

Original Investigation

Impact of Cognitive Behavioral Therapy for Social Anxiety Disorder on the Neural Dynamics of Cognitive Reappraisal of Negative Self-beliefs

Randomized Clinical Trial

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IMPORTANCE Cognitive behavioral therapy (CBT) for social anxiety disorder (SAD) is thought to enhance cognitive reappraisal in patients with SAD. Such improvements should be evident in cognitive reappraisal-related prefrontal cortex responses.

OBJECTIVE To determine whether CBT for SAD modifies cognitive reappraisal-related prefrontal cortex neural signal magnitude and timing when implementing cognitive reappraisal with negative self-beliefs.

DESIGN Randomized clinical trial of CBT for SAD vs wait-list control group during a study that enrolled patients from 2007 to 2010.

SETTING University psychology department.

PARTICIPANTS Seventy-five patients with generalized SAD randomly assigned to CBT or wait list.

INTERVENTION Sixteen sessions of individual CBT for SAD.

MAIN OUTCOME MEASURES Negative emotion ratings and functional magnetic resonance imaging blood oxygen-level dependent signal when reacting to and cognitively reappraising negative self-beliefs embedded in autobiographical social anxiety situations.

RESULTS During reactivity trials, compared with wait list, CBT produced (1) greater reduction in negative emotion ratings and (2) greater blood oxygen-level dependent signal magnitude in the medial prefrontal cortex. During cognitive reappraisal trials, compared with wait list, CBT produced (3) greater reduction in negative emotion ratings, (4) greater blood oxygen level-dependent signal magnitude in the dorsolateral and dorsomedial prefrontal cortex, (5) earlier temporal onset of dorsomedial prefrontal cortex activity, and (6) greater dorsomedial prefrontal cortex-amygdala inverse functional connectivity.

CONCLUSIONS AND RELEVANCE Modulation of cognitive reappraisal-related brain responses, timing, and functional connectivity may be important brain changes that contribute to the effectiveness of CBT for social anxiety. This study demonstrates that clinically applied neuroscience investigations can elucidate neurobiological mechanisms of change in psychiatric conditions.

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Social anxiety disorder (SAD) is characterized by high prevalence (12.1%),¹ early onset,² and low rates of spontaneous remission.³ Social anxiety disorder is linked to significant impairment in social, educational, and occupational functioning^{4,5} and represents a substantial problem for society.^{6,7} Individuals with SAD experience distressing levels of social fear, humiliation, and embarrassment⁸ and distorted beliefs about the social self.⁹

Cognitive Reappraisal in SAD

One factor thought to lead to heightened anxiety responses in SAD is a failure to successfully use cognitive reappraisal (henceforth “reappraisal”). Reappraisal is an emotion regulation strategy that entails reframing the meaning of an emotional stimulus to modify its impact. In healthy controls,^{10,11} neuroimaging studies of reappraisal show increased recruitment in brain networks implicated in cognitive control (dorsolateral, dorsomedial, and ventrolateral prefrontal cortex [DLPFC, DMPFC, and VLPFC]) and attention (precuneus, superior parietal lobule, right DLPFC, and dorsal anterior cingulate cortex),¹² as well as decreases in emotion processing brain regions, specifically the amygdala.¹³

Neuroimaging studies have found that, compared with healthy controls, patients with SAD show lesser blood oxygen level-dependent (BOLD) signal responses in cognitive control (DLPFC and DMPFC) and attention (medial precuneus, posterior cingulate, and bilateral dorsal parietal cortex) brain networks during reappraisal of social threat (harsh facial expressions).¹⁴ Furthermore, when reappraising self-generated negative self-beliefs (NSBs), compared with healthy controls, patients with SAD demonstrate temporally delayed prefrontal cortex (PFC) activation (DMPFC, bilateral DLPFC, and bilateral VLPFC) and less PFC-amygdala inverse functional connectivity.¹⁵ This inability to implement reappraisal in a timely manner and less successful PFC downregulation of amygdala responses may be related to heightened levels of anxiety that inhibit recruitment of PFC and/or deficient reappraisal implementation in the context of anxiety-inducing stimuli. What is not known is whether clinical interventions impact the magnitude, timing, and functional connectivity of reappraisal-related PFC responses.

Cognitive Behavioral Therapy for SAD

Individual cognitive behavioral therapy (I-CBT) for SAD, as developed by Hope and Heimberg,¹⁵ has been shown to be an effective treatment for SAD.^{16,17} One key component of CBT for SAD is cognitive restructuring, which involves reappraisal in the context of exposure to feared social situations and NSBs.¹⁸⁻²⁰ Behaviorally, increases in reappraisal self-efficacy during I-CBT have been shown to mediate the effect of I-CBT on improvement in severity of social anxiety symptoms and predict clinical status at 1 year posttreatment.¹⁷ Neurally, the first neuroimaging study of group CBT and citalopram treatment for SAD showed that regional cerebral blood flow decreases in the amygdala during public speaking were associated with clinical improvement 1 year later.²¹ A recent study

of group CBT demonstrated that pretreatment increases in functional magnetic resonance imaging (fMRI) BOLD signal in superior and inferior portions of the occipitotemporal cortex in response to angry vs neutral face stimuli predicted improvement in social anxiety symptoms.²² The current study builds on these prior studies by investigating whether I-CBT for SAD impacts BOLD signal magnitude, timing, and functional connectivity in PFC regions implicated in reappraisal of NSBs embedded in autobiographical social anxiety situations.

The Present Study

Our goal was to investigate the impact of I-CBT for SAD vs wait list on BOLD signal magnitude and temporal dynamics in a priori regions of interest (ROIs) in the DMPFC, DLPFC, and VLPFC (implicated in reappraising NSBs¹⁵) and in the amygdala (implicated in emotion generation¹³). Additionally, we used a context-dependent functional connectivity analysis to investigate whether CBT influenced PFC-amygdala connectivity. We expected that, compared with wait list, I-CBT would result in lesser negative emotion and amygdala responses to NSBs, greater and quicker responses in reappraisal-related PFC regions (DMPFC, DLPFC, and VLPFC), and greater inverse functional connectivity between the reappraisal-related PFC and the emotion-related amygdala.

Methods

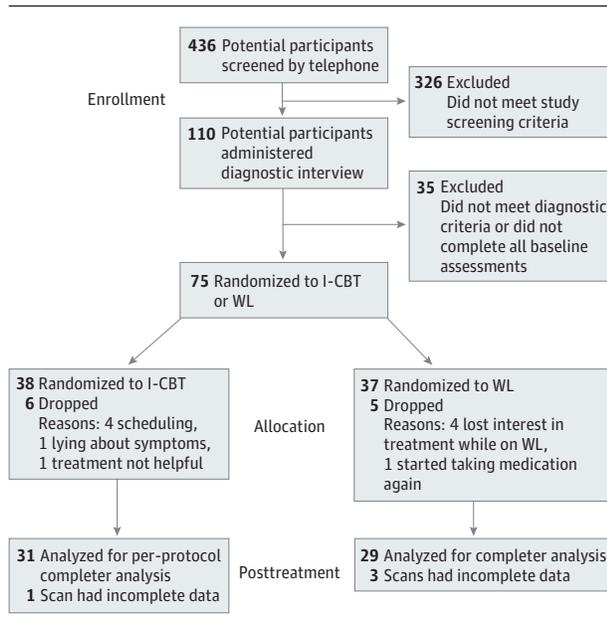
Participants

This study was approved by the institutional review board at Stanford University, and participants provided written informed consent. Participants met *DSM-IV*²³ criteria for a principal diagnosis of generalized SAD based on the Anxiety Disorders Interview Schedule for the *DSM-IV*: Lifetime Version (ADIS-IV-L).²⁴ Of 436 individuals assessed for eligibility, 110 were administered the ADIS-IV-L to determine eligibility (Figure 1). After 35 patients were excluded, the 75 patients who met *DSM-IV* criteria for a principal diagnosis of generalized SAD were randomly assigned to either immediate I-CBT (n = 38) or a wait-list control group (n = 37) who were subsequently offered I-CBT. After dropout from the I-CBT (n = 6) and wait list (n = 5) groups, and incomplete neuroimaging data after CBT (n = 1) and wait list (n = 3), the final sample for this fMRI study consisted of 31 CBT completers and 29 wait-list completers. Baseline data from 27 of the 60 patients with SAD examined in this study were reported in a previous article¹⁵ on differential SAD vs healthy control brain responses to NSBs.

Exclusion Criteria

Patients had to pass an MRI safety screen and be right handed as assessed by the Edinburgh Handedness Inventory.²⁵ They were excluded for current pharmacotherapy or psychotherapy, past CBT, and history of neurological disorders. Patients were also excluded if generalized SAD was not determined to be the principal clinical diagnosis. Patients were not excluded if they met diagnostic criteria for generalized anxiety disorder, agoraphobia without panic attacks, specific phobia, major depression, or dysthymia.

Figure 1. Consolidated Standards of Reporting Trials Diagram for a Randomized Clinical Trial of Individual Cognitive Behavioral Therapy (I-CBT) vs Wait List (WL)



Procedure

Patients were recruited through referrals and web listings. They had to pass a telephone screen, the ADIS-IV-L interview conducted in person, and all baseline assessments before being randomly assigned to I-CBT or wait list using the Efron biased coin randomization procedure,²⁶ which promotes equal sample sizes throughout the clinical trial. All participants completed the same measures at baseline and again 19 weeks later after I-CBT or wait list.

Clinical Assessment

To measure social anxiety symptoms, we administered the Liebowitz Social Anxiety Scale–Self-Report,^{27,28} which has good reliability and construct validity.²⁹ Its internal consistency (Cronbach $\alpha = .91$) was excellent in this study. To measure SAD-related disability in work, social, and family domains, we administered the Sheehan Disability Scale,³⁰ which has good internal consistency and validity³¹ and had good internal consistency ($\alpha = .67$) in this study.

I-CBT for SAD

Individual CBT was delivered by 4 PhD-level clinical psychologists trained by Heimberg using *Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach*, a manualized treatment protocol that included a therapist guide³² and a client workbook³³ and consisted of 16 individual 1-hour sessions (except for the first in-session exposure session, which lasted 1.5 hours) administered over 4 months. Individual CBT covered (1) psychoeducation and orientation to CBT; (2) cognitive restructuring skills; (3) graduated exposure to feared social situations, within session and as homework; (4) examination and modification of core beliefs; and (5) relapse prevention and termination.^{16,32,33}

All 16 sessions for each client were digitally recorded and rated using the Cognitive-Behavioral Therapy for Social Anxiety Disorder: Therapist Adherence Scale³² by research team members who had clinical training and extensive familiarity with the CBT treatment adherence. They rated each session according to various criteria, using a 5-point Likert-type scale ranging from 1 (ineffective) to 5 (extremely effective). Average adherence ratings had to be greater than 4 to be considered “in protocol.” All 4 study therapists achieved this standard for each therapy case (overall mean [SD], 4.61 [0.24]).

Experimental Task

Patients identified 4 personally salient autobiographical social situations characterized by social anxiety, humiliation, and embarrassment and composed (1) a single paragraph to describe each situation and (2) situation-specific NSBs that were used to probe reactivity and reappraisal.

Before scanning, patients were trained using methods developed by Ochsner et al^{34,35} to either “react” by considering how the NSB reflected something true about themselves or “reframe” by using reappraisal to “actively reframe the belief by thinking in a way that reinterprets the content of the belief and thereby make the belief less negative and toxic for you.” For example, if the NSB is “No one likes me,” reframing may be telling yourself “That is not always true,” “Some people like me,” or “This is only a thought, not a fact.”

During scanning, patients read their autobiographical social situations with NSBs embedded in the unfolding story. After each NSB, patients rated “How negative do you feel?” (1 = not at all to 5 = very much).

The task involved 5 situations. The first was an experimenter-composed neutral situation about cleaning a car that was used to obtain baseline emotion ratings and brain responses. The second through fifth situations were participant-generated autobiographical social anxiety situations with idiographic NSBs.

Three situations were presented in a first run lasting 9 minutes, 21 seconds, followed by 2 situations in a second run of 6 minutes, 24 seconds. The sequence of 5 situations was fixed (neutral, react NSB, reappraise NSB, react NSB, and reappraise NSB) for several reasons. First, we wanted to control for order effects at the pretreatment and posttreatment assessments. Second, we wanted to obtain an unbiased estimate of brain responses to neutral statements (prior to emotional reactivity). Third, we wanted to assess react NSB prior to reappraise to minimize the effect of reappraisal on reactivity. Negative emotion ratings during the first and second react NSB blocks did not differ ($P > .45$).

Each situation consisted of an instruction to react or reframe (6 seconds), 16 sentences describing the situation (3 seconds each) in white font against a black background, 10 NSBs (9 seconds each) embedded in the unfolding story in uppercase letters that flashed 9 times to maximize attentional engagement with the text (850 milliseconds on and 150 milliseconds off), and a negative emotion rating (3 seconds) after each NSB (Figure 2). The NSBs appeared in white font for react trials and green font for reframe trials as a visual reminder to react or reappraise.

The experimental task was administered during a 1.5-hour scanning session at baseline and again post-CBT/wait list. After scanning, patients rated (1) how successful they were at implementing reappraisal during reframe trials on a scale of 0% to 100% successful and (2) how often they used reappraisal during the react trials on a scale from 0 (not at all) to 50 (moderately) to 100 (always).

Image Acquisition

We used a GE 3-T Signa magnet with a T2*-weighted gradient echo spiral-in/out pulse sequence³⁶ to acquire 630 functional volumes from 22 axial slices (repetition time = 1500 milliseconds, echo time = 30 milliseconds, flip angle = 60°, field of view = 22 cm, matrix = 64 × 64, resolution = 3.438 mm² × 4.5 mm). High-resolution anatomical scans were acquired using fast spin-echo spoiled gradient recalled acquisition in a steady state (0.8594² × 1.5 mm; field of view = 22 cm; frequency encoding = 256).

fMRI Data Processing

We used AFNI software³⁷ to remove outliers, register, motion correct, spatially smooth (4-mm³ isotropic kernel), high-pass filter (0.011 Hz), linear detrend, and convert into percentage of signal change each functional run. No volumes demonstrated motion in the x, y, or z directions in excess of ±0.8 mm. There was no evidence of stimulus-correlated motion (all *P*s > .30).

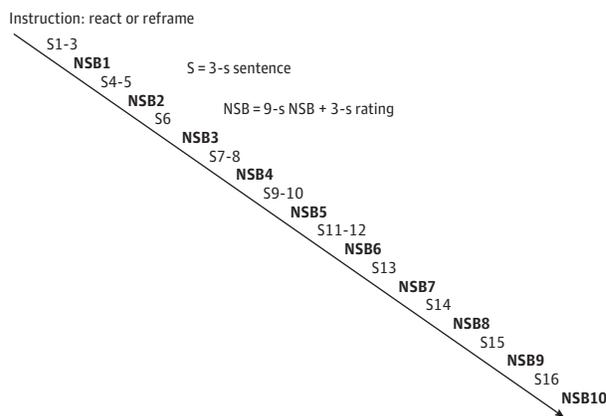
fMRI Statistical Analysis

We used 3dDeconvolve to conduct a multiple regression that included removal of mean, linear, and quadratic trends and motion-related variance in the BOLD signal. Regressors for the neutral statements, react, and reappraise were convolved with the gamma variate model³⁸ of the hemodynamic response function.

We converted brain maps into Talairach atlas space³⁹ and second-level group statistical parametric maps were produced according to a random-effects model. We investigated 10 a priori PFC ROIs in the DMPFC, dorsal anterior cingulate cortex, and bilateral medial anterior PFC, DLPFC, and VLPFC that were previously identified as more actively and rapidly recruited when reappraising NSBs in nonanxious healthy adults compared with patients with SAD.¹⁵ Because of its importance in anxiety disorders and emotional reactivity, we also investigated a priori Talairach atlas-defined amygdala ROIs.

We created spherical masks (radius = 7 mm, volume = 1437 mm³) centered on the peak x, y, z Talairach coordinates within each reappraisal-related ROI and amygdala masks, extracted mean BOLD responses, and conducted a multivariate analysis of variance with the Sidak correction for multiple comparisons to examine between-group differences in baseline to posttreatment BOLD signal changes for react NSBs vs neutral and reappraise NSBs vs neutral contrasts. We removed 1 participant from CBT and 1 from wait list with BOLD signal more than 3 SDs from the mean in the left amygdala. We also provide results for a supplemental whole-brain analysis of differential CBT vs wait list change for react NSBs vs neutral and reappraise NSBs vs neutral.

Figure 2. Experimental Design



Components and structure of 1 autobiographical social situation trial. After each negative self-belief (NSB), participants provide a negative emotion rating from 1 = not negative to 5 = extremely negative.

We investigated neural temporal dynamics in only the a priori ROIs that showed differential baseline to post-CBT/wait list change for react NSBs vs neutral (1 ROI) and reappraise NSBs vs neutral (2 ROIs). To do this, we conducted a 2 group (CBT and wait list) × 6 time (×1.5 seconds = 9 seconds) repeated-measures analysis of variance (ANOVA) (Huynh-Feldt corrected for autocorrelation in time series) on BOLD signal for each trial (with a 6-second shift to account for the temporal delay in the hemodynamic response). A follow-up paired *t* test tested for differential early (0-3 seconds) vs late (6-9 seconds) BOLD responses.

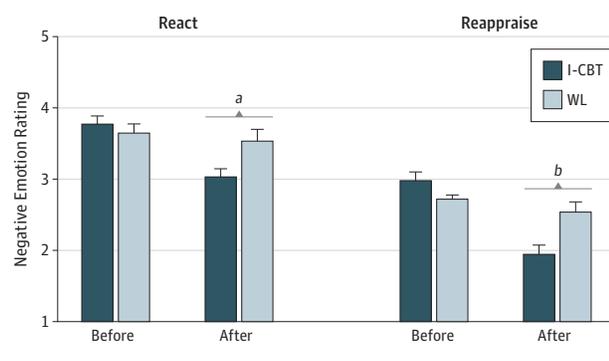
To investigate PFC-amygdala circuitry, we implemented a context-dependent functional connectivity analysis for each group at baseline and post-CBT/wait list for only 1 contrast (reappraise vs react NSBs). To reduce false-positive detection, the connectivity analysis was seeded to the single reappraisal-related a priori ROI (DMPFC) that showed both BOLD signal magnitude and timing results. We then computed baseline to posttreatment change scores and conducted a between-group *t* test to identify the interaction of group × time on PFC-amygdala connectivity. We focused the connectivity analysis within the a priori Talairach-defined amygdala search region using a *t* value associated with *P* < .03 and cluster volume of 160 mm³ or more.

Results

Preliminary Analyses

Patients in the I-CBT and wait list groups did not differ significantly in sex, age, education, ethnicity, yearly income, marital status, current or past Axis I comorbidity, past psychotherapy or pharmacotherapy, age at symptom onset, or years since symptoms onset (eTable 1 in Supplement). Ethnicity was self-reported by research participants in accordance with National Institutes of Health requirements.

Figure 3. Changes in Negative Emotion Intensity Ratings



Changes in negative emotion intensity ratings for react negative self-beliefs and cognitive reappraisal of negative self-beliefs in patients with social anxiety disorder before and after individual cognitive behavioral therapy (I-CBT) vs wait list (WL). 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, 4 = very much, and 5 = extreme). Error bars = standard error of the mean.

^a $P < .05$.

^b $P < .001$.

As reported elsewhere,¹⁷ an intent-to-treat analysis showed that, compared with wait list, I-CBT resulted in significantly greater reduction of social anxiety symptoms (Δ I-CBT = -29.7 vs Δ wait list = -8.2 ; $F_{2,73} = 20.0$; $P < .001$; $\eta_p^2 = 0.21$) and disability (Δ I-CBT = -9.3 vs Δ wait list = -1.2 ; $F_{2,73} = 5.6$; $P < .05$; $\eta_p^2 = 0.07$). Using the Jacobson and Truax⁴⁰ method, we determined that 19 of 31 patients (61.3%) who completed I-CBT and the fMRI assessments demonstrated clinically significant reduction in social anxiety symptoms.

As a manipulation check, at post-MRI scanning, we examined the self-reported success in implementing reappraisal of NSBs. A 2 group (I-CBT and wait list) \times 2 time (baseline and posttreatment) repeated-measures ANOVA yielded a significant group \times time interaction ($F_{2,55} = 18.14$; $P < .001$; $\eta_p^2 = 0.25$), no effect of group ($F_{1,56} = 1.81$; $P > .18$), but a significant effect of time ($F_{1,56} = 27.63$; $P < .001$; $\eta_p^2 = 0.33$). Follow-up paired t tests showed reappraisal success increased from baseline to post-I-CBT (mean [SD], baseline: 34.68 [21.09] vs post-I-CBT: 69.52 [17.62]; $t_{30} = 6.55$; $P < .001$; $\eta_p^2 = 0.59$) and did not change from baseline to post-wait list (mean [SD], baseline: 44.81 [19.97] vs post-wait list: 48.46 [23.48]; $t_{25} = 0.75$; $P > .46$). There was no significant difference between groups in reappraisal success at baseline ($t_{55} = 1.85$; $P > .07$).

We also examined post-MRI scanning self-reported use of reappraisal during react NSB trials when participants were not instructed to implement reappraisal (ie, uncued or spontaneous use of reappraisal). A 2 group (I-CBT and wait list) \times 2 time (baseline and posttreatment) repeated-measures ANOVA yielded a significant group \times time interaction ($F_{2,52} = 4.34$; $P < .05$; $\eta_p^2 = 0.08$), no effect of group ($F_{1,52} = 0.35$; $P > .56$), but a significant main effect of time ($F_{1,52} = 4.34$; $P < .05$; $\eta_p^2 = 0.08$). Follow-up t tests showed that spontaneous reappraisal during react NSBs increased from baseline to post-I-CBT (mean [SD], baseline: 23.67

[27.57] vs post-I-CBT: 37.75 [30.13]; $t_{29} = 2.91$; $P < .01$) but did not change in the wait list group (mean [SD], baseline: 26.88 [25.27] vs post-wait list: 26.88 [21.46]; $t_{23} = 0$; $P > .99$). There was no significant difference between groups in reappraisal during react trials at baseline ($t_{53} = 0.57$; $P > .57$).

Responses to NSBs

Behavioral Responses

A 2 group (I-CBT and wait list) \times 2 time (baseline and post-treatment) repeated-measures ANOVA on negative emotion ratings resulted in a group \times time interaction when reacting to NSB ($F_{2,58} = 8.63$; $P = .005$; $\eta_p^2 = 0.13$), a main effect of time ($F_{1,58} = 16.24$; $P = .001$; $\eta_p^2 = 0.23$), and no effect of group ($F_{1,58} = 1.37$; $P > .24$) (Figure 3). Follow-up t tests showed CBT-related decreases in negative emotion ($t_{30} = 5.18$; $P < .001$; $\eta_p^2 = 0.47$) and no change in the wait list group ($t_{27} = 0.74$; $P > .46$). There was no significant difference between groups at baseline ($t_{59} = 0.76$; $P > .45$).

Brain Response Magnitude

When we examined a priori amygdala ROI responses for the contrast of react NSBs vs neutral statements with a 2 group (CBT and wait list) \times 2 time (baseline and posttreatment) repeated-measures ANOVA, there were no interactions or main effects in the left (all P s $> .11$) or right amygdala (P s $> .06$).

For the 10 reappraisal-related a priori PFC ROIs, a multivariate analysis of variance with the Sidak correction for multiple comparisons on baseline to posttreatment BOLD signal change for react NSBs vs neutral statements yielded only a between-group difference in the medial PFC region ($F_{2,58} = 4.29$; $P < .05$; $\eta_p^2 = 0.07$), consisting of CBT increases ($t_{30} = 2.20$; $P < .05$; $\eta_p^2 = 0.14$) but no change in wait list ($t_{27} = 1.26$; $P > .21$).

Brain Response Temporal Dynamics

The examination of BOLD signal temporal dynamics in the medial PFC across the six 1.5-second points for react NSBs vs neutral yielded no interaction ($P > .80$) or main effects of group ($P > .39$) or time ($P > .35$).

Cognitive Reappraisal of NSBs

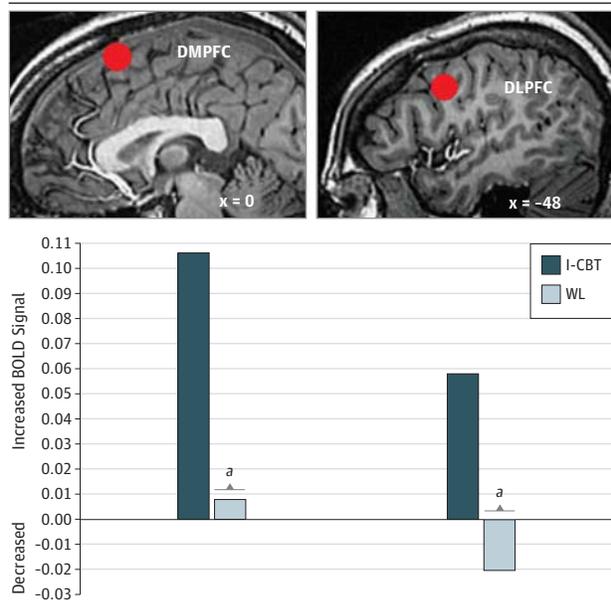
Behavioral Responses

A 2 group (I-CBT and wait list) \times 2 time (baseline and post-treatment) repeated-measures ANOVA on negative emotion ratings during reappraise NSBs resulted in a group \times time interaction ($F_{2,58} = 21.59$; $P < .001$; $\eta_p^2 = 0.28$), no effect of group ($F_{1,58} = 1.66$; $P > .20$), but a significant main effect of time ($F_{1,58} = 41.29$; $P < .001$; $\eta_p^2 = 0.42$) (Figure 3). Follow-up paired t tests showed CBT-related decreases in negative emotion (16.1%; $t_{30} = 8.93$; $P < .001$; $\eta_p^2 = 0.73$) and no change in the wait list group (1.7%; $t_{27} = 1.11$; $P > .27$). There was no difference between groups at baseline ($t_{59} = 1.59$; $P > .12$).

Brain Response Magnitude

For the a priori amygdala ROIs, a 2 group (CBT and wait list) \times 2 time (baseline and posttreatment) repeated-measures ANOVA on BOLD responses for reappraise NSBs vs neutral statements yielded no main or interaction effects in the left (all P s $> .15$) and right (all P s $> .06$) amygdala.

Figure 4. Changes in Brain Responses



Changes in brain responses in the dorsomedial prefrontal cortex (DMPFC) and left dorsolateral prefrontal cortex (DLPFC) a priori cognitive reappraisal-related prefrontal cortical brain regions of interest in patients with social anxiety disorder before and after individual cognitive-behavioral therapy (I-CBT) vs wait list (WL). The dot represents the spherical region of interest mask used in the analysis. Blood oxygen level-dependent (BOLD) signal represents before to after I-CBT and WL change scores in BOLD signal responses.

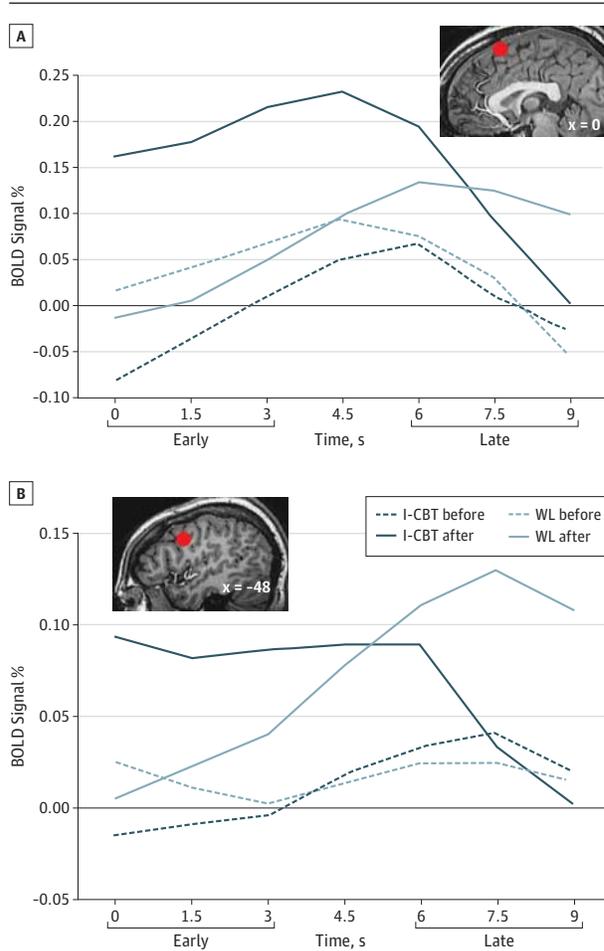
^a $P < .05$.

For the 10 reappraisal-related ROIs, a multivariate analysis of variance with the Sidak correction for multiple comparisons on baseline to posttreatment change for reappraise NSBs vs neutral statements yielded overall significance between groups ($F_{10,47} = 3.22; P = .003; \eta_p^2 = 0.41$). For the corrected model, there was evidence of between-group difference in only 2 regions: DMPFC ($\Delta = 0.10$; 95% CI, 0.01-0.19; $F_{2,58} = 4.70; P = .04; \eta_p^2 = 0.08$), consisting of CBT increases ($\Delta = 0.11; t_{30} = 3.36; P < .002; \eta_p^2 = 0.27$) but no change for wait list ($\Delta = 0.01; t_{27} = 0.23; P > .82$), and left DLPFC ($\Delta = 0.08$; 95% CI, 0.01-0.15; $F_{2,58} = 5.20; P < .03; \eta_p^2 = 0.09$), consisting of CBT increases ($\Delta = 0.06; t_{30} = 2.37; P < .05; \eta_p^2 = 0.16$) and no change for wait list ($\Delta = -0.02; t_{27} = 0.86; P > .39$) (Figure 4). The supplemental whole-brain analysis confirmed the ROI-based observation of increased BOLD responses in the DMPFC and left DLPFC (eTable 2 in Supplement).

Brain Response Temporal Dynamics

For the DMPFC, there was a significant interaction of group \times time ($F_{8,52} = 2.42; P < .05; \eta_p^2 = 0.04$) and no main effects of group ($P > .34$) or time ($P > .43$) (Figure 5). Follow-up baseline to posttreatment within-group paired t tests showed that the interaction was driven by linear changes ($t = 2.79; P = .007; \eta_p^2 = 0.12$) characterized by significantly increased early (0-3 seconds) vs late (6-9 seconds) responses in the I-CBT group (early: 0.23% vs late: 0.05%; $t_{30} = 2.22; P < .05$) and decreased early vs late responses in the wait list group (early:

Figure 5. Blood Oxygen Level-Dependent (BOLD) Signal Time Series



Blood oxygen level-dependent signal time series in the dorsomedial prefrontal cortex (A) and left dorsolateral prefrontal cortex (B) during reappraise negative self-beliefs vs read neutral statements. I-CBT indicates individual cognitive-behavioral therapy and WL, wait list.

–0.15% vs late: 0.01%; $t_{27} = 2.05; P < .05$). For the left DLPFC, the same analysis yielded no main or interaction effects (all P s $> .30$).

Context-Dependent Functional Connectivity

The DMPFC-seeded functional connectivity analysis for reappraise vs react NSBs showed that, compared with wait list, CBT produced greater inverse connectivity between the DMPFC and left amygdala and the right hippocampus and positive connectivity in the medial PFC and 2 DLPFC regions (Table and Figure 6).

Discussion

This study found that, compared with wait list, I-CBT for SAD resulted in reduction of negative emotions when reacting to and reappraising NSBs, no change in amygdala responses, and changes in BOLD signal magnitude, temporal dynamics, and

functional connectivity during cognitive reappraisal of NSBs in patients with SAD.

Responses to NSBs

When reacting to NSBs, compared with wait list, I-CBT resulted in a significant reduction of self-reported negative emotion. The absence of a change in negative emotion from baseline to post-wait list suggests that there was no habituation to

NSBs from the time 1 to time 2 assessments. Reduction in emotional reactivity to NSBs post-CBT may be associated with extensive practice in cognitive restructuring during exposures during CBT, which likely leads to greater skill in implementing reappraisal strategies. The decreases in negative emotion from baseline to post-CBT may reflect increased spontaneous (uncued) reappraisal during react trials, an interpretation that is consistent with CBT participants' greater reports of reappraisal during react trials.

Neurally, there were no interactions or main effects of group and time in the left or right amygdalae, suggesting that amygdala reactivity to NSBs remained consistent across time and across groups. While some studies have observed CBT-related reductions in amygdala responses using positron emission tomography during public speaking,²¹ the ability to detect changes in the amygdala using fMRI depends very much on task design, timing, and speed of habituation. Our baseline study showed rapid habituation of amygdala responses during both react and reappraise NSBs in both patients with SAD and healthy controls.¹⁵ There was, however, a single interaction of group × time in the medial PFC. This region is involved in reappraisal in general^{41,42} and is specifically implicated in reappraisal of negative emotion.¹⁵ Like the negative emotion ratings, this may reflect spontaneous implementation of reappraisal even when uninstructed.

Cognitive Reappraisal of NSBs

Behaviorally, during reappraisal of NSBs, compared with wait list, I-CBT resulted in greater reduction of self-reported negative emotion experience. The effect size (η_p^2) of this reduction was larger for reappraisal (0.73) than for react (0.47) NSBs, which may represent the differential impact of I-CBT on cued

Table. Differential Between-Group Baseline to Posttreatment Change in DMPFC-Seeded Context-Dependent Functional Connectivity of Cognitive Reappraisal vs React Negative Self-beliefs

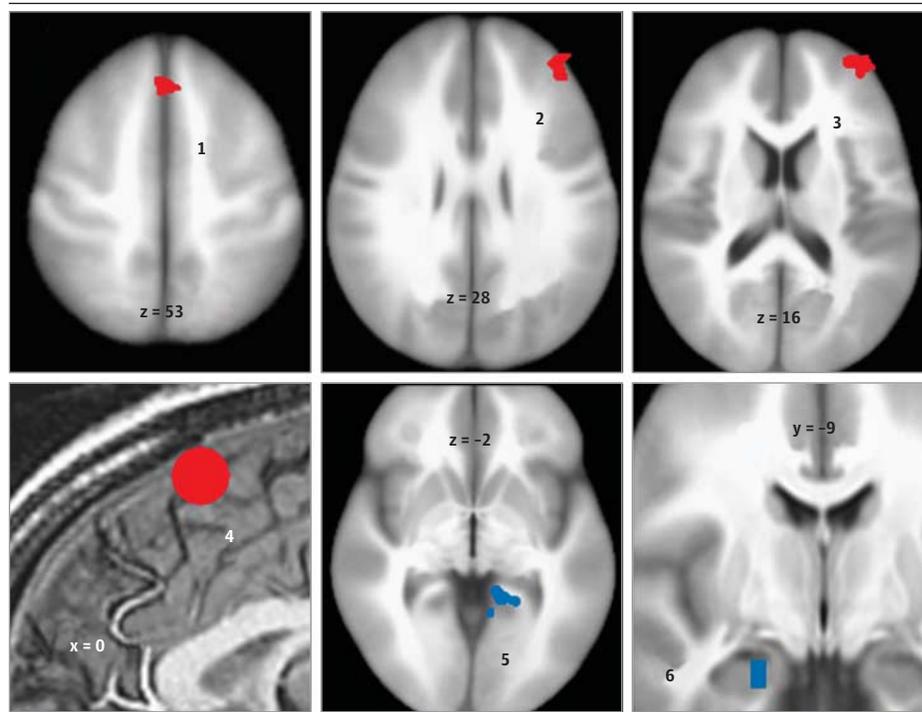
Brain Regions	Baseline to Posttreatment Change	x, y, z ^a	Volume, mm ³	t Value
Positive FC				
Medial PFC	CBT>WL	0, 25, 53	266	3.74
R DLPFC	CBT>WL	38, 45, 29	583	3.71
R DLPFC	CBT>WL	41, 56, 15	848	3.79
Inverse FC				
R posterior hippocampus	CBT<WL	21, -44, -2	583	3.50
L amygdala ^b	CBT<WL	-20, -9, -18	160	2.95

Abbreviations: CBT, cognitive behavioral therapy; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; FC, functional connectivity; L, left; PFC, prefrontal cortex; R, right; WL, wait list; x, y, z, Talairach coordinates.

^a t Value ≥ 2.91; per-voxel P < .005; minimum cluster volume threshold ≥ 266 mm³ (5 voxels × 3.44 mm² × 4.5 mm); and clusterwise P < .01.

^b For this cluster within the a priori Talairach-defined amygdala search region, FC was observed at a more lenient threshold consisting of t value ≥ 2.30; per-voxel P < .03; and minimum cluster volume threshold ≥ 160 mm³.

Figure 6. Differential Between-Group Baseline to Posttreatment Change



Differential between-group baseline to posttreatment change in dorsomedial prefrontal cortex-seeded context-dependent functional connectivity of cognitive reappraisal vs react negative self-beliefs. 1 Indicates medial prefrontal cortex; 2, right dorsomedial prefrontal cortex; 3, right middle frontal gyrus; 4, dorsomedial prefrontal cortex seed; 5, left hippocampus; and 6, left amygdala. For the whole-brain analysis, thresholding consisted of a per-voxel P < .005 and cluster volume threshold of 263 mm³ or more. Within the amygdala search region, thresholding consisted of a per-voxel P < .03 and cluster volume threshold of 160 mm³ or more.

reappraisal vs spontaneous reappraisal. These behavioral results are consistent with CBT participants' reports of greater success at using reappraisal. The absence of change in reappraisal-related reduction of negative emotion from baseline to post-wait list highlights the stability of reappraisal deficits in patients with SAD when untreated.

Neurally, group \times time interactions occurred in a priori DMPFC and left DLPFC ROIs, which were characterized by increases following I-CBT and no change following wait list. These regions are implicated in the cognitive control of emotion and usually coactivate when downregulating negative emotion.⁴² A recent meta-analysis of emotion regulation processes has shown that, in contrast to fear extinction and placebo control, reappraisal uniquely involves the left DLPFC and DMPFC.⁴¹

Prior investigations of neural temporal dynamics when implementing reappraisal of NSBs¹⁵ have demonstrated differential timing in reappraisal-related PFC regions consisting of quicker recruitment in healthy controls and delayed recruitment in patients with SAD. In the present study, post-wait list, patients with SAD continued to show delayed recruitment of the left DLPFC and DMPFC. Post-CBT, however, there was a shift to the normative earlier recruitment of DMPFC, which may be related to enhanced ability to access and implement reappraisal strategies and/or due to reduced emotional reactivity to NSBs (which might interfere with implementing reappraisal effectively). Figure 5 shows a post-CBT pattern of greater earlier recruitment of DLPFC and later nonrecruitment similar to DMPFC. However, the BOLD signal magnitude was too small to yield significance. This differential pattern raises the question of whether DLPFC and DMPFC serve different cognitive functions at different points during reappraisal.

The present findings, as well as those of other studies, suggest that the DMPFC plays a key role in emotion regulation. Studies have demonstrated that greater DMPFC activity is related to greater reappraisal success in both healthy controls and patients with SAD.^{14,43} In the present study, in addition to BOLD signal magnitude increases in DMPFC during reappraisal following I-CBT, there was evidence that CBT altered the link between DMPFC activity and amygdala response.

The DMPFC-seeded functional connectivity analysis showed a group \times time DMPFC-left amygdala interaction driven by inverse DMPFC-amygdala connectivity at post-CBT only and not at baseline in either group or after wait list. Interestingly, while there was no overall CBT-related BOLD signal magnitude change in amygdala responses, these results highlight that distributed rather than absolute changes in limbic-PFC patterns may be more reflective of underlying abnormalities in SAD and also in understanding 1 neurobiological mechanism of change during CBT. The DMPFC positive connectivity with 3 more PFC regions converges with prior evidence that DMPFC is important for effective top-down cognitive reappraisal of negative emotion in SAD.^{14,15,42} The inverse DMPFC-hippocampus connectivity may be related to lesser activation of memories associated with the autobiographical situation and NSBs.

Clinical Implications

Findings from this study highlight CBT-related enhancement of reappraisal, specifically, decreased negative emotion experience along with greater and quicker recruitment of reappraisal-related DMPFC neural responses, which are related to lesser amygdala responses to NSBs. This reinforces the clinical insight that emotion regulation and clinical symptoms are modified by CBT.

Modifiable temporal dynamics of reappraisal suggest that it might be clinically valuable to have clients record how quickly they can volitionally implement reappraisal following emotional triggers in social situations. This could be experimentally controlled during therapy sessions and measured during in vivo exposures outside of therapy sessions. Bringing attention to the timing of reappraisal and what factors enhance or interfere with more rapid implementation of reappraisal strategies could itself be a specific clinical insight that can be incorporated into the cognitive restructuring and exposure components of CBT protocols for treating anxiety disorders. Specifically, research needs to determine whether different forms of attention training (eg, that reduce self-focused attention) might impact the timing of reappraisal in SAD.

Equally intriguing is the finding indicating that CBT enhances not only cued reappraisal but also spontaneous reappraisal. This may be due to the generalization of the skills learned during CBT and may reflect a shift from initially effortful to subsequently spontaneous or automatic implementation of reappraisal. This raises intriguing questions about the extent to which the association of cued and spontaneous reappraisal (and their neural timing) is related to (1) clinical symptoms in patients with SAD and (2) immediate and longer-term treatment outcome of CBT.

Limitations and Future Directions

The current study is limited to inferences about reappraisal of participant-generated NSBs during autobiographical recall of personally meaningful events. Although this represents a key target of psychotherapy, it will be useful to investigate the impact of CBT on reappraisal of other-focused negative beliefs and to enhance positive experiences (ie, upregulate positive emotions), which may also be an important skill trained in CBT. Neurally, CBT for SAD yielded significant interactions in 3 of the 10 normative reappraisal-related a priori PFC ROIs. The functional connectivity analysis provided evidence for the coactivation in 3 more PFC regions implicated in cognitive reappraisal. Further research is necessary to identify which PFC regions contribute to longer-term treatment responses in SAD.

Our focus on 1 type of therapy for 1 type of disorder was dictated both by theory and the available literature. Future research could investigate how different forms of CBT (eg, individual vs group) and other clinical interventions for SAD influence the temporal dynamics of brain networks involved in different emotion regulation strategies. It will be important to examine how these therapeutic effects generalize to other disorders.

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