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Neural Bases of Social Anxiety Disorder: Emotional Reactivity and Cognitive Regulation During Social and Physical Threat

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Abstract

Context—Social anxiety disorder is thought to involve emotional hyper-reactivity, cognitive distortions, and ineffective emotion regulation. While the neural bases of emotional reactivity to social stimuli have been described, the neural bases of emotional reactivity and cognitive regulation during social and physical threat, and their relationship to social anxiety symptom severity, have yet to be investigated.

Objective—This study investigated behavioral and neural correlates of emotional reactivity and cognitive regulation in patients and controls during processing of social and physical threat stimuli.

Design—Participants were trained to implement cognitive-linguistic regulation of emotional reactivity induced by social (harsh facial expressions) and physical (violent scenes) threat while undergoing functional magnetic resonance imaging and providing behavioral ratings of negative emotion experience.

Setting—Academic psychology department.

Participants—15 adults with social anxiety disorder and 17 demographically-matched healthy controls.

Main Outcome Measures—Blood oxygen level dependent signal and negative emotion ratings.

Results—Behaviorally, patients reported greater negative emotion than controls during social and physical threat, but showed equivalent reduction in negative emotion following cognitive regulation. Neurally, viewing social threat resulted in greater emotion-related neural responses in patients than controls, with social anxiety symptom severity related to activity in a network of emotion and attention processing regions in patients only. Viewing physical threat produced no between-group differences. Regulation during social threat resulted in greater cognitive and attention regulation-related brain activation in controls compared to patients. Regulation during

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physical threat produced greater cognitive control-related response (i.e., right DLPFC) in patients compared to controls.

Conclusions—Compared to controls, patients demonstrated exaggerated negative emotion reactivity and reduced cognitive regulation related neural activation, specifically for social threat stimuli. These findings help to elucidate potential neural mechanisms of emotion regulation that might serve as biomarkers for interventions for social anxiety disorder.

Anxiety disorders are the most common psychiatric condition (with a lifetime prevalence of 28.8%[1]). Social anxiety disorder (SAD) is the most common subtype[2] with 7–13.3% lifetime prevalence[3]. SAD is characterized by heightened anxiety and avoidance during social interactions. It has an early onset (80% of cases occur before age 18[4]), and usually precedes other anxiety, mood, and substance abuse/dependence disorders[5–7]. SAD is associated with significant distress and functional impairment in work and social domains, and typically persists unless treated[8–12].

Emotional Reactivity and Regulation in SAD

Models of SAD[13,10,14] have highlighted the role of emotional hyper-reactivity, which is thought to arise from distorted appraisals of social situations. These maladaptive appraisals transform innocuous social cues into interpersonal threats, leading to inaccurate interpretations of self (e.g., as socially incompetent) and others (e.g., as critical judges). This induces a cascade of safety behaviors, somatic concerns, and negative emotional reactivity.

Another key feature of SAD is thought to be a failure of emotion regulation[15, 16]. Effective emotion regulation can reduce emotional reactions to stressful, anxiety-provoking situations[17–19]. Conversely, difficulties with emotion regulation have been postulated as a core mechanism underlying mood and anxiety disorders[20], and accordingly, many clinical treatments focus on enhancing use of emotion regulation to modulate emotional reactivity.

It is important to distinguish among various factors that might influence effective emotion regulation. For example, individuals with SAD may have problems with emotion regulation due to (a) exaggerated emotional reactivity to all types of potential threat stimuli, (b) a general deficit in down-regulating emotional reactivity, or (c) reactivity and regulation abnormalities that are specific to social threat stimuli only. One way to examine emotion regulation in SAD is to probe regulation skills in the context of reactivity to different types of threat stimuli. Thus, in addition to social threat, we also included physical threat as a comparison condition to investigate the specificity of emotional reactivity and emotion regulation abilities in SAD.

Neuroanatomical Model of Emotional Reactivity and Regulation in SAD

Numerous functional neuroimaging investigations of both healthy and clinical populations have contributed to an emerging neuroanatomical model of emotional reactivity and regulation[21–24]. In this limbic-cortical model, the ventral emotion system (i.e., limbic and paralimbic areas) detects personally relevant and affectively salient stimuli. A neural signal encoding potential threat is communicated to the rostral ACC which functions to monitor emotionally salient stimuli and trigger various cognitive regulatory processes[25] in the dorsal

medial and lateral prefrontal cortex (PFC)[21] that select, implement and monitor cognitive control strategies. While there is ample evidence for the neural bases of emotional reactivity, no published neuroimaging studies have directly investigated cognitive-linguistic regulation in SAD.

Effective communication between the dorsal regulatory system and ventral emotion system constitutes a finely balanced functional brain network that uses feedback mechanisms from the PFC to limbic regions to modulate the trajectory of an emotional response. When functioning successfully, this network confers psychological resilience, flexibility, and well-being. When not functioning optimally, the limbic-cortical network may produce acute responses that influence ongoing emotion experience, autonomic psychophysiology, cognition, and subsequent emotions.

Recent work has begun to elucidate the neural bases of emotional reactivity. This work has revealed a network of ventral emotion detection/generation-related limbic regions, including the amygdala, insula, and anterior cingulate cortex (ACC). Diverse PFC regions also have been implicated in specific dimensions of emotion processing, including valence (ventromedial and dorsomedial PFC), intensity (ventrolateral and dorsomedial PFC), and recognition (perigenual ACC)[26] as well as how task instruction (e.g., passive viewing versus judgment/rating) influence neural response to emotionally-evocative stimuli[27].

One common stimulus used to probe emotional reactivity in SAD is harsh facial expressions displaying, for example, anger and contempt. Such expressions can serve as a potent signal communicating social disapproval for individuals with SAD. Viewing harsh faces has been shown to reliably activate negative emotions and amygdala response in adults[28–30] and adolescents[31, 32] with SAD, with greater SAD symptom severity predicting stronger amygdala response[33, 34]. Evidence also suggests abnormal neural response in regions interconnected with the amygdala in SAD, including increased activity in insular cortex in response to angry faces[30, 35], in ACC in response to disgust faces[36], and in parahippocampal gyrus, left ventrolateral and medial PFC in response to harsh faces[28].

Other types of social threat stimuli also have been used to probe emotional reactivity in SAD. Anticipation and delivery of a speech have been shown to robustly activate fear processing in the amygdala[37] in adults with SAD[38, 39]. In fact, SAD patients who responded to either group cognitive-behavioral therapy or SSRI treatment demonstrated significant reduction from pre- to post-treatment in amygdala response during a speech task.[39] Additionally, post-treatment amygdala signal reduction during a speech task significantly predicted reduced social anxiety symptoms at one-year follow-up.

Despite advances in understanding emotional reactivity in SAD, the neuroanatomical model for emotion regulation has yet to be tested in SAD. Understanding PFC cognitive regulatory system recruitment in SAD during social threat may elucidate a functional neural profile that clarifies etiological and maintaining factors in SAD.

The Present Study

The goal of the present study was to extend our current understanding of the neural bases of SAD by probing emotional reactivity and regulation in adults with SAD compared to demographically-matched non-psychiatric healthy controls (HC). Previous fMRI studies in HC have found greater neural responses to violent scenes.[40] We included violent scenes (i.e., physical threat) as a comparison condition for harsh faces, in order to investigate differential emotion regulation for social (SAD-related) and physical (SAD-unrelated) threat. We expected to find (1) no difference in SAD and HC for emotional reactivity and regulation for physical threat, (2) greater reactivity to harsh faces in SAD than HC, and (3) deficits in regulation in SAD versus HC for social threat stimuli.

Methods

Participants

Participants were 15 (9 females) right-handed adults who met DSM-IV[41] criteria for current SAD and 17 (9 females) demographically-matched, right-handed healthy controls (HC) with no lifetime history of any DSM-IV psychiatric disorders. SAD and HC did not differ significantly in gender, age, education or ethnicity (Table 1). All participants provided informed consent in accordance with Stanford University's Human Subjects Committee guidelines.

Exclusion Criteria

All participants passed a MRI safety screen. Participants were excluded if they reported current use of any psychotropic medication, history of neurological or cardiovascular disorders, diabetes, hypo- or hyperthyroidism, or head trauma with loss of consciousness greater than five minutes. Both healthy and SAD participants were excluded if they had a lifetime diagnosis of a psychotic disorder, mania, hypomania, bipolar disorder, or substance/alcohol abuse. Due to potential effects on blood flow, participants were asked not to consume alcohol, recreational drugs, or pain killers during the 24-hour period before their MR scan and not to ingest caffeine at least five hours prior to the scan. Daily cigarette users were excluded from the study. SAD participants were excluded if they met criteria for any current DSM-IV Axis I psychiatric disorders other than social anxiety, generalized anxiety, agoraphobia, or specific phobia disorders.

Clinical Assessment

Clinical diagnostic assessments were conducted by a PhD-trained clinical psychologist using the Anxiety Disorder Inventory Schedule–IV (ADIS-IV[42]) to diagnose current and lifetime psychiatric disorders. This structured clinical interview is based on the DSM-IV, but has been extended to be more sensitive in differential diagnosis of anxiety disorders. Only SAD participants with a primary diagnosis of SAD or HC participants with no history of DSM-IV disorders were invited to participate.

As shown in Table 1, compared to HC, SAD reported greater social anxiety (Liebowitz Social Anxiety Scale, LSAS[43]), fear of negative evaluation (Brief Fear of Negative

Evaluation, BFNE[44]), depressive symptoms (Beck Depression Inventory-II, BDI-II[45]), state anxiety (Speilberger State-Trait Anxiety Inventory, STAI[46]), and negative affect (Positive and Negative Affect Schedule, PANAS[47]).

Procedure

Before scanning, participants were trained in accordance with methods developed by Gross and Ochsner[48, 49], and practiced with two stimuli (not used in the scanning experiment) per neutral, social and physical condition (a) to "just look" without trying to control or modulate their emotional reactivity, and (b) to "regulate" by actively thinking in a way that modifies the interpretation of the stimulus and thus reduces negative reactions. Specifically, they were instructed to re-interpret the content of the picture using cognitive-linguistic strategies including "This does not involve me," "This does not influence me," or "This does not impact me" for harsh faces, and "The person will be okay," "The person was not really hurt," and so forth for the violent scenes.

During MR scanning, stimuli were projected to a screen inside the head-coil that was placed six inches from the participant's eyes. Participants provided a negative emotion rating after each trial: "How negative do you feel?" (1=not at all, 2=slightly, 3=moderately, and 4=very much). Behavioral responses were made using a custom button box and recorded using Eprime software.

Experimental Task

The task consisted of 125 trials across three 9-minute functional runs (42, 42 and 41 trials, respectively) that were randomly ordered across participants. Within each run, stimuli were presented in a pseudo-randomized sequence (no more than two instances of the same condition in a row). There were 25 trials for each of five conditions: Look Harsh Face, Regulate Harsh Face, Look Violent Scene, Regulate Violent Scene, and Look Neutral Scene. Each 12s trial consisted of an instruction (Look or Regulate) (3s), stimulus (6s), and emotion rating (3s).

Stimuli

Prior fMRI studies have shown that direct-facing angry and contemptuous facial expressions produce strong neural responses in SAD[28, 33]. We thus trained actors to produce harsh expressions that combined angry and contempt facial expressions according to the Facial Action Coding System (FACS)[50]. Stimuli consisted of color photographs showing the actor's head against a black background. Two independent raters trained in FACS coded each face stimulus for the presence of action units associated with anger (action unit 4, drawing together of the eyebrows, and action unit 7, tightening of both upper and lower eyelids) and contempt (unilateral action unit 14, dimple-smirk with no teeth bared). Face stimuli for which both raters fully agreed on facial action units were used in the study. The final face stimulus set consisted of 25 male and 25 female unique actors with 70% Anglo-American, 10% Asian-American, 10% Latin-American, and 10% African-American actors, which were equally distributed across Look and Regulate Harsh Face conditions.

Physical threat scenes, especially those displaying violence, have been shown to capture attention and produce robust neural activation in HC[40]. Thus, physical threat stimuli consisted of color photos of a person being violently attacked (e.g., punched, clubbed, stabbed, burnt, shot) by one or more aggressors. These high arousal, visually complex stimuli were collected from internet sites.

Neutral scenes, used as the baseline comparison for both social and physical threat, consisted of non-arousing, non-social color photos of mundane scenes (e.g., pavement, garage door, wood siding). Neutral facial expressions were not used as a contrast to harsh faces because of evidence that individuals with SAD interpret neutral face stimuli more negatively then do HC[28, 51]. Examples of the three stimulus types are shown in Figure 1.

Image Acquisition

Imaging was performed on a GE 3-Tesla Signa magnet with a T2*-weighted gradient echo spiral-in/out pulse sequence[52] and a custom-built quadrature "dome" elliptical bird cage head-coil. Head movement was minimized using a bite-bar and foam padding. Across three functional runs, 1,114 functional volumes were obtained from 22 sequential axial slices [TR=1500 ms, TE=30 ms, flip angle=60 degrees, FOV=22 cm, matrix=64×64, single-shot, resolution=3.438 mm^2 × 5 mm]. 3D high-resolution anatomical scans were acquired using fast spin-echo SPGR (.8594^2 × 1.5 mm; FOV=22 cm, frequency encoding=256).

fMRI Data Preprocessing

Each functional run was subjected to preprocessing steps using AFNI[53] software: co-registration, motion correction, 4 mm^3 isotropic Gaussian spatial-smoothing, high-pass filtering (.011 Hz), and linear detrending. No volumes demonstrated motion in the x, y, or z directions in excess of ±0.5 mm. There was no evidence of stimulus-correlated motion, as assessed by correlations between condition-specific reference functions and x, y, z motion correction parameters (all *p*s>.5).

fMRI Statistical Analysis

A multiple-regression model implemented with AFNI 3dDeconvolve included baseline parameters to remove mean, linear and quadratic trends, and motion-related variance. BOLD responses during the 6s when looking or regulating were investigated using regressors (convolved with the gamma variate model[54] of the hemodynamic response function) for each of the five conditions (Look Neutral Scene, Look Harsh Face, Look Violent Scene, Regulate Harsh Face, Regulate Violent Scene). fMRI BOLD signal intensity was represented as percent signal change ((MR signal per voxel per time point / mean MR signal in that voxel for the entire functional run) × 100). The differential BOLD signal between target and comparison conditions (e.g., Regulate versus Look Harsh Face) is reported as BOLD percent signal change, an effect size measure.

Individual brain maps were converted to Talairach atlas space[55] and second-level group statistical parametric maps were produced according to a random-effects model. To correct for multiple comparisons, AlphaSim, a Monte Carlo simulation bootstrapping program in the AFNI library, was employed to protect against false positives[56]. This method uses a

voxel-wise and cluster volume joint-probability threshold to establish a cluster-wise false positive cluster detection level. For all contrasts, a threshold consisting of a voxel-wise $p<0.005$ and cluster volume >162 mm^3 (4 voxels × 3.438 mm^3) protected against false positive cluster detection at $p<0.01$.

Results

We examined the effects of emotional reactivity and cognitive regulation on both negative emotion ratings and fMRI BOLD signal during social (harsh face) and physical (violent scene) threat. Additionally, we investigated the relationship of social anxiety symptom severity with neural and behavioral indices of emotional reactivity and regulation.

Emotional Reactivity

Behavioral responses—A 2 (Group: SAD, HC) × 3 (Condition: Look Neutral Scene, Look Harsh Face, Look Violent Scene) repeated-measures ANOVA of negative emotion ratings resulted in no interaction of Group × Condition, $p>.42$. There were main effects of group, SAD>HC, $F(2,30)=7.32$, $p<.05$, eta^2 (η^2) =.20, and of condition, $F(2,30)=229.78$, $p<.001$, $\eta^2=.88$, with Violent Scene>Harsh Face>Neutral Scene ($p<.001$ for each comparison) as shown in Figure 2.

Neural responses—For social threat, a between-group t-test for the Look Harsh Face versus Neutral Scene contrast resulted in significantly greater BOLD responses in SAD versus HC in brain regions implicated in emotion (medial OFC, subgenual ACC, bilateral parahippocampal gyrus), ventral/dorsal visual processing (lingual and inferior occipital gyrus, superior and middle occipital gyrus, cuneus, superior parietal lobule), face-selective processing (lateral occipital cortex (LOC), but not fusiform face area (FFA)), and sensory processing (postcentral gyrus) (Table 2, Figure 3). Compared to SAD, HC had greater BOLD signal in regions implicated in attention processing (medial precuneus, left inferior parietal lobule and right supramarginal gyrus). Both groups had bilateral dorsal/extended amygdala and face-selective LOC responses for the contrast of Look Harsh Face versus Neutral Scene (Supplemental Table 1, 2). However, only SAD produced evidence of FFA responses. For physical threat, a between-group t-test for the Look Violent versus Neutral Scene found no between-group differences. Both groups had left dorsal/extended amygdala, bilateral FFA and LOC responses for the contrast of Look Violent versus Neutral Scene (Supplemental Table 3, 4).

Emotion Regulation

Behavioral responses—A 2 (Group: SAD and HC) × 2 (Condition: Regulate Violent Scene, Regulate Harsh Face) repeated-measures ANOVA of negative emotion ratings showed no evidence of an interaction, $p>.67$. There was a main effect of condition, Regulate Violent Scene>Regulate Harsh Face, $F(1,31)=47.19$, $p<.001$, $\eta^2=.61$, but no effect of group, $p>.10$. There were no group differences in the percent reduction in negative emotion following emotion regulation for social (HC=18.8%±17.3% vs. SAD=16.9%±19.0%, $p>.76$) or physical threat (HC=28.8%±14.8% vs. SAD=25.0%±16.3%, $p>.48$).

Neural Responses—For social threat (Table 3, Figure 4), a between-group t-test of the Regulate versus Look Harsh Face contrast showed that, compared to SAD, HC produced greater BOLD responses in brain regions implicated in cognitive control (dorsolateral PFC, dorsal ACC), visual attention (medial cuneus, posterior cingulate), attention areas (bilateral dorsal parietal), and visual feature detection (bilateral fusiform, superior temporal gyrus). No brain areas showed greater BOLD responses in SAD compared to HC. For physical threat (Table 4), a between-group t-test of the Regulate versus Look Violent Scenes contrast demonstrated that, compared to HC, SAD had greater BOLD response in right mid-dorsolateral PFC, and bilateral lentiform/caudate. Compared to SAD, HC produced greater BOLD responses for Regulate versus Look Violent Scene in a motor area of right middle frontal gyrus and left superior temporal gyrus.

Similar regions of activation for both groups during regulation of social threat included cognitive control regions (dorsomedial PFC and right superior frontal gyrus) and linguistic regions (left inferior frontal gyrus, left supramarginal gyrus, and bilateral posterior superior temporal gyrus). In SAD and HC, greater BOLD signal in dorsomedial PFC during cognitive regulation was associated with significant reduction in negative emotion ratings (Figure 5).

Emotional Reactivity, Regulation, and Social Anxiety Severity

Social anxiety severity (measured by the Liebowitz Social Anxiety Scale) was *positively* associated with BOLD signal in SAD and *inversely* with BOLD signal in HC during Look Harsh Face in left dorsal/extended amygdala, right middle occipital gyrus (Fisher's z-test *p*s<.05). When social anxiety severity was measured by the Brief Fear of Negative Evaluation, the same pattern of *positive* correlation in SAD and *inverse* correlation in HC during Look Harsh Face was observed in bilateral dorsal/extended amygdala, posterior cingulate and precuneus (Fisher's z-test *p*s<.05). There was no relationship of social anxiety symptom severity with BOLD responses (a) during looking at violent scenes, and (b) during emotion regulation.

Discussion

The goal of this study was to investigate the neural bases of emotional reactivity and cognitive regulation in adults diagnosed with SAD versus HC. Using both social and physical threat stimuli, we were able to examine the specificity of emotional reactivity and emotion regulation abnormalities in SAD. The primary finding was that, compared to demographically-matched HC, SAD demonstrated exaggerated negative emotion reactivity and reduced cognitive-linguistic regulation related neural activation specifically for social threat stimuli.

Emotional Reactivity

Behaviorally, compared to HC, SAD reported greater negative emotion experience for both social and physical threat, suggesting elevated emotional reactivity across these two types of threat stimuli. Neurally, while there was no between-group difference for physical threat, viewing social threat stimuli resulted in greater differential BOLD responses in SAD

compared to HC in emotion[21] (medial OFC, subgenual cingulate, parahippocampal gyrus), visual, face, and sensory processing brain regions. For both social and physical threat compared to neutral stimuli, both groups reported elevated negative emotion and enhanced BOLD signal in dorsal/extended amygdala, providing converging evidence for successful acute negative emotion induction. Additionally, while both groups had bilateral face-selective LOC responses for social threat, and bilateral LOC and FFA for physical threat, only SAD had FFA activation for social (harsh face) threat.

These results converge with prior findings of recognition bias and negative emotion reactivity to harsh faces in SAD[28, 33, 57–59], and neural bases of emotion processing in primates[60–62]. Medial PFC and parahippocampal activations have been observed in a previous study of reactivity to harsh faces[28] and may be related to higher-order neural representations of self-focused attention, perspective taking[63], and greater emotion intensity[26] that may be exaggerated in SAD. Insular responses to emotional face stimuli have also been observed in SAD[29] and are implicated in interoceptive processing of bodily sensations[64]. Both the FFA and LOC have subregions that are highly selective to faces and different objects[65, 66] which accounts for activation of these visual processing regions in both groups. However, elevated dorsal and ventral visual processing activations in general, and in the FFA specifically during harsh face processing in SAD versus HC confirms findings of enhanced visual processing in SAD for facial emotion stimuli[35].

Both groups produced dorsal/extended amygdala responses to harsh (i.e., mixed anger and contempt) facial expressions presented for 6s. While several prior studies of harsh facial expression have found greater amygdala response in SAD versus HC[28, 29, 33–35], the present study utilized a face displaying a mixed emotion (anger+contempt), and included longer stimulus presentation times. These stimulus parameters differentiate this study from prior studies, and may increase the likelihood that HC will, like SAD, evaluate the stimuli as threatening.

Social anxiety symptom severity was associated with significantly greater BOLD signal in response to viewing social threat (but not physical threat) in SAD versus HC in brain regions implicated in emotion (bilateral dorsal/extended amygdala)[37], visual attention (posterior cingulate cortex, and right middle occipital gyrus), and attentional control (right dorsolateral PFC)[67]. Our findings replicate previous studies that reported an association of social anxiety symptoms and amygdala response in adults[33] and adolescents[32] with SAD. Furthermore, recent neural models demonstrate that fear-related amygdala activity can directly modulate attentional process[68]. This aligns with cognitive information processing models of SAD that propose a vigilance-avoidance pattern involving automatic allocation of attention towards potential threat immediately followed by inhibition and avoidance of the threat signals[69, 70]. Accordingly, due to sensitivity to social threat cues, SAD should be associated with rapid initial orientating towards facial expressions that suggest social disapproval, and then turning attention away as an overlearned protective response.

Emotion Regulation

Behaviorally, SAD and HC reported similar reductions in negative emotion following cognitive regulation for both physical and social threat. However, because of greater initial

negative emotion for physical versus social threat, post-regulation negative emotion continued to be greater for physical versus social threat. This indicates that all participants were able to down-regulate negative emotion using cognitive-linguistic strategies, and that the physical threat scenes were emotionally more evocative than the social threat stimuli.

Neurally, during cognitive regulation both groups had neural activity in dorsomedial and dorsolateral PFC regions supporting cognitive regulation[21] (e.g., strategy selection, implementation, monitoring) and in a linguistic network including left inferior frontal, supramarginal, and posterior superior temporal regions[71]. These data are consistent with prior findings of cognitive down-regulation of emotion[17] and the neural bases of cognitive emotion regulation in non-psychiatric adults[48, 49, 72, 73]. Prior studies have also observed dissociation between self-report ratings and physiological responses during anxiety-inducing experimental tasks[74, 75]. Importantly, these findings demonstrate that, when cued in a controlled context, SAD can implement cognitive-linguistic regulation strategies.

Between-group analyses revealed that during regulation of social threat, compared to SAD, HC had a distributed pattern of neural activity implicated in cognitive regulation, attention, and visual processing. Specifically, during regulation of social threat, both compared to SAD and within-group, HC produced greater neural responses in both dorsomedial and dorsolateral PFC, suggesting an enhanced coordination of cognitive control circuitry not shown in SAD. Reciprocal modulation and attenuation in medial and lateral prefrontal cortex have previously been shown as a potential neural mechanism for emotion-cognitive interactions[76]. The differential pattern observed here in response to social threat stimuli suggests that greater emotional reactivity in SAD may be associated with enhanced medial PFC and concurrent attenuation of recruitment of dorsolateral PFC. In contrast, during regulation of physical threat, differential BOLD responses were observed in SAD in DLPFC and lentiform/caudate, and in HC in pre-motor and superior temporal cortex.

These results suggest that SAD may be less able to access and implement cognitive-linguistic emotion regulation strategies during social threat conditions, while showing relatively few differences from HC during regulation of physical threat. This supports the specificity of neural responses to disorder-relevant social threat stimuli in SAD. Furthermore, to compensate for high levels of initial reactivity, SAD may need to train in emotion regulation skills that specifically enhance the implementation and effectiveness of cognitive and attention regulation.

Implications for Psychopathology and Treatment

Exaggerated emotional reactivity and affective dysregulation are thought to be core features of many psychiatric problems[20]. The present study indicates that individuals with SAD (a) experience elevated negative emotion in response to social threat, (b) demonstrate the greatest difference from HC in cognitive control related brain regions during regulation of social threat, but (c) can implement emotion regulation during social and physical threat, *when cued to do so*.

These results suggest that SAD may be less able to access and implement cognitive-linguistic emotion regulation skills without an external cue during social threat conditions,

while showing relatively no difference in neural activation from HC during emotional reactivity and regulation of physical threat. This supports the specificity of neural responses to disorder-relevant social threat stimuli in SAD. Furthermore, in order to reduce negative emotional reactivity to the same levels as HC, SAD may need to train in emotion regulation strategies that specifically enhance the implementation and effectiveness of cognitive and attention regulation.

Thus, difficulties in regulation in SAD may be to lack of skill in applying regulation strategies. If this is correct, in addition to expanding the repertoire of emotion regulation strategies, clinical interventions need to increase accessibility and effective implementation of these regulation strategies. Training in implementing emotion regulation strategies in anticipation of and during social situations should enhance both accessibility and confidence in effective regulation. Understanding how social anxiety primes or entrains brain-behavioral systems towards emotional hyper-reactivity may help patients and clinicians better appreciate the experience of “limbic override” of PFC-related regulation attempts. Training in different forms of PFC-mediated cognitive and attentional control systems, for example, inhibition of cognitive elaboration, re-allocation of attentional focus, cognitive diffusion, may result in new forms of emotion learning and self-regulation instantiated by re-setting the relative weights of limbic and PFC systems, and modulating the trajectory of emotion experience.

Limitations

The current study is limited to inferences related to only one type of social threat (harsh facial expressions) and one type of non-social threat (violence scenes). This study used the same comparison condition (non-social neutral visual scenes) for both social and physical threat. It is important to note that the neutral scenes were not matched to violent scenes or harsh faces on a range of stimulus features, including number of actors, facial expressions, and complexity. Using neutral faces from the same set of actors who displayed harsh facial expressions, and the same people in a peaceful interaction in contrast to the physically violent interactions might serve as a better matched control for the social and physical threat, respectfully, in future studies. Still, using neutral scenes had the advantage that both types of threat were compared to the same comparison condition thereby reducing possible BOLD signal variability in the baseline comparison condition. One of the complexities associated with neutral faces is that prior studies indicate that they are not perceived as neutral by individuals with SAD[51]. Thus, some studies have used happy, not neutral, facial expressions as the comparison condition[28]. Investigating emotion regulation in response to a variety of threat stimuli and adding a non-SAD psychiatric comparison group will help identify the specificity of emotional reactivity and regulation in SAD. Similarly, comparison of different types of emotion regulation (e.g., linguistic, attention, distraction, visualization) will deepen our understanding of the typology of emotion regulation strategies. Additionally, the current study examined only a short duration of emotion regulation (6s) and punctate emotion experience ratings. Future studies may benefit from examining temporal dynamics of emotional reactivity and regulation by collecting continuous measures of emotion experience over durations longer than 6s with emotionally-evocative situations that more closely reflect real-life situations. Addressing these limitations will clarify the

neurobehavioral bases of emotional reactivity and regulation. This may in turn help clinical researchers and patients better understand the pre-onset risk, maintaining, and relapse prevention factors that characterize anxiety disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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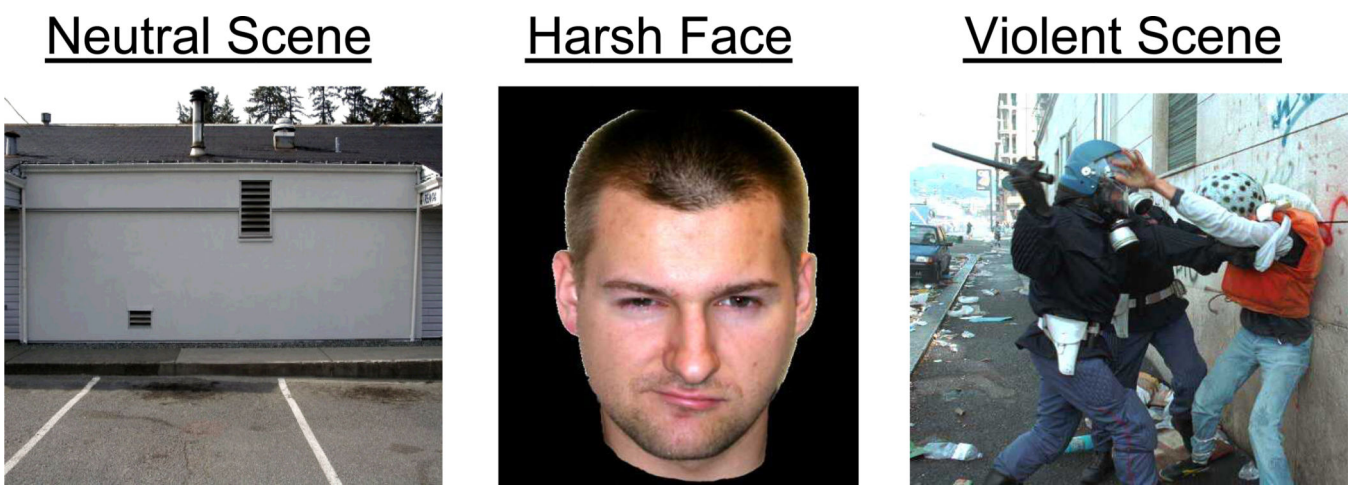

Figure 1.
Exemplars of Neutral, Harsh Faces, and Violent Scenes.

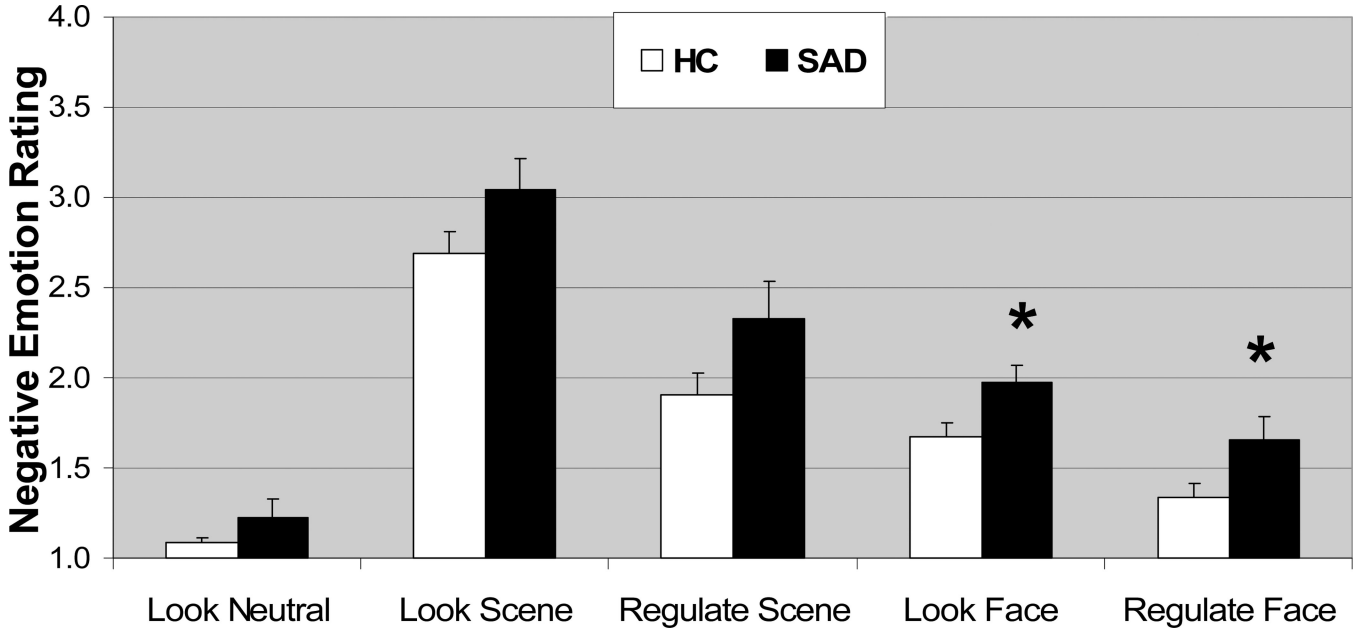

Figure 2.

Negative emotion ratings for Look Neutral Scenes, Look and Regulate Violent Scenes, and Look and Regulate Harsh Faces in SAD and HC. Negative emotion ratings after the offset of each stimulus were provided by participants in response to "How negative do you feel?" (1=not at all, 2=slightly, 3=moderately, and 4=very much).

* $p < 0.05$; Error bars = SEM

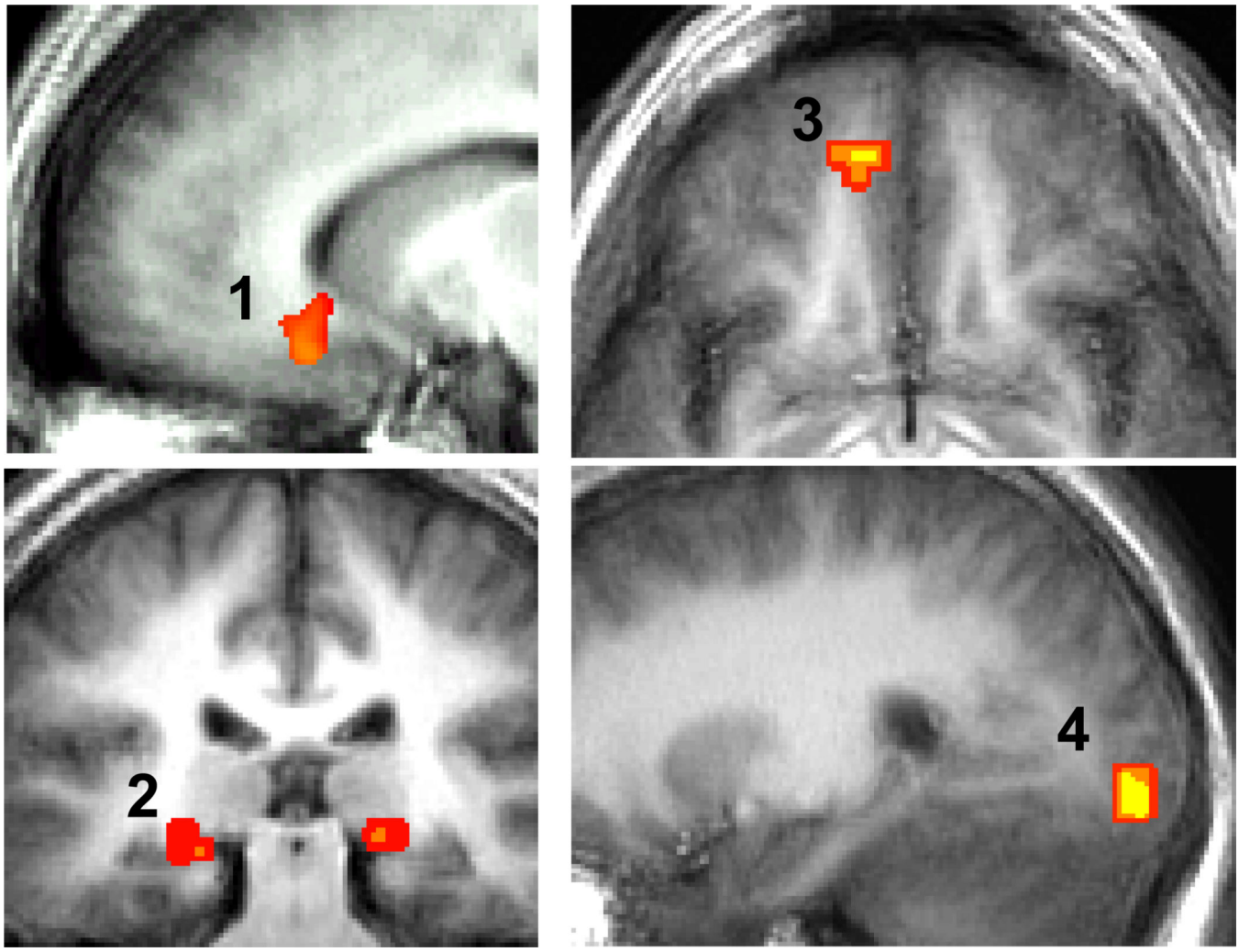

Figure 3.

SAD > HC BOLD Signal for Look Harsh Faces versus Neutral Scenes.

1. Subgenual Anterior Cingulate Cortex BA25, x=−10; 2. bilateral Parahippocampal Gyrus BA28, y=−27; 3. Medial Orbitofrontal Cortex BA11, z=−8; 4. Inferior Occipital Gyrus BA18, x=24

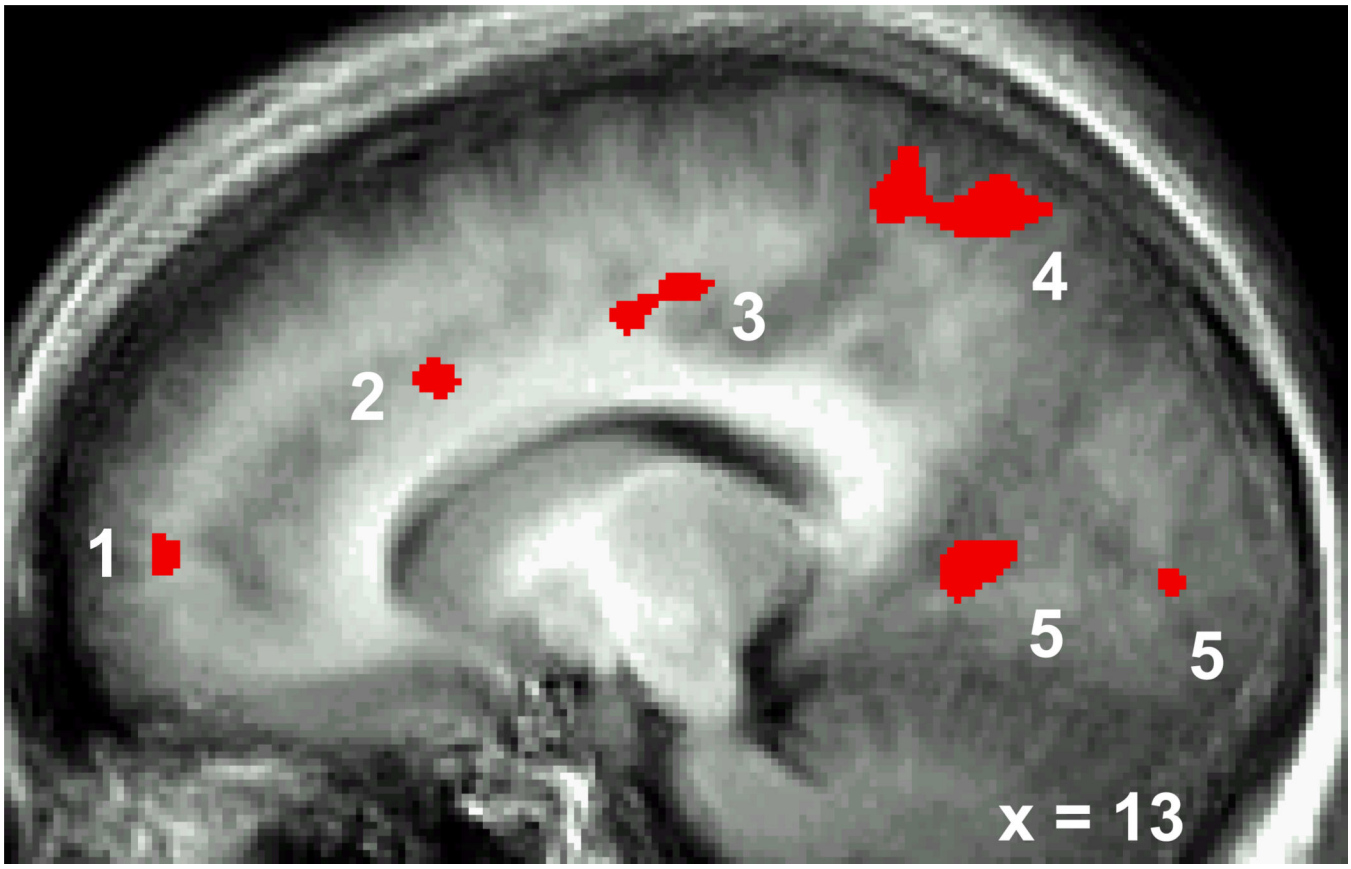

Figure 4.

HC > SAD BOLD Signal for Regulation versus Look Harsh Faces.

1. Medial Prefrontal Cortex, 2. Supragenual ACC, 3. Posterior Cingulate, 4. Precuneus/ Superior Parietal Lobule, 5. Lingual Gyrus

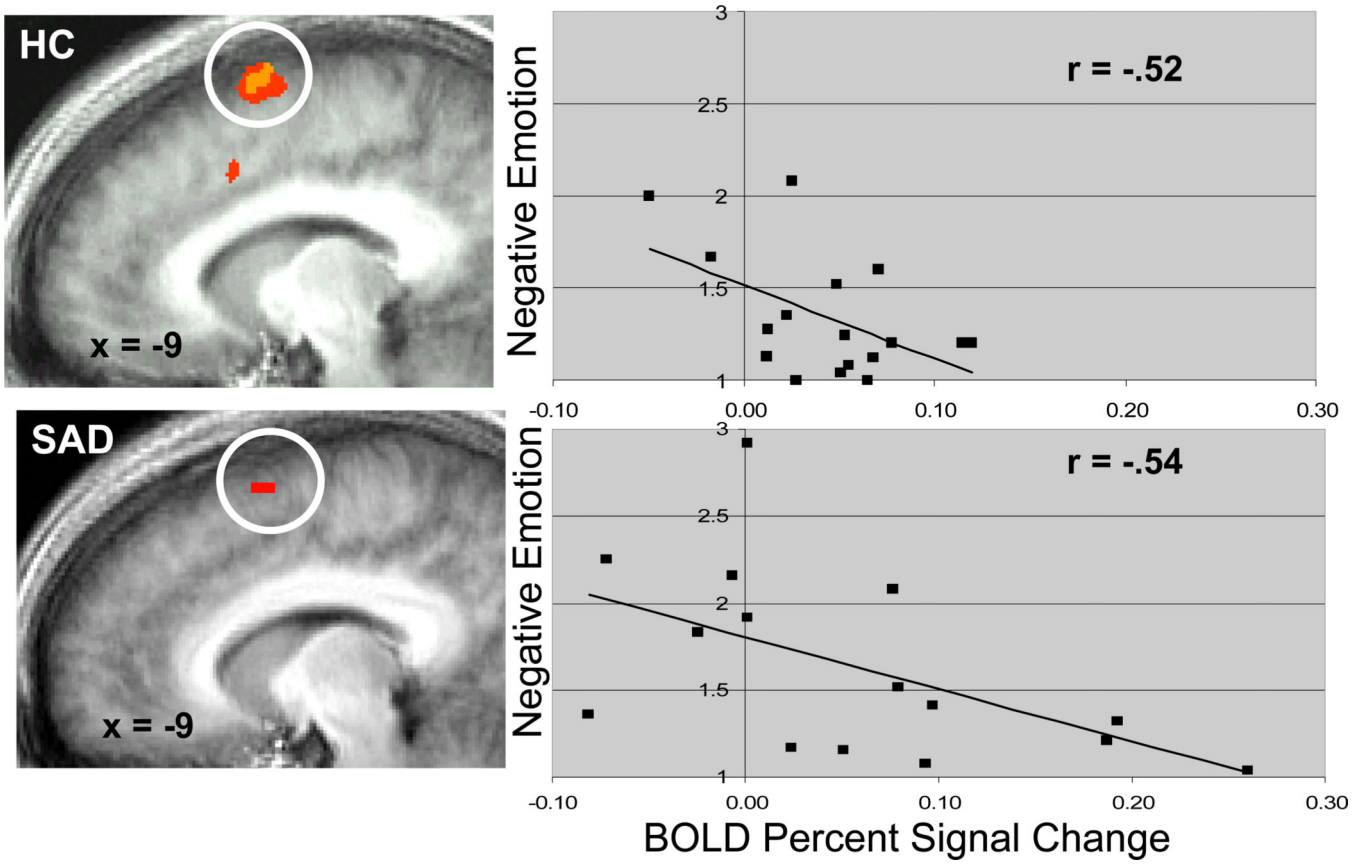

Figure 5.
Dorsomedial Prefrontal Cortical BOLD Activation During Regulation Predicts Reduction in Negative Emotion Experience Ratings.

Table 1

Demographic and Clinical Variables

	SAD n=15 Mean ± SD	**HC n=17 Mean ± SD**	**t-value, p**	**Partial eta^2**
Gender	9 female	9 females		
Age	31.6 ± 9.7	32.1 ± 9.3	1.15	.03
Education	16.3 ± 2.1	16.8 ± 2.4	1.01	.02
Ethnicity				
-Caucasian	53%	65%		
-Asian	33%	29%		
-Latino	13%	6%		
LSAS-SR	67.6 ± 21.1	29.3 ± 20.9	24.93 ***	.47
BFNE	44.1 ± 9.4	32.8 ± 5.2	16.36 ***	.37
BDI-II	11.9 ± 11.3	3.4 ± 2.6	7.99 **	.22
STAI-S	38.7 ± 11.3	30.0 ± 8.4	5.76 *	.17
PANAS-Neg	19.8 ± 9.6	13.7 ± 4.2	5.16 *	.16
PANAS-Pos	31.3 ± 8.03	33.5 ± 8.7	0.44	.02

* p<.05,

** p<.01,

*** p<.001

LSAS-SR=Liebowitz Social Anxiety Scale–Self-Report; BFNE=Brief Fear of Negative Evaluation; BDI-II=Beck Depression Inventory–II; STAI-S=Speilberger State Trait Anxiety Inventory-State Version; PANAS =Positive and Negative Affect Scale.

Table 2

Differential BOLD Responses for Look Harsh Faces versus Neutral Scenes in SAD versus HC

Brain Regions	BA	x y z of peak	Percent Change		Vol (mm^3)	t-value
			HC	SAD		
SAD > HC						
Frontal Lobes						
Medial OFC	11	−8 49 −9	.05	.22	244	4.06
L Subgenual ACC	25	−13 25 −12	.01	.12	813	3.37
Temporal Lobes						
L Parahippocampal Gyrus	28	−21 −27 −6	.06	.14	244	3.56
R Parahippocampal Gyrus	28	19 −28 −3	.05	.13	324	3.14
Parietal Lobes						
L Postcentral Gyrus	1, 3	−55 −24 56	−.07	.18	2723	3.16
L Postcentral Gyrus	3	−43 −17 49	−.04	.09	812	3.15
L Superior Parietal Lobule	7	−21 −55 67	−.03	.18	203	3.04
Occipital Lobes						
L Middle Occipital Gyrus	39	−40 −74 18	.04	.20	203	3.60
R Inferior Occipital Gyrus	18	24 −89 −5	.05	.29	610	3.44
R Lingual Gyrus	19	10 −55 −2	−.05	.14	244	3.36
R Cuneus	18	20 −79 28	.08	.25	366	3.52
HC > SAD						
Occipital Lobes						
L Medial Precuneus	31	7 −54 35	.8	−.03	203	3.13
L Inferior Parietal Lobule	40	−49 −55 48	.12	−.02	203	3.14
R Supramarginal Gyrus	40	60 −54 29	.15	.03	447	3.99

Note. t-value threshold≥3.034, voxel p<0.005, minimum cluster volume threshold ≥163 mm^3 (4 voxels × 3.438 mm^3), cluster-wise p<0.01. BA=Brodmann Area, ACC=anterior cingulate cortex, L=left, OFC=orbitofrontal cortex, R=right. Coordinates based on Talairach & Tournoux Deamon Atlas.

Table 3

Differential BOLD Responses for Regulate versus Look Harsh Faces in SAD versus HC

Brain Regions	BA	x y z of peak	Percent Change		Vol (mm^3)	t-value
			HC	SAD		
SAD > HC No results						
HC > SAD						
Frontal Lobes						
Medial PFC	10	7 51 8	.22	.2	560	3.55
Supragenual ACC	24	10 −6 43	.12	−.12	528	3.10
L Middle Frontal Gyrus	6	−24 −10 46	.12	−.12	528	3.04
R Posterior Insula	13	41 −20 5	.14	−.13	284	3.37
R Precentral Gyrus	4	41 −20 60	.13	−.18	163	2.80
Occipital Lobes						
Medial Cuneus	19	−7 −89 32	.15	−.13	406	3.42
R Lingual Gyrus	17	10 −89 5	.15	−.16	366	3.30
L Lingual Gyrus	19	−21 −61 1	.12	−.16	244	3.13
Parietal Lobes						
R Postcentral Gyrus	3	45 −20 53	.15	−.14	1300	2.73
R Posterior Cingulate, Cuneus	30	14 −58 8	.11	−.11	488	
R Superior Parietal Lobule	7	21 −65 63	.17	−.10	2845	3.79
R Superior Parietal Lobule	7	31 −48 63	.14	−.15	488	3.35
L Inferior Parietal Lobule	40	−41 −37 50	.11	−.16	244	2.67
R Posterior Cingulate	30	17 −58 15	.10	−.17	163	3.02
L Superior Parietal Lobule	7	−21 −48 70	.14	−.15	163	3.27
Temporal Lobes						
R Fusiform Gyrus	37	41 −55 −19	.16	−.16	406	3.30
L Superior Temporal Gyrus	42	−58 −17 12	.13	−.19	975	2.66
R Superior Temporal Gyrus	42	62 −17 15	.16	−.14	284	2.78
L Fusiform Gyrus	19	−24 −68 −19	.18	−.11	163	3.63
R Superior Temporal Gyrus	22	65 −13 5	.16	−.15	163	3.13

Note: t-value threshold≥3.034, voxel p<0.005, minimum cluster volume threshold ≥163 mm^3 (4 voxels × 3.438 mm^3), cluster-wise p<0.01. ACC=anterior cingulate cortex, L=left, PFC=prefrontal cortex, R=right. Coordinates based on Talairach & Tournoux Deamon Atlas.

Table 4

Differential BOLD Responses for Regulate versus Look Violent Scenes in SAD versus HC

Brain Regions	BA	x y z at peak	Percent Change		Vol (mm^3)	t-value
			HC	SAD		
SAD > HC						
Frontal Lobes						
R Mid-Dorsolateral PFC	9	21 49 29	.00	.16	463	3.07
Subcortical						
R Lentiform/Cuadate		10 4 −6	−.04	.13	244	3.79
L Lentiform/Caudate		−10 −4 −6	−.06	.12	285	3.04
HC > SAD						
Frontal Lobes						
R Middle Frontal Gyrus/Pre-motor Cortex	6	58 4 36	.14	−.06	203	3.11
Temporal Lobes						
L Superior Temporal Gyrus	22	−62 −20 5	.17	.00	263	3.41
L Superior Temporal Gyrus	41	−52 −27 12	.15	−.02	263	3.18

Note: t-value threshold≥3.034, voxel p<0.005, minimum cluster volume threshold ≥163 mm^3 (4 voxels × 3.438 mm^3), cluster-wise p<0.01. L=left, PFC=prefrontal cortex, R=right. Coordinates based on Talairach & Tournoux Deamon Atlas.