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Cognitive-Behavioral Therapy for Generalized Anxiety Disorder is Associated with Attenuation of Limbic Activation to Threat-Related Facial Emotions

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Abstract

Background—The neural processes underlying the benefits of cognitive behavioral treatment (CBT) for generalized anxiety disorder (GAD) are not well understood.

Methods—Twenty-one (n=21) adults with a principal diagnosis of GAD and eleven (n=11) non-anxious healthy controls (HC) underwent functional magnetic resonance imaging while completing a facial emotion processing task. Responses to threat-related emotionality (i.e., the contrast of fear and angry vs. happy faces) were assessed at pretreatment and again following 10 sessions of CBT in the GAD group and a comparable waiting period in the HC group.

Results—At pretreatment, GAD participants displayed blunted responses in the amygdala, insula, and anterior cingulate to the happy face-processing comparison condition, and greater amygdalo-insular connectivity. CBT was associated with attenuated amygdalar and subgenual anterior cingulate activation to fear/angry faces and heightened insular responses to the happy face

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CONFLICTS OF INTEREST

All of the authors report no financial conflicts of interest.

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comparison condition, but had no apparent effects on connectivity. Pre-treatment abnormalities and treatment-related changes were not associated with symptoms of worry.

Limitations—There was no active control condition (e.g., treatment waitlist) for comparison of treatment effects.

Conclusions—Taken together, these results provide evidence for a dual-process psychotherapeutic model of neural systems changes in GAD in which cingulo-amygdalar reactivity to threat cues is attenuated while insular responses to positive facial emotions are potentiated. Future work is needed to determine the clinical implications of these changes and their specificity to CBT.

Keywords

GAD; imaging; CBT; amygdala; psychotherapy

INTRODUCTION

Generalized anxiety disorder (GAD) is a prevalent and debilitating anxiety disorder (Kessler et al. 2005) characterized by chronic, pervasive, and uncontrollable worry as well as associated somatic symptoms (American Psychiatric Association 2000). Functional neuroimaging studies have demonstrated that GAD is associated with altered function of brain structures such as the amygdala (Etkin et al. 2009) and prefrontal cortex (Paulesu et al. 2010, Etkin et al. 2010) during paradigms that invoke processing of emotional content. The amygdala is crucial for the detection and processing of emotional stimuli (Kober et al. 2008) and has been found to display hyperactivity across a wide range of anxiety disorders (Etkin, Wager 2007). The prefrontal cortex is heavily implicated in higher-order regulatory mental functions (Campbell-Sills et al. 2011), which serve to inhibit limbic responsivity (Quirk et al. 2003, Milad, Quirk 2002). Prefrontal-limbic interactions may be particularly relevant to the pathophysiology of GAD given the role of these regions in worry behavior (Paulesu et al. 2010, Andreescu et al. 2011), existing findings for abnormal prefrontal-limbic connectivity in GAD during both a resting state (Etkin et al. 2009) and implicit emotion regulation paradigm (Etkin et al. 2010, Etkin, Schatzberg 2011), and their ability to differentiate GAD from major depressive disorder (Etkin, Schatzberg 2011) and social anxiety disorder (Blair et al. 2008).

Cognitive-behavioral therapy (CBT) is a widely utilized and efficacious treatment for GAD, but there are still a large number of individuals who do not respond (Mitte 2005). The neural functional changes underlying responses to treatment and changes in symptoms are also not well understood. Studies have observed that greater activity in the rostral anterior cingulate (ACC) during viewing of emotional faces and during anticipation of negative and neutral pictures predicted greater reduction in symptoms following pharmacotherapy with venlafaxine (Nitschke et al. 2009a, Whalen et al. 2008). However, with exception of one study in adolescents (Maslowsky et al. 2010), few studies have been conducted in GAD investigating neural functional changes following CBT and their relationship with changes in symptom manifestations. This is an important focus for research given: a) the relative paucity of information concerning the neural substrates responsive to CBT for anxiety

disorders; b) the potential to improve CBT treatment outcomes through a greater understanding of the neurobiological mechanisms underlying responses to CBT; and c) the potential to leverage this knowledge towards tracking of treatment progress and prediction of outcomes.

The purpose of this investigation was therefore threefold. First, we aimed to complement the existing literature by identifying functional abnormalities of limbic and prefrontal activation and connectivity in GAD using a widely-utilized facial emotion-processing paradigm that reliably engages relevant neurocircuitry (Hariri et al. 2005). Emotional faces, particularly those conveying anger and fear, readily engage neurocircuitry relevant to the pathophysiology of anxiety (Fusar-Poli et al. 2009), and are therefore useful experimental probes in this context. Second, we sought to determine the functional changes associated with CBT for GAD in and amongst relevant brain regions. Third, we attempted to characterize how CBT-related functional changes are associated with changes in worry following therapy. In accordance with existing evidence (Etkin et al. 2009, Paulesu et al. 2010, Nitschke et al. 2009a, McClure et al. 2007), we predicted that at pre-treatment GAD participants would display increased activation of the amygdala and decreased activation of the anterior cingulate/medial prefrontal cortical regions (ACC/mPFC) to threat-related stimuli. Following treatment, we predicted CBT would result in an attenuation of these amygdalar and ACC/mPFC group differences. Lastly, given that ACC/mPFC activity has been implicated in worry symptoms (Paulesu et al. 2010) and in prediction of treatment response in GAD (Nitschke et al. 2009a, Whalen et al. 2008), we predicted that reductions in worry symptoms would be associated with changes in activation in this region.

METHODS

Participants

Participants ages 18–55 were recruited through local online and print advertisement and referral from university-affiliated primary care clinics. Participants with GAD ($n=21$) were all treatment seeking and recruited to participate in an intervention study. Healthy control (HC) participants ($n=12$) were recruited to undergo functional magnetic resonance imaging (fMRI). Experienced clinicians established DSM-IV psychiatric diagnoses using the structured diagnostic Mini International Neuropsychiatric Interview (Sheehan et al. 1998). Though anxiety or mood disorder comorbidity was permitted for GAD participants, GAD had to be clinically predominant as judged by consensus of the research team. Psychiatric exclusion criteria included lifetime diagnosis of a psychotic disorder, organic mental disorder, mental retardation, bipolar I disorder, substance dependence in the past 12 months, and current (past-month) substance abuse. For the HC subjects, additional exclusion criteria included lifetime diagnosis of mood or anxiety disorders, eating disorders, or substance dependence. Urine screening was used to test for presence of illicit drugs. All participants were required to be psychotropic or antiepileptic medication-free for 6 weeks prior to recruitment (2 weeks for benzodiazepines). After complete description of the study to subjects, they provided written informed consent according to University of California-San Diego Human Research Protection Program guidelines. See Supplement for general/neurological exclusion criteria. See Table 1 for demographic and comorbidity information.

Self-Report Measures

Prior to undergoing fMRI scanning, all participants completed the Penn State Worry Questionnaire (PSWQ) (Meyer et al. 1990), the Overall Anxiety Severity and Impairment Scale (OASIS) (Norman et al. 2011, Campbell-Sills et al. 2009), and the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al. 2003). The GAD participants completed the measures again approximately 12 weeks later following completion of cognitive-behavioral therapy.

Cognitive-Behavioral Therapy

Following the initial pretreatment scan, all GAD participants underwent ten sessions of weekly cognitive-behavioral therapy (CBT) within a twelve week period (to allow for makeup of missed sessions) performed by an experienced masters or doctoral-level clinician. See Supplemental Methods for further details.

Task

Participants underwent scanning while completing a modified version of the Emotion Face Assessment Task (Hariri et al. 2005, Paulus et al. 2005) with angry, fearful, and happy faces. See Supplemental Methods for further details.

fMRI Data Acquisition

See Supplemental Methods.

Activation Preprocessing/Individual-Level Analysis

Data were processed using AFNI (Cox 1996). Voxel time-series data were coregistered to an intra-run volume, then to the anatomical image of each participant, and corrected for artifact intensity spikes. Those time points with greater than 2 standard deviations more voxel outliers than the subject's mean were excluded from analysis. Rotational parameters (roll, pitch, and yaw) were used as nuisance regressors for motion artifact. Time series data were normalized to Talairach coordinates (22), and a Gaussian smoothing filter with a full-width half max (FWHM) of 4 mm was applied to each participant's time series. A deconvolution analysis was conducted in which regressors of interest were target trials of: 1) happy faces; 2) angry faces; 3) fearful faces; and 4) shapes. The outcome measures of interest were activation magnitudes (%SCs) for the within-subject contrasts of each target emotion type vs. the shape-matching baseline condition.

Functional Connectivity Preprocessing/Individual-Level Analysis

Task-related activation in the amygdala during processing targeted towards threat (angry and fearful) vs. non-threat (happy) faces was chosen as a seed region, both for baseline analyses and for assessing changes following CBT. This region was specifically chosen due to *a-priori* hypotheses as well as significant activation differences between GAD and HC at baseline and changes in activation in GAD participants following CBT treatment. Functional connectivity analyses were conducted according to previously established methods (Fonzo et al. 2010) but slightly modified using a recently-published preprocessing pathway that

maps and removes sources of artifact in scanner signal (Jo et al. 2010). See Supplemental Methods for further details.

Task Effect, Group Difference, and Pre/Post-Treatment Analyses

To identify group differences, voxelwise activation and connectivity values were subjected to linear mixed effects analysis conducted within R (R Development Core Team 2011). To identify pre-treatment group activation differences, group and emotion type (i.e., angry vs. oval, fear vs. oval, etc.) were entered as model factors in conjunction with a random intercept resulting in a 2 (Group) x 3 (Emotion) factorial design. The outcome measure of interest was the group x emotion interaction effect for a contrast vector specifying the differences between fear and angry vs. oval and happy vs. oval (i.e., processing threat vs. non-threat emotional faces). We have chosen to explore the contrast of threat-related emotion for several reasons. First, our analyses of a large cohort of individuals with ($n = 162$) and without ($n = 96$) various anxiety disorders revealed that contrasts between emotional face-types produced greater between-group effect sizes in relevant limbic structures than contrasts with a sensorimotor control condition (mean voxelwise amygdala Cohen's D for fear vs. happy = 0.16, mean voxelwise amygdala Cohen's D for fear vs. oval = 0.07; unpublished data). Second, the contrast between emotional face-types provides greater specificity of emotion-related processing differences. Third, this contrast is most comparable with prior studies, which have used happy or neutral faces for comparison. As the target emotional expression on each trial occurs in the presence of a non-congruent emotional expression, effects elicited by this contrast should be interpreted as occurring within the context of emotional appraisal directed towards the predominant (i.e. target) and away from the non-congruent (i.e, distractor) emotional expression, hereafter referred to as targeting threat vs. non-threat faces. These contrasts have proven useful elsewhere for eliciting anxiety-related hyperactivity in relevant limbic structures (Fonzo et al. 2010). To identify pre-treatment connectivity differences, the Fisher Z -transformed correlation coefficients (rFz 's) for the PPI were entered into a linear mixed model with group as a fixed factor and a random model intercept.

To identify treatment-related changes, another mixed effects analysis was conducted in which Group, Emotion Type (i.e., angry vs. oval, fear vs. oval, etc.), and Time (pre or post-tx) were entered as model factors in conjunction with a random intercept resulting in a 2 (Group) x 3 (Emotion) x 2 (Time) factorial design. The outcome measure of interest was the group x time interaction effect for the same contrast vector specifying threat vs. non-threat emotion (i.e. voxels in which time-related changes to the threat vs. non-threat contrast were significantly different between GAD and HC). To identify treatment-related connectivity differences, the rFz 's for the PPI were entered into a linear mixed model with group and time point as model factors, along with a random model intercept. In addition to a whole-brain (WB) exploratory analysis, *a-priori* region of interest (ROI) analyses were conducted on emotion-processing brain regions previously implicated in studies of GAD: bilateral insula, bilateral amygdala, and anterior cingulate/medial prefrontal cortex (ACC/mPFC). Boundaries of these ROIs were based upon both anatomical criteria and standardized locations taken from the Talairach atlas (Talairach, Tournoux 1998). A threshold adjustment based upon Monte-Carlo simulations (using AFNI's program AlphaSim) was used to guard

against false positives in the WB and ROI analyses. See Supplemental Methods for further details.

Neural Correlates of Pre-Treatment Worry and Treatment-Related Change in Worry

In order to assess GAD activation abnormalities at pre-treatment and treatment-related changes which related to worry symptoms and change in worry, respectively, robust regressions conducted in R (R Development Core Team 2011, Wager et al. 2005, Huber 1964) were implemented by regressing %SCs for each contrast on PSWQ total scores and treatment-related changes in PSWQ total scores, respectively. Pre-treatment QIDS and OASIS scores, as well as changes in these measures following treatment, were also added as factors into the regression models to control for symptom relationships non-specific to worry. The voxelwise regression maps for the factor of interest (PSWQ) were then masked and error-protected, and the conjunction of the error-protected correlation map with the congruent error-protected group difference/treatment-related change map was examined for significant overlap (as determined through Monte-Carlo simulations on the cluster from the group difference map).

Behavioral and Self-Report Measure Statistical Analyses

All statistical analyses for behavioral and self-report measures were conducted using IBM SPSS Statistics 19.0 (SPSS Inc., an IBM company 2010). Pre-treatment behavioral data and symptom measures were subjected to a linear mixed model analysis with group as a fixed factor, task condition as a random and fixed factor (for behavioral data only), and a random intercept. Significant omnibus effects were followed up with pairwise comparisons using Bonferroni correction for multiple comparisons. The effect of treatment on behavioral data and symptom measures in GAD participants was assessed using a linear mixed model with group and time point as fixed factors, task condition as a random and fixed factor (for behavioral data only), and a random intercept.

RESULTS

Participant Demographics and Self-Report Measures

The GAD and HC groups did not differ with regard to age, ethnicity, gender, or years of education. At the pre-treatment assessment, the GAD participants displayed significantly higher levels of worry, anxiety, and depressive symptoms as demonstrated by higher total scores on the PSWQ, OASIS, and QIDS-SR (all p 's < 0.001; Table 1). A repeated-measures multivariate GLM revealed a significant effect of treatment ($F(3,18) = 10.903, p = 0.001$, partial $\eta^2 = 0.534$), and follow-up tests revealed a significant treatment-related attenuation of symptoms on all outcome measures (all p 's < 0.05; Table 1). Effect sizes for treatment (Cohen's D) were consistent with those reported in a meta-analysis of CBT treatments for GAD (Mitte 2005) and were as follows: PSWQ ($d = 0.38$), OASIS ($d = 1.18$), QIDS-SR ($d = 0.83$).

Behavioral Data

At pre-treatment, there was no effect of diagnosis on overall task accuracy, nor was there a significant diagnosis x condition interaction effect. There was a significant effect of

condition ($F(3,30)=3.883$, $p=0.019$) such that participants were more accurate for matching to happy faces relative to matching shapes ($p=0.036$, Bonferroni-corrected). There was a significant effect of diagnosis ($F(1,30)=5.197$, $p=0.03$) and condition ($F(3,30)=83.365$, $p<0.001$) on performance speed, but no significant diagnosis x condition interaction. Specifically, GAD participants had slower reaction times across all task conditions, and all participants matched trials from fastest to slowest in the following order: shapes, happy, angry, fear (all p 's < 0.05 , Bonferroni-corrected).

At post-treatment, there was no significant effect of diagnosis, condition, or time point on task accuracy, nor was there any significant interaction effects among these variables. In regards to task performance speed, there was a trend-level effect of diagnosis ($F(1,30.45)=3.889$, $p=0.058$) and significant omnibus effects of task condition ($F(3,31.18)=82.01$, $p<0.001$) and time point ($F(1,29.98)=6.182$, $p=0.019$), but no significant interaction effects. Post-hoc comparisons revealed a trend-level effect for slower performance in GAD participants, and faster performance across all participants at the second administration post-treatment. Furthermore, all participants performed the task from fastest to slowest in the following conditions: shapes, happy, angry, fear (all p 's < 0.003 , Bonferroni-corrected).

Pre-Treatment Activation

Task-Dependent Activation—In anatomical regions of interest, all participants activated the bilateral anterior insula for the effects-coded threat contrast (targeted processing of fear and angry vs. happy). In the whole brain (WB) analysis, additional activation was seen in the bilateral dorsolateral PFC, dorsomedial PFC, and temporoparietal regions, See Table S1 for complete results.

Group Activation Differences—In regions of interest, significant group x threat processing effects were observed in the perigenual ACC (pgACC), right posterior insula, left amygdala, and left anterior insula (Table 2 and Figure 1). Post-hoc extractions revealed group differences reflected greater activation in GAD participants to the threat contrast, but decomposition of the threat contrast into separate emotion processing conditions revealed the effects in all implicated regions were due primarily to greater activation in HC participants to the happy face condition. Thus, although GAD participants displayed a greater magnitude of activation to the threat-related contrast, these effects were driven primarily by blunted responses to the happy face comparator condition. To further explore whether this finding could be related to levels of depressive symptoms, which might attenuate the neural circuitry response to positively valenced stimuli, we correlated QIDS total score at baseline with extracted activation values in these clusters. However, there were no significant relationships between QIDS scores in GAD participants and magnitude of activation in these regions to the happy face comparison condition (all p 's > 0.05).

In the whole brain (WB) analysis, additional group x threat processing effects were observed in the posterior cingulate, bilateral dorsolateral PFC, right postcentral gyrus, bilateral middle temporal gyri, right paracentral lobule, and left parahippocampal gyrus (Table 2). Extractions also revealed these effects were due to greater activation in GAD participants to

the threat contrast, but decomposing these effects into the component emotion conditions revealed they were driven primarily by greater activation in HC participants to the happy face condition.

Pre-Treatment Worry Correlates—Conjunction analyses revealed no group activation differences in GAD participants that were significantly associated with worry symptoms at pre-treatment.

Pre-Treatment Connectivity

Task-Dependent Amygdala Connectivity—In anatomical regions of interest, there were no significant regions that displayed task-dependent connectivity with the left amygdala seed region. In the WB analysis, the left amygdala seed displayed significant positive connectivity with the right precuneus. See Table S2 for complete results.

Amygdala Connectivity Group Differences—Focusing on anatomical regions of interest, GAD participants displayed increased connectivity between the left amygdala seed region and the left anterior insula (Table 2 and Figure 2). In the WB analysis, GAD participants displayed increased connectivity between the left amygdala seed and the right cerebellum.

Post-Treatment Activation

Treatment-Related Activation Changes—In anatomical regions of interest, there were significant group $\times$ time effects for the threat-related contrast of interest in the right anterior insula, subgenual ACC, left amygdala, and right posterior insula (Table 3 and Figure 3). Post-hoc extractions revealed all effects were due to reduced activation in GAD participants to the threat contrast following treatment, but decomposition of the threat contrast into separate emotion processing components revealed effects in the subgenual ACC and amygdala were due primarily to reductions in activation to angry and fearful trials in the GAD group following treatment, while effects in the right anterior insula and posterior insula were due primarily to increases in activation to the happy face trials in GAD participants following treatment. These increases in activation in the insula were also unrelated to changes in depression symptoms indexed by QIDS total scores (all p 's > 0.05). Thus, activation changes in GAD participants in the amygdala and subgenual ACC following treatment were arising from the processing of fearful and angry stimuli.

In the WB analysis, additional effects were seen in the brainstem, visual cortex, cerebellum, and right dorsolateral PFC (Table 3). Post-hoc extractions revealed these effects were also due to attenuated activation in GAD participants to the threat contrast following treatment, but decomposition of the contrast revealed effects in the brainstem, visual cortex, and cerebellum were due primarily to greater activation to the happy face condition in GAD participants following treatment, while the effect in the right dorsolateral PFC was due to attenuated activation to angry and fearful faces in GAD participants. See Table 3 for details.

Treatment-Related Worry Correlates—Conjunction analyses revealed no regions in which treatment-related changes in activation were also related to treatment-related reductions in worry symptoms.

Post-Treatment Connectivity

Treatment-Related Amygdala Connectivity Changes—There were no significant effects observed for the group x time interaction effect in anatomical regions of interest or in a WB analysis. That is, there were no regions in which connectivity with the left amygdala changed differently between GAD and HC participants from pre-treatment to post-treatment.

Testing Effects of Comorbidity

To increase confidence that effects were not influenced by the presence of comorbid mood/anxiety disorders in GAD participants, post-hoc extracted values for the threat-related contrast from clusters displaying significant group differences and treatment-related changes were compared between GAD individuals with ($n = 11$) and without comorbidity ($n = 10$) using t-tests. These analyses revealed that all of the aforementioned effects did not significantly differ between GAD individuals with and without comorbid mood/anxiety disorders, suggesting these effects were unlikely to be driven entirely by comorbidity within the GAD group.

Discussion

To our knowledge, this is the first study to investigate functional brain changes in adults with GAD following the administration of a course of CBT. This investigation yielded three main findings. First, at baseline GAD individuals showed blunted responses in the amygdala, insula, and ACC during processing of positive social cues. Second, prior to treatment GAD individuals displayed greater connectivity between the amygdala and anterior insula compared to HC subjects. Third, activation in the amygdala and subgenual ACC to threat cues was attenuated following CBT, while activation in the insula was heightened in response to positive facial emotions; no changes in connectivity from pre- to post-treatment were observed. Taken together, these results provide evidence for a psychotherapeutic neural-systems model of CBT for GAD reflecting two complementary mechanisms of therapeutic benefit—an attenuation of reactivity of limbic brain structures to stimuli signaling potential threat, and a potentiation of interoceptive responses to positive facial emotional cues.

Consistent with existing evidence for amygdalar abnormalities in GAD (Etkin et al. 2010, Nitschke et al. 2009b), we observed blunted activation of this structure during the processing of happy facial emotions, which could not be accounted for by level of depressive symptoms as measures by the QIDS. Prior studies have observed no differences in amygdala activation between GAD and healthy comparison subjects (Whalen et al. 2008, Palm et al. 2011), as well as reduced activation in face processing paradigms (Blair et al. 2008). These findings, in aggregate, suggest the pathophysiology of amygdala functioning in GAD is perhaps distinct from the typical amygdala hyperactivity observed in other anxiety disorders (Etkin, Wager 2007), which may relate to altered patterns of widespread brain connectivity with

amygdalar subregions in GAD and the presence of compensatory networks (Etkin et al. 2009). Similarly, to the authors' knowledge this study is the first to report insula abnormalities in GAD in the context of a face-processing paradigm, which may also relate to the ability for this task to robustly engage insular cortex and a prior lack of an *a-priori* focus on this anatomical region. The insula plays a crucial role in homeostatic integration of internal body states with diverse mental processes and is highly implicated in emotional awareness, somatic/physiological states such as pain and disgust, and top-down attentional control (Craig 2009). Over recent years, its role in anxiety and fear states has become increasingly recognized and supported by meta-analytic (Etkin, Wager 2007) and experimental evidence (Paulus et al. 2005, Stein et al. 2007, Simmons et al. 2006), though it is also known to be involved in processing of rewards and other positive emotions (Craig 2009), consistent with these findings. The amygdala and insula share reciprocal connections (Reynolds, Zahm 2005) and are found to be part of an interconnected functional neural network that displays frequent coactivations in imaging studies (Kober et al. 2008, Mutschler et al. 2009), highlighting complementary roles for these regions in salient stimulus detection and emotional responding. Consistent with this, we observed that GAD participants display increased connectivity of these two regions at pre-treatment, though given the observed pattern of blunted activation responses to the happy face comparison condition it is difficult to disambiguate the processes that may underlie this hyperconnectivity. To the authors' knowledge, this is the first demonstration of altered amygdalo-insular connectivity in GAD participants during facial emotion processing, a finding that parallels a recent report of enhanced amygdalo-insular connectivity in GAD during fear conditioning (Greenberg et al. 2013). These findings suggest a bottom-up network-level dysfunction in GAD during the processing of facial emotional cues and are in accord with a broader implication for amygdalo-insular dysfunction in anxiety and traumatic-stress disorders (Etkin, Wager 2007).

After CBT, GAD participants displayed an attenuation of symptoms and activation in the left amygdala and subgenual ACC to threat-related emotional cues. The observation of amygdalar changes following CBT is consistent with treatment studies in other anxiety-disordered samples (Furmark et al. 2002, Felmingham et al. 2007) and supports the contention that changes in amygdalar function may index successful treatment outcomes across various anxiety disorders. Changes in insular function following completion of psychotherapy parallels a report of decreased insular activation in GAD following citalopram treatment during processing of worry statements (Hoehn-Saric, Schlund & Wong 2004). However, the current findings suggest a potentiation of insular responses to positive facial emotions characterizes successful CBT treatment.

To our knowledge, this study reports the first findings regarding neural functional changes in adult GAD following psychotherapeutic treatment and is consistent with the notion that successful psychotherapeutic treatment of symptoms may involve two complementary neural processes—a reduction of activation in a core limbic network (amygdala/subgenual ACC) to expressions of threat-related emotions, and a potentiation of activity in a lateral paralimbic network (anterior/posterior insula) to positive facial emotions. Thus, these and other findings regarding neural changes following treatment of anxiety disorders provide an

important transdiagnostic context through which brain changes in functional paradigms can be linked to underlying neurobehavioral processes that may be shared across different diagnostic manifestations of similar dysfunction. The findings presented here are indicative of changes in neural processes underlying emotional face processing in GAD following cognitive-behavioral therapy, which likely represents only one neural component of a successful therapeutic response to an efficacious intervention. It is important to note the behavioral paradigm utilized in this study selectively targets brain regions underlying a bottom-up, stimulus-driven manipulation and is therefore poised to detect changes that primarily involve this type neurobehavioral response. Therefore, the absence of observed relationships between neural dynamics during this type of emotion processing and worry symptoms, a more top-down manifestation of anxiety symptomatology, both at pre-treatment and in response to CBT suggests that other behavioral paradigms that more robustly engage cognitive systems may be better able to delineate the neural changes associated with this cardinal symptom of GAD.

This study has several limitations. Most importantly, we did not have an active control condition for GAD participants to rule out CBT non-specific effects (e.g., a treatment waitlist or non-CBT treatment condition). Therefore, these results must be interpreted with caution until replicated by future studies with appropriate comparison conditions, as changes in brain function could be due to factors other than the active ingredients of CBT. Second, GAD participants with comorbid depressive/anxiety disorders were not excluded, which may limit specificity of findings. However, GAD was established as the basis for treatment enrollment and experienced clinicians confirmed the principality of this disorder as the most debilitating psychiatric condition. Inclusion of these subjects is also most consistent with the high degree of comorbidity among anxiety disorders observed in the population (Kessler et al. 2005), and exclusion of these participants may have yielded non-generalizable findings. Third, the task used here does not directly isolate effects related to the target emotional expression due to the presence of a non-congruent face (i.e., the distractor) on each trial. Participants must engage in several mental computations for matching, and group differences may arise due to the assessment of the target/matching face, inhibition of the distractor, or both. Thus, the results of this study are not directly comparable to those presenting single faces.

Taken together, these results offer initial evidence concerning functional brain changes that may underlie the therapeutic effects of CBT for GAD. They also highlight the importance of conceptualizing GAD from a network perspective emphasizing coordinated interactions of several brain regions. In particular, we offer evidence that implicates attenuation of limbic reactivity to threat as one neurobehavioral outcome of successful CBT treatment in GAD, a finding that converges with studies in other anxious populations (Furmark et al. 2002, Felmingham et al. 2007) to suggest common neurobiological changes may underlie psychotherapeutic interventions transdiagnostically. Future studies in GAD utilizing behavioral paradigms that tap a wider variety of neurobehavioral processes are needed to illuminate the full spectrum of neural changes effected by psychotherapeutic interventions. Such affective neuroscience studies will be crucial to the identification and development of biomarkers that may be used to develop an effective approach to individualized treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- The neural changes following CBT for GAD are not well understood.
- Before CBT, GAD participants had less insula activation to happy faces vs. controls.
- CBT decreased cingulate and amygdala activation to threat cues in GAD participants.
- CBT also increased insula activation to happy faces in GAD participants.
- Symptom change following CBT for GAD likely reflects multicomponent neural processes.

Figure 1.

Error bars represent ± 1 standard error; Graphs depict average % signal changes for each condition composing the threat contrast of matching to fearful or angry vs. happy faces; a.u.=arbitrary units; GAD=generalized anxiety disorder; HC=healthy comparison.

Figure 2.

Error bars represent ± 1 standard error; GAD=generalized anxiety disorder; HC=healthy comparison.

Figure 3.

Error bars represent ± 1 standard error; Graphs in middle depict mean % signal change at each timepoint for the threat contrast of fearful and angry vs. happy faces; Graphs on bottom depict % signal changes for each emotion processing condition pre-and post-treatment in the GAD group; GAD=generalized anxiety disorder; HC=healthy comparison.

Table 1

Demographic and Pre-/Post-Treatment Self-Report and Behavioral Data Statistics

Measure	GAD (<i>n</i> =21) μ , σ	HC (<i>n</i> =12) μ , σ	F/χ^2 , p-value	Partial η^2
Pre-Treatment				
Age (yrs)	34.29, 11.27	27.58, 3.00	3.180, 0.084	0.093
Yrs of Educ.	15.76, 2.07	15.08, 0.55	0.984, 0.329	0.031
Gender	16 female, 5 male	7 female, 5 male	1.057, 0.405	--
	1 Asian-American	3 Asian American		
	1 Latino/Hispanic	2 Latino/Hispanic		
	1 Native American	0 Native American		--
Ethnicity	18 Caucasian	6 Caucasian	1.362, 0.291	
	0 African-American	0 African-American		
	0 Mixed/Other	1 Mixed/Other		
OASIS	10.38, 3.68	1.08, 0.89	69.637, <0.001	0.692
PSWQ	17.90, 2.36	12.42, 0.57	59.060, <0.001	0.656
QIDS	8.76, 4.17	1.83, 0.98	31.790, <0.001	0.506
	1. SAD			
	2. SAD			
	3. SAD			
	4. OCD			
	5. SAD			
Comorbidity	6. MDD, SAD	--	--	--
	7. SAD			
	8. MDD, SAD			
	9. MDD			
	10. PD			
	11. PD, SAD			
Post-Treatment				
OASIS	6.21, 3.37	--	25.436, <0.001	0.560
PSWQ	16.90, 2.84	--	4.468, 0.047	0.183
QIDS	5.38, 4.01	--	24.131, <0.001	0.547

Each number in the comorbidity row indicates a subject in the GAD group with comorbid conditions; educ=education; IUS=Intolerance of Uncertainty Scale; μ = mean; OASIS=Overall Anxiety Severity and Impairment Scale; PSWQ=Penn State Worry Questionnaire; QIDS=Quick Inventory of Depressive Symptoms; σ = standard deviation; yrs=years.

Table 2
Activation/Connectivity Differences at Pre-Treatment for GAD vs. HC Participants

Seed	Mask	Hem.	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats			Extracted %SC/rFz
								t	p	GAD	HC
--	ROI	L/R	Anterior Cingulate (pg)	2944	0	40	12	6.04 (2.23)	0.024 (0.013)	0.09	-0.29
--	ROI	R	Insula (p)	896	33	-18	18	6.05 (2.09)	0.023 (0.01)	0.10	-0.12
--	ROI	L	Amygdala	768	-23	-6	-15	6.49 (1.90)	0.019 (0.014)	0.23	-0.13
--	ROI	L	Insula (a)	768	-33	17	5	5.84 (1.60)	0.023 (0.013)	0.31	0.01
--	WB	L/R	Posterior Cingulate	8832	-4	-54	17	10.28 (2.62)	0.004 (0.003)	0.21	-0.33
--	WB	L	Middle/Medial/Superior Frontal Gyrus (dl)	5632	-26	12	46	9.39 (2.21)	0.005 (0.003)	0.16	-0.13
--	WB	R	Middle/Medial/Superior Frontal Gyrus (dl)	3328	26	11	49	9.33 (1.94)	0.005 (0.003)	0.20	-0.10
--	WB	R	Postcentral Gyrus	2432	42	-27	45	8.80 (1.31)	0.005 (0.002)	0.15	-0.15
--	WB	R	Middle Temporal Gyrus	1664	47	-21	-8	9.45 (1.66)	0.004 (0.003)	0.21	-0.17
--	WB	L	Superior/Middle Frontal Gyrus (dl)	1664	-31	46	15	9.36 (2.31)	0.005 (0.003)	0.21	-0.16
--	WB	R	Paracentral Lobule	1600	6	-34	62	8.97 (1.59)	0.005 (0.002)	0.16	-0.20
--	WB	L	Middle Temporal Gyrus	1536	-52	-26	-3	10.04 (1.86)	0.003 (0.003)	0.16	-0.19
--	WB	R	Superior Frontal Gyrus (dm)	1216	14	37	42	10.49 (3.25)	0.004 (0.003)	0.17	-0.18
--	WB	L	Parahippocampal Gyrus	1152	-20	-14	-17	10.30 (1.67)	0.003 (0.002)	0.26	-0.35
--	WB	L	Medial Frontal Gyrus (SMA)	1024	-17	-21	54	8.94 (1.22)	0.005 (0.002)	0.12	-0.08
L Amyg	ROI	L	Insula (a)	704	-32	18	10	6.19 (1.20)	0.022 (0.013)	0.02	-0.06
L Amyg	WB	R	Culmen	1344	8	-42	-21	12.63 (5.33)	0.003 (0.003)	0.03	-0.06
L Amyg	WB	R	Cerebellar Tonsil	1216	11	-57	-39	10.82 (3.21)	0.004 (0.003)	0.02	-0.05

X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean t and p value with standard deviations in parentheses; Extracted values for each group represent the average activation or connectivity cluster value for the threat contrast; Locational descriptors in parentheses do not denote actual anatomical distinctions but are based upon the relative location of the cluster in standardized space; a=anterior; dl=dorsolateral; dm=dorsomedial; GAD=generalized anxiety disorder; HC=healthy control; Hem=hemisphere; L=left; LAmyg=left amygdala; p=posterior; %SC=percent signal change; rFz=Fisher-Z transformed correlation coefficient; R=right; ROI=region of interest masks; sd=standard deviation; SMA=supplementary motor area; Vol. = volume; WB=whole-brain masks.

Table 3

Activation Changes in GAD Participants Following Cognitive-Behavioral Therapy

Mask	Hem.	Region	Vol. (μl)	X	Y	Z	Voxelwise Stats Mean (sd)			Extracted %SC (Pre, Post)	
							F	p		GAD	HC
ROI	R	Insula (a)	1088	39	10	5	7.31 (2.86)	0.015 (0.013)		0.19, -0.13	0.10, 0.06
ROI	L/R	Anterior Cingulate (sg)	704	2	23	-6	7.08 (3.00)	0.016 (0.012)		-0.05, -0.28	-0.16, -0.20
ROI	L	Amygdala	576	-22	-4	-17	7.36 (3.17)	0.016 (0.016)		0.21, -0.22	-0.12, -0.13
ROI	R	Insula (p)	576	38	-20	13	5.81 (1.28)	0.021 (0.014)		0.06, -0.19	-0.15, -0.13
WB	L/R	Brainstem	2560	-1	-29	-24	12.69 (3.93)	0.002 (0.002)		0.14, -0.14	-0.01, -0.05
WB	R	Inferior Occipital	2496	18	-87	1	11.53 (3.68)	0.002 (0.002)		0.10, -0.01	-0.01, -0.06
		Gyrus/Lingual									
		Gyrus/Cuneus									
WB	R	Middle Frontal	1408	25	35	38	10.46 (3.20)	0.003 (0.003)		0.10, -0.17	-0.05, -0.16
		Gyrus/Superior Frontal									
WB	L	Gyrus (dl)	1216	-23	-80	-26	12.87 (6.33)	0.003 (0.004)		0.18, -0.03	0.05, -0.07

X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean F and p value with standard deviations in parentheses; Locational descriptors in parentheses do not denote actual anatomical distinctions but are based upon the relative location of the cluster in standardized space; a=anterior; dl=dorsolateral; Hem=hemisphere; L=left; p=posterior; %SC=percent signal change; Pre=pretreatment; Post=posttreatment; R=right; ROI=region of interest masks; sd=standard deviation; Vol. = volume; WB=whole-brain mask.