or ACT) and completed all necessary assessments (N=36), as described below.

2.3. Procedures

Approximately two weeks after completing an initial clinical interview and questionnaires, participants underwent an fMRI session at the UCLA Ahmanson-Lovelace Brainmapping Center. SAD participants were then randomized to either 12 weeks of CBT (N=25), 12 weeks of ACT (N=25), or a 12-week waitlist period (N=20). Following treatment, SAD participants completed questionnaires and a second fMRI session. This manuscript includes fMRI data from pre-treatment scans only, along with pre- and post-treatment questionnaire data. The complete pre-post fMRI results of will be presented in a separate manuscript (in preparation).

2.4. Questionnaires

The Liebowitz Social Anxiety Scale - Self Report Version (LSAS-SR; Fresco et al., 2001; Heimberg et al., 1999; Liebowitz, 1987) was used to index overall social anxiety severity (at baseline) as well as treatment outcome (using pre-post difference scores). The Social Interaction Anxiety Scale (SIAS; Mattick & Clarke; 1998) was included to assess social interaction anxiety severity specifically as this is the component of social anxiety that is targeted with the rejection stimuli used in this study. We also measured depression symptoms using the Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995) given possible impacts of comorbid depression (Burklund et al., 2015). Questionnaire data were missing from three SAD participants who were excluded from related analyses.

2.5. Behavioral treatments

Both CBT and ACT treatments involved twelve weekly one-hour, manualized, individual therapy sessions (for details see Craske et al., 2014). CBT and ACT were matched on the extent of exposure practice but differed in the theoretical framing of the intent of exposure; CBT emphasized the development of cognitive restructuring skills whereas ACT emphasized the development of acceptance and mindfulness in the pursuit of a value-driven life. Clinical outcomes of the larger parent study have been previously published (Craske et al., 2014). Of the 70 SAD participants with baseline fMRI data, 25 were randomized to receive CBT, with a completion rate of 68% (N=17), and 25 were randomized to receive ACT, with a completion rate of 76% (N=19). There were significant reductions in LSAS scores from pre to post for both CBT [M(SD)=24.57(20.28); $t(15)=4.85$, $p<.001$] and ACT [M(SD)=25.00(15.84), $t(19)=7.06$, $p<.001$], and a treatment group (CBT vs. ACT) by time (pre vs. post) interaction analysis was not significant [$F(1,34)=.005$, $p=.943$], suggesting that CBT and ACT were similarly effective.

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2.6. fMRI dynamic social threat task

While being scanned, participants viewed blocks of video clips of actors saying rejecting and neutral phrases and were instructed to imagine that the people in the videos were speaking directly to them. Specifically, in the Rejection condition, participants viewed video clips of individuals (actors) saying disapproving, rejecting, and other negative comments such as “No one likes you,” “Everyone is laughing at you,” or “I don't like you.” In the Neutral condition, participants viewed video clips of individuals saying neutral comments such as “It's warm today” or “I need a pen.” The Neutral condition was designed as a comparison condition for the Rejection videos by controlling for the non-emotional aspects of the stimuli, including visual, language, social, and auditory processing, thereby isolating neural processes specific to social rejection. Participants did not make any button presses or other behavioral responses while viewing the videos. Sample screenshots of each condition are shown in Figure 1. Four other conditions were included in the task but not analyzed for this manuscript, including two conditions in which participants viewed rejection videos and were asked to respond using emotion regulation strategies, one condition involving positive phrases, and another with non-social stimuli.

The task utilized a blocked design and was presented across two functional scans. There were two blocks of each of the condition types, with each block consisting of six 5-second video clips of different people saying phrases of a single type (e.g., six different people saying rejecting comments). Thus, there were a total of 12 different video clips (presented in 2 blocks/runs) per condition. Blocks were 30 seconds long, a length appropriate to maximize MR signal (Huettel et al., 2004). Each block was preceded by a 5-second instruction cue indicating the block type (i.e., Rejection, Neutral, etc.), and followed by an 11-second rating period and a 10-second fixation crosshair. During the rating period, participants were presented with two rating screens and asked to provide subjective ratings of how distressed they felt when watching the videos in the preceding block (0 = not at all, 1 = somewhat, 2 = moderately, 3 = extremely), and how successful they thought they were in imagining the video clips as real (0 = not at all, 1 = somewhat, 2 = moderately, 3 = extremely). Three random orders of the conditions were generated and counterbalanced across participants.

Video clips of 18 actors (9 female) were filmed and edited by the experimenters using a Sony digital video recorder and a Macintosh G5 iMac with iMovie software. Each actor was seen no more than three times across all videos. Across the entire task, there were 30 unique phrases, with each repeated exactly once and said by a different actor each time.

Stimuli for the Video Task were presented on a Macintosh MacBookPro computer using MacStim 3.2.1 software (WhiteAnt Occasional Publishing, www.brainmapping.org/WhiteAnt) and high-resolution magnet-compatible goggles (Resonance Technology, Inc). Button press responses were collected using an MR-compatible button box connected to the Macintosh via a custom USB interface.

2.7. fMRI image acquisition

Magnetic resonance images were acquired using a Trio 3.0 Tesla MRI scanner at the UCLA Ahmanson-Lovelace Brainmapping Center. For each participant, a high-resolution structural

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T2-weighted echo-planar imaging volume (spin-echo, TR=5000ms, TE=34ms, matrix size=128×128, resolution 1.6 × 1.6 × 3mm, FOV=200mm, 36 slices, 3mm thick, flip angle=90°, bandwidth=1302 Hz/Px) was acquired coplanar with the functional scans. Two functional scans were acquired (gradient-echo, TR=3000ms, TE=25ms, flip angle=90°, matrix size=64×64, resolution 3.1 × 3.1 × 3.0mm, FOV=200mm, 36 slices, 3mm thick, bandwidth=2604 Hz/Px). Slice orientation was oblique axial for all scans.

2.8. fMRI data preprocessing

The imaging data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). All images were first reoriented along a horizontal AC-PC line, with image origin at the anterior commissure. Functional images were then realigned to the mean within each run to correct for head motion. High-resolution T2-weighted structural images were co-registered to a mean EPI for each subject and normalized using the segmentation method in SPM8 to warp them into MNI space (resampled at 3×3×3mm; Mazziotta et al., 2001). Resulting normalization parameters were applied to functional images which were subsequently smoothed using an 8-mm Gaussian kernel, full-width half-max. Co-registered and normalized images were visually inspected for quality control.

2.9. fMRI statistical analysis

2.9.1. GLM—General linear models for each subject were determined by pre-specified timing parameters based on task design. Each model included regressors for each condition of interest (Rejection and Neutral) along with nuisance regressors for conditions of non-interest to the current manuscript, task instruction and rating periods, and the rotational and translational movement parameters. Blocks were modeled as box-car functions convolved with the canonical double-gamma hemodynamic response function (HRF). Custom scripts were used to model out volumes containing movement spikes ≥1.5mm as well as volumes representing global signal intensity change ≥ 2.5 standard deviations from the run mean. High pass filters were set at 128s. All analyses were corrected for serially correlated errors by fitting a first-order autoregressive process (AR(1)) to the error term. Linear contrasts were computed for each participant using a fixed-effects model for the contrast Rejection vs. Neutral to specifically isolate neural signatures of social rejection.

2.9.2. ROI-restricted search analyses—Contrast images from subject-level models were used to conduct group-level random-effects analyses using the SPM8-based GLM Flex statistical software package (http://mrtools.mgh.harvard.edu, June 22 2014). Voxels with missing data from some participants were analyzed using adjusted degrees of freedom, with reported p-values adjusted automatically within GLM Flex to reflect the equivalent p-value dependent upon the full model. Voxels missing data from more than 10% of participants were eliminated from analyses. First-level contrast images were pooled together for within- and between-group voxel-wise t-tests, thresholded at $p<.005$ and corrected for multiple comparisons using a restricted search approach involving extent thresholds of 5 ($135mm^3$), 16 ($432mm^3$), and 18 ($486mm^3$) contiguous voxels for activations observed in bilateral amygdala, insula, and ACC, respectively, each corresponding to a false-positive discovery rate of 5% in each region as estimated by 10,000 Monte Carlo simulations using AlphaSim

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(http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html). The amygdala, insula, and ACC regions were defined a priori by the AAL anatomical atlas (Tzourio-Mazoyer et al., 2002), with ACC additionally constrained to the regions specifically associated with rejection in a recent meta-analysis which include the dorsal anterior, pregenual, and subgenual portions (i.e., y>4.5 in Talairach space; Rotge et al., 2014). For completeness, activations beyond our regions of interest were also reported, thresholded at p<.005 and 42 (1,134mm^3) contiguous voxels, corresponding to a false-positive discovery rate of 5% across the whole brain as estimated by 10,000 Monte Carlo simulations using AlphaSim.

2.9.3. ROI-averaged analyses—We also completed analyses focused on amygdala, insula, and dACC ROIs wherein parameter estimates were extracted and averaged across each ROI and subjected to analyses in SPSS. Specifically, functional ROIs were defined by significant clusters of activation in these regions observed in the HC within-group analysis contrasting Rejection vs. Neutral described above, thereby representing functional ROIs of normative rejection responses. We used MarsBaR (Brett et al., 2002) to compute and extract the ROI parameter estimates using averaged activity across the voxels that comprised each functional ROI, and then imported them into SPSS for t-tests to examine corresponding patterns in these normative rejection-related regions in the SAD group, thresholded at p<.05. For completeness, if no significant functional clusters were observed in analyses for Rejection vs. Neutral in the HC group for the amygdala, insula, or dACC, ROIs were then defined anatomically based on the AAL anatomical atlas (Tzourio-Mazoyer et al., 2002) with dACC additionally constrained as per Rotge et al. (2014).

We also examined moderation of neural activity by baseline (pre-treatment) SAD severity (i.e., using LSAS and SIAS scores in separate analyses) as well as baseline depression symptoms (i.e., using MASQ subscores) within the SAD group in both restricted-search regression analyses as well as regression analyses using the extracted ROI averaged parameter estimates in SPSS, using the significance thresholds described for each method above.

Finally, to examine baseline neural activity that was associated with treatment responses, we completed regression analyses within the SAD group examining activations that correlated with LSAS difference scores (i.e., $LSAS_{pre} - LSAS_{post}$), controlling for baseline LSAS scores. We completed such regression analyses using a restricted-search approach as well as using the extracted ROI averaged parameter estimates in SPSS, using the significance thresholds described for each method above.

3. Results

3.1. Self-reported data

Participants provided ratings of how successful they thought they were at “imagining the videos as real” in the scanner following each block. A group (HC vs SAD) by condition (Rejection vs. Neutral) ANOVA of these success ratings did not yield any significant effects, including interactions, main effects, or simple main effects, suggesting that participants felt they were able to imagine the stimuli as real equivalently well across groups and conditions – all at a level between “somewhat” and “moderately.” (See Figure 2.)

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Participants also rated their distress following each block of videos in the scanner. As shown in Figure 3, a group (HC vs SAD) by condition (Rejection vs. Neutral) ANOVA of distress ratings revealed significant main effects of group with SAD>HC ($F(1,77)=17.986$; $p<.001$) and condition with Rejection>Neutral ($F(1,77)=89.679$; $p<.001$), and a significant interaction such that the difference between conditions was greater for the SAD group ($F(1,77)=4.584$; $p=.035$). There were also significant simple main effects of higher distress for Rejection videos relative to Neutral videos within both groups (SAD: $t(62)=12.470$; $p<.001$; HC: $t(15)=4.869$; $p<.001$) as well as higher distress reported by SAD participants relative to HC participants for both Rejection ($t(78)=4.312$; $p<.001$) and Neutral videos ($t(80.288)=4.234$; $p<.001$).

3.2. Neural results for ROI-restricted search

Comparing Rejection with Neutral videos in order to isolate activity associated with the experience of rejection specifically, the HC group showed significantly greater activity to Rejection videos in left anterior insula (extending across inferior frontal cortex/LVLPFC) and dACC, as predicted (see Table 2 and Figures 4 & 5). Conversely, HCs showed significantly less activity in the left middle occipital/parietal region in response to the Rejection videos compared to Neutral videos. No significant activations or deactivations were seen in the amygdala.

As shown in Table 3, in response to Rejection videos relative to Neutral videos, SAD participants exhibited significantly greater activity exclusively in the occipital cortex. Conversely, and contrary to predictions, SAD participants also showed significantly *less* activity in several regions, including a large cluster spanning right amygdala, hippocampus, parahippocampal gyrus, and superior temporal gyrus, a cluster spanning right inferior and middle frontal gyrus (including VLPFC), clusters in right posterior temporal/occipital gyrus, one cluster in left posterior temporal gyrus, and left parahippocampal gyrus/fusiform gyrus (see Table 3 and Figure 6). Additional regions of reduced activation in response to Rejection vs. Neutral videos included right middle frontal gyrus, subcallosal gyrus, posterior cingulate/lingual gyrus, and motor and sensory regions including paracentral lobule and postcentral gyrus. No significant activations or deactivations were seen in the insula or dACC.

In direct between-group comparisons, there were no significant differences between the SAD and HC groups in response to Rejection vs. Neutral videos.

In regression analyses completed with SAD participants only, LSAS scores pre-treatment were positively correlated with activity in right precuneus/parietal (6, -55, 52; $t=3.45$; 68 voxels) and precentral gyrus (51, -13, 52; $t=3.45$; 42 voxels) during Rejection relative to Neutral. No regions were negatively correlated with LSAS scores. SIAS scores and MASQ-anhedonic depression scores were not positively or negatively correlated with any regions during Rejection relative to Neutral.

Regression analyses were also completed to examine baseline neural activity that predicted treatment responses to CBT and ACT. As shown in Table 4, increased activity in pregenual ACC/VMPFC/middle frontal gyrus (Figure 8), left amygdala (Figure 9), bilateral parietal, and occipital regions during Rejection relative to Neutral predicted better CBT response

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(i.e., reductions in LSAS symptoms). In contrast, ACT treatment response was predicted only by increased posterior insula activity during Rejection relative to Neutral (Figure 10).

3.3. ROI-averaged analyses

ROI analyses were completed using functionally-defined ROIs based on the significant dACC and left anterior insula activation clusters for the HC group in Rejection vs. Neutral, as described above. For mean parameter estimates extracted from both the dACC and left anterior insula ROIs, in contrast to the HC group, the SAD group did not exhibit significantly different activity between Rejection and Neutral (Figures 4 & 5). In independent-samples t-tests conducted on these mean extracted values, the differences between Rejection and Neutral for each group were significantly different from each other for both dACC ($t(43.40)=2.76$; $p=.008$) and insula ($t(45.62)=2.99$; $p=.004$), with greater differences for HCs as expected. Since there was no significant activation in the amygdala for the HC within-group Rejection vs. Neutral analysis, we were not able to create a functionally-defined amygdala ROI. Thus, for completeness, we completed ROI analyses for the amygdala using mean parameter estimates extracted from anatomically-defined bilateral ROIs (Figure 7). Within-group t-tests conducted on mean parameter estimates extracted from bilateral amygdala ROIs revealed significantly greater activity during Neutral relative to Rejection in the SAD group for both left ($t(66)=-3.41$; $p=.001$) and right ($t(66)=-3.38$; $p=.001$) amygdala but no differences within the HC group. In separate independent-samples t-tests, the differences between Rejection and Neutral for SAD vs. HC did not reach significance (left amygdala: $t(82)=1.80$; $p=.075$; right amygdala: $t(82)=1.53$; $p=.129$).

LSAS, SIAS, and MASQ-anhedonic depression scores were not correlated with mean parameter estimates extracted from the dACC, insula, or amygdala ROIs for any contrasts. Additionally, mean extracted parameter estimates from the ROIs were not associated with treatment response for either CBT or ACT.

Given unexpected findings for the amygdala, including null findings for the HC group, greater activation for Neutral relative to Rejection in the SAD group, and no significant group differences, we completed additional exploratory analyses examining activity separately for the first and second halves of the Rejection and Neutral blocks of videos to examine possible habituation confounds. Parameter estimates were extracted from anatomically-defined amygdala ROIs for contrasts comparing early vs. late Rejection, early vs. late Neutral, early Rejection vs. early Neutral, and late Rejection vs. late Neutral, plotted in Figure 11, and subjected to t-tests in SPSS ($p<.05$). As shown in Figure 11, there was a consistent pattern of greater amygdala activity in the later periods relative to the early periods for both groups, providing evidence against habituation generally. In direct between-group comparisons of Rejection vs. Neutral focused on only the early or late period, we found no differences in amygdala activity for the early period, and a marginal effect for the later period in the right amygdala ($p=.052$), which was driven specifically by greater amygdala activity in the SAD group during the later half of Neutral videos relative to Rejection.

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4. Discussion

4.1. Overview and within-group findings

In this fMRI study, we first sought to examine how healthy controls and individuals with SAD responded to dynamic social threat stimuli conveying rejection. We examined neural activity in response to rejection videos compared to similarly-formatted neutral social videos in order to isolate neural activity specific to the experience of social threat or rejection. For the HC group, this revealed activations in dACC and anterior insula. The dACC has been shown to be involved in monitoring and appraisal of potential threat and emotion conflict (Etkin et al., 2011). The insula is central to the integration of perceptual, emotional, and cognitive information into subjective experiences (Craig, 2011; Kurth et al., 2010). In particular, anterior insula, which was observed here, has been shown to be involved in social and emotional experiences, including both elicited emotion as well as recognizing emotions in others (Kurth et al., 2010). Additionally, and importantly, much previous work has implicated both dACC and anterior insula as playing a central role in social pain (see Eisenberger 2012 for a review). In particular, dACC and anterior insula have been shown to be involved in experiences of social rejection (e.g., Eisenberger et al., 2003), social evaluation (e.g., Eisenberger et al., 2011; Takahashi et al., 2009; Wager et al., 2009), and exposure to nonverbal cues of rejection (e.g., Burklund et al., 2007). Interestingly, the rejection stimuli in this study did not evoke greater activations in the amygdala for the healthy control group, even when examining early and late responses separately. This is not entirely unexpected (see Cacioppo et al., 2013). While the amygdala is central to fear responding, is commonly observed in response to cues of potential threat, and is often seen to be hyperactive in anxiety disorders (LeDoux, 1998), its role in experiences of rejection and social pain is less clear. Thus, overall, neural findings for the healthy control group appear to validate the paradigm as an effective means of evoking activations specifically in core rejection response regions. That the healthy controls also rated the rejection stimuli as significantly more distressing than the neutral control stimuli further validates the task at an experiential level.

Comparison of rejection vs. neutral social stimuli in SAD yielded more complex and unexpected results. No significant activations were observed in insula or dACC in response to rejection vs. neutral stimuli for SAD participants. In fact, the only region more activated in response to rejection relative to neutral social stimuli was visual cortex. In contrast, there were several regions *less* activated in response to rejection relative to neutral videos, including the amygdala and other regions we predicted would have the opposite pattern including parahippocampal gyrus, VLPFC, and posterior temporal and occipital regions.

One potential explanation for the counterintuitive findings of relatively *greater* activations to the neutral stimuli in SAD is that the neutral social stimuli were not actually “neutral” and instead may have represented a more complex and subtle social threat that required more extensive processing in order to fully ascertain its threat value. Although we designed the neutral videos to present non-threatening social information, they may have held potential threat-value to the SAD group who are more likely to perceive neutral or ambiguous stimuli as threatening (Amir, Foa, & Coles, 1998; Cooney et al., 2006; Yoon et al., 2008).

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Additionally, some of the neutral expressions signified a need for a response (e.g., “I need a pen”) and this may have represented a potential threat in the form of implied performance/interaction expectations. Furthermore, some of the same actors were included in rejection and neutral videos and therefore, previous exposure to a “rejecting” individual may have contaminated a subsequent “neutral” encounter with the individual for SAD participants or created further ambiguity. As such, neural responses to the neutral stimuli may have reflected relatively greater demands for perception and interpretation of face-related stimuli (e.g., posterior temporal and occipital regions; Haxby et al., 2000; Kanwisher et al., 1997; Rossion et al., 2003), retrieval and integration of emotional contextual information from memory (e.g., parahippocampal gyrus; Aminoff et al., 2013; Smith et al., 2004), regulatory processes to appraise and react to the complex stimuli as necessary (e.g., RVLPFC; Buhle et al., 2014; Kalisch, 2009; Kohn et al., 2014; Ochsner et al., 2009), and perhaps even interpretation of sarcasm (parahippocampal gyrus; Rankin et al., 2009). In fact, to the extent that the generally increased processing of the neutral stimuli reflected increased focus on the neutral faces, this also provides a possible explanation for the increased amygdala activity seen for neutral videos, given research suggesting that attended faces yield greater amygdala activity than unattended faces (Pessoa et al., 2002).

Nevertheless, it is important to note that the enhanced processing during neutral videos seen in the SAD group does not imply that the neutral stimuli elicited greater distress or were consciously perceived as more threatening than the rejection stimuli. In fact, SAD participants rated the rejection stimuli as more distressing than the neutral stimuli. Furthermore, no differences (activations or deactivations) were observed in insula or dACC during rejection vs. neutral stimuli.

4.2. Differences between SAD and healthy control participants

Despite interesting patterns within each group, direct between-group comparisons of SAD and healthy participants' neural data yielded no significant differences. Contrary to predictions, averaged-ROI analyses investigating activity in targeted anterior insula and dACC rejection-related regions revealed greater activity during rejection vs. neutral stimuli for healthy controls compared to those with SAD. The lack of neural *hyper*activity in SAD and overall lack of significant group differences observed here conflicts with previous work comparing SAD individuals with healthy controls (Brühl et al., 2014; Freitas-Ferrari et al., 2010). However, a more focused investigation of previous research specifically examining rejection-related experiences suggests that our findings are consistent with closely related work.

Only a handful of fMRI studies have investigated responses to rejection-related experiences in SAD and, overall, these studies have reported remarkably few differences between SAD and healthy participants. Ziv and colleagues (2013) examined responses to dynamic social rejection stimuli and to viewing personalized phrases reflecting negative self-beliefs, and found no group differences for either task in the amygdala or insula using an ROI approach. Whole-brain results comparing the SAD group with healthy controls were not presented.[1] Blair and colleagues completed two studies in which SAD and healthy control participants viewed negative phrases about themselves (e.g., “You are an idiot”) while imagining the

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phrases being said by someone whose opinion they cared about (Blair et al., 2008a, 2011b). In the first study, relative to healthy controls, SAD participants exhibited greater activity in MPFC and bilateral amygdala but amygdala results were seen only at a liberal threshold of $p<.05$, uncorrected (Blair et al., 2008a). In the second study (Blair et al., 2011b), SAD participants exhibited greater activity in a similar region of MPFC and mid frontal gyrus relative to healthy controls, but no group differences were observed in the amygdala or insula, or any other regions. Thus, overall, the lack of SAD hyperactivity in amygdala and insula and minimal differences in other regions observed in our study is consistent with previous research focused on rejection experiences.

An interesting question remains, however, as to how results presented here (and in other rejection-based work) can be reconciled with much other previous work demonstrating hyperactivity in multiple regions in SAD relative to healthy controls. First, the lack of observed group differences in amygdala activity in particular may be, in part, a function of the relatively complex social rejection task. A review of previous SAD neuroimaging findings suggests that amygdala group differences are more likely to emerge in simple threat "reactivity" tasks (e.g., Phan et al., 2013) that typically are less likely to evoke explicit distress rather than in more complex evocative paradigms that may provoke variable combinations of threat reactivity and spontaneous regulation (down or up).[2] In our study, participants with SAD and healthy controls reported different levels of explicit distress and therefore also likely had differential spontaneous regulation needs and/or tendencies.

Another issue is that group differences may be more of a function of differential timing (e.g., Campbell et al., 2007; Goldin et al., 2009; Sladky et al., 2012). In our study, we used a blocked design to maximize the signal to noise ratio (Huettel et al., 2004). However, with this approach, differences in the timing of responses are not readily apparent, and differences between SAD and healthy control participants at specific time points following exposure to social threat would be obscured. In analyses examining the early and late periods of rejection and neutral videos separately, results suggested a general pattern of increased amygdala activity over time for both groups, arguing against habituation as a primary factor obscuring group differences.

4.3. Clinical implications of neural data for SAD

Despite the paucity of formal group differences, neural responses to this task for the SAD group nonetheless appear to have important clinical implications. As noted above, there were no differences in activity in key rejection response regions (i.e., anterior insula and dACC) between the Rejection and Neutral stimuli for SAD participants. Even in targeted

[1]Ziv et al. (2013) presented results for secondary whole-brain analyses comparing the healthy controls with a subgroup of the SAD participants with the most severe social anxiety (LSAS mean= 99), however, given the biased subsample selection, these results address a different research question that what is explored here. Whether these analyses were presented precisely because no whole-brain group differences were found when comparing all SAD participants with healthy controls is unclear.

[2]In one recent review of task-based neural differences between participants with SAD and healthy controls (Brühl et al., 2014), roughly half of the studies included (17/38) reported significant group differences in the amygdala. Of these 17 studies finding group differences, 10 utilized static facial expressions in simple paradigms involving passive viewing, perceptual matching, or identification (Blair et al., 2008b, 2011a; Cooney et al., 2006; Evans et al., 2008; Gentili et al., 2008; Hahn et al., 2011; Klumpp et al., 2012; Prater et al., 2013; Phan et al., 2013; Yoon et al. 2007), 3 used other simple emotion stimuli such as generally negative but non-social images or words (Brühl et al., 2011; Schmidt et al., 2010; Shah et al., 2009), and only 4 used more complex, potentially emotionally-evocative tasks (e.g. imaging feared social situations; Blair et al., 2008a, 2010, 2011b; Boehme et al., 2013).

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ROI analyses focused on specific subregions that were differentially activated in healthy controls using a relatively lower statistical threshold failed to yield any differences in these regions for the SAD group. There was also a main effect of relatively greater activity in the amygdala in response to the *neutral* stimuli. Together, these findings imply that there may be an impairment in differentiating between rejection and neutral (i.e, harmless/ambiguous) stimuli, as well as heightened sensitivity to neutral/ambiguous stimuli in SAD. This underscores the significance of maladaptive responses to subtle indications of potential or ambiguous threat, rather than overt rejection, as a key mechanism of SAD. That is, most people would feel social pain in the face of overt rejection – it is feeling this pain *when there is no rejection* that is problematic. These findings are consistent with decades of research characterizing SAD as being largely a function of distortions and biases in the processing of social/evaluative information, (e.g., Craske et al., 2009; Rapee & Heimberg, 1997).

These results may also illustrate the contribution of intolerance of uncertainty in SAD to the extent the neutral stimuli were interpreted as ambiguous. While not widely emphasized as a specific mechanism of SAD, intolerance of uncertainty has been shown to explain a significant proportion of variance in social anxiety symptoms (e.g., Boelen & Reijntjes, 2009; Carleton et al., 2010) and may be related to catastrophizing and other maladaptive interpretive biases in SAD in the context of ambiguous social situations. As such, maladaptive responses to the neutral video stimuli may have reflected discomfort with its ambiguity; clearly negative communications may be easier to deal with than ambiguous statements that may or may not represent a threat. Alternatively, these findings are also reminiscent of psychophysiolgoical research in which anxious individuals have been shown to exhibit elevated threat responding to safety signals in the context of threat (Craske et al., 2008; Grillon et al., 1998; Lissek et al., 2010), with such heightened responding predicting the subsequent onset of anxiety disorders (Craske et al., 2012). Such findings of sensitivity to neutral or safe stimuli have been suggested to reflect an inability to appropriately inhibit aversive responding in situations involving both threatening and non-threatening (safety) stimuli (Craske et al., 2012), which may have played a role in this study.

Differential sensitivity to the rejecting vs. ambiguous social stimuli also played a role in predicting treatment response to CBT. Specifically, greater pre-treatment levels of pregenual ACC activity during rejection relative to neutral stimuli predicted better treatment outcomes following CBT. Like dACC, pregenual ACC has been implicated in social pain and rejection (Rotge et al., 2014), as well as during the regulation of emotional conflicts (Etkin et al., 2011), and responses to social-evaluative threat (Wager et al., 2009). Similarly, increased amygdala activity to rejection vs. neutral stimuli also predicted better CBT treatment outcomes. Thus, pre-treatment tendencies to exhibit increased differential sensitivity to overtly rejecting vs. ambiguous social stimuli in rejection and threat detection regions predicted better response to CBT. In this study, CBT focused on decreasing maladaptive cognitions and behavioral responses to social situations in large part via exposure therapy. The observed neural patterns may reflect an attentional or appraisal process of greater discrimination between what is safe and what is dangerous, and this may have benefitted participants throughout exposure therapy as they had to learn to associate “safety” with cues that were previously erroneously perceived as dangerous. That is, individuals with an intact mechanism for discriminating between threatening and non-threatening stimuli may have

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been able to benefit more from a treatment that focused on recognizing and internalizing such distinctions. Activations in perceptual regions (occipital and angular gyri) in response to the rejection stimuli also predicted outcomes following CBT, consistent with previous research (e.g., Doerhmann et al., 2013; Klumpp et al., 2013).

Finally, the pattern of neural activity associated with greater treatment response to ACT was quite different. Specifically, greater activation in posterior insula in response to rejection stimuli relative to neutral stimuli predicted greater improvement following ACT. In contrast to CBT, one of the core components of ACT is the development of acceptance and mindfulness in the pursuit of a value-driven life, which involves an objective awareness of one's thoughts, feelings, and behaviors without trying to change them. The posterior insula region observed to predict responses to ACT is a multimodal sensory region (Kurth et al., 2010; Zu Eulenburg et al., 2013). Thus, greater pre-treatment reactivity in this region may have facilitated the effectiveness of ACT through an enhanced dispositional sensory awareness.

4.4. Limitations and Conclusions

Limitations of this study include the lack of data obtained from participants regarding their interpretations and responses to the videos beyond fMRI signal and self-reported distress and experiential success. Data regarding precisely how such stimuli are explicitly interpreted and how participants respond physiologically (e.g., arousal via skin conductance response) would likely provide important insights. Although emerging evidence suggests that ACT is as effective as CBT for anxiety disorders (Craske et al., 2014), including in this sample, ACT is relatively newer and is supported by less evidence than CBT with respect to outcomes and mediators. Other issues that should be addressed in future work include the lack of available data regarding the specific timing of neural responses, different subjective experiences with the task for healthy vs. SAD participants, and contributing influences of medication and comorbidities.

In summary, we used fMRI to investigate responses to novel dynamic socially-threatening stimuli in individuals with SAD and healthy controls, finding few statistically significant differences between groups, despite qualitatively distinct experiences with the task. Nevertheless, responses to the rejection and neutral social stimuli related to clinical outcomes in unique ways. Future research is needed to further tease apart effects, and may benefit from optimizing design to examine differential temporal dynamics of neural responses, and considering the modulating role of individual difference variables.

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Highlights

- Both healthy controls and SAD participants reported greater distress to novel dynamic rejection stimuli compared to neutral social stimuli.
- While healthy controls exhibited greater activations in social pain/rejection regions to rejection stimuli, the SAD group evidenced a different pattern, with no differences in rejection regions and relatively greater activations in the amygdala and other regions to neutral stimuli.
- The lack of differential responses in rejection regions to rejection vs. neutral stimuli, as well as heightened sensitivity to neutral stimuli (which may have represented ambiguous threat), were related to CBT outcomes in SAD participants.
- Results suggest that a generalized “rejection” response in SAD to both overt rejection and ambiguous/possible rejection may represent an inability to effectively differentiate between threat and safety signals that hinders success with CBT.
- Enhanced neural reactivity in sensory-focused posterior insula related to success with ACT, which although similarly effective as CBT, entails a very different theoretical basis that emphasizes awareness and acceptance of subjective experiences.

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Figure 1.
Example clips conveying (a) Rejection and (b) Neutral social communications.

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Figure 2.

Participants provided ratings of how successful they thought they were at “imagining the videos as real” in the scanner following each block. A group (HC vs SAD) by condition (Rejection vs. Neutral) ANOVA of these success ratings did not yield any significant effects, including interactions, main effects, or simple main effects, suggesting that participants felt they were able to imagine the stimuli as real equivalently well across groups and conditions. 0=“Not at all” 1=“Somewhat” 2=“Moderately” and 3=“Extremely”

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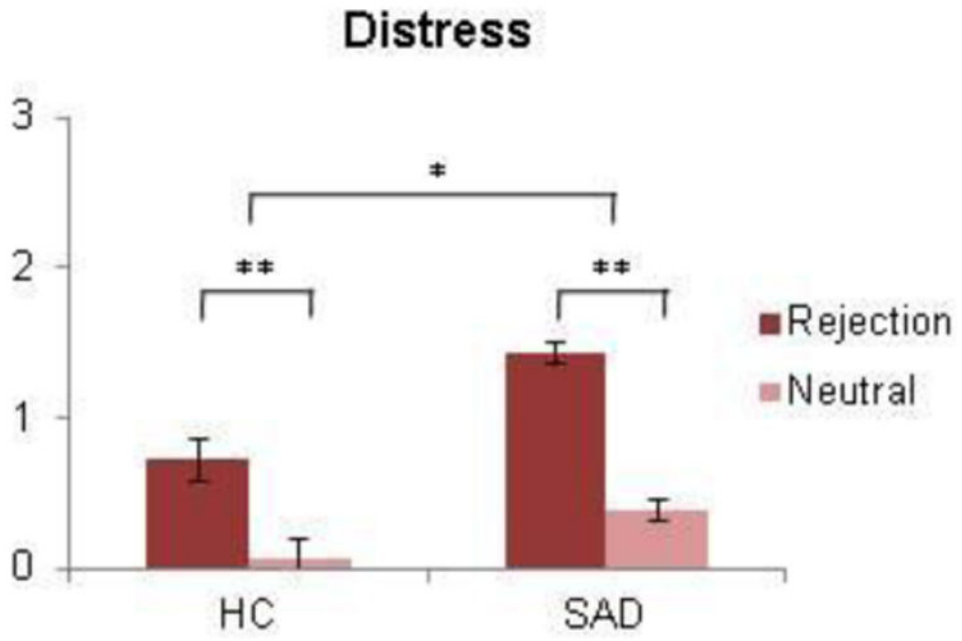

Figure 3.

Self-reported ratings of distress were provided immediately following each block of videos while still in the scanner. In a group (HC vs SAD) by condition (Rejection vs. Neutral) ANOVA, there was a significant interaction ($F(1,77)=4.584$; $p=.035$), significant main effect of group ($F(1,77)=17.986$; $p<.001$), and significant main effect of condition ($F(1,77)=89.679$; $p<.001$), as well as simple main effects of higher distress for Rejection videos relative to Neutral videos within both groups (SAD: $t(62)=12.470$; $p<.001$; HC: $t(15)=4.869$; $p<.001$) and higher distress reported by SAD participants relative to HC participants for both Rejection ($t(78)=4.312$; $p<.001$) and Neutral videos ($t(80.288)=4.234$; $p<.001$). *$p<.05$ **$p<.005$ 0="Not at all," 1="Somewhat," 2="Moderately," and 3="Extremely."

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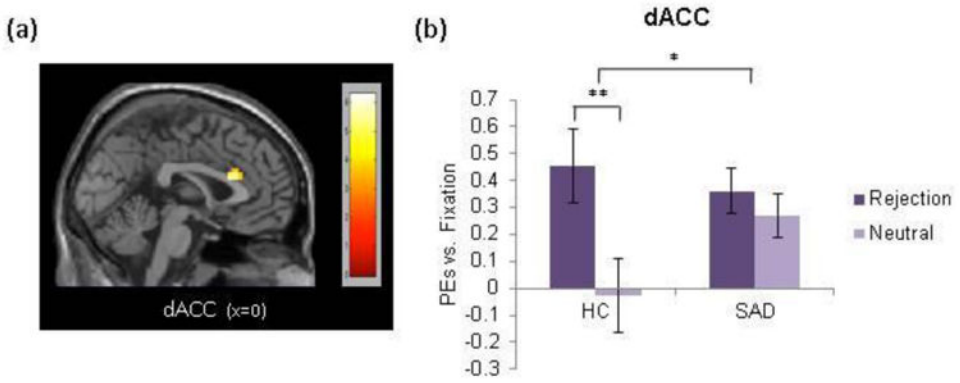

Figure 4.

(a) MR image showing greater neural activity in dACC in healthy controls during Rejection>Neutral ($p<.005$), and (b) parameter estimates (PEs) extracted from this region for each group, plotted relative to the low-level fixation baseline for illustration. Error bars represent standard errors within each group and condition. In contrast to the HC group, the SAD group did not exhibit significantly different activity between Rejection and Neutral in this dACC region. In an independent-samples t-test, the differences between Rejection and Neutral were significantly different between the two groups ($t(43.40)=2.76$; $p=.008$). *$p<.05$ **$p<.005$.

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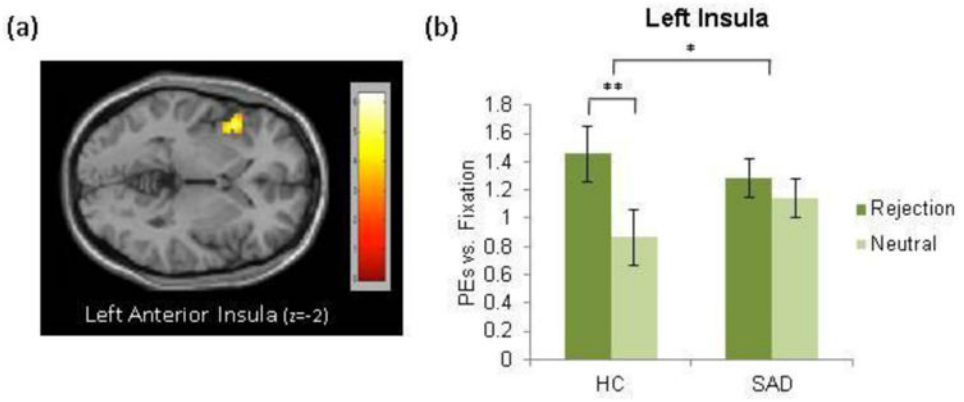

Figure 5.

(a) MR image showing greater neural activity in left anterior insula in healthy controls during Rejection>Neutral (p<.005), and (b) parameter estimates (PEs) extracted from this region for each group, plotted relative to the low-level fixation baseline for illustration. Error bars represent standard errors within each group and condition. In contrast to the HC group, the SAD group did not exhibit significantly different activity between Rejection and Neutral in this insula region. In an independent-samples t-test, the differences between Rejection and Neutral were significantly different between the two groups (t(45.62)=2.99; p=.004). **p<.005.

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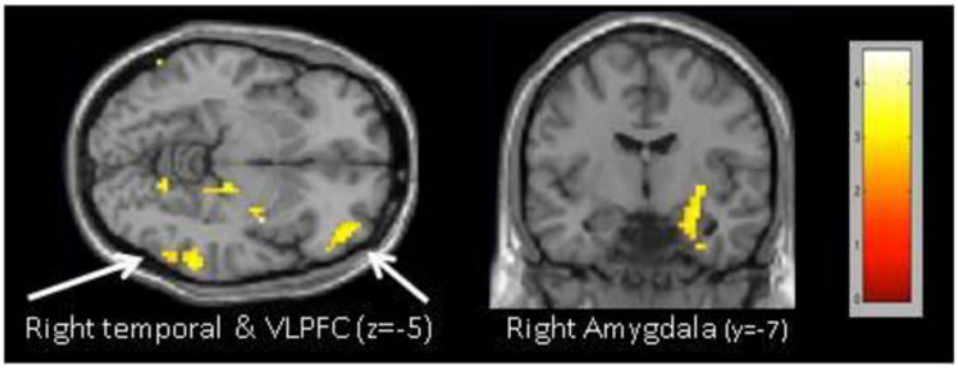

Figure 6.

MR images showing greater neural activity in right middle temporal gyrus, RVLPFC, and right amygdala for SAD during Neutral>Rejection.

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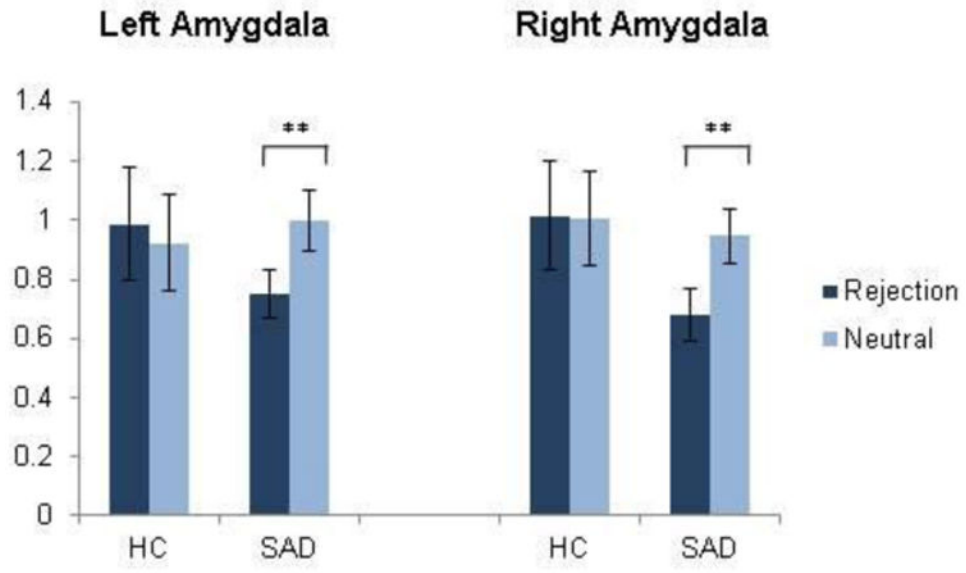

Figure 7.

Parameter estimates were extracted from anatomically-defined bilateral amygdala ROIs during each condition and plotted relative to the low-level fixation baseline for illustration. Error bars represent standard errors within each group and condition. Within-group t-tests revealed significantly greater activity during Neutral relative to Rejection in the SAD group for both left ($t(66)=-3.41$; $p=.001$) and right ($t(66)=-3.38$; $p=.001$) amygdala but no differences within the HC group. In separate independent-samples t-tests, the differences between Rejection and Neutral for SAD vs. HC did not reach significance (left amygdala: $t(82)=1.80$; $p=.075$; right amygdala: $t(82)=1.53$; $p=.129$). **$p<.005$.

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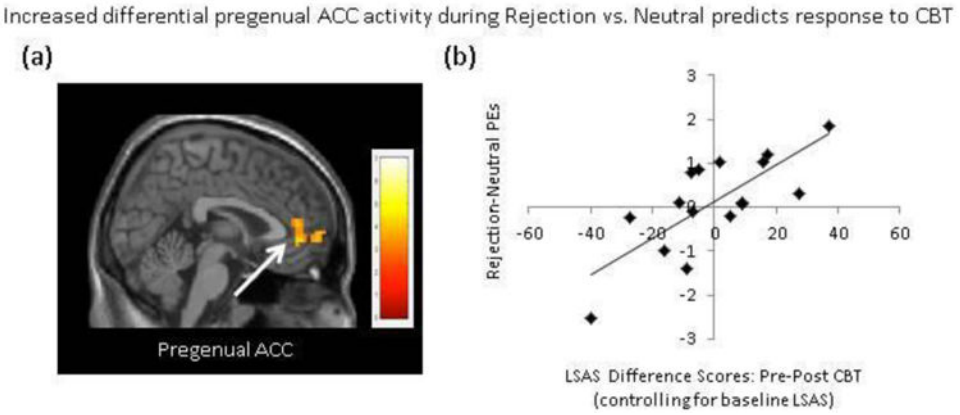

Figure 8.

(a) MR image showing activation cluster in pregenual ACC during Rejction vs. Neutral that predicted CBT response ($p<.005$); and (b) parameter estimates (PEs) extracted from this region and plotted vs. LSAS difference scores (controlling for baseline LSAS scores), indicating that larger differential activity in this region during Rejection vs. Neutral was associated with better CBT outcomes.

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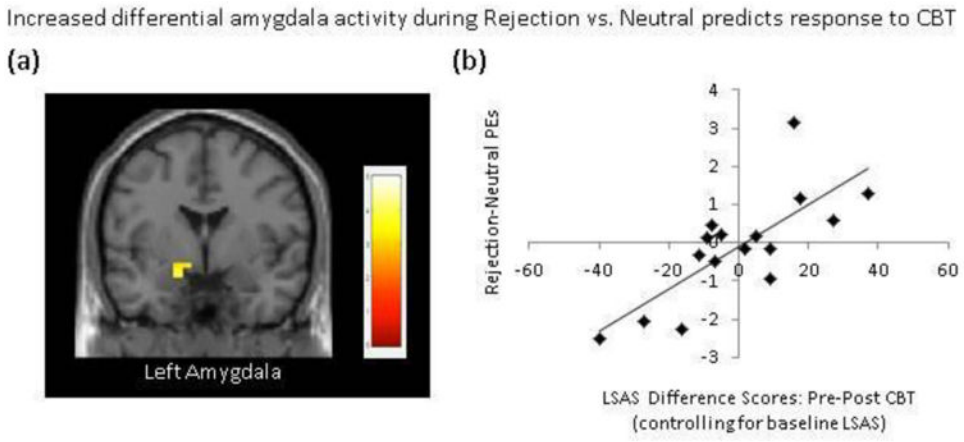

Figure 9.

(a) MR image showing activation cluster in left amygdala during Rejction vs. Neutral that predicted CBT response ($p<.005$); and (b) parameter estimates (PEs) extracted from this region and plotted vs. LSAS difference scores (controlling for baseline LSAS scores), indicating that greater activity in this region during Rejection vs. Neutral was associated with better CBT outcomes.

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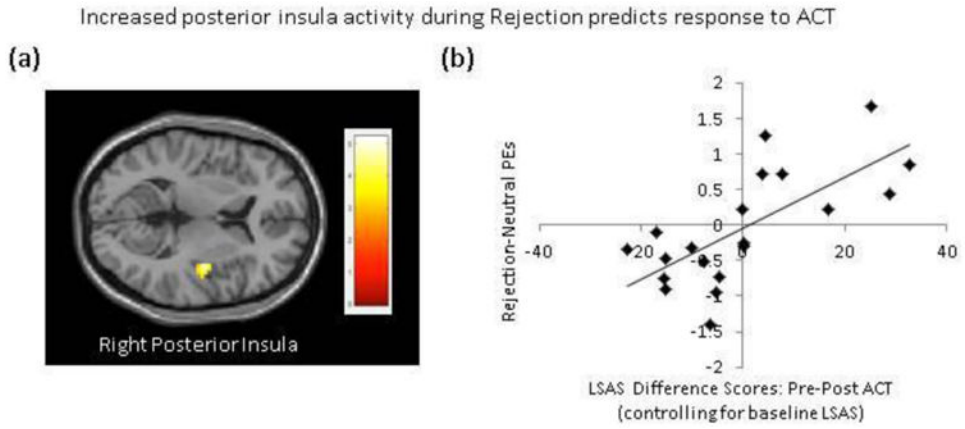

Figure 10.

(a) MR image showing activation cluster in right posterior insula during Rejction vs. Neutral that predicted ACT response ($p<.005$); and (b) parameter estimates (PEs) extracted from this region and plotted vs. LSAS difference scores (controlling for baseline LSAS scores), indicating that greater activity in this region during Rejection vs. Neutral was associated with better ACT outcomes.

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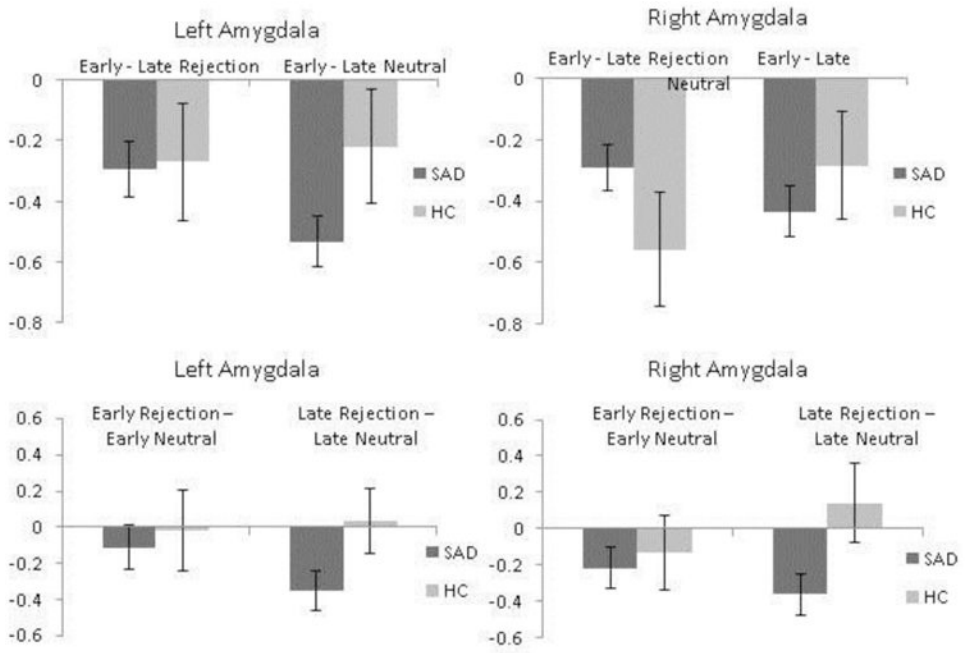

Figure 11.

Parameter estimates were extracted from anatomically-defined bilateral amygdala ROIs separately for the first and second halves (“Early” and “Late”) for contrasts of interest. Error bars represent standard errors within each group and condition. No between-group comparisons were significant (all ps>.1) apart from one marginally significant difference for Late Rejection – Late Neutral in the right amygdala (p=.052).

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Table 1

Demographic and Clinical variables.

	HC	SAD	HC vs SAD
N	17	70	
Gender (male/female)	7/10	36/34	
Age (mean(sd))	28.05(6.93)	27.74(7.88)	t(85)=.148, ns
Ethnicity			
Asian	6	13	
Hispanic	0	14	
White	9	31	
African American	0	2	
Other	1	10	
Mixed	1	0	
LSAS-SR (Pre-treatment)	17.68(7.70)	81.94(19.20)	t(66.20)=21.53, p<.001 †
SIAS (Pre-treatment)	11.88(6.00)	53.19(11.92)	t(51.59)=20.07, p<.001 †
MASQ-Anhedonic Depression (Pre-treatment)	26.18(11.14)	44.96(14.27)	t(82)=5.04, p<.001
Comorbid disorders			
Dysthymia		7	
Major Depressive Disorder		12	
Generalized Anxiety Disorder		17	
Specific Phobia (e.g., heights, animals, etc.)		13	
Panic Disorder with or without Agoraphobia		8	
Obsessive Compulsive Disorder		2	
Hypochondriasis		1	
Adjustment Disorder		1	
Total number of comorbid disorders			
0		30	
1		26	
2		9	
3		4	
4		1	
Current Medication Status			
Stable dose		8	
As needed		3	
None		57	
Missing data		2	

LSAS-SR: Liebowitz Social Anxiety Scale - Self Report Version; SIAS: Social Interaction Anxiety Scale; MASQ: Mood and Anxiety Symptom Questionnaire.

† Degrees of freedom adjusted for unequal sample variances.

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Table 2

Significant Activations within the HC group in response to Rejection vs. Neutral videos.

Contrast/Region	R/L	x	y	z	t	k
Rejection >Neutral						
	R/L	0	20	19	5.34	33
Dorsal ACC		3	26	22	4.33	*
		-3	23	22	4.38	*
Inf frontal gyrus (LVLPFC)	L	-45	17	1	5.1	52
Anterior insula	L	-42	14	-5	4.21	*
Neutral>Rejection						
Mid occipital/parietal	L	-42	-76	37	5.09	75

*Additional peak voxel in same cluster as line above

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Table 3

Significant Activations within the SAD group in response to Rejection vs. Neutral videos.

Contrast/Region	R/L	x	y	z	t	k
Rejection >Neutral						
Mid occipital gyrus	L	-24	-94	13	4.00	96
Neutral>Rejection						
Ant sup temporal gyrus	R	42	11	-23	4.16	113
Amygdala (19 voxels)	R	27	-4	-23	3.39	*
Parahippocampal gyrus	R	24	-1	-29	3.10	*
Hippocampus	R	27	-4	-23	3.39	*
Subcallosal gyrus	L/R	-3	5	-11	3.39	53
Parahippocampal gyrus/fusiform gyrus	L	-24	-40	-14	3.71	66
Inf/mid/orbitofrontal gyrus	R	27	41	-8	3.64	190
Orbitofrontal gyrus	R	18	32	-14	3.55	*
Inf frontal gyrus (RVLPFC)	R	54	35	-5	2.74	*
Inf frontal gyrus (RVLPFC)	R	45	44	-5	3.43	*
Mid frontal gyrus	R	45	47	7	3.30	*
Inf frontal gyrus	R	54	32	13	3.33	*
Mid frontal gyrus	R	27	14	55	3.18	43
Paracentral lobule/Med frontal gyrus	R	0	-22	73	3.31	44
Parietal/postcentral gyrus	R	45	-31	61	3.52	43
	R	51	-61	19	4.59	126
Mid/sup temporal/mid occipital gyrus	R	42	-73	25	3.37	*
	R	60	-58	10	4.10	*
Inf/mid temporal gyrus	R	60	-58	-11	4.05	120
Inf temporal gyrus/fusiform gyrus	L	-48	-46	-8	3.49	48
Post cingulate/lingual gyrus	R	9	-58	4	3.69	114
	R	12	-70	13	3.43	*

*Additional peak voxel in same cluster as line above

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Table 4

Regions that predicted CBT and ACT treatment response (Pre-Post LSAS change scores, controlling for baseline LSAS scores) for the SAD group in response to Rejection vs. Neutral.

Contrast/Region	R/L	x	y	z	t	k
CBT Treatment Response Positive Correlations during Rejection>Neutral (OR CBT Treatment Response Negative Correlations during Neutral>Rejection)						
Amygdala	L	-15	2	-14	5.02	16
Mid frontal gyrus	L	-39	59	1	6.97	320
Medial prefrontal	L	-12	59	4	6.23	*
Pregenual ACC	R	3	47	-2	4.27	*
Pregenual ACC	L	-3	47	10	4.75	*
Precuneus/parietal	L	-9	-82	40	5.25	56
Parietal/angular	L	-45	-70	43	4.33	43
Mid occipital/parietal	R	39	-79	31	5.82	78
Occipital	R	6	-97	16	5.60	97
CBT Treatment Response Negative Correlations during Rejection>Neutral (OR CBT Treatment Response Positive Correlations during Neutral>Rejection)						
None						
ACT Treatment Response Positive Correlations during Rejection>Neutral (OR ACT Treatment Response Negative Correlations during Neutral>Rejection)						
Posterior Insula	R	42	-10	7	5.55	32
ACT Treatment Response Negative Correlations during Rejection>Neutral (OR ACT Treatment Response Positive Correlations during Neutral>Rejection)						
None						

*Additional peak voxel in same cluster as line above