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Attention retraining in social anxiety disorder: an fMRI study

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ATTENTION RETRAINING IN SOCIAL ANXIETY DISORDER: AN fMRI STUDY

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ATTENTION RETRAINING IN SOCIAL ANXIETY DISORDER:

AN fMRI STUDY

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ABSTRACT

Research suggests that patients with social anxiety disorder (SAD) have an attentional bias toward socially threatening stimuli, and recent studies have shown that computerized interventions designed to train attention away from such stimuli decrease attentional bias and SAD symptomatology. The current study sought to replicate findings from previous attention retraining studies and to examine neural mechanisms underlying attentional biases in SAD using functional magnetic resonance imaging (fMRI). Thirty-two SAD patients were randomized to complete either eight 15-minute sessions of a probe detection task designed to train attention away from disgust faces (n=16), or a placebo control task (n=16). Before and after these sessions, patients completed an fMRI probe detection task. Sixteen matched healthy controls also completed this fMRI task on one occasion. Study hypotheses were as follows: (a) post-intervention, SAD patients in the retraining condition would show greater reductions in attentional bias and SAD symptomatology compared to patients in the placebo condition; (b) SAD patients would show greater amygdala activation, and less prefrontal cortex (PFC) activation, when

viewing negative faces than healthy controls; and (c) post-intervention, SAD patients in the retraining condition would show less amygdala activation, and greater PFC activation, when viewing negative faces than patients in the placebo condition. Results showed no between-group differences in attentional bias or SAD symptomatology post-intervention, with both groups showing significant symptom reduction. However, attentional bias change was significantly correlated with symptom change across the entire SAD sample (N=32) and was predictive of Liebowitz Social Anxiety Scale scores at post-intervention. Neuroimaging results showed hypo-activation in the orbitofrontal cortex and anterior cingulate cortex at pre-treatment for the SAD group compared to healthy controls. At post-treatment, this difference was no longer significant across the entire SAD group (N=32). Finally, results indicated that activation at pre-treatment in the posterior cingulate cortex/precuneus was significantly correlated with symptom change across the entire SAD sample. These results suggest that SAD patients may not be engaging higher-level cortical regions as readily as healthy controls and add to the recent growing body of research suggesting that attention retraining may not be an effective treatment for patients with SAD.

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List of Abbreviations

ACC: anterior cingulate cortex

ACQ: Anxiety Control Questionnaire

AC-PC: anterior commissure – posterior commissure

ANOVA: analysis of variance

ANTS: Advanced Normalization Tools

ART: Artifact Detection Tools

ASQ*:* Affective Style Questionnaire

BDI-II: Beck Depression Inventory II

BOLD: blood oxygen-level dependent

BU: Boston University

CARD: Center for Anxiety and Related Disorders

CBT: cognitive behavioral therapy

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

EPI: echo-planar imaging

FDR: false-discovery rate

fMRI: functional magnetic resonance imaging

FSL: FMRIB Software Library

GAD: generalized anxiety disorder

IAPS: International Affective Picture System

LIFE-RIFT: Range of Impaired Functioning Tool

LSAS: Liebowitz Social Anxiety Scale

MADRS: Montgomery-Asberg Depression Rating Scale

Mini-ADIS-IV: Anxiety Disorders Interview Schedule for DSM-IV- Treatment follow-up version

MIT: Massachusetts Institute of Technology

MPRAGE: magnetization-prepared rapid acquisition with gradient echo

ms: millisecond

OCD: obsessive-compulsive disorder

OFC: orbitofrontal cortex

PD: panic disorder

PCC: posterior cingulate cortex

PFC: prefrontal cortex

ROI: Region-of-Interest

SAD: social anxiety disorder

SCID: Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition

SDS: Sheehan Disability Scale

SPAI: Social Phobia Anxiety Inventory

SPIN: Social Phobia Inventory

SPM: Statistical Parametric Mapping

STAI-S: Spielberger State-Trait Anxiety Inventory

Introduction

Social Anxiety Disorder (SAD) is defined as a marked and persistent fear of negative evaluation in one or more social or performance situations (American Psychiatric Association, 2000). SAD has an estimated 6.8% prevalence rate among the general population and is the second most common anxiety disorder behind only specific phobia (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). SAD is highly comorbid with other psychiatric conditions (Kessler et al., 2005), often has an early age of onset, and is characterized by a chronic, unremitting course if left untreated (Dewit, Ogborne, Offord, & MacDonald, 1999; Neal & Edelmann, 2003). The disorder results in significant distress and impairment, is associated with economic burden (Stein & Kean, 2000), and has a negative impact on educational attainment (Katzelnick & Greist, 2001) and overall quality of life (Saarni et al., 2007).

Attentional Biases in SAD

Attentional bias is a term that refers to exhibiting preferential attention to specific types of stimuli in one's environment, either internal or external (Harvey, Watkins, Mansell, & Shafran, 2004). Attentional biases have been proposed to contribute significantly to the etiology and maintenance of anxiety disorders, including SAD (Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Hofmann, 2007). A recent meta-analysis of 172 studies confirmed that attentional biases towards threat are reliably linked with anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Beck and colleagues (1985) postulated that anxiety disorders are uniquely associated with a bias in the initial stimulus registration phase of cognitive processing:

attention is rapidly and automatically deployed toward threatening information. Indeed, anxious individuals have been shown to exhibit vigilance towards threatening stimuli during the initial stages of processing (e.g., 16-500 ms post stimulus onset) (Bar-Haim et al, 2007). Although this shift toward threatening information is evolutionarily adaptive, it becomes problematic when it leads to hypervigilence, as is proposed to occur in anxiety disorders (Mogg & Bradley, 1998). Beck's content-specificity hypothesis stipulates that each emotional disorder can be characterized by cognitive content specific to that disorder (Beck, 1976; Beck, Brown, Steer, Eidelson, & Riskind, 1987). According to this theory, patients with SAD have distorted cognitions relative to social contexts and are hypersensitive to threatening information that is social in nature (e.g., critical faces) (Coles & Heimberg, 2005; Lundh & Öst, 1996). Empirical evidence supports this hypothesis and suggests that patients with SAD detect signals of social threat with greater speed and accuracy than healthy controls (Amir, Freshman, & Foa, 2002; Hope, Rapee, Heimberg, & Dombeck, 1990; Maidenberg, Chen, Craske, Bohn, & Bystritsky, 1996; Mattia, Heimberg, & Hope, 1993; Mogg & Bradley, 2002). In addition to exhibiting a hypervigilence towards threat, it has also been shown that patients with SAD have difficulty disengaging from socially-threatening stimuli (Amir, Elias, Klumpp, & Przeworski, 2003; Buckner, Maner, & Schmidt, 2010).

Why Study Treatments that Manipulate Attentional Bias in SAD?

Despite the high prevalence of SAD in the general population, only 20% of individuals with the disorder receive treatment (Coles, Turk, Jindra, & Heimberg, 2004), and of those individuals who do receive treatment, only 60% respond positively

(Liebowitz, Ninan, & Blanco, 2005). Meta-analyses show consistent results, with less than 60% of patients showing a significant response to treatment (e.g., Federoff & Taylor, 2001). In light of these findings and the significant room for improvement in outcomes, the importance of developing, evaluating, and understanding novel treatments for SAD cannot be overemphasized. One such novel treatment is attention retraining (also known as attention bias modification).

Assessing and Manipulating Attention

Attention retraining is an intervention that manipulates attentional biases by training participants to attend to certain types of stimuli by using visual probe detection tasks (Posner, Snyder, & Davidson, 1980). The dot-probe is one such task and involves simultaneously presenting two stimuli that vary in emotional content (e.g., a threatening word and a neutral word) on a computer screen, removing the stimuli, and then replacing one of the stimuli with a probe. The participant is instructed to identify an aspect of the probe as quickly as possible. It is assumed that participants will be faster at detecting an aspect of a probe that replaces the stimulus to which the participant was attending before the probe appeared. Visual probe detection tasks were first used to *assess* attentional bias. For example, the faster a participant responded to a probe that replaced a threatening stimulus as compared to a probe that replaced a neutral stimulus, the greater the participant's attentional bias towards threat.

In recent years, visual probe detection tasks have also been used to *manipulate* attentional biases. In attention retraining paradigms, a strong contingency is built by pairing probes with either threatening or neutral stimuli, thereby changing attentional bias

over repeated trials. For anxious populations, this technique has recently gained popularity as a intervention – in these interventions, the probes consistently replace the neutral stimulus in neutral-threat stimuli pairs, thus training attention away from threat and towards neutral. Unlike psychotherapy, which seeks to alter cognitions on a conscious level, attention retraining interventions are believed to alter attentional biases on a more implicit level. Typically, participants are unaware of the contingency between the placement of probes and stimuli; therefore, the training is assumed to alter attentional processes not under volitional control (MacLeod & Mathews, 2012).

Recently, attention retraining has gained increasing empirical support for its ability to effectively manipulate attention. For example, MacLeod and colleagues (2002) successfully manipulated attention in a non-clinical sample by training participants to attend to threatening words using a dot-probe task. In this experiment, one group of participants was trained to attend to threatening words (i.e., the probe always replaced the threat word) while the other group was trained to attend to neutral words (i.e., the probe always replaced the neutral word). Post-training, the participants in the threat group exhibited faster reaction times to probes replacing new threatening words. Additionally, at post-training those participants in the threat group reported higher levels of negative mood and anxiety during a stressful task than participants in the neutral group. This study provides support for the notion that there may be a causal relationship between attentional biases toward threat and a vulnerability to experience anxiety.

There is increasing evidence that training patients with anxiety disorders, including SAD, to attend away from threat may decrease anxiety. Because increased

attention to social threat and difficulty disengaging from threat are believed to be involved in the etiology and maintenance of SAD, elimination or reduction of attentional bias may decrease associated anxiety symptoms. Recent studies examining this hypothesis indeed indicate that attention retraining may be an effective intervention for individuals with SAD. In numerous studies, after completion of an attention retraining intervention, individuals with SAD showed less attentional bias toward threat cues and decreased SAD symptomatology (e.g., Amir et al., 2009; Amir, Weber, Beard, Bomyea, & Taylor, 2008; Li, Tan, Qian, & Lui, 2008; Schmidt, Richey, Buckner, & Timpano, 2009).

Attention Retraining as a Treatment for SAD – Previous Study Findings

Studies employing attention retraining interventions have demonstrated impressive results with regard to decreasing SAD symptomatology. For example, Amir and colleagues (2008) examined the effect of a single session of attention retraining on response to a public speaking challenge in a group of individuals with SAD. In this study, all participants demonstrated elevated scores (minimum score = 26) on the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) at baseline. Participants were randomized into an active retraining condition ($N = 47$) or a control condition ($N = 47$) and completed one session of training on a dot-probe task before engaging in a challenging speech task. Specifically, participants had two minutes to prepare a speech on a controversial topic and then spoke on the topic for up to five minutes. Results showed that participants did not differ on levels of anxiety prior to training as measured by the Spielberger State-Trait Anxiety Inventory, state version (STAI-S; Spielberger, Gorsuch, Lushene, Vagg, &

Jacobs, 1983) but immediately following the training session participants did differ, with the attention retraining group showing lower levels of anxiety compared to the control group. Additionally, blind assessors rated the speeches of the participants in the retraining group as better than those of the control group.

More recently, Amir and colleagues (2009) conducted a randomized double-blind placebo-controlled trial examining the effects of attention retraining on individuals with SAD. In this study, participants were randomized into an active retraining condition (N = 22) or a control condition (N = 26) and completed eight sessions of training on a dot-probe task. Post-intervention, the patients in the active retraining condition versus control condition demonstrated a decrease in anxiety symptoms as measured by the LSAS, the Social Phobia Anxiety Inventory (SPAI; Turner, Beidel, Dancu, & Stanley, 1989), and the Sheehan Disability Scale (SDS; Leon, Olfson, Portera, Faber, & Sheehan, 1997). Furthermore, at post-intervention, 50% of patients in the attention retraining group no longer met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR; American Psychiatric Association, 2000) diagnostic criteria for SAD as compared to 14% of patients in the control condition. This reduction in SAD symptomatology was maintained for patients in the attention retraining condition at 4-month follow-up.

A recent study by Schmidt and colleagues (2009) also suggests that attention retraining has a strong therapeutic effect. In this study, SAD patients were randomized into two groups: one group received active attention retraining and the other received training on a control dot-probe task. Post-treatment, patients in the retraining condition showed decreased SAD symptoms compared to those patients in the control condition.

Specifically, 72% of the patients in the active retraining condition no longer meet DSM-IV diagnostic criteria for SAD, as compared to 11% of patients in the control condition.

The majority of attention bias modification intervention studies involving individuals with social anxiety disorder, as well as other anxiety disorders (e.g., generalized anxiety disorder), show promising results. The results from these studies formed the basis for **Aim 1, *Hypothesis* 1** of the current study: After completing the attention retraining intervention, SAD patients assigned to the active retraining condition will show greater reductions in attentional bias (as measured by reaction time and accuracy) compared to SAD patients in the placebo control condition. They also formed the basis for **Aim 1, *Hypothesis* 2**: Patients in the active retraining condition will show greater reductions in SAD symptomatology at post-intervention as compared to SAD patients in the placebo control condition.

Given the growing interest in attention retraining interventions in recent years, numerous meta-analyses have been published quantifying the results of attention retraining studies (e.g., Beard, Sawyer, & Hofmann, 2012; Hakamata et al., 2010; Hallion & Ruscio 2011). These reviews, however, have arrived at somewhat discrepant findings. For example, a review by Hakamata et al. (2010), based on 12 studies, concluded that attention retraining interventions produced a large effect on attentional bias (Cohen's d = 1.16) and a medium effect on anxiety (Cohen's d = 0.61), whereas a review by Hallion and Ruscio (2011), based on 21 studies, revealed small but reliable effects on attention (Hedges' g = .29), and anxiety (Hedges' g = .23). The most recent meta-analysis to examine attention retraining studies (Beard et al., 2012) showed that for studies that

assessed changes in symptoms following a multi-session attention retraining protocol, and trained towards neutral, the average pre–post effect size estimate was Hedges' g = 0.41. Therefore, the Beard et al. (2012) meta-analysis confirmed the results of the Hakamata (2010) review and suggests that attention retraining has a large and reliable effect on attentional bias. However, with regard to symptom change, although both reviews showed moderate effects, these results must be interpreted with caution, as the fail-safe N calculations were not robust in either review. Therefore, both reviews suggest that there is currently insufficient data to determine the effect of attention retraining on subjective experience.

Since the proposal of the current study and the publication of the above-mentioned meta-analyses (Beard et al., 2012; Hakamata et al., 2010; Hallion & Ruscio, 2011), four attention retraining intervention studies reporting null findings have been published (Boettcher, Berger, & Renneberg, 2012; Carlbring et al., 2012; Julian, Beard, Schmidt, Power & Smits, 2012; Neubauer et al., 2013). Three of the studies examined home-based attention retraining programs (Boettcher et al., 2012; Carlbring et al., 2012; Neubauer et al., 2013). Carlbring and colleagues conducted a double-blind randomized controlled study in which 79 participants diagnosed with SAD were assigned to either an active attention training condition or a placebo control condition. Both conditions involved 8 training sessions of the computerized intervention conducted in participants' homes. Results revealed an overall effect of time on all domains measured (e.g., social anxiety symptoms, depression symptoms, overall anxiety levels, and quality of life), but no group x time interactions, suggesting no difference between the active and placebo

conditions. Interestingly, this study used the same stimuli as the Amir et al. (2009) study that showed significant group differences in favor of the active condition. Both the Boettcher et al. (2012) study ($N = 68$) and the Neubauer et al. (2013) study ($N = 56$) also employed an internet-delivered home-based intervention and showed similar results; again, there was a small reduction in symptoms (i.e., social anxiety and depressive symptoms), but no evidence for superiority of the active retraining condition.

The final study reporting null findings was conducted in the laboratory and examined the effect of a single-session of attention retraining in conjunction with exercise or rest on a group of socially anxious undergraduates (LSAS scores >26) (Julian et al., 2012). Participants ($N = 112$) were randomized to one of the four following conditions: (1) active attention retraining + exercise; (2) active attention retraining + rest; (3) placebo training + exercise; and (4) placebo training + rest. Exercise and rest were added to the study design in light of evidence suggesting that exercise has beneficial effects on attentional control. Participants completed behavioral assessments, exercise (20 min) or rest (30 min), and then the attention retraining or control paradigm. Finally, all participants completed a behavioral assessment that consisted of a 5-minute speech. This study sought to replicate the results of the Amir and colleagues (2008) single-session study that showed robust results in favor of the active attention retraining condition, and therefore used the same stimuli and training procedures. However, results revealed no replication. The authors state, “Our findings do not support the hypotheses. Specifically, there were no singular effects of attention retraining on attention bias or anxiety reactivity and no interactive effects of attention training and exercise on attention

bias or anxiety reactivity, nor did these hypothesized effects vary as a function of attention bias at baseline" (p.356).

Taken together, findings from individual studies and meta-analyses suggest that attention retraining may be an efficacious clinical intervention for SAD; however, as highlighted by the meta-analyses and recent publications reporting null findings, more multi-session treatment interventions employing attention retraining are necessary to determine the efficacy of attention retraining at reducing anxiety symptoms. The current study is one such treatment study; it builds upon the results of previous research examining symptom change, and contributes to the body of knowledge on attentional biases in SAD by examining neural changes that occur as the result of attention retraining.

Why Study Changes in Brain Function as a Result of Attention Retraining?

Although there is evidence for the efficacy of attention retraining as a treatment for SAD, no studies have yet examined associated changes in brain function. Investigating the effects of attention retraining at the neural level through the use of functional magnetic resonance imaging (fMRI) is an important first step towards gaining a greater understanding of the functional pathways of attentional bias in individuals with SAD. To date, neuroimaging techniques have played a crucial role in clarifying the pathophysiology of SAD. Specifically, these techniques have helped elucidate abnormalities in brain function and circuitry that lead to deficits in information processing and emotion regulation underlying the disorder (e.g., Freitas-Ferrari et al., 2010; Mennin, McLaughlin, & Flanagan, 2009). Gaining a better understanding of the

neural underpinnings of SAD, by identifying abnormal processes and neural pathways, has major clinical implications for improving upon and devising new treatments directly targeting these deficits.

Amygdala - Prefrontal Cortex Circuit

There is an emerging body of research implicating the importance of connectivity between the amygdala and prefrontal cortex (PFC) in the neural circuitry guiding attention to threat (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Bishop, 2007; Bishop, Duncan, Brett, & Lawrence, 2004). The relationship between amygdala and PFC activity in the development and persistence of anxiety was first elucidated by findings from studies in animal models (e.g., Caldji, Diori, & Meaney, 2003) and has subsequently been extended to humans (e.g., LeDoux, 2000). Neuroimaging studies examining this circuitry suggest that bottom-up amygdalar signals promote initial vigilance towards threat, while top-down PFC signals later modulate and regulate these signals. Anxiety disorders appear to be characterized by disrupted limbic-prefrontal circuitry; specifically, exaggerated limbic amygdalar response to threat, coupled with deficient PFC activity (Bishop, 2007).

Role of amygdala in face processing and attentional bias in SAD. The amygdala is a region of the limbic system known to serve broad functions in the processing of emotional information and has consistently been implicated in the normal processing of emotional facial expressions (e.g., Phillips et al., 2001). Face processing, particularly of negative facial expressions, is thought to be an area of deficit in individuals with SAD (e.g., Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). Given that individuals with SAD have information processing biases for negative social stimuli, it is

not surprising that studies consistently find that these individuals show hyperactivation in the amygdala in response to socially threatening stimuli (Blair et al., 2008; Gentili et al., 2008; Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein et al., 2002; Straube, Mentzel, & Miltner, 2005).

The first study to examine neural activity associated with emotional face processing in SAD found greater activation in the left amygdala in SAD patients as compared to healthy controls when viewing angry or contemptuous faces (Stein et al., 2002). In this study, 15 patients with SAD (generalized) and 15 healthy controls completed an fMRI task in which they viewed a series of angry, fearful, contemptuous, happy, or non-expressive facial expressions, and were asked to identify the gender associated with each stimulus. Results indicated that SAD patients produced significantly greater blood oxygen-level dependent (BOLD) responses in the left anterior medial temporal lobe region (which includes the amygdala, uncus, and parahippocampal gyrus) than healthy controls while viewing angry and contemptuous faces versus happy faces. There was no difference in BOLD signals for fearful or non-expressive faces compared to happy faces. These results suggest that SAD patients may exhibit a hyperactive amygdala response to socially salient facial expressions (i.e., contemptuous and angry faces) as compared to other non-disorder specific facial expressions (i.e., happy and neutral faces).

The degree of hyperactivation in regions of the limbic system in SAD patients has been shown to be correlated with SAD symptom severity (Phan et al., 2006; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009). Phan and colleagues (2006) conducted a study comparing BOLD signals between 10 SAD patients and 10 healthy controls during

an fMRI task in which participants viewed blocks of faces of different emotional expressions (i.e., angry, disgusted, fearful, and happy). Results indicated that compared to healthy controls, SAD patients exhibited greater activation in the right amygdala when viewing negative faces (i.e., angry, disgust, and fearful) relative to happy faces. Furthermore, level of amygdala activation was positively correlated with SAD symptom severity. Shah and colleagues (2009) conducted a similar study with 11 SAD patients and 11 healthy controls in which participants were asked to view blocks of positive, negative, and neutral pictures (IAPS images). Results showed that SAD patients exhibited greater bilateral amygdala and insula activation than healthy controls while viewing negative images. Within the SAD group, the level of amygdala activation was positively correlated with SAD symptom severity.

There is also evidence to suggest that the amygdala may be hyper-responsive to positive as well as negative social stimuli in SAD populations (Straube et al., 2005). Straube and colleagues (2005) conducted a study in which brain activations of nine SAD patients were compared to nine healthy controls on an fMRI task in which participants viewed blocks of happy, angry, or neutral pictures. Results showed that SAD patients as compared to healthy controls had greater right amygdala activation to happy faces as well as angry faces. These findings suggest that the amygdala may play a more general role in the processing of emotional information, and that for SAD patients, the amygdala may be involved in the processing of safety signals (e.g., happy faces) as well as the processing of emotional threat (e.g., angry faces).

In search of a disorder-specific neurobiological deficit in SAD, meta-analyses have examined neuroimaging findings in individuals with SAD and confirmed the presence of dysfunctional hyperactivation in the amygdala, insula, and visual areas of the brain (Etkin & Wager, 2007; Freitas-Ferrari et al. (2010). However, these meta-analyses highlight discrepant findings across studies. For example, studies show differences in lateralization; some studies have shown hyperactivation in the *right* amygdala (e.g., Phan et al., 2006), while others have shown it in the *left* amygdala (e.g., Stein et al., 2002; Straube et al., 2004) and others *bilaterally* (e.g., Shah et al., 2008). The Freitas-Ferrari et al. (2010) meta-analysis states that such discrepancies may in part be due to methodological differences between the studies. For example, studies that employ fMRI tasks requiring participants to respond to certain aspects of a stimulus may recruit greater attentional resources and require greater support from higher cortical regions than tasks simply requiring the participant to view the stimulus without responding. Such differences make it challenging to draw meaningful comparisons across studies.

Role of prefrontal cortex in attentional bias in SAD. Signals from the PFC also play an important role in the neural circuitry guiding attention to threat. As stated above, top-down signals from the PFC are believed to flexibly modulate bottom-up signals generated by the amygdala (Bishop, 2007; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003).

Neuroimaging studies examining the neural mechanisms of attentional bias in clinically anxious populations are beginning to emerge. For example, Monk and colleagues (2006) examined neural correlates of attentional bias in a sample of

adolescents with generalized anxiety disorder (GAD). In this study, 18 adolescents and 15 matched healthy controls (age range 7-19 years) underwent a dot probe fMRI task (using angry and neutral faces stimuli) on one occasion. Results indicated that relative to the healthy controls, patients with GAD exhibited greater attentional bias away from angry faces ($F = 4.90$, $df = 30$, $p < 0.05$) and increased right ventrolateral PFC activation while viewing angry faces ($t = 3.91$, $df = 30$, $p < 0.001$). (It is important to take into consideration developmental age when interpreting these results, particularly in terms of attentional bias; studies examining attentional bias in adult (≥ 18 years) GAD patients show an attentional bias *towards* threat). Ten of the 18 GAD patients in this study had comorbid SAD, and secondary analyses were conducted to explore the effect of social anxiety symptoms on neural activation. Results of these analyses revealed no differences between the two patient groups with regard to level of ventrolateral PFC activation ($t = 0.35$, $df = 16$, $p = 0.73$). Within the entire GAD group, ventrolateral PFC activity was inversely related to anxiety severity, suggesting that the greater the hypo-reactivity in the PFC, the more severe the symptom presentation. The authors suggest that patients with more severe GAD may not be recruiting resources as effectively from the ventrolateral PFC in order to modulate abnormal limbic responses. No group differences in the amygdala were found.

The relationship between activation in the lateral PFC and the amygdala was further examined by the same research team using masked angry faces in a sample of children and adolescents with GAD (Monk et al., 2008). In this study, 17 youth with GAD and 12 healthy controls participated in a dot-probe task using masked angry and

neutral faces. Results indicated that the patients with GAD exhibited increased right amygdala activation in response to the angry faces compared to healthy controls and that the level of amygdala activation was positively correlated with GAD symptom severity. Additionally, results of the entire sample revealed a strong negative relationship between amygdala activation and right ventrolateral PFC activation when viewing angry faces. In the GAD group, this relationship was not as strong, suggesting that GAD patients were not recruiting as much compensatory response from the PFC as the healthy control group.

PFC activity and attentional bias has also been examined in late-life (age ≥ 60) GAD patients (Price, Eldreth, & Mohlman, 2011). In this study, 16 GAD patients (mean age = 66 yrs) and 12 age-matched healthy controls completed an emotional Stroop task in the scanner. Results indicated that during the presentation of negative words (in comparison to neutral words), the GAD patients exhibited decreased activation in the PFC whereas the healthy controls exhibited increased activation in this region. Across all participants, greater attentional bias for negative words was correlated with decreased PFC recruitment.

The effect of attention training *interventions* on neural function has just recently begun to be explored. Only one such fMRI study has been published to date; it examined the effects of a single attention-retraining session in healthy individuals and showed changes in prefrontal attention mechanisms post-training (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). In this study, 53 healthy participants (age ≥ 18) were randomly assigned to either train attention towards threat (i.e., "attend-threat" condition) or train attention away from threat (i.e., "avoid-threat" condition). Each participant

completed one computerized training session using threat and neutral words. Following the training, approximately half of the total sample completed a behavioral assessment of the training outside the scanner, and the other half completed an fMRI assessment of the training. Both assessments used faces rather than words. The fMRI assessment task consisted of faces flanked by two bars in different orientations. One face (either fearful or neutral) and two bars appeared on each trial. The participant was instructed to respond to the gender of the face, or the orientation of the flanking bars (depending on the direction of attention that was being manipulated (i.e., either toward or away from the face)). Results indicated that for the subsample that completed the fMRI assessment, the training had altered lateral frontal activation to emotional stimuli. Specifically, lateral PFC activity was greatest on trials when participants were asked to attend to the stimulus opposite of their trainings (i.e., when the "attend-threat" group attended to neutral stimuli, and the "avoid-threat" group attended to threat stimuli). This study suggests that a single session of attention retraining can modify frontal control over the processing of emotional stimuli in healthy individuals. To date, no studies have been published examining the effect of attention retraining on neural activity in clinical populations, including SAD.

The results from the studies described above form the basis for the following hypotheses: **Aim 2**, ***Hypothesis 1***: Both patients and controls will show activation in the amygdala and PFC during the presentation of angry faces as compared to neutral faces; and **Aim 2**, ***Hypothesis 2***: Patients with SAD will show greater activation in the amygdala, and less activation in the PFC during the presentation of angry faces than healthy controls.

Implications of Gaining a Better Understanding of the Neural Correlates of Attention Retraining in Individuals with SAD

Given the promise of attention retraining in effectively mitigating the symptoms of SAD, it is important to gain insight into changes in neural activity as a result of the intervention. This led to the development of the ***Hypothesis*** **of Aim 3**: SAD patients randomly assigned to the active retraining condition will show attenuation of activation in the amygdala, and increased activation in the PFC, during the presentation of angry faces at post-treatment compared to SAD patients assigned to the placebo control condition. The current study is the first to examine neural changes in patients with SAD as the result of an attention retraining intervention. Understanding the ways in which attention retraining exerts an influence at the neural level in SAD patients may be particularly valuable in light of evidence from neuroscience (detailed above) implicating hyperactivity in limbic structures and hypoactivity in the PFC (Etkin & Wager, 2007). These findings suggest that interventions that modify neural activity in these structures may be necessary to achieve long-term treatment gains and to prevent relapse. Overall, investigating the neurobiology of individuals with SAD will generate a deeper understanding of the disorder and may lead to more effective treatment.

Specific Aims of the Current Study

The present study sought to use fMRI in a sample of patients with SAD to measure neural changes as the result of an attention retraining intervention. Specifically, patients with SAD were randomly assigned to an active retraining condition or a placebo control condition and underwent fMRI before and after eight, 15-minute training sessions

of a validated attention retraining paradigm or a placebo dot-probe task. The main scientific goal of the current study was to identify neural changes as the result of an experimental manipulation of attention, and to examine the effects of this intervention on SAD symptoms.

This investigation had three specific aims:

Aim 1: To experimentally manipulate attentional bias in patients with SAD through an attention retraining intervention.

Hypothesis 1: Post-intervention, SAD patients assigned to the active retraining condition will show greater reductions in attentional bias (as measured by reaction time) compared to SAD patients in the placebo control condition.

Hypothesis 2: Patients in the active retraining condition will show greater reduction in SAD symptomatology at post-intervention compared to SAD patients in the placebo control condition.

Aim 2: To examine neural differences in patients with SAD vs. healthy controls during an fMRI dot-probe task.

Hypothesis 1: Both patients and controls will show greater activation in the amygdala and PFC during the presentation of angry faces as compared to neutral faces.

Hypothesis 2: Patients with SAD will show greater activation in the amygdala, and less activation in the PFC, during the presentation of angry faces than healthy controls.

Aim 3: To examine changes in neural activity as a result of the attention retraining intervention.

***Hypothesis**:* SAD patients randomly assigned to the active retraining condition will show attenuation of activation in the amygdala, and increased activation in the PFC, during the presentation of angry faces at post-treatment compared to SAD patients assigned to the placebo control condition.

Method

Research Design

The current study used a 2 (condition: attention retraining vs. placebo control) x 2 (time: pre-intervention, post-intervention) design. After meeting inclusion criteria (described below), informed consent was obtained. All patients with SAD completed an initial set of clinician-administered and self-report measures to assess baseline symptom severity. All patients with SAD participated in two identical scanning sessions pre- and post-intervention at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research, Massachusetts Institute of Technology (MIT), detailed below. Following the first pre-intervention fMRI scanning session, patients were randomized into either the active attention retraining condition or the placebo control condition. Regardless of condition, all participants completed eight, 15-minute computerized training sessions at the Center for Anxiety and Related Disorders (CARD) at Boston University (BU). Training sessions took place twice weekly, for a total of four weeks of training. Subsequent to the last training session, participants completed the 2nd scanning session. The sequence of the study for SAD patients was as follows:

Session #	**Procedures**	**Location**
Session 1	• Administration of symptom measures • 1st scanning session	MIT
Sessions 2-9	• Administration of symptom measures • Attention retraining intervention or placebo • (Before the 1st and after the 8th training session, patients completed a computerized test of attentional bias)	CARD
Session 10	• Administration of symptom measures • 2nd scanning session	MIT

The participation of healthy control subjects (n = 16) was limited to only one scanning session (i.e., they did not participate in the intervention or 2nd scanning session).

The sequence of the study for healthy control participants was as follows:

Session #	**Procedures**	**Location**
Session 1 (only session)	• Scanning session	MIT

Participants

A total of 32 subjects meeting DSM-IV diagnostic criteria for SAD, generalized subtype, participated in the study. Sixteen of these patients were randomized into the active retraining condition and 16 into the placebo condition. Additionally, 16 subjects with no psychopathology participated as healthy controls and completed one scanning session in order to examine differences in brain activation between healthy controls and SAD patients at pre-treatment.

Patients with Social Anxiety Disorder. The minimum severity level for inclusion into the study was a DSM-IV diagnosis of SAD, generalized subtype, according to the SCID or ADIS-IV (i.e., a clinician's severity rating of ≥4, on a 0-8 scale) and a LSAS total score of ≥ 60. Patients seeking treatment at CARD who met eligibility criteria were invited to participate while they remained on the treatment waitlist. Patients were also recruited through advertisements in the community.

Healthy Control subjects. Healthy Controls were recruited from the general community by advertisement and were age, gender, and handedness matched to the SAD patient group. All healthy volunteers were screened for current and lifetime psychopathology using the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, First, Spitzer, Gibbon, & Williams, 1996). To be eligible, subjects must have had no current or lifetime diagnosis of a psychiatric illness.

Inclusion and Exclusion Criteria

All screening was completed by the principal investigator. All patients were ≥18 years of age with a primary diagnosis of SAD, generalized subtype. All healthy controls were ≥18 years of age with no history of psychopathology. If a subject agreed to participate, informed consent was obtained following consideration of the following exclusion criteria based on current recommendations for fMRI studies as implemented at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research at MIT:

- History of head injury resulting in prolonged loss of consciousness
- History of prior neurosurgical procedure
- Metal in the head, metal injury to the eyes
- Signs of increased intracranial pressure
- Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, or ventriculo-peritoneal shunt
- Current pregnancy
- Chronic treatment with medications
- Claustrophobia

Additional exclusion criteria were as follows:

- Current suicidal or homicidal ideation
- History of or current psychosis
- Current diagnosis of alcohol or substance dependence, excluding nicotine

- Current use of "as-needed" psychiatric medications for the reduction of anxiety symptoms

The decision to exclude patients using "as-needed" psychiatric medication was based upon concerns that these medications would artificially alter neural patterns of emotional responding. Because we were interested in identifying patterns of neural activation during emotional processing in a clinical population, the effect of "as-needed" medication represented a significant confound. However, patients on a stable dose of psychiatric medication (i.e., on a consistent dose and timing regimen for 3 months prior to study initiation) were included in the study.

Assessment Instruments

A battery of clinician-administered and self-report measures was administered in order to assess severity of SAD symptoms and to screen formally for suicidality.

Clinician administered measures:

Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P; First et al., 1996). This semi-structured interview has good psychometric properties and focuses on all major psychiatric illnesses. This instrument was used to screen healthy controls to determine eligibility for participation (i.e., no current or lifetime diagnosis of a psychiatric illness).

Anxiety Disorders Interview Schedule for DSM-IV- Treatment follow-up version (Mini-ADIS-IV; Brown, DiNardo, & Barlow, 1994). This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use.

Diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms/impairment) to 8 (extremely severe symptoms/impairment), with a rating of 4 or above indicating that DSM diagnostic criteria has been met. This measure has demonstrated excellent inter-rater reliability for the anxiety and mood disorders.

Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). The MADRS is designed to measure the overall severity of depressive symptoms and has demonstrated good reliability as well as good specificity for depression compared to anxiety symptomatology.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). The LSAS is a 24-item scale that provides separate scores for fear and avoidance in social and performance situations. This measure shows very good psychometric properties.

Range of Impaired Functioning Tool (LIFE-RIFT; Leon et al., 1999). This clinician administered measure assesses functional impairment in the following areas: work (includes employment, household, and student); interpersonal relations (includes spouse, children, other relatives, and friends); satisfaction; and recreation. This measure can be used on a variety of populations.

Self-report measures:

Social Phobia Inventory (SPIN; Connor et al., 2000). The SPIN is a 17-item self-report measure originally created as a screening tool to identify individuals with social anxiety disorder, and to assess avoidance, fear, and physiological responses to social and performance situations. The reliability, validity, and test-retest reliability of SPIN has been demonstrated in both clinical and non-clinical samples.

Beck Depression Inventory II (BDI-II: Beck, Steer, & Brown, 1996). The BDI-II is a 21-item measure of depression symptoms. It has been shown to reliably assess aspects of depressive symptoms, including suicidality.

Affective Style Questionnaire (ASQ; Hofmann & Kashdan, 2010). The ASQ is a 20-item questionnaire used to measure individual differences in emotion regulation. The measure has three major subscales examining different emotion regulation strategies: *Concealing* subscale (8 items), *Adjusting* subscale (7 items), and *Tolerating* subscale (5 items). The measure shows satisfactory internal consistency.

Anxiety Control Questionnaire (ACQ; Rapee, Craske, Brown, & Barlow, 1996). The ACQ assesses perceived control over external threats and emotional reactions. Participants rate beliefs on a scale from 0 (strongly disagree) to 5 (strongly agree). This measure consists of 30 items, 14 of which make up the "reactions" subscale (e.g., "When I am in a stressful situation, I am able to stop myself from breathing too hard"), and 16 of which make up the "events" subscale (e.g., "I can usually influence the degree to which a situation is potentially threatening to me"). The ACQ total score has demonstrated good test–retest reliability, internal consistency, and convergent validity.

Experimental Tasks

Assessment and intervention tasks delivered at BU

Attentional bias assessment task. To assess attentional bias at pre- and post-intervention, patients completed two 20-minute sessions of a modified Posner task (Posner, 1980), once before and once after completing the eight training sessions. The stimuli used during this assessment task were five social threat words (e.g., ignored,

foolish), five physical threat words (e.g., ambulance, assault), and five neutral words (e.g., flag, plumbing), Words were chosen for this assessment task, rather than faces, to prevent any confound with the training trials (which used faces). During each trial, the participant saw a fixation cross and two small rectangles, one to the left of the fixation cross and one to the right. On each trial, a word (either socially-threatening, physically-threatening, or neutral) appeared within one of the rectangles while the other rectangle remained blank. The word appeared for 600 ms and then disappeared. Then a probe (an arrow, either "↑" or "↓") appeared in one of the rectangles. The participant was instructed to note the orientation of the arrow as quickly and accurately as possible by clicking the left or right mouse button (left for ↑, right for ↓). Upon responding, the next trial commenced. Each assessment session consisted of 288 trials. One-hundred ninety-two trials (two-thirds of the trials) were valid in which the probe appeared in the position previously occupied by the word, 48 trials (one-sixth of the trials) were invalid in which the probed appeared in the empty rectangle, and 48 trials (one-sixth of the trials) were un-cued in which no probe appeared. Reaction times to invalid and valid trials were used to calculate each participant's attentional bias (see Results section for formula).

Instructions for this assessment task read: "In this task you will see a cross (+) in the middle of the screen and two rectangles on either side of the cross. Please focus on the cross during the entire experiment. The screen will then clear and you will see a word in the left or right rectangle. The word will then be followed by an arrow that will usually appear on the same side of the screen as the word. However, once in a while the target arrow will appear on the opposite side of the screen from the word. Your job is to press

the left button on the mouse if the arrow is facing up and the right button on the mouse if the arrow is facing down. That is, regardless of the location of the arrow, press the left button if the arrow if facing up and the right button if the arrow is facing down."

Attentional bias modification training task. Participants were randomly assigned to participate in the attention retraining condition or the placebo control condition. Patients were blind to the condition they were assigned. Regardless of treatment condition, participants completed eight training sessions (each lasting approximately 15 minutes) of a modified dot-probe task at BU (see Figure 1). The training intervention used in the current study was identical to that used by Amir and colleagues (2009). The modified dot-probe task was as follows: A fixation cross (+) appeared on the computer screen. After 500 ms the cross disappeared and two pictures appeared, one above and one below where the fixation cross had previously been. The pictures were neutral faces (i.e., expressionless) or disgust faces (i.e., socially threatening). After 500 ms the faces disappeared and either the letter "F" or "E" appeared where one of the faces had previously been. The participant was instructed to indicate as quickly and accurately as possible which letter was presented by pressing the left or right button on the computer mouse. Immediately after the participant responded, a new fixation cross appeared and the next trial commenced. Each training session consisted of 160 trials comprising all combinations of probe type (E or F), probe position (top or bottom), and face type (neutral or disgust). Thirty-two of the trials (20% of the trials) included only neutral faces in order to prevent participants from guessing the mechanism underlying the training

paradigm. The remaining 128 trials (80% of the trials) included one neutral and one disgust face.

The faces used during the trainings were selected from a standardized face set of emotional expressions (Matsumoto & Ekman, 1989). The faces consisted of eight individuals, four men and four women. A threatening (i.e., disgust) and neutral expression was used from each individual. Disgust expressions, rather than other emotional expressions (e.g., anger) were chosen for the following reasons: disgust conveys rejection and dislike – a central concern of patients with SAD; research has shown a strong attentional bias toward disgust in socially anxious individuals (Pishyar, Harris, & Menzies, 2004); and disgust has shown the most dramatic training effects in previous trials (Amir et al., 2008; Schmidt et al., 2009).

Instructions for the attention retraining sessions read: "In this section you will be asked to perform a practice task. No computer knowledge is required for performing the task. Simply view photographs and decided whether a letter is an E or an F. Specifically, after you press Start, you will see a plus sign ("+") in the center of the screen. Please focus on this plus sign. The plus sign will then disappear and you will be presented with two faces, one on top and one on bottom. Your task is to look at the top face. Then, the faces will disappear and a letter will appear replacing the top or the bottom face. The letter will with be an "E" or an "F". If the letter is an "E" press the button on the mouse corresponding to the letter E (left mouse button). If the letter is an F, press the button on the mouse corresponding to the letter F (the right mouse button). After you make your decision, the next trial will begin with a plus sign. Please work as quickly and accurately

as you can. Please rest your fingers on the mouse buttons, index finger on the left button and middle finger on the right button. Also leave your mouse pointer on the button that will appear labeled "E" or "F"."

Attention retraining condition. In the active attention retraining condition, on trials including one neutral and one disgust face (i.e., 80% of the trials), the probe always replaced the neutral face, thereby training the participant to focus attention on the neutral (i.e., non-threatening) stimulus. This condition was designed to enhance attentional engagement away from social threat cues (i.e., disgust faces).

Placebo control condition. In the placebo control condition, on trials including one neutral face and one disgust face, the probe was always paired equally with neutral faces and disgust faces.

fMRI Task

fMRI dot probe paradigm. Participants completed a modified dot-probe task in the scanner at pre- and post-intervention. The task was modeled after Pourtois et al. (2006), with the exception that angry (i.e., socially-threatening) faces were used instead of fearful faces. Face stimuli were grayscale photographs from Ekman and Friesen (1976) of eight different individuals (4 males, 4 females), each with three possible expressions (neutral, happy, angry). Faces were calibrated for low-level visual properties (i.e., luminance, size, and spatial frequency) for the different emotion conditions. Pairs of faces were displayed, one face on the right of the screen and one face on the left. These face pairs always consisted of one emotional face (i.e., happy or angry) and one neutral face. The emotional face appeared with equal frequency (i.e., 50% of the time) in the

right and the left visual fields. Four different pair conditions (2 emotions × 2 sides) were created to yield four different bilateral face displays. For each condition, 24 pairs were obtained by combining each individual with two other individuals. The actual task was as follows (see Figure 2): A fixation cross (+) remained centered at the bottom of the screen throughout the task. A pair of faces appeared on the screen and remained for 100 ms before disappearing. A dim gray bar (the target) then appeared in the former location of either the emotional face or the neutral face. The target was a single rectangular bar displayed either in a horizontal or vertical orientation. The target unpredictably replaced either the emotional face (50% of the time – valid cue type [i.e., probe appears in the location of the cue]) or neutral face (50% of the time – invalid cue type [i.e., probe appears in the location opposite the cue]). When the target was presented, either the horizontal or the vertical line segment of the fixation cross at the bottom of the screen thickened. The participant was instructed to indicate on the response box whether the target was in the same or different orientation as the thickened line segment of the fixation cross. This ensured that participants oriented covertly to the peripheral bars, while maintaining fixation on the central cross throughout the experiment. Each trial took 2000 ms to complete (1000 ms face phase, 1000 ms target phase). A total of 600 trials were presented in random order in an event-related design: 100 angry valid, 100 angry invalid, 100 happy valid, 100 happy invalid, 100 angry cue only, 100 happy cue only. The entire task took approximately 25 minutes to complete (3 runs of approximately 8 minutes). Participants practiced this task outside of the scanner prior to each scanning session.

Instructions for this task in the scanner read: “Welcome! In this experiment, you will see a series of face pairs, most of which will be followed by a line either at the top left or top right corner. If the orientation of the line at the top is the same as the orientation of the thicker line of the cross in the middle, press 1. If they are not the same, press 2. If there is no line, fixate upon the cross in the middle. Get Ready.”

Image Acquisition for fMRI

Data acquisition. Image acquisition was conducted at the A.A. Martinos Imaging Center at MIT, and performed on a Siemens 3T MAGNETOM Trio, A TimSystem (Siemens Healthcare, Erlangen, Germany). A 32-channel phased array head coil was employed for the purpose of capitalizing on the increased sensitivity afforded by high magnetic field strength and increased spatial resolution (Triantafyllou, Polimeni, & Wald, 2011). Head immobilization was achieved using foam pads, and sound attenuation was provided by earplugs. Automatic slice prescription, based on alignment of localizer scans to a multi-subject atlas, was used to achieve a consistent head position across subjects. The visual stimulus system for fMRI studies used a Hitachi (CP-X1200 series) projector. The image was projected through a wave guide and was displayed on a rear projection screen. Responses were collected through an MRI-compatible response button box.

Anatomical MRI. Anatomical scans (whole-head, high-resolution T1-weighted multiecho MPRAGE volumes) were acquired prior to functional scanning for anatomical co-registration with fMRI (acquisition parameters: TR = 2530 ms, TE = 3.39 ms, flip angle = 7°, TI = 1100 ms, 1.3x1.3x1.3 mm3). The anatomical scanning sequence lasted 4 minutes.

Dot Probe fMRI. BOLD functional data were acquired using a gradient-echo T2*-weighted echo-planar imaging (EPI) sequence. Thirty-two 4mm thick slices were acquired positioned parallel to the AC-PC line (imaging parameters: TR = 6sec, TE = 30msec, flip angle = 90°, bandwidth = 2300, echo spacing = 0.5, field of view = 200x200, matrix size = 64x64). Prior to each scan, four images were acquired and discarded to allow for longitudinal magnetization to reach equilibrium. Participants completed 3 runs of the task (total time = approximately 25 minutes).

Data Analysis

Behavioral data from attention retraining intervention. To examine whether random assignment created differences in baseline characteristics across the active training group and the placebo control group, chi-square tests were conducted for categorical variables, and t-tests were conducted for continuous variables.

To assess the efficacy of the attention retraining intervention on symptoms, a 2 (group: attention retraining vs. placebo control) x 2 (time: pre-intervention score vs. post-intervention score) mixed between-within analysis of variance (ANOVA) with repeated measures for time was conducted. These analyses were conducted for anxiety measures (i.e., LSAS, SPIN) and depression measures (i.e., BDI-II, MADRS). Effect sizes (i.e., partial eta squared (η_p^2)) were interpreted based on the following guidelines suggested by Cohen (1988, pp. 284-7): .01 = small effect, .06 = medium effect, .14 = large effect.

Attentional bias scores were calculated for each participant using the following difference formula described by MacLeod and Mathews (1988): (Mean reaction time to probes replacing neutral stimuli) – (Mean reaction to probes replacing threatening

stimuli) = Attentional bias towards threat. Using this formula, positive scores indicate an attentional bias towards threat, whereas negative scores indicate an attentional bias away from threat. A score of zero indicates neither vigilance nor avoidance of threatening stimuli (i.e., no attentional bias). To assess the efficacy of the attention retraining intervention on decreasing attentional bias towards threat, a 2 (group: attention retraining vs. placebo control) x 2 (time: pre-intervention attentional bias score vs. post-intervention attentional bias score) mixed between-within ANOVA with repeated measures for time was conducted. These results were interpreted using Cohen's guidelines as described above.

Standard multiple regression was used to assess the ability of certain independent variables (group, pre LSAS score, change in attention bias) to predict LSAS score at post-treatment. Additionally, the relationship between change in social anxiety symptoms (as measured by LSAS change scores) and other variables (e.g., attentional bias, pre-treatment LSAS score) was investigated using Pearson product-moment correlation coefficient. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Interpretation of correlation values were made using the following guidelines suggested by Cohen (1988, pp. 79-81): small = .10 to .29 =; medium = .30 to .49; and large = .50 to 1.0.

fMRI data analysis. Behavioral results (i.e., movement in the scanner (motion outliers), accuracy rates) across the SAD group and the healthy control group were examined using independent-samples t-tests. Attentional bias scores for the dot-probe task performed in the scanner were calculated using the same formula by MacLeod and

Mathews (1988) described above [i.e., (Mean reaction time to probes replacing neutral stimuli) – (Mean reaction to probes replacing threatening stimuli) = Attentional bias towards threat].

Data were analyzed using Nipype v0.4 (Neuroimaging in Python: Pipelines and Interfaces; http://nipy.org/nipype; Gorgolewski et al., 2011), a neuroimaging data processing framework. Nipype provides interfaces to multiple existing neuroimaging software (e.g., Statistical Parametric Mapping (SPM), Freesurfer, FMRIB Software Library (FSL)), thereby allowing the use of different software packages to execute different components of the analysis in a single workflow. For the current study, structural data (cortical reconstruction and parcellation of anatomical images) were analyzed using the default processing stream Freesurfer v5.1.0 (Dale, Fischl, & Sereno, 1999; http://surfer.nmr.mgh.harvard.edu/). Functional data were analyzed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) using workflows in Nipype v0.4. Image preprocessing consisted of motion correction (rigid-body realignment to the mean EPI image from the first functional run) and spatial smoothing (6mm isotropic FWHM 3D Gaussian kernel). Slice timing correction was performed using SPM8. Motion and intensity outliers (functional volumes exceeding 1mm in differential motion or differing from the mean image intensity by > 3 SD) were identified using the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/). Model design was implemented using the modelgen algorithm in Nipype.

Subject-specific first-level analysis was applied using a general linear model approach. Regressors for each of the experimental conditions were entered into the

design matrix, as well as motion parameters and outliers (as detected by ART). The following 15 experimental conditions were examined: (1) task > rest; (2) Angry Valid; (3) Angry Invalid; (4) Angry Cue Only; (5) Happy Valid; (6) Happy Invalid; (7) Happy Cue Only; (8) Angry Cue Only > Happy Cue Only; (9) Angry Invalid > Angry Valid; (10) Angry Invalid > Happy Invalid; (11) Happy Invalid > Happy Valid; (12) Angry Invalid > Angry Cue Only; (13) Happy Invalid > Happy Cue Only; (14) Angry Valid > Angry Cue Only; (15) Happy Valid > Happy Cue Only. "Valid" indicates that the probe replaced the emotional face during an emotional/neutral face pair, whereas "Invalid" indicates that the probe replaced the neutral face. "Cue Only" indicates that no probe appeared after the presentation of a face pair.

Within-subject estimation of the general linear model and contrasts were conducted in participants' native Echo Planar Imaging (EPI) space. The co-registration transformation between each participant's mean functional EPI volume and their T1-weighted structural image was calculated using Freesurfer's BBRegister program. These transforms were applied to the contrast images from each participant's first-level analysis to insure accurate co-registration between functional data and high-resolution anatomy. Participants' high-resolution structural images were aligned to a common space (the 1mmisotropic MNI152 template from FSL v4.1.6 (http://www.fmrib.ox.ac.uk/fsl/)) using nonlinear symmetric diffeomorphic mapping implemented in ANTS v.1.5 (Avants, Epstein, Grossman, & Gee, 2008; http://www.picsl.upenn.edu/ANTS/). The transformation matrix and deformation field from this spatial normalization were applied to each participant's co-registered first-level contrast images to align them to the common

space. Beta values from selected data files at specific regions of interest were extracted using the region-of-interest toolbox (Rex) and submitted to further analysis for contrasts of interests. Second-level (group comparisons) were performed using SPM8, thresholded at $p < 0.05$, and corrected for multiple comparisons via topographic false-discovery rate (FDR) correction at $q = 0.05$.

Results

Participant Characteristics for Attention Retraining Intervention

A total of 34 SAD patients entered the study. Two of these participants were excluded due to diagnostic reasons that became apparent as the study progressed (i.e., both over-reported symptoms at the outset of the study). Analyses were performed on treatment completers (active group = 15, placebo control group = 16); this decision was based on the fact that only one participant did not complete the study (from active group). The demographic and clinical characteristics of the SAD study participants are provided in Table 1. Attentional bias assessment data (assessed with the Posner task) was not collected on one patient in the active group (due to computer malfunction) and one patient in the control group (the task was added after this first subject started the study).

To examine whether random assignment created differences in baseline characteristics between individuals in the active condition as compared to the placebo control condition, chi-square tests were conducted for categorical variables, and t-tests were conducted for continuous variables. The active attention retraining condition and the placebo control condition did not differ on any demographic or clinical characteristics at baseline (ps > .33).

Attention Retraining Intervention Results

Effect of intervention on social anxiety symptoms. To assess the efficacy of the attention retraining intervention on symptoms of social anxiety, a 2 (group: attention retraining vs. placebo control) x 2 (time: pre-intervention LSAS score, post-intervention LSAS score) mixed between-within ANOVA with repeated measures for time was

conducted. Results revealed a significant main effect for time (Wilks' Lambda = .51, F (1, 28) = 26.89, $p < .001$, $\eta_p^2 = .49$), with both groups showing a reduction in LSAS scores from pre to post (see Table 2; Figure 3). However, in contrast to most previously published studies, and contrary to current study expectations, results did not reveal a significant interaction between group and time (Wilks' Lambda = .97, F (1, 28) = .75, p = .39, $\eta_p^2 = .03$). The main effect comparing the two training groups was not significant (F (1, 28) = .44, p = .52, $\eta_p^2 = .015$), suggesting no differences in the effectiveness of the two training conditions (i.e., active training vs. placebo). Therefore, results indicate that the overall sample experienced a decrease in symptoms, however, this was not related to group. Thus, this study failed to provide support for ***Aim 1, Hypothesis 2*** that patients in the active retraining condition would show greater reduction in SAD symptomatology at post-intervention than those patients assigned to the placebo control condition.

The same result was seen when examining scores on the SPIN, a self-report measure of SAD symptomatology. Again, a mixed between-within ANOVA revealed a significant main effect for time (Wilks' Lambda = .78, F (1, 28) = 8.13, p = .008, η_p^2 = .23), with both groups showing a reduction in SPIN scores from pre to post. Results did not reveal a significant interaction between group and time (Wilks' Lambda = .99, F (1, 28) = .16, p = .69, $\eta_p^2 = .006$). The main effect comparing the two training groups was not significant (F (1, 28) = .44, p = .54, $\eta_p^2 = .019$), again suggesting no differences in the effectiveness of the two training conditions.

Effect of intervention on depressive symptoms. Social anxiety and depression are highly comorbid disorders (Kessler et al., 2005); therefore, changes in depression

symptomatology were also explored. Changes in depressive symptoms were similar to that of SAD symptoms. Specifically, when examining BDI-II scores, results revealed a significant main effect for time (Wilks' Lambda = .71, F (1, 28) = 11.52, p = .002, η_p^2 = .29), with both groups showing a significant reduction in BDI-II scores from pre to post (see Table 2; Figure 4). However, results did not reveal a significant interaction between group and time (Wilks' Lambda = .89, F (1, 28) = 3.20, p = .08, η_p^2 = .12). The main effect comparing the two training groups was not significant (F (1, 28) = .30, p = .59, η_p^2 = .011). The MADRS, a clinician-administered measure of depression, was also examined, and results again revealed a significant main effect for time (Wilks' Lambda = .86, F (1, 28) = 4.6, p = .041, η_p^2 = .14), but no significant interaction between group and time (Wilks' Lambda = .99, F (1, 28) = .13, p = .72, η_p^2 = .005). The main effect comparing the two training groups was not significant (F (1, 28) = .56, p = .46, η_p^2 = .02), again suggesting no differences in the effectiveness of the two training conditions.

Effect of intervention on attentional bias. A 2 (group: attention retraining vs. placebo control) x 2 (time: pre-intervention attention bias score, post-intervention attention bias score) mixed between-within ANOVA with repeated measures for time was conducted to examine the effects of the intervention on attention bias. Results revealed neither a significant main effect for time (Wilks' Lambda = .99, F (1, 28) = .115, p = .737, η_p^2 = .004), nor a significant interaction between group and time (Wilks' Lambda = .98, F (1, 28) = .55, p = .47, η_p^2 = .02). The main effect comparing the two training groups was also not significant (F (1, 28) = .03, p = .86, η_p^2 = .001). Therefore, the results of the study do not support ***Aim 1, Hypothesis 1*** that at post-intervention, SAD

patients assigned to the active retraining condition would show greater reductions in attentional bias (as measured by reaction time) compared to SAD patients in the placebo control condition.

There was, however, a significant correlation between change in attentional bias to social threat words and change in LSAS scores across groups (i.e., when all SAD patients were examined together). There was a strong, positive correlation between the two variables ($r = .699$, $p < .0001$), with greater changes in attentional bias associated with greater LSAS change. According to Cohen's (1988) guidelines for interpretation, these results indicate a large correlation between change in LSAS score and change in attentional bias to social threat words.

The correlation between SAD symptom change and attentional bias change was significant when each training group (i.e., active training group and placebo control group) was examined separately. For the active group, the correlation between change in attentional bias and change in LSAS was $r = .501$, $p = .03$, and for the placebo control group it was $r = .767$, $p < .001$.

Correlations between change in attentional bias to the other stimulus words used (i.e., neutral words, physical threat words) and change in LSAS scores were examined to determine specificity of the result to socially relevant stimuli. Results indicated non-significant correlations between attentional bias change to non-socially relevant stimuli and LSAS change [(neutral words: $r = -.207$, $p = .28$); (physical threat words: $r = -.141$, $p = .47$)].

In light of a recent study reporting that attentional bias at pretreatment was predictive of treatment response (Amir, Taylor, & Donohue, 2011), standard multiple regression was used to assess the ability of certain independent variables (i.e., pretreatment attentional bias, pre LSAS score, group, change in attentional bias) to predict LSAS scores at post-treatment. The total variance in post-treatment LSAS scores explained by the model as a whole was 50.2%, F (4, 25) = 6.05, p = .002. Examining each independent variable's contribution, pre LSAS scores made the strongest unique contribution to explaining post LSAS scores (beta coefficient = .88; p >.001), and uniquely explained 49% of the variance in post LSAS scores. Change in attentional bias also made a unique significant contribution (beta coefficient = -.49; p =.02), and explained 13% of the variance in post LSAS scores. Finally, neither group (i.e., active or placebo control; beta coefficient = -.025; p = .86),) nor pre-treatment attentional bias score (beta coefficient = .018, p = .91) made a statistically significant unique contribution to the equation. These findings suggest that LSAS severity at pre-treatment, as well as change in attentional bias, were predictive of SAD symptomatology at post-treatment.

fMRI Results

Sixteen healthy control subjects completed one fMRI scanning session to allow the direct comparison of brain activation in healthy controls to patients with SAD. The mean age of the healthy controls was 25.1 years (SD = 7.8). The majority of the sample was Caucasian (n=10), followed by Asian (n=5), and Black/African American (n=6), and half the sample was female. The healthy control group was intentionally matched closely

with the SAD group, and there were no between group differences between the SAD group and healthy control group at baseline.

Motion outliers and accuracy rates. The number of motion outliers was small for both the SAD patients [pre (M = 3.13; SD = 6.56); post (M = 1.84; SD = 3.55)] and the healthy controls (M = 1.83; SD = 1.85). The groups did not differ in number of outliers at baseline, $t(46) = .77$, $p = .45$. There were also no group differences in number of motion outliers between the SAD patients in the active group [pre (M = 2.48; SD = 4.36); post (M = 1.87; SD = 3.36)] as compared to those in the placebo control group [pre (M = 3.77; SD = 8.31); post (M = 1.82; SD = 3.85)]. The training groups did not differ in number of outliers at baseline, $t(30) = -.55$, $p = .59$.

Individual reaction times for errors (i.e., incorrect responses) were excluded from the analyses. Additionally, trials in which response latencies were less than 50 ms or greater than 1200 ms were considered outliers and excluded from the analyses. The number of inaccurate responses was small for both the SAD patients [pre (M = 9.05; SD = 11.38); post (M = 7.42; SD = 9.12)] and the Healthy Controls (M = 13.31; SD = 11.73). The groups did not differ in number of inaccurate responses, $t(46) = -1.21$, $p = .23$.

fMRI attentional bias data. As noted above, attentional bias is inferred when responses to probes replacing an emotional stimulus (e.g., threat or happy face) in emotional-neutral pairs are faster than responses to probes replacing the neutral stimulus. Attentional bias towards threat was similar for both the SAD patients [pre (M = -6.61; SD = 17.94)] and the Healthy Controls (M = 4.10; SD = 17.42) at baseline. The groups did not differ in levels of threat vigilance at baseline, $t(46) = -1.97$, $p = .06$. This finding is

contrary to current study expectations in which initial threat vigilance (at baseline) was expected to be greater for the SAD group than the Healthy Control group. There were also no group differences in vigilance between the SAD patients in the active group [pre (*M* = -4.95; *SD* = 14.78); post (*M* = 6.73; *SD* = 12.46)] as compared to the SAD patients in the placebo control group [pre (*M* = -8.27; *SD* = 21.01); post (*M* = -0.90; *SD* = 14.33)]. These groups did not differ in threat vigilance at baseline, *t(*30) = -.52, *p* = .61, or at post-treatment *t(*29) = 1.58, *p* = .13.

Attentional bias towards happy faces was also examined using reaction time data. Attention towards happy faces was again similar for the SAD patients (*M* = 1.50; *SD* = 11.51) and the Healthy Controls (*M* = 2.01; *SD* = 19.64) at baseline. The groups did not differ in levels of attention towards happy faces at baseline, *t(46*) = -.12, *p* = .90. There were also no group differences in attention to happy faces between the SAD patients in the active group [pre (*M* = 0.71; *SD* = 12.17); post (*M* = 8.09; *SD* = 15.15)] as compared to those in the placebo control group [pre (*M* = 2.29; *SD* = 11.16); post (*M* = 9.92; *SD* = 11.23)]. These groups did not differ in attention to happy faces at baseline, *t(*30) = -.38, *p* = .71, or at post-treatment *t(*29) = -.38, *p* = .71.

SAD group (at baseline) compared to Healthy Control group. Commensurate with findings from previous studies (e.g., Amir et al., 2009; Schmidt et al., 2009), it was hypothesized that SAD patients in the active training group would experience a greater decrease in SAD symptoms and attentional bias as a result of the intervention than the placebo control group. However, as stated above, this hypothesis was not supported in the current study. As a result of this unexpected finding, and the finding that for the entire

sample change in attentional bias was highly correlated with LSAS change scores and predicted treatment outcome, fMRI analyses were conducted including the entire SAD sample, rather than examining the training groups separately.

Analyses revealed significant differences in BOLD levels between the SAD patients and healthy controls at pre-treatment in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) for the following experimental conditions: Happy Invalid > Happy Valid and Happy Invalid > Happy Cue Only. Only contrasts involving happy face stimuli (not angry face stimuli) showed these results. An independent-samples t-test was conducted to compare the beta values for the SAD group at pre-treatment and the healthy control group in this Region-of-Interest (ROI) showing significant between-group differences. There was a significant difference in scores for the SAD pre group (M = -.60, SD = .79) and the Healthy Control group (M = -.09, SD = .45); $t(45) = -2.36$, p = .02. The magnitude of the differences in the means (mean difference = -.51, 95% CIs [-.945, -.074]) was large (eta squared = 0.11). This finding indicates hypo-activation in the OFC and ACC at pre-treatment for the SAD group as compared to the Healthy Control group (see Figure 5).

SAD group (at post-treatment) compared to Healthy Control group. An independent-samples t-test was conducted to compare the beta values in the OFC and ACC for the SAD group at post-treatment and the Healthy Control group. At post-treatment, there was no longer a significant difference in scores between the SAD group (M = -.21, SD = .61) and the Healthy Control group (M = -.09, SD = .45); $t(45) = -.68$, p = .50). The magnitude of the differences in the means (mean difference = -.119, 95% CIs

[-.469, .23] was small (eta squared = 0.01). Therefore, at post-intervention the SAD group beta values were no longer significantly different than the healthy control group, suggesting that levels of BOLD activation for the SAD group had normalized (see Figure 6). A paired-samples t-test was conducted to evaluate the difference in beta values for the SAD sample from pre to post. There was a statistically significant increase in beta values from pre (M = -.60, SD = .80) to post (M = -.21, SD = .61); $t(30)$ = -2.342, p = .03. The mean decrease in beta values was -.39 (95% CIs [-.73, -.05]). The eta squared statistic (.15) indicated a large effect size.

The relationship between change in beta scores for the SAD group and change in LSAS was investigated using Pearson product-moment correlation coefficient. There was a small non-significant correlation between the two variables, r = .158, N = 31, p = .397. The relationship between change in beta scores and change in attentional bias was also examined, and results again showed a non-significant correlation (r = .001, N = 29, p = .99).

SAD symptom change and brain activation. Analyses conducted on the whole brain level revealed that change in SAD symptomatology (as measured by LSAS change from pre to post treatment) was significantly correlated with activation in the precuneus at pre-treatment (mean ΔLSAS = 12.58 (SD = 13.93); mean BOLD signal = -.114 (SD = .88); r = .555, p = .001, N = 31). Only contrasts including angry faces resulted in this correlation; the contrast with the highest correlation was Angry Invalid > Happy Invalid (see Figure 7). On the dot probe task, the Angry Invalid trials consisted of an angry/neutral face pair where the probe replaced the neutral face; the Happy Invalid trials

consisted of a happy/neutral face pair where the probe replaced the neutral face. Thus, the Angry Invalid > Happy Invalid condition examined where activation was greater in response to Angry Invalid trials as compared to Happy Invalid trials.

Discussion

Principal Findings

The present study sought to replicate and extend findings from previous studies suggesting that attention retraining reduces attentional bias and anxiety symptoms among patients diagnosed with SAD. Furthermore, the study was the first to examine neural activation in SAD patients before and after an attention retraining intervention. Analyses of the current study provided confirmation for some proposed hypotheses; however, they also yielded several unexpected findings.

Contrary to study hypotheses, results indicated no difference between the active and placebo control groups in attentional bias or SAD symptomatology as a result of the attention retraining intervention. Change in attentional bias was significantly correlated with change in SAD symptomatology across the entire SAD sample ($r = .699$, $p < .0001$). Initial SAD severity (i.e., LSAS at pre-treatment) and change in attentional bias were predictive of post-intervention SAD severity (i.e., LSAS at post-treatment). Consistent with previous findings, neuroimaging results indicated a significant difference in brain activation in the OFC and ACC at pre-treatment between SAD patients and healthy controls; at post-treatment, this difference was no longer significant, suggesting that BOLD activations in the SAD group had normalized. Finally, results indicate that activation at pre-treatment in the PCC/precuneus, an area of the brain implicated in self-referential processing, was significantly correlated with SAD symptom change across the entire sample.

Attention Retraining Intervention

With regard to the attention retraining intervention, the results of the current study did not support the hypothesis that those individuals randomly assigned to the active retraining condition would exhibit greater reductions in attentional bias and SAD symptomatology compared to those randomly assigned to the placebo control condition. Both groups experienced a significant decrease in SAD symptoms, but no interaction was found between group and time. Results indicated, however, that change in attentional bias towards social threat words was highly and significantly correlated with change in social anxiety symptoms across the entire sample. This finding supports the theory that attentional biases towards social threat and SAD symptomatology are closely linked (Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Hofmann, 2007). Moreover, non-significant correlations were found between changes in attentional bias to non-socially relevant stimuli (i.e., physical threat words, neutral words) and LSAS change, further supporting this theory.

In light of the current study's findings, it is important to note that across all clinical trials to-date examining attention retraining as a treatment for SAD, patients in the placebo control condition, as well as those in the active condition, have improved. For example, in the Schmidt et al. (2009) study, 11% of the patients in the placebo control condition no longer met diagnostic criteria for SAD (compared to 72% of patients in the active condition). Similarly, in the Amir et al. (2009) study, 14% of patients in the placebo control condition no longer met DSM-IV diagnostic criteria for SAD (compared to 50% of patients in the attention retraining group).

When the current study was first proposed, no studies examining attention retraining interventions for SAD populations had reported null findings (i.e., no effect of group on reduction in SAD symptoms). As mentioned above (see Introduction), four such studies reporting null findings have recently been published (i.e., Boettcher et al., 2012; Carlbring et al., 2012; Julian et al., 2012; Neubauer et al., 2013). The publication of these studies is important, particularly when considering that results of recent meta-analyses (Beard et al., 2012; Hakamata et al., 2010) examining the efficacy of attention retraining interventions on symptom change were inconclusive due to non-robust fail-safe N calculations. It is plausible that publication bias may have existed in the past, whereby only studies reporting significant results were accepted for publication, while those with null findings are kept in the "file-drawer".

Possible Explanations for Study Findings

Given that the current study did not find hypothesized group differences (and recent studies have also reported null findings), the question must be raised as to why.

Placebo response. It is plausible that factors unrelated to the training paradigm, such as a placebo response, may have played a role in the results of the current study. The term "placebo response" refers to the apparent improvement in the clinical condition of patients assigned to the placebo arm of a randomized controlled trial. The placebo response is a common phenomenon in research and medicine, and it has been widely accepted as influential in the treatment of multiple conditions, such as chronic pain, impaired motor functioning, as well as psychiatric conditions such as mood and anxiety

disorders (Shapiro & Shapiro, 1997; Walsh, Seidman, Sysko, & Gould, 2002; Wampold, Minami, Tierney, Baskin, & Bhati, 2005).

When an active treatment condition and a placebo result in similarly high response rates, it is difficult to conclude that the active treatment is, in fact, not efficacious. This is particularly true within the field of anxiety disorder research where the placebo response rates for many disorders are high (e.g., Stein, Baldwin, Dolberg, Despiegel, & Bandelow, 2006). A review of 15 clinical trials showed that patients with SAD had a moderately large benefit from placebo (mean $d = 0.46$; Oosterbaan, van Balkom, Spinhoven, & van Dyck, 2001). Specifically, the percentage of responders for placebo conditions was 23.5% (SD = 7.9, range = 8 - 33%), as compared to 53.5% (SD = 19.2, range = 18 – 78%) for the active drug conditions. More recently, Huppert and colleagues examined the placebo response for SAD patients compared to patients with panic disorder (PD) and obsessive-compulsive disorder (OCD) (Huppert et al., 2004). This study examined the effects of placebo across three randomized controlled trials comparing cognitive behavioral therapy (CBT), medication, and their combination (i.e., CBT + medication) to placebo. Results showed that patients with SAD and PD showed significantly larger placebo responses than patients with OCD. The relatively high placebo response rate for SAD is important to consider when interpreting the results of the current study. It is possible that in the current study, there was simply a high placebo response rate, such that the patients in the placebo condition improved similarly to those in the active retraining condition.

It has been proposed that placebo effects may act on a number of mechanisms including anxiety reduction, conditioning, social support, increased sense of mastery and control, increased self-efficacy, and expectancy. The role of expectancy is thought to play a major role in the placebo response among anxiety disorders. The "expectancy theory" posits that the placebo response is related to patients' expectations of improvement (Gladstein, 1969; Kirsch, 1990). Patient expectancy is defined as a patient's beliefs about how a given treatment will affect them and may influence outcomes. Expectancy may also bring about increased self-esteem and improved coping. Expectancy effects have been studied widely in psychiatry and the social sciences, and it is believed that expectations may help account for the placebo effects seen in many randomized clinical trials across many disorders (Stewart-Williams & Podd, 2004). For example, expectancy effects have been linked to greater improvement of symptoms in trials examining depression (e.g., Krell, Leuchter, Morgan, Cook, & Abrams, 2004; Meyer et al., 2002; Rutherford, Wager, & Roose, 2010), and other clinical problems, such as irritable bowel syndrome (e.g., Kaptchuk et al., 2009).

A major advantage of attention retraining interventions is the maintenance of a valid blind (i.e., the placebo control condition appears identical in all aspects to the active condition aside from the contingency created between probe positions). Indeed, patients and researchers are typically completely unaware of which condition the patient is assigned, thereby greatly reducing interference from demand characteristics and expectancy effects. However, despite this advantage, expectancy of therapeutic gain may still play a role in symptom improvement. In the current study, all participants were told

that the study was examining the effects of a novel "*treatment"* on symptoms of social anxiety. They were told that they had a 50% chance of being randomly assigned to the active condition or the placebo control condition, Moreover, they were told that previous research studies had shown the active condition to be effective in mitigating symptoms of social anxiety, although given individual differences it was unknown how they would respond if assigned to the active condition. This knowledge alone may have created an expectancy of change, thereby leading some patients in the placebo control group to report symptom reductions.

Control (placebo) condition serves as a weak intervention. Another possible explanation for the fact that there were no group differences in the current study lies with the placebo control condition. The placebo control condition of the dot probe task pairs probes with neutral and threatening stimuli with equal frequency. There is no contingency between probes and stimulus type; therefore, no training is thought to occur. However, the placebo condition assumes that the participant has a neutral bias (i.e., no bias towards or away from threat), and that this bias will therefore remain unchanged because no training occurs. However, if a participant has a bias towards threat, the placebo may potentially serve as a weak intervention. In essence, in the placebo control condition, the 50% of the trials where the probe replaces the neutral face could be seen as training trials, while the other 50% where probes replace the threatening face would not. Although one would still assume that the participants receiving the active training would improve more than those in the placebo control condition, it is plausible that the patients assigned to the placebo condition might also improve as a result of receiving this

"watered down" intervention. This may explain why in the current study and in previous published studies, participants in both the active and placebo groups improved (e.g., Schmidt et al., 2009; Amir et al., 2009). Perhaps the placebo control condition was a less robust intervention than the active intervention, but an intervention nonetheless.

Placebo control condition = exposure to threatening faces. Another potential explanation for the current study findings is that patients in the placebo control group may have experienced symptom improvement simply from exposure to threatening faces. Symptom reductions may reflect desensitization to repeatedly presented threat stimuli. Unfortunately there is no way to test this hypothesis within the current study. One way around this potential problem in future studies would be to employ control conditions with neutral-neutral face pairs as have been used in recent studies (Eldar et al., 2012); therefore, not exposing patients in the placebo control group to threatening faces.

Intervention provided social contact/exposure. It is also plausible that the frequent study visits (i.e., twice per week) provided more occasions for social interactions than many of the patients would have experienced normally. Participants in the current study completed two fMRI scanning sessions and eight training sessions for a total of 10 study visits. Each of these study visits could be seen as an exposure in which patients faced their fears and interacted with others. Furthermore, the frequent study sessions could have served as behavioral activation.

Aspects of Attention Retraining Paradigms (technical parameters)

The impressive results in symptom reductions seen in some attention retraining intervention studies and the null findings seen in others beg the question of what are the

most effective parameters for attention retraining intervention protocols, and can differences in these parameters account for differences in outcome. Recent meta-analyses (Beard et al., 2012; Hakamata et al., 2010) indicate that studies that employ words (rather than pictures) and present stimuli in a top/bottom (rather than left/right) orientation resulted in the greatest therapeutic change (in the current study, pictures where presented in a top/down orientation). Additionally, it appears that the greater the number of training sessions, the greater the effect size. Differences in parameters across studies may account for some discrepancies in outcome; however, they cannot explain why studies employing the exact same stimuli and presentation parameters have found very different results. For example, the training intervention used in the current study was identical to that used by Amir and colleagues (2009), but failed to replicate the findings of that study. The explanation for differences in outcome between these studies remains unknown.

Given that SAD patients appear to vary in their response to attention retraining interventions, a recent study attempted to illuminate what demographic, clinical, and cognitive disturbance characteristics (e.g., attentional bias) predict treatment response (Amir et al., 2011). This study consisted of 112 patients with SAD, randomized to the active retraining condition ($n = 55$) or the placebo control condition ($n = 57$). Results indicated that ethnicity predicted response across both groups, with patients identifying as non-Caucasian displaying better treatment response, as measured by change in LSAS scores, than those identifying as Caucasian ($t(96) = 4.20$, $p < .001$, 2.86 ± 0.68). Additionally, results showed that level of attentional bias at pretreatment was predictive of treatment response (i.e., LSAS change), with greater attentional bias at baseline

predicting greater treatment response ($t(90) = -3.06$, $p = .003$, -0.07 ± 0.02). Results showed no other variables as predictive of treatment outcome. Overall, these results suggest that there may exist a subset of patients for which attention retraining interventions may be most beneficial. In the current study, the *N* was too small to examine ethnicity, but other potential predictors were examined. Current study findings showed that level of attentional bias at baseline did not predict treatment response (i.e., LSAS change); however, pre-treatment LSAS score, as well as change in attentional bias, were predictive of treatment response.

Neural Activation

Differences between SAD group and Healthy Control group at pre and post treatment. Results of the current study revealed significant group differences at pre-treatment between the SAD patients and Healthy Controls in the OFC and ACC. As noted earlier (see Introduction), the PFC plays a crucial role in threat detection and is thought to modulate initial vigilance signals generated by the amygdala. In the current study, the SAD patients show *less* activation in the OFC and ACC compared to the Healthy Controls at pre-treatment, suggesting that the SAD patients may not be engaging higher level cortical regions as readily as the Healthy Controls. This finding is consistent with other fMRI studies in anxious populations showing such deficiencies (Monk et al., 2006; Monk et al., 2008; Price et al., 2011).

Results of the current study revealed that at post-treatment there were no longer significant differences in BOLD activations in the OFC and ACC between the SAD group and the Healthy Control group. This finding suggests that at post-treatment, the

levels of activation in the SAD group had normalized and that the SAD group was more readily able to recruit higher order cognitive processes/regions. However, neither change in LSAS nor change in attentional bias was correlated with change in activation in this ROI for the SAD group.

The differences in activation in the OFC and ACC seen between the SAD patients and healthy controls were observed only during experimental conditions of the dot probe task that involved happy face stimuli (i.e., Happy Invalid > Happy Valid; Happy Invalid > Happy Cue Only). This finding is contrary to study hypotheses that predicted more pronounced group differences during trials involving angry face stimuli (conveying disapproval and likely evoking a fear response and negative cognitions) as compared to happy or neutral face stimuli. Past fMRI studies in SAD samples have shown that stimuli of different emotional valences (e.g., happy, angry) elicit greater neural responses in SAD patients as compared to Healthy Controls (e.g., Straube et a., 2005). It is possible that SAD patients may process positive stimuli (i.e., happy faces) as safety signals. Or perhaps they may process them as construing ridicule or as an invitation for later rejection. SAD is characterized by a fear of embarrassment, and both criticism and praise have been shown to result in embarrassment. Campbell and colleagues (2009) conducted a study in which SAD patients rated happy faces as less approachable than Healthy Controls. Results also indicated that among the SAD group, symptom severity was negatively correlated with rated approachability. The SAD patients included in the current study had generalized SAD at a severe level (LSAS $\geq$ 60), and it is possible that happy faces may have been construed as negative or threatening. Unfortunately, this

cannot be tested as information regarding approachability and likeability of the face stimuli was not obtained.

There were no differences in amygdala activation between the SAD group and the Healthy Control group in the current study as hypothesized. Other neuroimaging studies have found similar results, with pronounced differences in PFC activity between anxious populations and Healthy Controls without accompanying differences in amygdalar activity (e.g., Monk et al., 2006). Although differences in amygdala activation between the SAD patient group and healthy control group were frequently reported in early neuroimaging studies of SAD populations, it has become increasingly common in recent years that studies do not find such differences (e.g., Doehrmann et al., 2013; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). A recent study by Ziv and colleagues (2013) highlights the fact that abnormalities in amygdala response (and the limbic system more generally) among patients with SAD may not define the disorder as originally thought. In this study, 67 SAD patients and 28 matched healthy controls participated in fMRI tasks in which they viewed harsh faces, social criticism (delivered by actors via videotape), and negative self-beliefs. Results indicated no differences in levels of activation between the SAD group and the Healthy Control group in the amygdala or insula. Additionally, despite no differences in neural response, the SAD group reported heightened negative emotion as compared to the control group. The authors concluded that this difference in emotional response between the two groups was likely driven by dysfunction in higher cognitive processes. The results from this study are consistent with

the current study's findings of dysfunctional activity in the PFC with no accompanying abnormalities in limbic activity.

One methodological reason behind the current study's amygdala findings may pertain to the design of the fMRI dot probe paradigm used. Most studies that found differences in amygdala activation between SAD populations and healthy controls employed fMRI paradigms in block designs (e.g., Phan et al., 2006; Shah et al., 2008). Block designs present stimuli in sets; for example, a series of 10 fearful faces will be presented in succession, following by the a series of 10 neutral faces presented in succession. Since BOLD has delayed temporal resolution, block designs increase power and are thought to be more sensitive to the detection of functional activation compared to event-related designs, which present stimuli in random/varied order (Liu & Frank, 2004). The current study employed an event-related design because a block design was not appropriate given the nature of the dot-probe task. It is important to note, however, that some studies showing no differences in amygdala activation between SAD patients and healthy controls have used block designs. Furthermore, in the Freitas-Ferrari et al. (2010) meta-analysis, results showed that studies employing event-related designs showed similar areas and patterns of activation as those employing block designs. Therefore, although possible, it is unlikely that the design used in the current study could fully explain the fact that no between-group differences in amygdala activation were found.

Brain Activation and SAD Symptom Change. The finding that BOLD activation in the precuneus and PCC at pre-treatment was significantly correlated with LSAS symptom change scores was not expected in the current study, but is consistent

with previous work suggesting that these brain regions may play a role in SAD pathophysiology (e.g., Gentili, 2009; Goldin, Ziv, Jazaiere, & Gross, 2012; Pannekoek et al., 2013; Warwick, 2008). The precuneus is a brain region located in the posterior region of the medial parietal cortex and is thought to be involved in higher order cognitive functions such as self-processing, experience of agency, first-person perspective taking, episodic memory retrieval, and visuo-spatial imagery (Cavanna & Trimble, 2006). Given that SAD is characterized by excessive self-scrutiny, self-consciousness, and fear of negative judgments by others, it is not surprising that aberrant BOLD signals in this brain area have appeared in other fMRI studies of SAD populations and were positively correlated with symptom change in the current study. Only fMRI contrasts in the current study involving the presentation of angry faces resulted in a significant correlation of symptom change (i.e., LSAS change) with precuneus activation at pre-treatment. This is consistent with study expectations that angry face stimuli would result in higher levels of BOLD activation for the SAD patients as compared to healthy controls.

Numerous neuroimaging studies of SAD patients have shown BOLD activation in the precuneus in response to self-referential verbal stimuli (Blair et al., 2008), and faces versus nonsense pictures (Gentili et al., 2009). More recently, treatment studies in SAD samples have shown that BOLD signal levels in the precuneus decrease following treatment. For example, a recent study examining the effect of mindfulness-based stress reduction on patients with SAD showed a decrease in precuneus activation during a self-referential encoding task from pre- to post-treatment (Goldin et al., 2012). Precuneus

deactivation has also been shown in SAD patients following a course of paroxetine treatment (Schneier, Pomplun, Sy, & Hirsch, 2011).

It is important to note that in the current study, the correlation between pre-treatment LSAS scores and symptom change (as measured by LSAS change scores; r = .593, p > .001, N = 31) was slightly greater than the correlation between activation in the precuneus and symptom change (r = .555, p = .001, N = 31). Although using neural activation as a treatment prediction tool may be useful in the future, it is premature based of the results of the current study to conclude that levels of activation in precuneus should be used in this way.

Current Study Limitations

Ideally, the current study would have included a waitlist control condition. The effects of time alone on attentional bias and symptom change are unknown in the current study. By employing a waitlist control group, it would have been possible to see whether the active and placebo control groups outperformed the waitlist control condition in terms of symptom reduction and thereby prove that time alone was not a contributing factor. It also would also have been interesting to include a non-socially anxious clinical comparison group (e.g., patients with obsessive-compulsive disorder) in order to help clarify disorder specificity. Unlike other fMRI studies that excluded SAD patients with comorbidities (e.g., Shah et al., 2009; Phan et al., 2006), the current study included such patients as long as they had a primary diagnosis of generalized SAD. Unfortunately, resource limitations precluded the use of a waitlist control group or clinical control group for the purposes of this study.

The current study included a small number of participants with SAD. This small sample size of participants in the active (n = 16) and control (n = 16) conditions may have contributed to the failure to find between group differences in the attention retraining intervention. The sample size for the current study was chosen based upon power curves generated by Desmond and Glover (2002), estimating minimal sample size for fMRI studies. With percent signal changes at approximately 0.05% and spatial smoothing at full-width half-maximum of 5mm, it is recommended that a minimum of 12 subjects be included to ensure 80% power at a $\alpha = 0.05$ level. This sample size was also deemed appropriate to account for occasional malfunctioning of fMRI recording systems, and noisy or unreliable data. Therefore, the sample size was chosen specifically for the fMRI portion of the study and not to optimize power for the attention retraining intervention. It is important to note, however, that all recent studies reporting null findings (Boettcher et al., 2012; Carlbring et al, 2012; Julian et al., 2012; Neubauer et al., 2013) included large samples (N = 68, 79, 112, and 56, respectively). Therefore, it is possible, but unlikely, that with a larger sample the between group attention retraining results of the current study would have changed.

Finally, as mentioned earlier, a methodological limitation is the lack of formal assessment of expectancy of change. Ideally, the current study would have measured this at the outset of the study, as it is possible that the patients who anticipated improving the most were the ones who showed the greatest symptom reductions. To better tease apart the role of expectancy effects in attention retraining interventions, future studies could assess and manipulate expectancy effects. This could be achieved by varying the

instructions across patients; for example, half the sample might be told they may receive a treatment for SAD (as in the current study), while the other half might be told they may receive an intervention completely unrelated to SAD (e.g., to increase visual acuity).

Future Directions

The current study proposed that a computerized attention retraining intervention would result in reduced attentional bias and SAD symptomatology among patients diagnosed with generalized SAD. The lack of support for the beneficial role of attention retraining in this study warrants further investigation. Future studies employing larger samples of SAD patients and multiple training sessions are needed. Future research should consider what aspects of the stimuli and their presentation have been shown to lead to the greatest change (e.g., words vs. pictures), and employ what has been shown to be most efficacious. Studies directly examining and comparing specific parameters also need to be conducted, as do studies examining the effects of various types of placebo control conditions. For example, in addition to examining control conditions with neutral-neutral face pairs, studies should examine the effects of geometric shapes and other inanimate objects (Eldar et al., 2012).

Given the results of the current study, that changes in attentional bias are highly and significantly correlated with reductions in SAD symptoms, it is important to further explore this relationship. One way to achieve this would be to examine the influence of empirically supported treatments for SAD (e.g., CBT) on changes in attentional bias by measuring attentional bias pre- and post-intervention. Attention to threat is an explicit target of CBT, as cognitive biases are directly challenged through cognitive restructuring

and the implementation of in vivo exposures. Therefore, it would be interesting to examine whether patients who respond to CBT also experience a decrease in attentional bias towards social threat. Also, if future studies show that attention retraining is indeed an efficacious treatment for SAD, it may offer an additional tool to augment CBT treatments. Although some studies have already examined the effect of adding attention retraining to CBT and did not show added benefit (e.g., McEvoy & Perini, 2009), more research is necessary.

Attentional bias interventions have many advantages over conventional psychotherapeutic approaches, as they are easy to administer, cost-effective, and minimize patient burden (e.g., side effects, negative emotional experiences). Also, given their administration over the computer and Internet, they have the potential for wide-reaching and rapid dissemination. However, despite these advantages, it appears premature to employ attention retraining as a standard treatment. The current study contributes to the evidence base for attention retraining as a novel treatment for SAD and highlights the necessity of replication studies. Future studies are necessary to establish a firm empirical basis for the efficacy of attention retraining in SAD populations.

More research is also necessary investigating the neurobiology of SAD. Research to date has led to a deeper understanding of the disorder, and in the future neuroimaging will hopefully lead to more effective treatments. Ideally, in the future fMRI imaging may show neuromarkers for treatment response in SAD as well as aid in choosing the most effective treatment (e.g., CBT, psychotropic medication) given certain neural disruptions. More research is needed, however, before patients exhibiting certain patterns of neural

activation can be matched to specific interventions in an individualized medicine approach.

Table 1. SAD Participant Demographic and Clinical Characteristics at Baseline.

Characteristic	Overall Sample	Active Retraining Group	Placebo Control Group
Gender (M/F)	17/15	8/8	9/7
N	32	16	16
Age	26.7 (9.6) [range 18-59]	26.9 (9.8)	26.8 (10.4)
Age of onset	12.4 (4.6)	11.7 (5.1)	13.1 (4.0)
Patients with comorbid anxiety disorder	9	5	4
Patients with comorbid mood disorder	8	5	3
Patients taking psychotropic medication	8	5	3
Anxiety Measures:			
LSAS total	76.25 (16.24)	73.38 (14.02)	79.13 (18.19)
SPIN	43.31 (8.52)	44.63 (8.32)	42.0 (8.79)
STAI – T	53.75 (10.19)	54.63 (8.67)	52.87 (11.73)
STAI – S	46.41 (12.68)	45.94 (14.74)	46.87 (10.71)
Depression Measures:			
BDI-II	15.25 (11.33)	17.0 (12.19)	13.50 (10.49)
MADRS	6.31 (5.08)	6.63 (5.33)	6.00 (4.98)
Qualilty of life measure:			
LIFE-RIFT	9.87 (1.48)	10.06 (1.48)	9.69 (1.49)
ACQ	31.50 (10.32)	30.69 (10.03)	32.31 (10.87)
ASQ	54.03 (11.61)	54.69 (12.57)	53.38 (10.94)

Table shows means (standard deviations).

Note. ACQ = Anxiety Control Questionnaire (Rapee, Craske, Brown, & Barlow, 1996); ASQ = Affective Style Questionnaire (Hofmann & Kashdan, 2010); BDI-II = Beck Depression Inventory II (Beck, Steer, & Brown, 1996); LIFE-RIFT = Range of Impaired Functioning Tool (Leon et al., 1999); LSAS = Liebowitz Social Anxiety Scale (Liebowitz, 1987); MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); SPIN = Social Phobia Inventory (Connor et al., 2000); STAI-S = State-Trait Anxiety Inventory, state version (Spielberger, 1983); STAI-T = State-Trait Anxiety Inventory, trait version (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Table 2. Means and Standard Deviations of Social Anxiety and Depression Measures at Pre and Post Intervention.

Measure	Active Training Group (n = 15)		Placebo Control Group (n = 16)	
	Pre-assessment	Post-assessment	Pre-assessment	Post-assessment
Social Anxiety Measures				
LSAS	72.80 (14.32)	61.87 (13.54)	78.13 (18.38)	62.80 (11.92)
SPIN	41.87 (9.08)	38.2 (7.18)	44.33 (8.52)	39.47 (7.41)
Depression Measures				
BDI-II	15.80 (11.60)	10.27 (10.15)	12.00 (8.91)	10.33 (8.02)
MADRS	6.47 (5.48)	4.87 (4.72)	5.13 (3.70)	4.00 (3.317)

Table shows means (standard deviations).

Note. BDI-II = Beck Depression Inventory II (Beck, Steer, & Brown, 1996); LSAS = Liebowitz Social Anxiety Scale (Liebowitz, 1987); MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); SPIN = Social Phobia Inventory (Connor et al., 2000).

Figure 1. Attention Retraining Task. Figure depicts a Valid Threat trial (i.e., the probe replaces the disgust face).

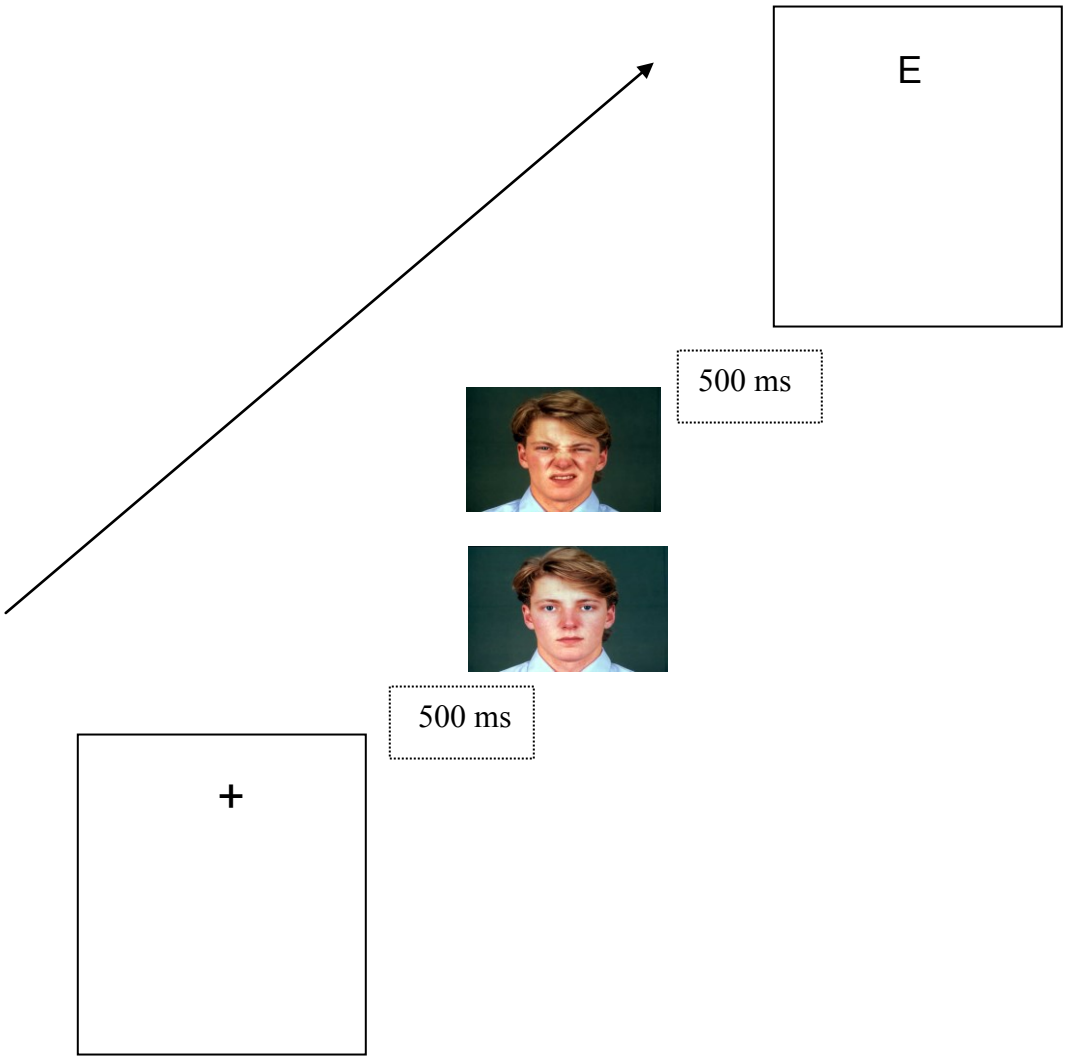


Figure 2. Modified Dot Probe Task.

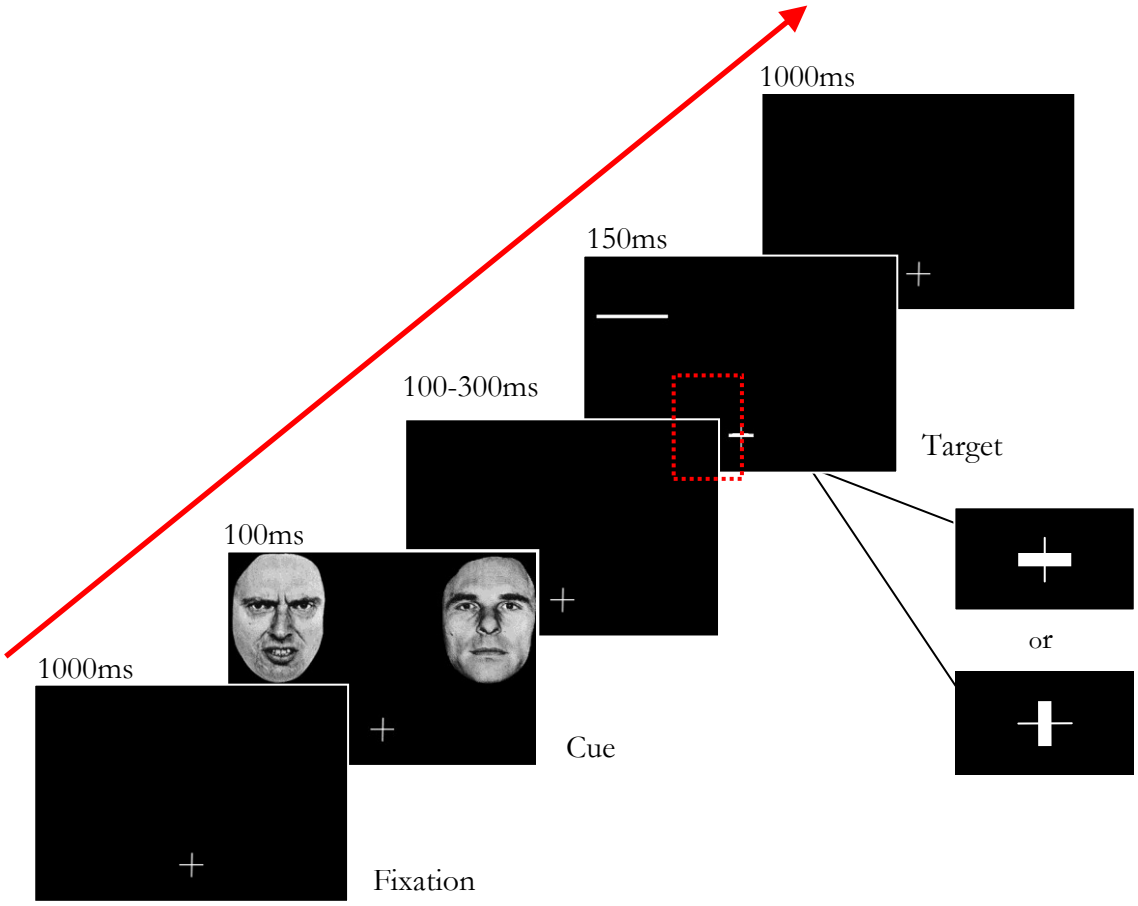


Figure 3. Comparison of Group Changes in LSAS Scores Across Training Sessions. Standard Errors are shown.

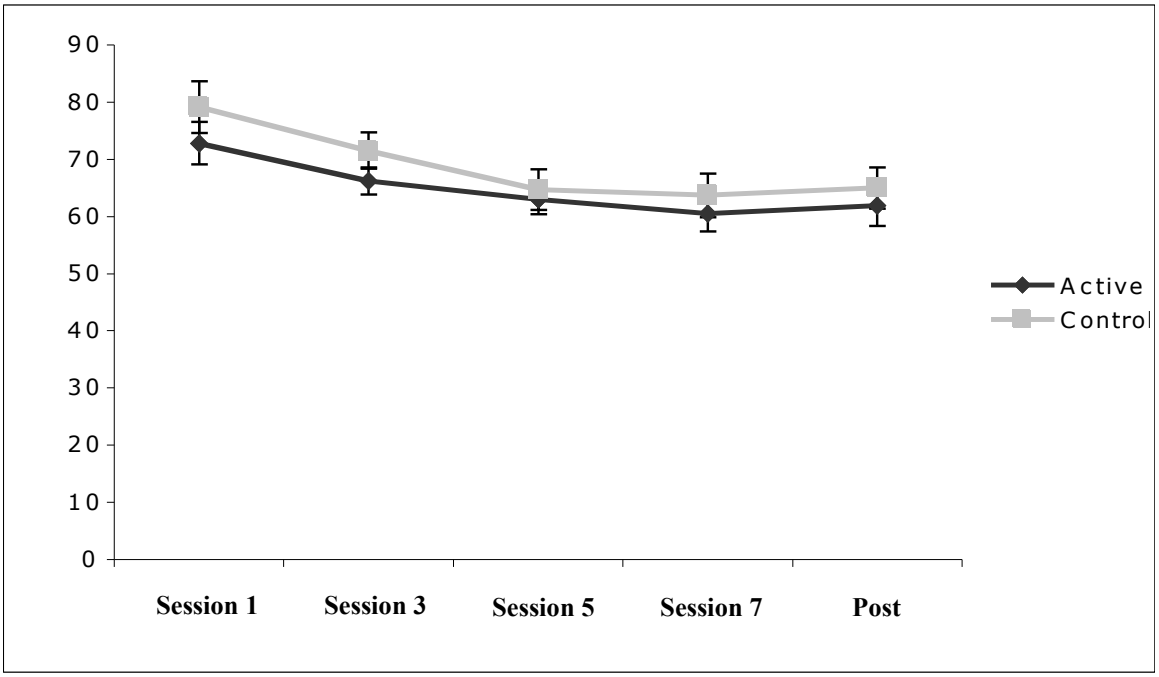


Figure 4. Comparison of Group Changes in BDI-II Scores Across Training Sessions. Standard Errors are shown.

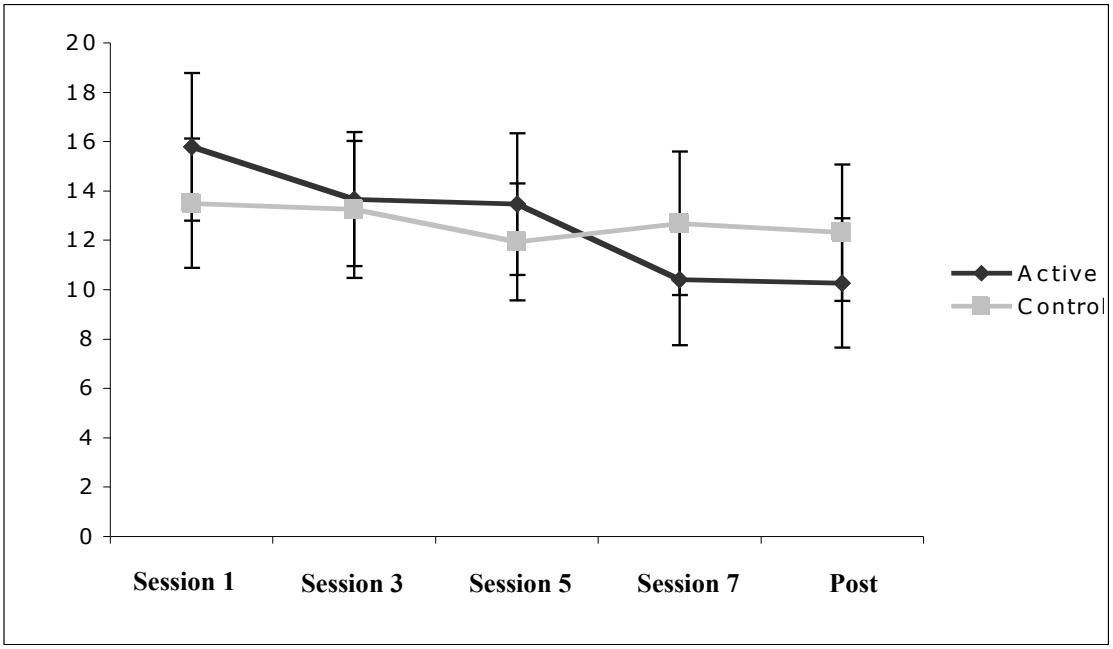


Figure 5. Cortical representation of hypo-activation in the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) at pre-treatment for the SAD group compared to the Healthy Control group. Happy Invalid > Happy Valid contrast is depicted.

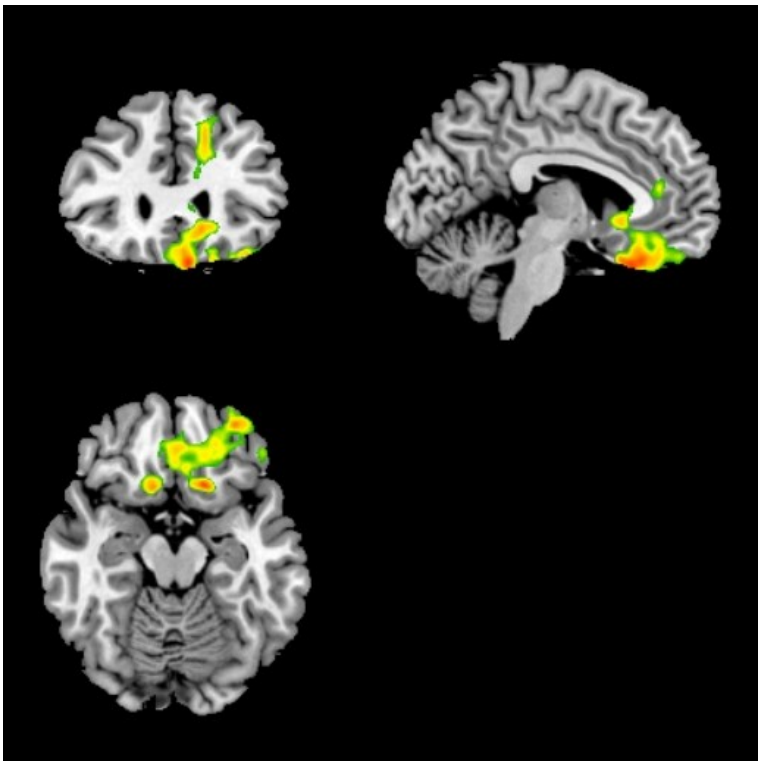


Figure 6. Change in activation in the OFC/ACC from pre- to post-treatment for the SAD group compared to the Healthy Control group. At pre-intervention, SAD patients showed significantly less activation in the OFC/ACC compared to healthy controls. At post-intervention, the SAD group beta values were no longer significantly different than the healthy control group. The Y-axis shows level of brain activation in beta values. Standard Errors are shown.

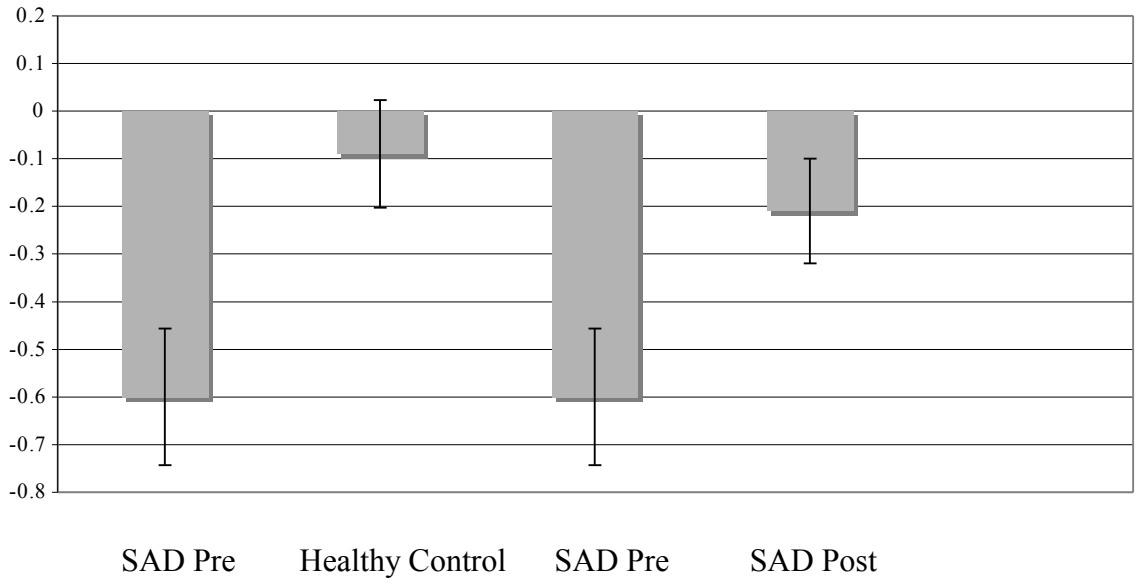
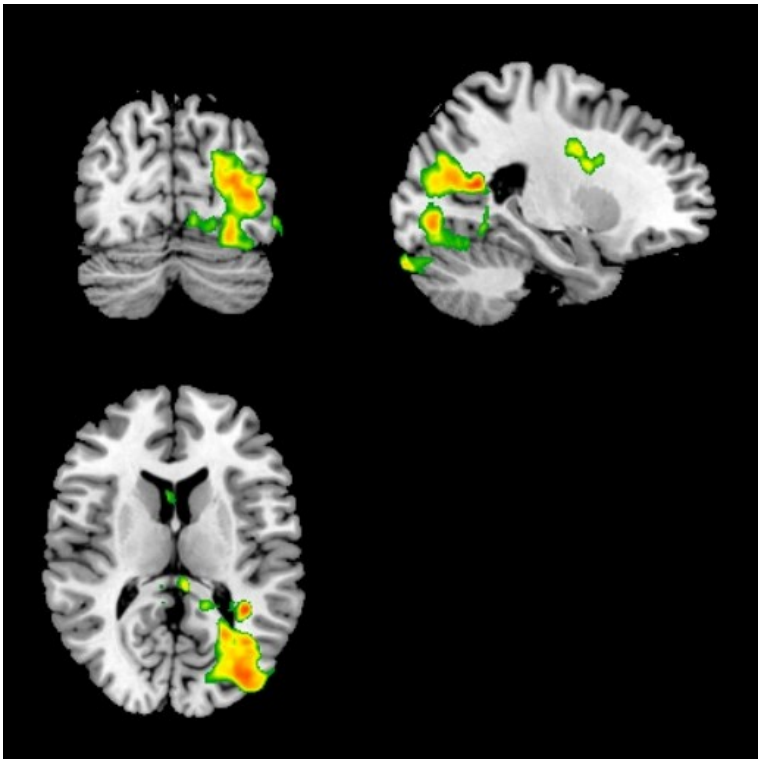


Figure 7. Cortical representation of areas of activation in the posterior cingulate cortex (PCC) and precuneus at pre-treatment that were significantly correlated with LSAS change scores. Only contrasts including angry faces resulted in this correlation.



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