ORIGINAL ARTICLE

Neural Bases of Social Anxiety Disorder

Emotional Reactivity and Cognitive Regulation During Social and Physical Threat

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Context: Social anxiety disorder is thought to involve emotional hyperreactivity, 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: To investigate 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: Fifteen 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 with patients. Regulation during physical threat produced greater cognitive control–related response (ie, right dorsolateral prefrontal cortex) in patients compared with controls.

Conclusions: Compared with 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.

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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 a 7% to 13.3% lifetime prevalence.[3] Social anxiety disorder is characterized by heightened anxiety and avoidance during social interactions. It has an early onset (80% of cases occur before age 18 years[4]) and usually precedes other anxiety, mood, and substance abuse/dependence disorders.[5-7] Social anxiety disorder 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[10,13,14] have highlighted the role of emotional hyperreactivity, 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 (eg, as socially incompetent) and others (eg, 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-

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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 because of (1) exaggerated emotional reactivity to all types of potential threat stimuli, (2) a general deficit in downregulating emotional reactivity, or (3) 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 (ie, limbic and paralimbic areas) detects personally relevant and affectively salient stimuli. A neural signal encoding potential threat is communicated to the rostral anterior cingulate cortex (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 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 (eg, passive viewing vs judgment/rating) influences 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 and 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, patients with SAD who responded to either group cognitive behavioral therapy or selective serotonin reuptake inhibitor treatment demonstrated significant reduction from pretreatment to posttreatment in amygdala response during a speech task.[39] Additionally, posttreatment amygdala signal reduction during a speech task significantly predicted reduced social anxiety symptoms at 1-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 with demographically matched nonpsychiatric healthy controls. Previous functional magnetic resonance imaging (fMRI) studies in healthy controls have found greater neural responses to violent scenes.[40] We included violent scenes (ie, physical threat) as a comparison condition for harsh faces to investigate differential emotion regulation for social (SAD-related) and physical (SAD-unrelated) threat. We expected to find (1) no difference in participants with SAD and healthy controls for emotional reactivity and regulation for physical threat, (2) greater reactivity to harsh faces in participants with SAD than healthy controls, and (3) deficits in regulation in participants with SAD vs healthy controls for social threat stimuli.

METHODS

PARTICIPANTS

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

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Table 1. Demographic and Clinical Variables

	Mean (SD)			
	SAD (n=15)	HC (n=17)	*t* Value	Partial η^2
Female, No.	9	9		
Age, y	31.6 (9.7)	32.1 (9.3)	1.15	0.03
Education, y	16.3 (2.1)	16.8 (2.4)	1.01	0.02
Ethnicity, %				
White	53	65		
Asian	33	29		
Latino	13	6		
LSAS-SR[42]	67.6 (21.1)	29.3 (20.9)	24.93[a]	0.47
BFNE[43]	44.1 (9.4)	32.8 (5.2)	16.36[a]	0.37
BDI-II[44]	11.9 (11.3)	3.4 (2.6)	7.99[b]	0.22
STAI-S[45]	38.7 (11.3)	30.0 (8.4)	5.76[c]	0.17
PANAS[46]-Neg	19.8 (9.6)	13.7 (4.2)	5.16[c]	0.16
PANAS-Pos	31.3 (8.03)	33.5 (8.7)	0.44	0.02

Abbreviations: BDI-II, Beck Depression Inventory–II; BFNE, Brief Fear of Negative Evaluation Scale; HC, healthy controls; LSAS-SR, Liebowitz Social Anxiety Scale–Self-Report; Neg, negative affect; PANAS, Positive and Negative Affect Schedule; Pos, positive affect; SAD, social anxiety disorder; STAI-S, Spielberger State-Trait Anxiety Inventory–State Version.

[a] $P < .001$.

[b] $P < .01$.

[c] $P < .05$.

EXCLUSION CRITERIA

All participants passed an MRI safety screen. Participants were excluded if they reported current use of any psychotropic medication or history of neurological or cardiovascular disorders, diabetes mellitus, hypothyroidism or hyperthyroidism, or head trauma with loss of consciousness greater than 5 minutes. Both healthy controls and participants with SAD were excluded if they had a lifetime diagnosis of a psychotic disorder, mania, hypomania, bipolar disorder, or substance/alcohol abuse. Because of potential effects on blood flow, participants were asked not to consume alcohol, recreational drugs, or pain killers during the 24-hour period before their magnetic resonance (MR) scan and not to ingest caffeine at least 5 hours prior to the scan. Daily cigarette users were excluded from the study. Participants with SAD 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 (P.R.G.) using the Anxiety Disorders Interview Schedule for *DSM-IV*[47] 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 participants with SAD with a primary diagnosis of SAD or healthy controls with no history of *DSM-IV* disorders were invited to participate.

As shown in Table 1, compared with healthy controls, participants with SAD reported greater social anxiety (Liebowitz Social Anxiety Scale[42]), fear of negative evaluation (Brief Fear of Negative Evaluation Scale[43]), depressive symptoms (Beck Depression Inventory–II[44]), state anxiety (Spielberger State-Trait Anxiety Inventory[45]), and negative affect (Positive and Negative Affect Schedule[46]).

PROCEDURE

Before scanning, participants were trained in accordance with methods developed by Ochsner et al[48,49] and practiced with 2 stimuli (not used in the scanning experiment) per neutral, social, and physical condition to (1) "just look" without trying to control or modulate their emotional reactivity and (2) "regulate" by actively thinking in a way that modifies the interpretation of the stimulus and thus reduces negative reactions. Specifically, they were instructed to reinterpret 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 6 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 E-Prime software (Psychology Software Tools, Inc, Pittsburgh, Pennsylvania).

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 pseudorandomized sequence (no more than 2 instances of the same condition in a row). There were 25 trials for each of 5 conditions: look harsh face, regulate harsh face, look violent scene, regulate violent scene, and look neutral scene. Each 12-second trial consisted of an instruction (look or regulate) (3 seconds), stimulus (6 seconds), and emotion rating (3 seconds).

STIMULI

Prior fMRI studies have shown that direct-facing angry and contemptuous facial expressions produce strong neural responses in participants with 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.[50] Stimuli consisted of color photographs showing the actor's head against a black background. Two independent raters trained in the Facial Action Coding System 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, 70% Anglo American, 10% Asian American, 10% Latin American, and 10% African American, who 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 healthy controls.[40] Thus, physical threat stimuli consisted of color photographs of a person being violently attacked (eg, 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 nonarousing, nonsocial color photographs of mundane scenes (eg, pavement, garage door, wood siding). Neutral facial expressions were not

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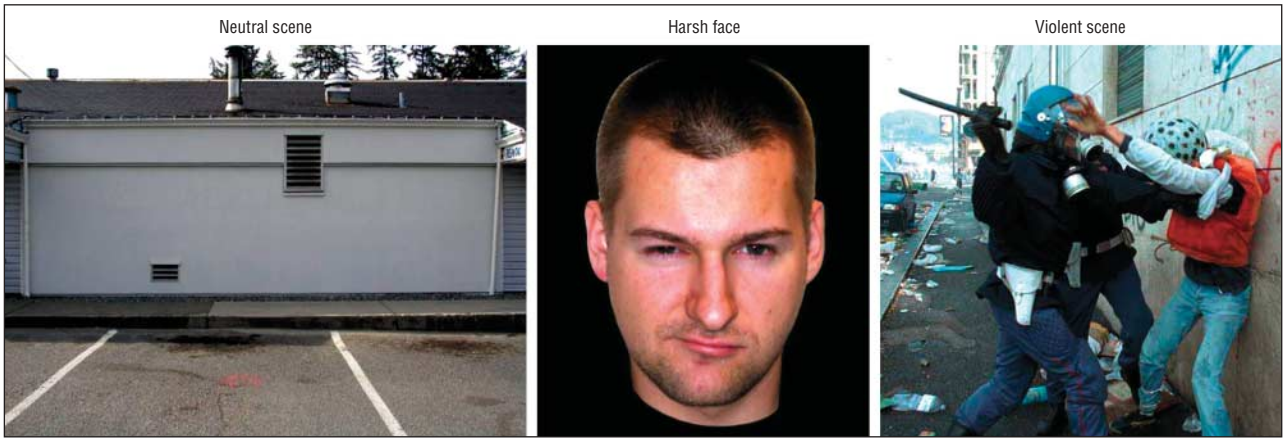

Figure 1. Exemplars of neutral, harsh faces, and violent scenes.

used as a contrast to harsh faces because of evidence that individuals with SAD interpret neutral face stimuli more negatively then do healthy controls.[28,51] Examples of the 3 stimulus types are shown in **Figure 1**.

IMAGE ACQUISITION

Imaging was performed on a GE 3-T Signa magnet with a T2*-weighted gradient echo spiral–in/out pulse sequence[52] and a custom-built quadrature "dome" elliptical birdcage head coil (GE Healthcare, Milwaukee, Wisconsin). Head movement was minimized using a bite bar and foam padding. Across 3 functional runs, 1114 functional volumes were obtained from 22 sequential axial slices (repetition time = 1500 milliseconds, echo time = 30 milliseconds, flip angle = 60°, field of view = 22 cm, matrix = 64 × 64, single shot, resolution = 3.438 $mm^2 \times 5$ mm). Three-dimensional high-resolution anatomical scans were acquired using fast spin-echo spoiled gradient recall ($0.8594^2 \times 1.5$ mm; field of view = 22 cm, frequency encoding = 256).

fMRI DATA PREPROCESSING

Each functional run was subjected to preprocessing steps using AFNI[53] software: coregistration, motion correction, 4-mm^3 isotropic gaussian spatial smoothing, high-pass filtering (0.011 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 ($P > .50$ for all).

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. Blood oxygen level–dependent (BOLD) responses during the 6 seconds when looking or regulating were investigated using regressors (convolved with the gamma variate model[54] of the hemodynamic response function) for each of the 5 conditions (look neutral scene, look harsh face, look violent scene, regulate harsh face, regulate violent scene). Functional MRI BOLD signal intensity was represented as percentage of signal change [(MR signal per voxel per point/mean MR signal in that voxel for the entire functional run) × 100]. The differential BOLD signal between target and comparison conditions (eg, regulate vs look harsh face) is reported as BOLD percentage of 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 used 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 $P < .005$ and cluster volume higher than 162 mm^3 (4 voxels × 3.438 mm^3) protected against false-positive cluster detection at $P < .01$.

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 indexes of emotional reactivity and regulation.

EMOTIONAL REACTIVITY

Behavioral Responses

A 2 (group: participants with SAD and healthy controls) × 3 (condition: look neutral scene, look harsh face, look violent scene) repeated-measures analysis of variance of negative emotion ratings resulted in no interaction of group × condition ($P > .42$). There were main effects of group (SAD > healthy controls, $F_{2,30} = 7.32$; $P < .05$; $\eta^2 = 0.20$) and condition ($F_{2,30} = 229.78$; $P < .001$; $\eta^2 = 0.88$), with violent scene having a higher rating than harsh face, which had a higher rating than 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 vs neutral scene contrast resulted in significantly greater BOLD responses in participants with SAD vs healthy controls in brain regions implicated in emotion (medial orbitofrontal cortex, subgenual ACC, bilateral parahippocampal gyrus), ventral/dorsal visual process-

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ing (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 with participants with SAD, healthy controls 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 vs neutral scene (eTable 1 and eTable 2, http://www.archgenpsychiatry.com). However, only participants with SAD produced evidence of FFA responses. For physical threat, a between-group *t* test for the look violent vs neutral scene found no between-group differences. Both groups had left dorsal/extended amygdala and bilateral FFA and LOC responses for the contrast of look violent vs neutral scene (eTable 3 and eTable 4).

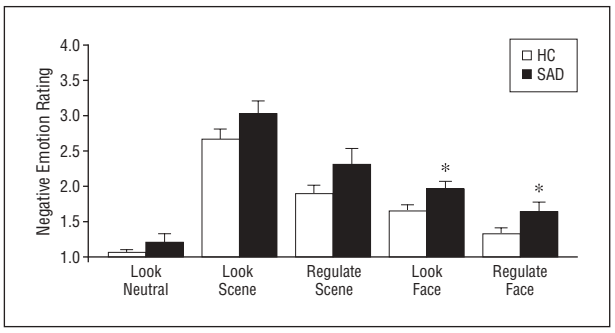

Figure 2. Negative emotion ratings for look neutral scenes, look and regulate violent scenes, and look and regulate harsh faces in participants with social anxiety disorder (SAD) and healthy controls (HC). Negative emotion ratings after the offset of each stimulus were provided by participants in response to "How negative do you feel?" (1 = not at all, 2 = slightly, 3 = moderately, and 4 = very much). Error bars represent standard error of the mean. *$P < .05$.

EMOTION REGULATION

Behavioral Responses

A 2 (group: participants with SAD and healthy controls) × 2 (condition: regulate violent scene, regulate harsh face) repeated-measures analysis of variance 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, $F_{1,31} = 47.19$; $P < .001$; $\eta^2 = 0.61$) but no effect of group ($P > .10$). There were no group differences in the percentage of reduction in negative emotion following emotion regulation for social (mean [SD], healthy controls, 18.8% [17.3%] vs SAD, 16.9% [19.0%]; $P > .76$) or physical threat (mean [SD], healthy controls, 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 vs look harsh face contrast showed that, compared with participants with SAD, healthy controls 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 participants with SAD compared with

Table 2. Differential BOLD Responses for Look Harsh Faces vs Neutral Scenes in Participants With SAD vs HC[a]

Brain Region	BA	At Peak x	At Peak y	At Peak z	Change, % HC	Change, % SAD	Volume, mm³	*t* Value
SAD > HC								
Frontal lobes								
Medial OFC	11	−8	49	−9	0.05	0.22	244	4.06
L subgenual ACC	25	−13	25	−12	0.01	0.12	813	3.37
Temporal lobes								
L parahippocampal gyrus	28	−21	−27	−6	0.06	0.14	244	3.56
R parahippocampal gyrus	28	19	−28	−3	0.05	0.13	324	3.14
Parietal lobes								
L postcentral gyrus	1, 3	−55	−24	56	−0.07	0.18	2723	3.16
L postcentral gyrus	3	−43	−17	49	−0.04	0.09	812	3.15
L superior parietal lobule	7	−21	−55	67	−0.03	0.18	203	3.04
Occipital lobes								
L middle occipital gyrus	39	−40	−74	18	0.04	0.20	203	3.60
R inferior occipital gyrus	18	24	−89	−5	0.05	0.29	610	3.44
R lingual gyrus	19	10	−55	−2	−0.05	0.14	244	3.36
R cuneus	18	20	−79	28	0.08	0.25	366	3.52
HC > SAD								
Occipital lobes								
L medial precuneus	31	7	−54	35	0.8	−0.03	203	3.13
L inferior parietal lobule	40	−49	−55	48	0.12	−0.02	203	3.14
R supramarginal gyrus	40	60	−54	29	0.15	0.03	447	3.99

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood oxygen level dependent; HC, healthy controls; L, left; OFC, orbitofrontal cortex; R, right; SAD, social anxiety disorder.

[a] *t* Value threshold ≥3.034, voxel $P < .005$, minimum cluster volume threshold ≥163 mm³ (4 voxels × 3.438 mm³), and clusterwise $P < .01$. Coordinates based on Talairach and Tournoux Daemon Atlas.

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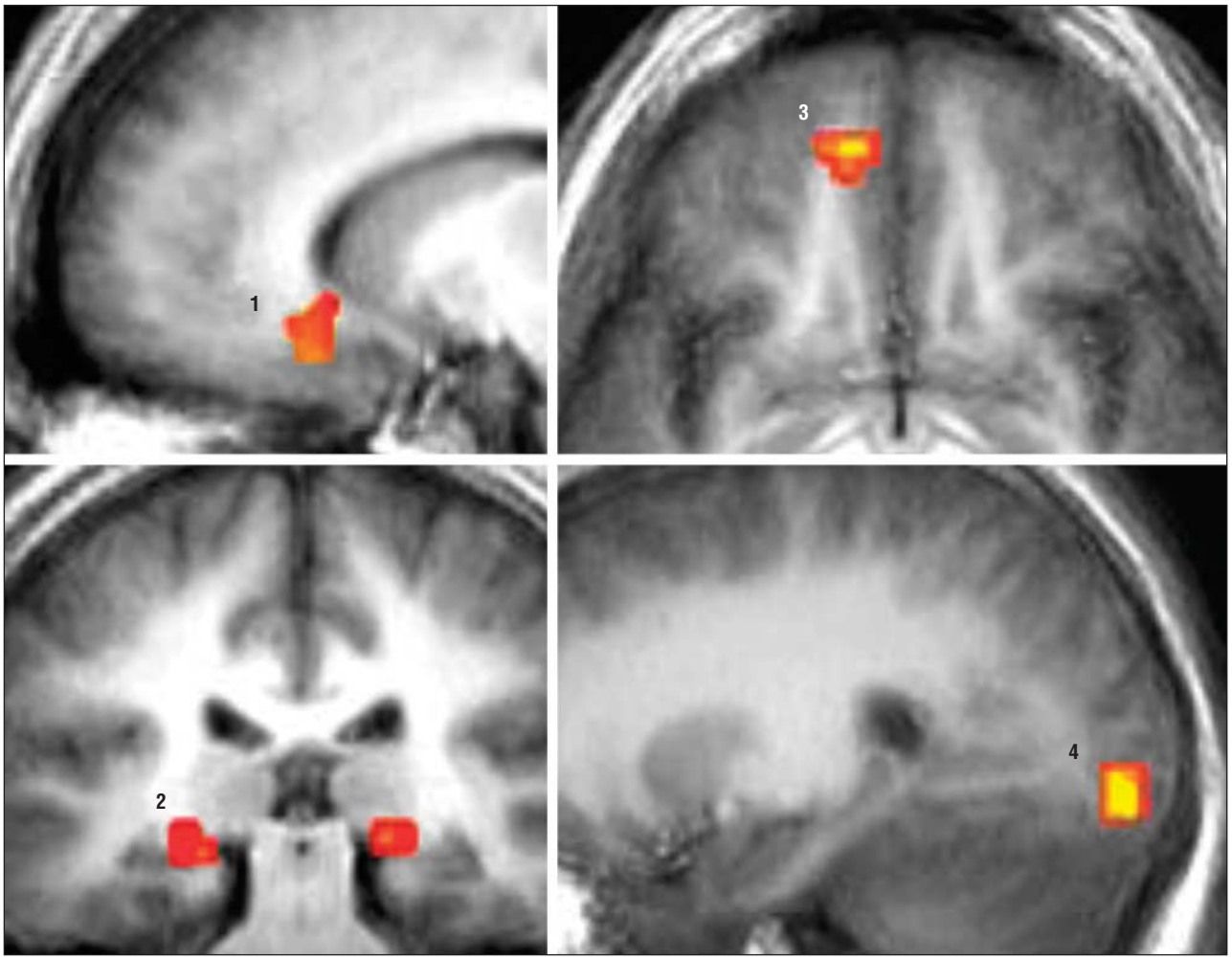

Figure 3. Participants with social anxiety disorder had significantly greater blood oxygen level–dependent responses vs healthy controls for the look harsh faces vs neutral scenes. 1 indicates subgenual anterior cingulate cortex, Brodmann area (BA) 25, x=−10; 2, bilateral parahippocampal gyrus, BA 28, y=−27; 3, medial orbitofrontal cortex, BA 11, z=−8; 4, inferior occipital gyrus, BA 18, x=24.

healthy controls. For physical threat (**Table 4**), a between-group *t* test of the regulate vs look violent scenes contrast demonstrated that, compared with healthy controls, participants with SAD had greater BOLD response in right mid-dorsolateral PFC and bilateral lentiform/caudate. Compared with participants with SAD, healthy controls produced greater BOLD responses for regulate vs 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 [eTable 5 and eTable 6]). In participants with SAD and healthy controls, 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 participants with SAD and inversely with BOLD signal in healthy controls during look harsh face in left dorsal/extended amygdala and right middle occipital gyrus (Fisher *z* test $P<.05$ for all). When social anxiety severity was measured by the Brief Fear of Negative Evaluation Scale, the same pattern of positive correlation in participants with SAD and inverse correlation in healthy controls during look harsh face was observed in bilateral dorsal/extended amygdala, posterior cingulate, and precuneus (Fisher *z* test $P<.05$ for all). There was no relationship of social anxiety symptom severity with BOLD responses (1) during looking at violent scenes and (2) during emotion regulation.

COMMENT

The goal of this study was to investigate the neural bases of emotional reactivity and cognitive regulation in adults diagnosed with SAD vs healthy controls. Using both social and physical threat stimuli, we were able to examine the specificity of emotional reactivity and emotion regulation abnormalities in participants with SAD. The primary finding was that, compared with demographi-

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Table 3. Differential BOLD Responses for Regulate vs Look Harsh Faces in Participants With SAD vs HC[a]

Brain Region	BA	At Peak x	At Peak y	At Peak z	Change, % HC	Change, % SAD	Volume, mm³	*t* Value
SAD > HC: no results								
HC > SAD								
Frontal lobes								
Medial PFC	10	7	51	8	0.22	0.2	560	3.55
Supragenual ACC	24	10	–6	43	0.12	–0.12	528	3.10
L middle frontal gyrus	6	–24	–10	46	0.12	–0.12	528	3.04
R posterior insula	13	41	–20	5	0.14	–0.13	284	3.37
R precentral gyrus	4	41	–20	60	0.13	–0.18	163	2.80
Occipital lobes								
Medial cuneus	19	–7	–89	32	0.15	–0.13	406	3.42
R lingual gyrus	17	10	–89	5	0.15	–0.16	366	3.30
L lingual gyrus	19	–21	–61	1	0.12	–0.16	244	3.13
Parietal lobes								
R postcentral gyrus	3	45	–20	53	0.15	–0.14	1300	2.73
R posterior cingulate, cuneus	30	14	–58	8	0.11	–0.11	488	
R superior parietal lobule	7	21	–65	63	0.17	–0.10	2845	3.79
R superior parietal lobule	7	31	–48	63	0.14	–0.15	488	3.35
L inferior parietal lobule	40	–41	–37	50	0.11	–0.16	244	2.67
R posterior cingulate	30	17	–58	15	0.10	–0.17	163	3.02
L superior parietal lobule	7	–21	–48	70	0.14	–0.15	163	3.27
Temporal lobes								
R fusiform gyrus	37	41	–55	–19	0.16	–0.16	406	3.30
L superior temporal gyrus	42	–58	–17	12	0.13	–0.19	975	2.66
R superior temporal gyrus	42	62	–17	15	0.16	–0.14	284	2.78
L fusiform gyrus	19	–24	–68	–19	0.18	–0.11	163	3.63
R superior temporal gyrus	22	65	–13	5	0.16	–0.15	163	3.13

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood oxygen level dependent; HC, healthy controls; L, left; PFC, prefrontal cortex; R, right; SAD, social anxiety disorder.

[a] *t* Value threshold ≥3.034, voxel $P < .005$, minimum cluster volume threshold ≥163 mm³ (4 voxels × 3.438 mm³), and clusterwise $P < .01$. Coordinates based on Talairach and Tournoux Daemon Atlas.

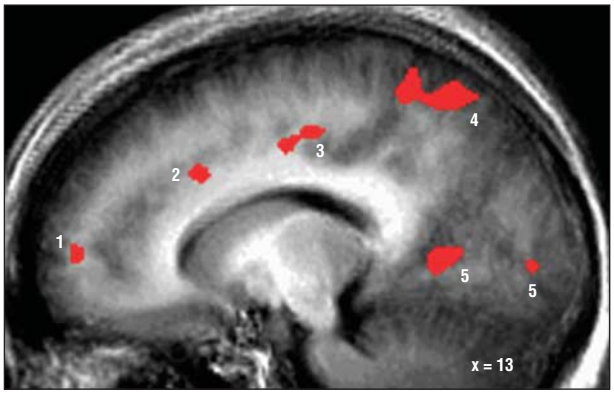

Figure 4. Healthy controls had greater blood oxygen level–dependent responses vs participants with social anxiety disorder for regulation vs look harsh faces. 1 indicates medial prefrontal cortex; 2, supragenual anterior cingulate cortex; 3, posterior cingulate; 4, precuneus/superior parietal lobule; 5, lingual gyrus.

cally matched healthy controls, participants with SAD demonstrated exaggerated negative emotion reactivity and reduced cognitive-linguistic regulation–related neural activation specifically for social threat stimuli.

EMOTIONAL REACTIVITY

Behaviorally, compared with healthy controls, participants with SAD reported greater negative emotion experience for both social and physical threat, suggesting elevated emotional reactivity across these 2 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 participants with SAD compared with healthy controls in emotion-[21] (medial orbitofrontal cortex, subgenual cingulate, parahippocampal gyrus), visual-, face-, and sensory-processing brain regions. For both social and physical threat compared with 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 participants with 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 participants with 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

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Table 4. Differential BOLD Responses for Regulate vs Look Violent Scenes in Participants With SAD vs HC[a]

Brain Region	BA	At Peak x	At Peak y	At Peak z	Change, % HC	Change, % SAD	Volume, mm³	*t* Value
SAD > HC								
Frontal lobes								
R mid-dorsolateral PFC	9	21	49	29	0	0.16	463	3.07
Subcortical								
R lentiform/caudate		10	4	−6	−0.04	0.13	244	3.79
L lentiform/caudate		−10	−4	−6	−0.06	0.12	285	3.04
HC > SAD								
Frontal lobes								
R middle frontal gyrus/premotor cortex	6	58	4	36	0.14	−0.06	203	3.11
Temporal lobes								
L superior temporal gyrus	22	−62	−20	5	0.17	0	263	3.41
L superior temporal gyrus	41	−52	−27	12	0.15	−0.02	263	3.18

Abbreviations: See Table 3.
[a] *t* Value threshold ≥3.034, voxel $P < .005$, minimum cluster volume threshold ≥163 mm³ (4 voxels × 3.438 mm³), and clusterwise $P < .01$. Coordinates based on Talairach and Tournoux Daemon Atlas.

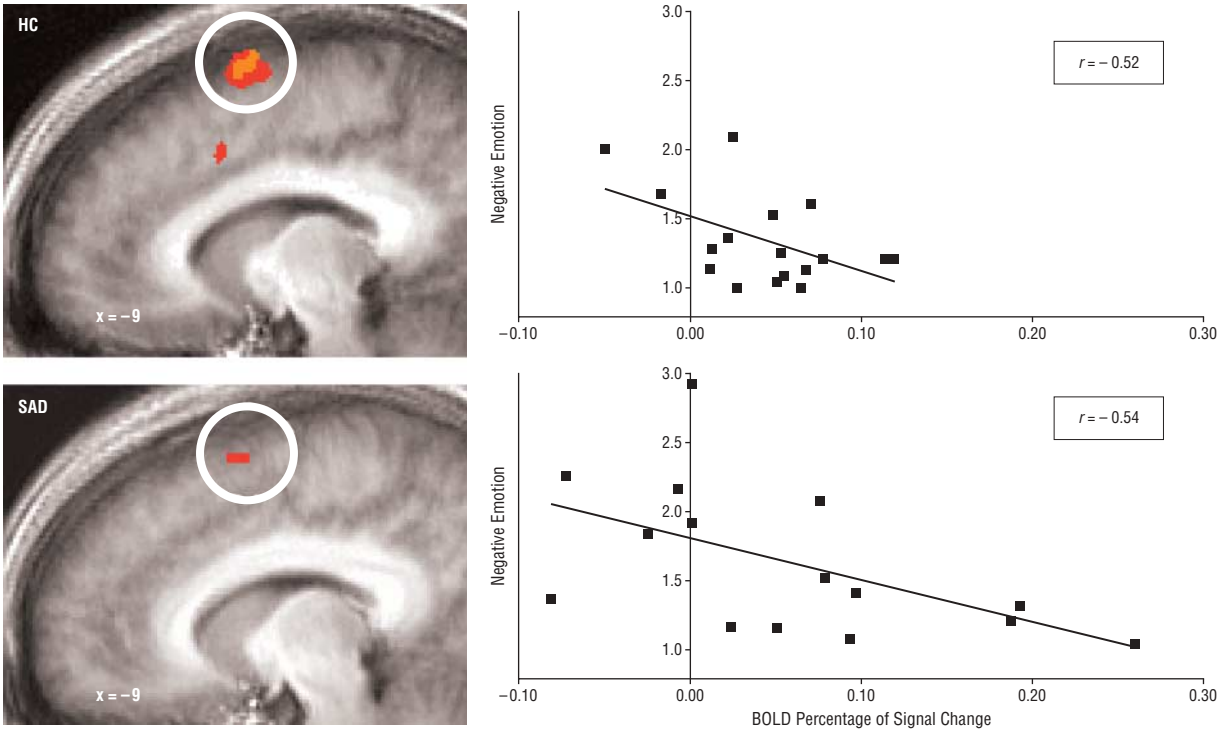

Figure 5. Dorsomedial prefrontal cortical blood oxygen level–dependent (BOLD) activation during regulation predicts reduction in negative emotion experience ratings. HC indicates healthy controls; SAD, social anxiety disorder.

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 participants with SAD vs healthy controls confirms findings of enhanced visual processing in SAD for facial emotion stimuli.[35]

Both groups produced dorsal/extended amygdala responses to harsh (ie, mixed anger and contempt) facial expressions presented for 6 seconds. While several prior studies of harsh facial expression have found greater amygdala response in individuals with SAD vs healthy controls,[28,29,33-35] the present study used 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 healthy controls will, like participants with 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 partici-

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pants with SAD vs healthy controls 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 toward potential threat immediately followed by inhibition and avoidance of the threat signals.[69,70] Accordingly, because of sensitivity to social threat cues, SAD should be associated with rapid initial orienting toward facial expressions that suggest social disapproval and then turning attention away as an overlearned protective response.

EMOTION REGULATION

Behaviorally, participants with SAD and healthy controls reported similar reductions in negative emotion following cognitive regulation for both physical and social threat. However, because of greater initial negative emotion for physical vs social threat, postregulation negative emotion continued to be greater for physical vs social threat. This indicates that all participants were able to downregulate 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] (eg, 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 downregulation of emotion[17] and the neural bases of cognitive emotion regulation in nonpsychiatric 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, individuals with SAD can implement cognitive-linguistic regulation strategies.

Between-group analyses revealed that during regulation of social threat, compared with participants with SAD, healthy controls had a distributed pattern of neural activity implicated in cognitive regulation, attention, and visual processing. Specifically, during regulation of social threat, both compared with participants with SAD and within group, healthy controls 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 herein 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 participants with SAD in dorsolateral PFC and lentiform/caudate and in healthy controls in premotor and superior temporal cortex.

These results suggest that individuals with SAD may be less able to access and implement cognitive-linguistic emotion regulation strategies during social threat conditions, while showing relatively few differences from healthy controls 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, individuals with 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 (1) experience elevated negative emotion in response to social threat and (2) demonstrate the greatest difference from healthy controls in cognitive control–related brain regions during regulation of social threat but (3) can implement emotion regulation during social and physical threat, when cued to do so.

These results suggest that individuals with 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 healthy controls during emotional reactivity and regulation of physical threat. This supports the specificity of neural responses to disorder-relevant social threat stimuli in SAD. Furthermore, to reduce negative emotional reactivity to the same levels as healthy controls, individuals with 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 individuals with SAD may be due 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 affective regulation. Understanding how social anxiety primes or entrains brain behavioral systems toward emotional hyperreactivity 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, reallocation of attentional focus, and cognitive diffusion, may result in new forms of emotion learning and self-regulation instantiated by resetting the rela-

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tive 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 nonsocial threat (violence scenes). This study used the same comparison condition (nonsocial neutral visual scenes) for both social and physical threat. 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 with 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 (eg, 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 (6 seconds) 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 6 seconds 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 preonset risk, maintaining, and relapse prevention factors that characterize anxiety disorder.

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