HHS Public Access

Author manuscript

Depress Anxiety. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Depress Anxiety. 2019 May ; 36(5): 453–464. doi:10.1002/da.22859.

Transdiagnostic Neural Correlates of Volitional Emotion Regulation in Anxiety and Depression

Jacklynn M. Fitzgerald[a], **Heide Klumpp**[b,c], **Scott Langenecker**[b,c], and **K. Luan Phan**[b,c,d]

[a]University of Wisconsin - Milwaukee, Department of Psychology, Milwaukee, WI

[b]University of Illinois at Chicago, Department of Psychiatry, Chicago, IL

[c]University of Illinois at Chicago, Department of Psychology, Chicago, IL

[d]University of Illinois at Chicago, Department of Anatomy and Cell Biology and the Graduate Program in Neuroscience, Chicago, IL

Abstract

Background: Individuals who suffer from anxiety and/or depression have difficulty adaptively managing emotional responses, while accumulating evidence suggests impaired emotion regulation is a transdiagnostic feature of psychopathology. Effectual regulation in the context of negative stimuli is characterized by engagement of the prefrontal cortex (PFC) coupled with reduced amygdala reactivity. In anxiety disorders and major depression, PFC under-engagement and atypical PFC-amygdala connectivity has been observed, although patient findings based on case-control studies have been mixed with regard to magnitude, locality and extent of dysfunction. As anxiety disorders and major depression are heterogeneous disorders and frequently comorbid with one another, delineating relationships between reappraise-related substrates and symptoms may advance our understanding of emotion dysregulation in these populations.

Methods: We examined PFC activation and its functional connectivity (FC) to the amygdala using functional magnetic resonance imaging (fMRI) in a large sample of patients (N=174) with primary generalized anxiety disorder (n=47), social anxiety disorder (n=78), or major depressive disorder (n=49) during a reappraisal-based emotion regulation task. Comorbidity was permitted and the majority of participants had a concurrent psychiatric illnesses.

Results: Across participants, whole-brain results showed that: 1) greater anxiety and depression symptom severity was related to less engagement of the dorsal anterior cingulate cortex (dACC); and 2) less FC between the amygdala and ventrolateral prefrontal cortex. Results were driven by anxiety, while depression symptoms were not significant.

Conclusion: These findings demonstrate that individual differences in anxiety and depression may help explain ACC and PFC dysfunction during emotion regulation observed across anxiety and depressive disorders.

Corresponding Author: Jacklynn M. Fitzgerald, PhD, University of Wisconsin - Milwaukee, Department of Psychology, 2441 E Hartford Ave, Milwaukee, WI 53211, P: (262) 370-6212, fitzgejm@uwm.edu.

Keywords

Anxiety/anxiety disorders; Depression; Functional MRI; SAD/social anxiety disorder/social phobia; GAD/generalized anxiety disorder

Introduction

Anxiety and depressive disorders are prevalent, disabling, and highly co-morbid (Hirschfeld, 2001). For instance, up to 75% of individuals with depression meet diagnostic criteria for an anxiety disorder in their lifetime, while nearly 79% of those with an anxiety disorder also have lifetime history of major depression (Alonso, Lepine, & ESEMeD/MHEDEA 2000 Scientific Committee, 2007). Frequent comorbidity is due, in part, to a polythetic-categorical diagnostic taxonomy that allows for each disorder to be defined by a combination of multiple symptoms (Krueger & Bezdjian, 2009), while more than one symptom is shared across diagnostic boundaries (Zbozinek et al., 2012). Thus, although treated categorically, the presence of shared symptoms increases likelihood of dual-diagnoses. As shared symptoms are rational targets for remediation—given they hold the potential to simultaneously reduce both anxiety and depression symptom burden—more research is needed to evaluate the underlying neurobiological mechanisms associated with them. In particular and in the wake of accumulating evidence from neuroimaging studies demonstrating the utility of transdiagnostic neurobiological models to understand shared psychiatric disorders (Cuthbert, 2014, 2015), more information is needed on whether individual differences in anxiety and depression severity map onto similar neurobiological aberrations.

One such example of symptom overlap across those with anxiety and depressive disorders is emotion dysregulation, as evinced by reports of negative biases (Beck & Clark, 1997; Gotlib, Krasnoperova, Yue, & Joormann, 2004) and difficulty managing negative emotions in ways that are adaptive (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Amstadter, 2008; Fernandez, Jazaieri, & Gross, 2016; Hostinar, Nusslock, & Miller, 2017; Shapero, Abramson, & Alloy, 2016; Tripp, McDevitt-Murphy, Avery, & Bracken, 2015; Tull, Bardeen, DiLillo, Messman-Moore, & Gratz, 2015). A well-studied form of emotion regulation is cognitive reappraisal, an antecedent emotion regulation strategy that occurs prior to or when an emotional experience is unfolding and involves the cognitive transformation (e.g., re-interpretation) of an emotional experience in order to change its emotional meaning (Gross, 1998). In healthy individuals, cognitive reappraisal in the context of negative information is associated with positive health and well-being (Cutuli, 2014); thus, deficiency or inefficiency in use of cognitive reappraisal has garnered significant attention in psychiatrically-ill populations.

In healthy individuals, cognitive reappraisal is associated with increased neural activation across a network of brain regions involving the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC), dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (VMPFC), middle and superior temporal gyri, and the

inferior parietal lobe (IPL) (Buhle et al., 2014; Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Messina, Bianco, Sambin, & Viviani, 2015; Ochsner, Silvers, & Buhle, 2012). Engagement of dorsal and lateral regions of the PFC likely sub-serves in the selection of a reappraisal strategy (Yamagishi et al., 2016) and generation of inner speech that aids the reappraisal process (Geva et al., 2011; Jones & Fernyhough, 2007; Morin & Hamper, 2012). By contrast, involvement of the medial and ventral regions of the PFC as well as the dACC are important for the conflict monitoring between competing responses and automatic regulation of a "bottom-up" affective response (Bush, Luu, & Posner, 2000; Etkin, Egner, & Kalisch, 2011; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Paradiso et al., 1999; Quirk & Gehlert, 2003). Greater reappraisal-related engagement in frontal and parietal cortices is associated with reductions in amygdala responding (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; M. Beauregard, Levesque, & Bourgouin, 2001; Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan et al., 2005; Schaefer et al., 2002; Urry, 2006), a region involved in the generation of negative affect (Costafreda, Brammer, David, & Fu, 2008). Thus, a functional relationship between frontoparietal structures and the amygdala are thought to characterize effectual reappraisal.

In support of this hypothesis, functional connectivity (FC) studies assessing the correlation of neural activity across spatially distributed brain regions during reappraisal have found that, using the amygdala as a seed region, greater activation within the amygdala is positively related to increased engagement to the DLPFC (Banks et al., 2007; Paschke et al., 2016), inferior frontal gyrus corresponding to the VLPFC (Morawetz, Bode, Baudewig, & Heekeren, 2016), DMPFC (Banks et al., 2007; Sripada et al., 2014), VMPFC (Delgado, Nearing, LeDoux, & Phelps, 2008), MPFC (Paschke et al., 2016), ACC (Banks et al., 2007), and IPL (Banks et al., 2007). During reappraisal, positive correlations between the amygdala and cortical regions is also related to greater reduction in self-reported negative affect in some studies (Banks et al., 2007; Morawetz et al., 2016) providing support that amygdala-PFC coupling represents successful regulation. Based on findings from both activation and connectivity studies, the neural profile of cognitive reappraisal is defined by greater engagement of the PFC, decreased excitability of the amygdala, and increased FC between these regions.

Findings from discrete fMRI studies investigating the neural profile of emotion dysregulation via reappraisal in those with anxiety or depression demonstrate atypical engagement of the PFC and aberrant PFC-amygdala connectivity in these populations. Compared to healthy controls (HCs), individuals with generalized anxiety disorder (GAD) and social anxiety disorder (SAD) under-engage the dACC (Blair et al., 2012; Goldin, Manber, Hakimi, Canli, & Gross, 2009), DMPFC (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013), and DLPFC (Ball et al., 2013; Goldin, Manber, et al., 2009) when using reappraisal to make negative images appear less negative or to down-regulate response to threatening faces. Again during reappraisal, individuals with SAD display less FC between the amygdala and the DLPFC and VLPFC compared to HCs (Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009), while individuals with MDD do not exhibit any significant FC between the amygdala and PFC that is present in HCs (Erk et al., 2010). Other work shows that those with MDD over-recruit the dACC during reappraisal in response to sad film clips (Beauregard, Paquette, & Levesque, 2006) and over-engage the lateral PFC during

reappraisal to negative images (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007), demonstrating somewhat mixed findings with regard to direction of effects in those with depression. When directly comparing disorders, one study by Blair and colleagues found that individuals with GAD and SAD were similarly characterized by under-engagement of the dACC compared to HCs (Blair et al., 2012). Similarly, Ball and colleagues demonstrated that individuals with GAD do not differ from those with panic disorder (PD) in under-engagement of the DMPFC and DLPFC during reappraisal (Ball et al., 2013). In addition to these neural findings, individuals with GAD (Fitzgerald et al., 2017) and SAD (Goldin, Manber-Ball, et al., 2009) report feeling more negative when viewing negative stimuli compared to healthy participants. Yet, when engaging in cognitive reappraisal, results are less consistent. Individuals with GAD report more negative affective state when using reappraisal than healthy controls (Fitzgerald et al., 2017) whereas those with SAD have a similar decrease in negative response as healthy participants (Goldin, Manber-Ball, et al., 2009; Goldin, McRae, Ramel, & Gross, 2008). Also, individuals with MDD do not differ from HCs in self-reported affect during reappraisal but indicate a greater level of difficulty in the process (Beauregard et al., 2006). In general, individuals with anxiety or depression have intact regulation capability though certain disorders may be more prone to deficiencies or find it more difficult to use reappraisal. In addition, patients with anxiety and depression may be similar to one another with regard to aberrant PFC and ACC engagement during reappraisal, although mixed findings with regard to depression means that more research is needed. In addition, we are not aware of an investigation that has assessed neural engagement during reappraisal in the context of individual differences in anxiety and depression symptoms within a diverse patient sample.

The current study extends the literature by examining the relationship between reappraisal-related activity and variance in anxiety and depressive symptoms in a sample of individuals with primary anxiety disorder (i.e., SAD, GAD) or depressive disorder (i.e., MDD). We tested for (i) group effects, (ii) individual differences across participants, and (iii) whole-brain FC with bilateral amygdala as the seed region during cognitive reappraisal in this study. With regard to group effects, we anticipated no group differences would emerge owing to significant comorbidity within the sample. Second, we examined the extent to which anxiety and depression symptoms across participants was linked to frontal or subcortical neurofunctional activity. Based on prior research, we hypothesized that illness severity in both dimensions (anxiety, depression) would be related to less engagement of the PFC and more amygdala reactivity when using reappraisal to make negative images appear less negative. In addition, we hypothesized that during reappraisal both anxiety and depression symptoms would relate to negative connectivity between the amygdala and PFC.

Materials and Methods

Participants

Participants were included if they were (1) between the ages of 18–65, (2) able to give informed consent, (3) free from alcohol or drugs on the day of testing as confirmed by a urinary drug screen, (4) and had severe enough mood disturbances to warrant treatment as determined by a consensus panel that included a psychiatrist and psychologist. Exclusion

criteria included (1) history of congenital brain defects, (2) history or presence of severe psychiatric illness (e.g., schizophrenia, bipolar disorder), (3) substance dependence, and (4) active treatment either in the form of psychotherapy or medication. For fMRI testing, additional exclusion criteria included (1) the presence of ferromagnetic objects within the body, (2) being pregnant or actively trying to become pregnant, (3) fear of enclosed spaces (e.g., claustrophobia), and (4) inability to lie still in an enclosed space for up to one hour. All participants completed a consent form approved by the local Institutional Review Board at the University of Illinois at Chicago. Participants were compensated for their time and all procedures complied with the Helsinki Declaration.

Patients were assessed for presence of an Axis I anxiety or depressive disorder through the use of an in-person Structured Clinical Interview for Diagnostic Statistical Manual-IV (SCID-IV; (First, Spitzer, Gibbon, & Williams, 2002) conducted at screening by a clinically trained master's or PhD-level researcher. Individuals in the present study were required to have a primary anxiety disorder or major depression, however, comorbidity was permitted. Severity of anxiety symptoms was assessed using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) and, for depression symptoms, the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960).

A total of N=174 patients were eligible for entry into this study based on Axis I diagnosis of GAD (n=47), SAD (n=78), or MDD (n=49) , a sub-set of which were included in prior publications (Klumpp, Fitzgerald, et al., 2017; Klumpp, Roberts, et al., 2017) that did not evaluate the relationship between neural engagement and connectivity during reappraisal and symptoms of anxiety and depression. Range of HAM-A (1–41) and HAM-D (0–26) scores reflected a distribution of no/minimal to severe symptoms. Participants with a principal diagnosis of MDD had greater HAM-D (M=15.31, SD=4.80) scores than those with SAD (t(125)=7.47, p<0.001; M=8.60, SD=5.00) and GAD (t(88.95)=5.80, p<0.001; M=10.30, SD=3.61). In addition, participants with a principal diagnosis of MDD (M=13.86, SD=7.78) had greater HAM-A symptoms than those with SAD (t(125)=4.69, p=0.001; M=13.89, SD=7.78) and GAD (t(94)=2.58, p=0.011; M=15.02, SD=6.09). Participants with a principal diagnosis of SAD and GAD did not differ from one another in terms of HAM-A scores (p>0.36), while participants with GAD had greater HAM-D scores than those with SAD (t(118.96)=2.19, p=0.030). Table 1 displays participant demographics.

fMRI Task

During fMRI scanning, participants completed a well-validated block-design Emotion Regulation Task (ERT) that utilized cognitive reappraisal as a regulation strategy (Fitzgerald et al., 2016, 2017; MacNamara et al., 2016; Phan et al., 2005; Rabinak et al., 2014). During ERT, participants were shown 64 negative and 32 neutral images from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008) across three conditions (Reappraise, Look-Negative, Look-Neutral). Participants were instructed to: 1) use a cognitive strategy to reduce negative affect to aversive images ('Reappraise' condition); 2) attend to the emotional state elicited by aversive images ('Look-Negative' condition); or 3) view neutral images ('Look-Neutral' condition). Task instructions are provided in full in Supplementary material. Prior to scanning, participants were instructed on the strategy of

cognitive reappraisal (Ochsner et al., 2002; Phan et al., 2005) and all conditions were practiced with eight images not used in the fMRI experiment to confirm understanding of task instructions.

The task consisted of four 20 s blocks of each condition (four images presented for 5 s each without inter-stimulus interval). Blocks were interspersed by a rest period in which 20 s blocks of a white fixation cross were shown on a black background to enable the hemodynamic response to return to baseline. Block order was pseudo-randomized over the course of two separate runs, with each run lasting a total of five minutes. Prior to each block, an instruction screen ("Reappraise" or "Look") was presented for 5 s. To assess self-reported negative affect in the form of behavioral responses, following each block, participants viewed a screen that asked them to answer the question "How negative do you feel?". Participants indicated their response on a 5-item Likert scale (1=not at all; 5=extremely) via a 5-button response with their dominant hand.

FMRI scanning was performed on a 3 Tesla GE Discovery System (General Electric Healthcare; Milwaukee, WI) using a standard radiofrequency coil. Whole-brain functional images (i.e., BOLD) were collected using the following parameters: TR=2s, TE=25 ms, flip angle=90°, field of view=22 × 22 cm^2, acquisition matrix 64 × 64; 44 axial, 3-mm-thick slices with no gap. The first 4 volumes from each run were discarded to allow magnetization to reach equilibrium.

Behavioral Analysis

Self-reported negative affect following each condition (Reappraise, Look-Negative, Look-Neutral) was averaged across blocks and runs within individuals. First, we investigated whether there were differences in self-reported affect across conditions and groups using a condition-by-group repeated measures ANOVA. In the event of a significant effect of condition, planned comparisons included paired samples *t*-tests to evaluate differences in self-reported affect between Look-Neutral and Look-Negative, as well as Reappraise and Look-Negative. Subsequently, we examined the relationship between self-reported negative affect using difference scores reflecting (a) Look-Negative > Look-Neutral and (b) Reappraise > Look-Negative and symptom severity. Utilization of difference scores was done to mimic analysis plan involving fMRI contrast comparisons (see below). Finally, in post-hoc analyses we examined whether self-reported affect, again using two difference calculations, correlated with significant clusters of activation derived from focal analyses or significant amygdala connectivity derived from connectivity analyses.

fMRI Preprocessing

Conventional preprocessing steps were completed in Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London www.fil.ion.ucl.ac.uk/spm). Images were temporally corrected to account for slice time acquisition differences and spatially realigned to the mean image. Motion realignment parameters were entered as regressors of no-interest to control for minimal head movement during scanning, however functional images from all participants included in analysis met criteria for high-quality with minimal motion correction (e.g., movements were < 3 mm and < 3 degrees rotation in any

one direction). Images were subsequently normalized to a Montreal Neurological Institute (MNI) template using the echo-planar imaging template, resampled to 2 × 2 × 2 voxels and smoothed using an 8 mm isotropic Gaussian kernel.

A general linear model (GLM) was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Hemodynamic response during instruction, rest, collection of self-reported negative affect, and blocks of Reappraise, Look-Negative, and Look-Neutral were modeled separately, the effects of which were estimated for each voxel for each participant. Our primary objective was to measure neural functioning during cognitive reappraisal, controlling for variability in negative affect. Therefore, neural activity during Reappraise > Look-Negative was modeled as a primary contrast of-interest and taken to the second level for random effects analysis. In addition, analyses were also tested using a Look-Negative > Look-Neutral contrast to assess for a relationship between anxiety and depression severity during unregulated affect responding.

fMRI Analysis

Whole-Brain Analyses: Using the Reappraise > Look-Negative contrast, we evaluated group differences (GAD vs. SAD vs. MDD) using a whole-brain ANCOVA, controlling for age, gender, and education. To examine individual differences, a regression analysis for Reappraise > Look-Negative was performed with symptom measures. Specifically, owing to high concordance between HAM-A and HAM-D scores (r=0.82, p<0.001), the summation of HAM-A and HAM-D total scores was the covariate of interest (Klumpp, Hosseini, et al., 2018; Klumpp, Kinney, et al., 2018) while age, education, gender, and diagnostic status (dummy coded) were added as covariates of no-interest. Analyses also controlled for age, education, and gender. To test whether anxiety (HAM-A) and/or depression (HAM-D) were more significant in driving neural activity, post-hoc analyses were performed. That is, beta-weights in arbitrary units were extracted from significant clusters using the SPM MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002) and subjected to stepwise linear regression in the Statistical Package for the Social Sciences (version 25.0) (SPSS) to determine if results were explained more by either symptom domain. In these analyses, neural activity was the dependent variable and HAM-A total scores, HAM-D total scores, age, gender, education, and diagnosis were the independent variables.

PPI Analyses: Generalized PPI analyses (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) was completed using SPM8 for the contrast Reappraise > Look-Negative only given *a priori* hypotheses regarding the relationship between amygdala and PFC connectivity during reappraisal. In this approach, a (i) 'psychological' variable representing the epoch of cognitive reappraisal, (ii) a 'physiological' variable representing timecourse of activation in the bilateral amygdala, and (iii) the interaction of these two variables were modeled at the individual level. The interaction term provided a measure of which brain regions were statistically correlated with the bilateral amygdala as a function of cognitive reappraisal. First, condition onset times for Look-Neutral, Look-Negative, Reappraise, the preceding instruction screen, and the following affect rating period were separately convolved with the canonical hemodynamic response function for each condition to create psychological regressors. Next, deconvolved time series was extracted from a

bilateral anatomical amygdala based on Anatomical Automatic Labeling (AAL)-defined mask using the SPM toolbox to create the physiological variable. Finally, interaction terms (e.g., PPIs) were computed by multiplying the psychological and physiological variables. Effects representing connectivity values with bilateral amygdala were estimated for each voxel for each participant and taken to the second level for random effects analysis in an identical fashion to focal fMRI analyses listed above (e.g., we first evaluated group differences among patients and subsequently the relationship to severity of anxiety and depression scores). As before, all analyses controlled for age, education, gender, and diagnostic status.

In all analyses, significant clusters of activation were identified correcting for multiple comparisons across the entire brain (p<0.05 family-wise error [FWE]) using a gray matter mask excluding the cerebellum (MacNamara, Klumpp, Kennedy, Langenecker, & Phan, 2017). This correction displayed clusters that were significant based on a height thresholds of F=12.56 and F=13.42 when evaluating group differences in focal neural engagement and connectivity, respectively; height thresholds of T=4.38 and T=4.60 were used when evaluating significant relationships between symptoms and focal neural engagement and connectivity, respectively.

Results

Behavioral Data

Ratings of self-reported negative affect were available for n=172/174 participants due to missing responses from two SAD participants. Results from repeated measures ANOVA demonstrated a significant effect of condition (F(2,338)=417.47, p<0.001) but no effect of group (p>0.85) or group-by-condition interaction (p>0.17). To explore condition effects, paired samples t-tests confirmed that negative affect ratings were higher following Look-Negative (M=2.97±0.75) compared to Look-Neutral (M=1.34±0.46) conditions (t(171)=26.74, p<0.001) and that negative affect reduced following Reappraise (M=2.62±0.75) conditions compared to Look-Negative (t(171)=6.50, p<0.001). Symptom severity was not related to negative affect ratings following the Look-Negative > Look-Neutral (p>0.92) or Reappraise > Look-Negative (p>0.85) conditions.

fMRI Group Results

The ANCOVA did not reveal group differences in terms of brain response during Reappraise > Look-Negative or Look-Negative > Look-Neutral, nor did groups differ in terms of whole-brain amygdala connectivity during Reappraise > Look-Negative (p's>0.05 FWE-adjusted).

fMRI Whole-brain Results: Association with Symptom Severity

Within the Reappraise > Look-Negative contrast, there was no positive association between symptoms and focal brain activation (p>0.05 FWE-adjusted). By contrast, there was a negative relationship between symptoms and the supplementary motor area (SMA; peak MNI: −6, 10, 72; T=−4.78; Z=−4.62; volume=272 mm^3), precental gyrus (peak MNI: −38, −2, 30; T=−4.65; Z=−4.50; volume=104 mm^3), cuneus (peak MNI: 24, −86, 6; T=−4.60; Z=−4.46; volume=80 mm^3), and dACC (peak MNI: −8, 24, 30; T=−4.46; Z=−4.33; volume=56

mm^3). Figure 1 displays location of dACC cluster and scatterplot reflecting relationship between focal neural engagement and severity of symptoms. No significant negative or positive relationship with symptoms were found for the Look-Negative > Look-Neutral contrast (p's>0.05 FWE-adjusted).

Post-hoc stepwise linear regressions in SPSS demonstrated that symptoms of anxiety (e.g., HAM-A) predicted decreased precentral gyrus ($b = -0.01$, $p < 0.001$), cuneus ($b = -0.02$, $p < 0.001$) and dACC activation ($b = -0.02$, $p < 0.001$), while symptoms of depression (e.g., HAM-D) were not related to these regions ($p > 0.30$). By contrast, symptoms of depression predicted decreased SMA activation ($b = -0.05$, $p < 0.001$), while symptoms of anxiety were not related ($p > 0.07$).

fMRI Connectivity with Amygdala: Association with Symptom Severity

There was no positive relationship between symptoms and whole-brain amygdala connectivity (p>0.05 FWE-adjusted). By contrast, there was a negative relationship between symptoms and amygdala connectivity with the right (peak MNI: 30, 60, 2; T=−6.22; Z= −5.89; volume=4,360 mm^3) and left VLPFC (peak MNI: −20, 62, 18; T=−5.32; Z=−5.11; volume=1,336 mm^3). Figure 2 displays location of right-lateralized significant connectivity with amygdala and scatterplot reflecting relationship to symptoms. No other significant negative relationship with symptoms were found (p's>0.05 FWE-adjusted).

Post-hoc stepwise linear regressions, results showed anxiety symptoms (e.g., HAM-A) predicted less amygdala-right VLPFC connectivity ($b = -0.14$, $p < 0.001$) and amygdala-left VLPFC connectivity ($b = -0.12$, $p < 0.001$). Again, symptoms of depression (e.g., HAM-D) were not related to clusters representing amygdala functional connectivity (p's>0.21).

Relationship with Self-reported Negative Affect

No significant relationships were found between clusters identified in focal and connectivity analyses and self-reported negative affect following Look Negative (> Look-Neutral) (p>0.66) or Reappraise (> Look-Negative) (p>0.35).

Discussion

The current study investigated reappraisal-specific neurobiological correlates of individual differences in anxiety and depressive symptoms in a heterogeneous sample of patients with GAD, SAD, and MDD as primary diagnoses. Three main findings emerged from this investigation: (i) severity of anxiety and depression, when combined, was associated with deficits in recruiting the dACC, and (ii) reduced connectivity between the amygdala and bilateral VLPFC when using cognitive reappraisal to make negative images appear less negative. In post-hoc analyses we found that (iii) these results were significantly driven by anxiety symptoms and not significantly driven by depression symptoms. Behaviorally, all participants reported feeling more negative during the viewing of negative images compared to viewing neutral images and reduced their negative affect after reappraisal indicating patients successfully regulated emotion. Behaviorally, all participants reported feeling more negative during the viewing of negative images compared to viewing neutral images and reduced their negative affect after reappraisal, indicating patients successfully regulated

emotion. No group differences in self-reported affect were found, nor did we find evidence that severity of anxiety and depression symptoms were related to self-reported affect.

The result that under-engagement of the dACC during cognitive reappraisal was related to anxiety and depression severity replicates prior findings of under-engagement of this region in those with GAD (Blair et al., 2012) and SAD (Ball et al., 2013; Blair et al., 2012) when using cognitive reappraisal to reduce negative affect. The dACC is involved in conflict control, response selection, and error detection (Bush et al., 2000; Etkin et al., 2011) and forms little direct connection to the amygdala (Beckmann, Johansen-Berg, & Rushworth, 2009). In the context of cognitive reappraisal, the dACC is likely involved in monitoring and balancing the mismatch between bottom-up affective responses generated in limbic and sub-cortical regions with top-down reappraisals occurring in lateral portions of the cortex (Shenhav, Botvinick, & Cohen, 2013). While lateral prefrontal regions (e.g., DLPFC, VLPFC) are heavily implicated in cognitive reappraisal, the involvement of the dACC is to allocate control and attentional resources over incoming stimuli in light of interoceptive affective states (Shenhav et al., 2013). Together, diminished dACC activation may portend deficits in conflict-related processing in the wake of cognitive and affective demands. This deficiency as it specifically relates to anxiety symptoms replicates recent meta-analytic work completed by Zilverstand and colleagues, which found that individuals with anxiety disorders (e.g., GAD, SAD), consistently under-engaged the dACC during reappraisal in response to negative images (Zilverstand, Parvaz, & Goldstein, 2016).

Outside of the ACC, we also found that greater symptom severity was related to less engagement in the SMA, precentral gyrus, and cuneus. As cognitive reappraisal engages a wide network of brain regions (Kohn et al., 2014; Messina et al., 2015; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), the present results suggest that anxiety and depression are negatively associated with deficiencies recruiting a broader neural network. Specifically, prior work confirms involvement of the SMA (Etkin, Büchel, & Gross, 2015; Kohn et al., 2014; Wager et al., 2008) and precentral gyrus (Picó-Pérez, Radua, Steward, Menchón, & Soriano-Mas, 2017) during reappraisal. These regions are hypothesized to govern the behavioral output of reappraisal, as the SMA integrates input from frontal regions responsible for the formation of an internal representation of regulation goals with a behavioral response (Etkin et al., 2015), and the precentral gyrus governs internal emotional experiences that help guide motoric output (Hardee et al., 2017). Although involvement of the cuneus during reappraisal is not well-documented, this region is implicated in visual processing (Parker, Zalusky, & Kirbas, 2014). Deficiencies in cuneus recruitment may therefore suggest deficits associated with visual appraisal of emotional material instrumental for the reappraisal process (Gross, 1998), perhaps related to mid-level visual processing associated with attention (Corbetta et al., 1998).

In addition, we found that less connectivity between the amygdala and bilateral VLPFC during cognitive reappraisal was related to greater anxiety and depression symptoms, similar to prior work that found less connectivity between the amygdala and PFC in SAD (Goldin, Manber-Ball, et al., 2009) and MDD (Erk et al., 2010). The VLPFC is involved in semantic processing (Marumo et al., 2014), memory for semantic information (Nozari & Thompson-Schill, 2016), and categorization of objects (Corbetta, Patel, & Shulman, 2008; Corbetta &

Shulman, 2002). During cognitive reappraisal, engagement of the left VLPFC may help in the generation of inner speech (Geva et al., 2011; Jones & Fernyhough, 2007; Morin & Hamper, 2012), which helps individuals categorize emotions for the reappraisal process (Kohn et al., 2014). That less connectivity between the VLPFC and amygdala was driven by anxiety severity therefore hints at the possibility that anxiety is also related to deficiency in the relationship between emotional responding, sub-served by amygdala, and language processing for either the appraisal or re-appraisal process, sub-served by VLPFC.

In hypothesized regions (e.g., deficiency in dACC recruitment and negative amygdala-VLPFC connectivity), neurobiological aberrations were only significantly driven more significantly by anxiety symptom severity, despite the fact that anxiety and depression severity were highly correlated in this sample. In addition, both disorders are associated with deficiency in emotion regulation and use of cognitive reappraisal based on prior research. This points to the possibility that although the manifestation of emotion dysregulation as seen within clinical settings appears similar across the two disorders, they may be dissimilar in the underlying neural mechanisms that make regulating negative states difficult. This possibility is supported by the fact that while prior neuroimaging studies in anxiety uniformly report under-engagement of the dACC and PFC during cognitive reappraisal of negative affect (Ball et al., 2013; Blair et al., 2012; Goldin, Manber, et al., 2009), findings with regard to MDD are inconsistent (e.g., under-recruitment (Erk et al., 2010) and over-recruitment (Beauregard et al., 2006) of these regions are both reported). Therefore, in depression, deficiency in recruiting frontal regions during reappraisal may reflect co-occurring anxiety severity. Under-engagement of additional cortical regions outside the PFC and ACC (e.g., precentral gyrus, cuneus) was also associated with anxiety symptom severity, suggesting even greater non-specificity and widespread deficiencies in the reappraisal process tied to anxiety. By contrast, the SMA was the only region associated with depression symptom severity in the present study. Prior research has found less SMA engagement during reappraisal in those with depression (Davis, Foland-Ross, & Gotlib, 2018) and anxiety disorders (e.g., GAD, SAD, Panic Disorder, Posttraumatic Stress Disorder) (Wang et al., 2018). Comorbid depression was allowed in this latter study, while the effects of anxiety versus depressive symptoms were not disentangled (Wang et al., 2018). Findings of the present study support the conclusion that under-engagement of the SMA, involved in integrating regulation goals with behavioral response, is specific to depression, more so than anxiety.

Notably, we did not find evidence of a relationship between amygdala activation and anxiety or depression symptom severity. The failure to find group differences in the amygdala replicates prior work using a similarly-crafted large, trans-diagnostic sample of GAD, SAD, and MDD participants during exposure to negative stimuli but outside the context of reappraisal (MacNamara et al., 2017). In addition, although numerous prior studies report over-active amygdala in response to varied negative stimuli (e.g., scenes, faces, words), there are also number of studies that fail to find such effects in those with GAD and SAD (Blair et al., 2008; Burklund, Torre, Lieberman, Taylor, & Craske, 2017; Davies et al., 2017; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014; Nakao et al., 2011; Palm, Elliott, McKie, Deakin, & Anderson, 2011; Strawn et al., 2012; Whalen et al., 2008) or MDD (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010;

Beauregard et al., 2006; Davidson, Irwin, Anderle, & Kalin, 2003; Grimm et al., 2008; Irwin et al., 2004; Lawrence et al., 2004; Townsend et al., 2010). Lack of amygdala differentiation between patients and controls is also consistent with prior studies that did not find amygdala differences between HCs and those with GAD (Fitzgerald et al., 2017) or HCs and those with MDD (Erk et al., 2010) during reappraisal specifically. In addition, recent meta-analytical work found no elevated amygdala reactivity during reappraisal in individuals with anxiety and depressive disorders (Picó-Pérez et al., 2017). As a result, amygdala response to these types of stimuli may not be strongly associated with anxiety and depression symptoms, suggesting that this neural trait may not best characterize these disorders (Hägele et al., 2016).

Finally, failure to find group differences in brain engagement during emotional responding and cognitive reappraisal underscores the need for individual differences approach in the study of emotion dysregulation in these populations. That is, when treated as a homogenous group, individuals with GAD, SAD, MDD did not differ extensively in neural engagement during emotional responding or regulation. Nevertheless, individual differences in anxiety and depression symptom severity related to neural deficiencies in expected regions across the patient sample (e.g., dACC, VLPFC). These findings are consistent with similar studies that have failed to find categorical diagnostic differences in brain functioning but found that individual and trans-diagnostic measures of anxiety and depression related to differences in brain functioning in tasks of emotion processing (MacNamara et al., 2017). Extending this work, we provide the first account of a similar relationship during a task of active explicit regulation in the form of cognitive reappraisal.

Results of the present study should be considered in light of several limitations. First, the current study did not include positive stimuli. Prior research suggests that the processing of positive stimuli, along with negative stimuli, may be disrupted be MDD (Grotegerd et al., 2014; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Matthews, Strigo, Simmons, Yang, & Paulus, 2008; van Tol et al., 2012). Therefore, neural deficits during cognitive reappraisal may be pronounced when using positive images in this population, perhaps as it relates to using reappraisal to up-regulate positive affect. Second, only individuals with GAD, SAD, and MDD were included. Thus, results cannot be generalized to other anxiety disorders like panic disorder and specific phobia. Third, HAM-A and HAM-D may be more sensitive to measuring symptom severity in some groups, but not others. Specifically failure to find a robust relationship between depression severity and neural functioning may be tied to qualities of the HAM-D as an instrument for measuring depression psychopathology (Watson et al., 2007). Fourth, despite high comorbidity across patients, the majority were diagnosed with a primary anxiety disorder; therefore, it will be important to replicate findings in a patient sample matched on primary diagnoses. Fifth, due to high comorbidity and shared variance in depression and anxiety symptoms, results may not generalize to ‘pure’ (e.g., GAD only) diagnostic groups.

Conclusion

In conclusion, we found that anxiety symptoms were related to under-engagement of the dACC and to less connectivity between the amygdala and the VLPFC during cognitive

reappraisal of negative affect in a diverse sample of patients. Results suggest that while trans-diagnostic disturbances in neural engagement are related to measures of anxiety and depression severity, neural deficits in cortical recruitment may be more closely tied to anxiety symptoms. Findings offer added insight into neurobiology underlying emotion dysregulation in anxiety and depression. Ultimately, results underscore the fact that deficits in ability to explicit down-regulate negative affect in those with principal anxiety and depressive disorders may be tied to aberrations in cortical regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures: Research reported in this publication was supported by the National Institutes of Health grants K23MH093679 (to HK), R01MH101497 (to KLP), S10RR028898 and Center for Clinical and Translational Science (CCTS) UL1RR029879.

References

Aldao A, Nolen-Hoeksema S, & Schweizer S (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clinical Psychology Review, 30(2), 217–237. 10.1016/j.cpr.2009.11.004 [PubMed: 20015584]

Almeida JRC, Versace A, Hassel S, Kupfer DJ, & Phillips ML (2010). Elevated Amygdala Activity to Sad Facial Expressions: A State Marker of Bipolar but Not Unipolar Depression. Biological Psychiatry, 67(5), 414–421. 10.1016/j.biopsych.2009.09.027 [PubMed: 19931855]

Alonso J, Lepine JP, & ESEMeD/MHEDEA 2000 Scientific Committee. (2007). Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). Journal of Clinical Psychiatry, 68(Suppl 2), 3–9.

Amstadter A (2008). Emotion regulation and anxiety disorders. Journal of Anxiety Disorders, 22(2), 211–221. 10.1016/j.janxdis.2007.02.004 [PubMed: 17349775]

Ball TM, Ramsawh HJ, Campbell-Sills L, Paulus MP, & Stein MB (2013). Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. Psychological Medicine, 43(07), 1475–1486. 10.1017/S0033291712002383 [PubMed: 23111120]

Banks SJ, Eddy KT, Angstadt M, Nathan PJ, & Phan KL (2007). Amygdala–frontal connectivity during emotion regulation. Social Cognitive and Affective Neuroscience, 2(4), 303–312. 10.1093/scan/nsm029 [PubMed: 18985136]

Beauregard M, Levesque J, & Bourgouin P (2001). Neural correlates of conscious self-regulation of emotion. Journal of Neuroscience, 21, 1–6.

Beauregard Mario, Paquette V, & Levesque J (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. Neuroreport, 17(8), 843–846. [PubMed: 16708026]

Beck AT, & Clark DA (1997). An information processing model of anxiety: automatic and strategic processes. Behav Res Ther, 35(1), 49–58. [PubMed: 9009043]

Beckmann M, Johansen-Berg H, & Rushworth MFS (2009). Connectivity-Based Parcellation of Human Cingulate Cortex and Its Relation to Functional Specialization. Journal of Neuroscience, 29(4), 1175–1190. 10.1523/JNEUROSCI.3328-08.2009 [PubMed: 19176826]

Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, Pine DS (2012). Reduced Dorsal Anterior Cingulate Cortical Activity During Emotional Regulation and Top-Down Attentional Control in Generalized Social Phobia, Generalized Anxiety Disorder, and Comorbid Generalized Social Phobia/Generalized Anxiety Disorder. Biological Psychiatry, 72(6), 476–482. 10.1016/j.biopsych.2012.04.013 [PubMed: 22592057]

Blair K, Shaywitz J, Smith BW, Rhodes R, Geraci M, Jones M, Pine DS (2008). Response to Emotional Expressions in Generalized Social Phobia and Generalized Anxiety Disorder: Evidence

for Separate Disorders. American Journal of Psychiatry, 165(9), 1193–1202. 10.1176/appi.ajp.2008.07071060 [PubMed: 18483136]

Brett M, Anton J-L, Valabregue R, & Poline J-B (2002). Region of Interest Analysis Using an SPM Toolbox [Abstract]. In NeuroImage (Vol. 16(2)).

Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, Ochsner KN (2014). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cerebral Cortex, 24(11), 2981–2990. 10.1093/cercor/bht154 [PubMed: 23765157]

Burklund LJ, Torre JB, Lieberman MD, Taylor SE, & Craske MG (2017). Neural responses to social threat and predictors of cognitive behavioral therapy and acceptance and commitment therapy in social anxiety disorder. Psychiatry Research: Neuroimaging, 261, 52–64. 10.1016/j.pscychresns.2016.12.012 [PubMed: 28129556]

Bush G, Luu P, & Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences, 4(6), 215–222. [PubMed: 10827444]

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, Shulman GL (1998). A Common Network of Functional Areas for Attention and Eye Movements. Neuron, 21(4), 761–773. 10.1016/S0896-6273(00)80593-0 [PubMed: 9808463]

Corbetta M, Patel G, & Shulman GL (2008). The reorienting system of the human brain: from environment to theory of mind. Neuron, 58(3), 306–324. [PubMed: 18466742]

Corbetta M, & Shulman GL (2002). CONTROL OF GOAL-DIRECTED AND STIMULUS-DRIVEN ATTENTION IN THE BRAIN. Nature Reviews Neuroscience, 3(3), 215–229. 10.1038/nrn755

Costafreda SG, Brammer MJ, David AS, & Fu CHY (2008). Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. Brain Research Reviews, 58(1), 57–70. 10.1016/j.brainresrev.2007.10.012 [PubMed: 18076995]

Cuthbert BN (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry, 13(1), 28–35. [PubMed: 24497240]

Cuthbert BN (2015). Research Domain Criteria: toward future psychiatric nosologies. Dialogues in Clinical Neuroscience, 17(1), 89. [PubMed: 25987867]

Cutuli D (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Frontiers in Systems Neuroscience, 8 10.3389/fnsys.2014.00175

Davidson RJ, Irwin W, Anderle MJ, & Kalin NH (2003). The neural substrates of affective processing in depressed patients treated with venlafaxine. American Journal of Psychiatry, 160(1), 64–75. [PubMed: 12505803]

Davies CD, Young K, Torre JB, Burklund LJ, Goldin PR, Brown LA, Craske MG (2017). Altered time course of amygdala activation during speech anticipation in social anxiety disorder. Journal of Affective Disorders, 209, 23–29. 10.1016/j.jad.2016.11.014 [PubMed: 27870942]

Davis EG, Foland-Ross LC, & Gotlib IH (2018). Neural correlates of top-down regulation and generation of negative affect in major depressive disorder. Psychiatry Research: Neuroimaging, 276, 1–8. 10.1016/j.pscychresns.2018.04.001 [PubMed: 29689500]

Delgado MR, Nearing KI, LeDoux JE, & Phelps EA (2008). Neural Circuitry Underlying the Regulation of Conditioned Fear and Its Relation to Extinction. Neuron, 59(5), 829–838. 10.1016/j.neuron.2008.06.029 [PubMed: 18786365]

Erk S, Mikschl A, Stier S, Ciaramidaro A, Gapp V, Weber B, & Walter H (2010). Acute and Sustained Effects of Cognitive Emotion Regulation in Major Depression. Journal of Neuroscience, 30(47), 15726–15734. 10.1523/JNEUROSCI.1856-10.2010 [PubMed: 21106812]

Etkin A, Büchel C, & Gross JJ (2015). The neural bases of emotion regulation. Nature Reviews Neuroscience, 16(11), 693–700. [PubMed: 26481098]

Etkin A, Egner T, & Kalisch R (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences, 15(2), 85–93. 10.1016/j.tics.2010.11.004 [PubMed: 21167765]

Etkin A, Prater KE, Hoeft F, Menon V, & Schatzberg AF (2010). Failure of Anterior Cingulate Activation and Connectivity With the Amygdala During Implicit Regulation of Emotional

Processing in Generalized Anxiety Disorder. American Journal of Psychiatry, 167(5), 545–554. 10.1176/appi.ajp.2009.09070931 [PubMed: 20123913]

Fernandez KC, Jazaieri H, & Gross JJ (2016). Emotion Regulation: A Transdiagnostic Perspective on a New RDoC Domain. Cognitive Therapy and Research, 40(3), 426–440. 10.1007/s10608-016-9772-2 [PubMed: 27524846]

First M, Spitzer R, Gibbon M, & Williams J (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York.

Fitzgerald JM, MacNamara A, Kennedy AE, Rabinak CA, Rauch SAM, Liberzon I, & Phan KL (2016). Individual differences in cognitive reappraisal use and emotion regulatory brain function in combat-exposed veterans with and without PTSD. Depression and Anxiety. 10.1002/da.22551

Fitzgerald JM, Phan KL, Kennedy AE, Shankman SA, Langenecker SA, & Klumpp H (2017). Prefrontal and amygdala engagement during emotional reactivity and regulation in generalized anxiety disorder. Journal of Affective Disorders, 218, 398–406. 10.1016/j.jad.2017.05.013 [PubMed: 28501740]

Geva S, Jones PS, Crinion JT, Price CJ, Baron J-C, & Warburton EA (2011). The neural correlates of inner speech defined by voxel-based lesion-symptom mapping. Brain, 134(10), 3071–3082. 10.1093/brain/awr232 [PubMed: 21975590]

Goldin PR, Manber T, Hakimi S, Canli T, & Gross JJ (2009). Neural Bases of Social Anxiety Disorder: Emotional Reactivity and Cognitive Regulation During Social and Physical Threat. Archives of General Psychiatry, 66(2), 170 10.1001/archgenpsychiatry.2008.525 [PubMed: 19188539]

Goldin PR, Manber-Ball T, Werner K, Heimberg R, & Gross JJ (2009). Neural Mechanisms of Cognitive Reappraisal of Negative Self-Beliefs in Social Anxiety Disorder. Biological Psychiatry, 66(12), 1091–1099. 10.1016/j.biopsych.2009.07.014 [PubMed: 19717138]

Goldin PR, McRae K, Ramel W, & Gross JJ (2008). The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. Biological Psychiatry, 63(6), 577–586. 10.1016/j.biopsych.2007.05.031 [PubMed: 17888411]

Gotlib IH, Krasnoperova E, Yue DN, & Joormann J (2004). Attentional biases for negative interpersonal stimuli in clinical depression. Journal of Abnormal Psychology, 113(1), 127.

Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Northoff G (2008). Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. Biological Psychiatry, 63(4), 369–376. 10.1016/j.biopsych.2007.05.033 [PubMed: 17888408]

Gross JJ (1998). Antecedent-and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. Journal of Personality and Social Psychology, 74(1), 224. [PubMed: 9457784]

Grotegerd D, Stuhrmann A, Kugel H, Schmidt S, Redlich R, Zwanzger P, Dannlowski U (2014). Amygdala excitability to subliminally presented emotional faces distinguishes unipolar and bipolar depression: An fMRI and pattern classification study: An fMRI and Pattern Classification Study. Human Brain Mapping, 35(7), 2995–3007. 10.1002/hbm.22380 [PubMed: 24038516]

Hägele C, Friedel E, Schlagenhauf F, Sterzer P, Beck A, Bermpohl F, Heinz A (2016). Affective responses across psychiatric disorders—A dimensional approach. Neuroscience Letters, 623, 71–78. 10.1016/j.neulet.2016.04.037 [PubMed: 27130821]

Hamilton M (1959). The assessment of anxiety states by rating. British Journal of Medical Psychology, 32, 50–55. [PubMed: 13638508]

Hamilton M (1960). A rating scale for depression. Neurosurgery Psychiatry, 23, 56–62.

Hardee JE, Cope LM, Munier EC, Welsh RC, Zucker RA, & Heitzeg MM (2017). Sex differences in the development of emotion circuitry in adolescents at risk for substance abuse: a longitudinal fMRI study. Social Cognitive and Affective Neuroscience, 12(6), 965–975. 10.1093/scan/nsx021 [PubMed: 28338724]

Hirschfeld RA (2001). The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim Care Companion J Clin Psychiatry., 3(6), 244–254. [PubMed: 15014592]

Hostinar CE, Nusslock R, & Miller GE (2017). Future Directions in the Study of Early-Life Stress and Physical and Emotional Health: Implications of the Neuroimmune Network Hypothesis. Journal of Clinical Child & Adolescent Psychology, 1–15. 10.1080/15374416.2016.1266647

Irwin W, Anderle MJ, Abercrombie HC, Schaefer SM, Kalin NH, & Davidson RJ (2004). Amygdalar interhemispheric functional connectivity differs between the non-depressed and depressed human brain. NeuroImage, 21(2), 674–686. 10.1016/j.neuroimage.2003.09.057 [PubMed: 14980569]

Johnstone T, van Reekum CM, Urry HL, Kalin NH, & Davidson RJ (2007). Failure to Regulate: Counterproductive Recruitment of Top-Down Prefrontal-Subcortical Circuitry in Major Depression. Journal of Neuroscience, 27(33), 8877–8884. 10.1523/JNEUROSCI.2063-07.2007 [PubMed: 17699669]

Jones SR, & Fernyhough C (2007). Neural correlates of inner speech and auditory verbal hallucinations: A critical review and theoretical integration. Clinical Psychology Review, 27(2), 140–154. 10.1016/j.cpr.2006.10.001 [PubMed: 17123676]

Kanske P, Heissler J, Schonfelder S, Bongers A, & Wessa M (2011). How to Regulate Emotion? Neural Networks for Reappraisal and Distraction. Cerebral Cortex, 21(6), 1379–1388. 10.1093/cercor/bhq216 [PubMed: 21041200]

Keedwell PA, Andrew C, Williams SCR, Brammer MJ, & Phillips ML (2005). The Neural Correlates of Anhedonia in Major Depressive Disorder. Biological Psychiatry, 58(11), 843–853. 10.1016/j.biopsych.2005.05.019 [PubMed: 16043128]

Klumpp H, Fitzgerald JM, Kinney KL, Kennedy AE, Shankman SA, Langenecker SA, & Phan KL (2017). Predicting cognitive behavioral therapy response in social anxiety disorder with anterior cingulate cortex and amygdala during emotion regulation. NeuroImage: Clinical, 15, 25–34. 10.1016/j.nicl.2017.04.006 [PubMed: 28462086]

Klumpp H, Hosseini B, & Phan KL (2018). Self-Reported Sleep Quality Modulates Amygdala Resting-State Functional Connectivity in Anxiety and Depression. Frontiers in Psychiatry, 9 10.3389/fpsyt.2018.00220

Klumpp H, Kinney KL, Kennedy AE, Shankman SA, Langenecker SA, Kumar A, & Phan KL (2018). Trait attentional control modulates neurofunctional response to threat distractors in anxiety and depression. Journal of Psychiatric Research, 102, 87–95. 10.1016/j.jpsychires.2018.03.011 [PubMed: 29674271]

Klumpp H, Roberts J, Kapella MC, Kennedy AE, Kumar A, & Phan KL (2017). Subjective and objective sleep quality modulate emotion regulatory brain function in anxiety and depression. Depression and Anxiety. 10.1002/da.22622

Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, & Habel U (2014). Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. NeuroImage, 87, 345–355. 10.1016/j.neuroimage.2013.11.001 [PubMed: 24220041]

Krueger RF, & Bezdjian S (2009). Enhancing research and treatment of mental disorders with dimensional concepts: toward DSM-V and ICD-11. World Psychiatry, 8(1), 3–6. [PubMed: 19293948]

Lane RD, Reiman EM, Ahern GL, Schwartz GE, & Davidson RJ (1997). Neuroanatomical correlates of happiness, sadness, and disgust. American Journal of Psychiatry, 154(7), 926–933. [PubMed: 9210742]

Lang P, Bradley M, & Cuthbert BN. (2008). International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual Technical Report A-8. Gainesville, FL.

Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Phillips ML (2004). Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biological Psychiatry, 55(6), 578–587. 10.1016/j.biopsych.2003.11.017 [PubMed: 15013826]

MacNamara A, Klumpp H, Kennedy AE, Langenecker SA, & Phan KL (2017). Transdiagnostic neural correlates of affective face processing in anxiety and depression: Depression and Anxiety. 10.1002/da.22631

MacNamara A, Rabinak CA, Kennedy AE, Fitzgerald DA, Liberzon I, Stein MB, & Phan KL (2016). Emotion regulatory brain function and SSRI treatment in PTSD: neural correlates and predictors of change. Neuropsychopharmacology, 41(2), 611–618. [PubMed: 26111649]

Marumo K, Takizawa R, Kinou M, Kawasaki S, Kawakubo Y, Fukuda M, & Kasai K (2014). Functional abnormalities in the left ventrolateral prefrontal cortex during a semantic fluency task, and their association with thought disorder in patients with schizophrenia. NeuroImage, 85, 518–526. 10.1016/j.neuroimage.2013.04.050 [PubMed: 23624170]

Matthews SC, Strigo IA, Simmons AN, Yang TT, & Paulus MP (2008). Decreased functional coupling of the amygdala and supragenual cingulate is related to increased depression in unmedicated individuals with current major depressive disorder. Journal of Affective Disorders, 111(1), 13–20. 10.1016/j.jad.2008.05.022 [PubMed: 18603301]

Messina I, Bianco S, Sambin M, & Viviani R (2015). Executive and semantic processes in reappraisal of negative stimuli: insights from a meta-analysis of neuroimaging studies. Frontiers in Psychology, 6 10.3389/fpsyg.2015.00956

Mochcovitch MD, da Rocha Freire RC, Garcia RF, & Nardi AE (2014). A systematic review of fMRI studies in generalized anxiety disorder: Evaluating its neural and cognitive basis. Journal of Affective Disorders, 167, 336–342. 10.1016/j.jad.2014.06.041 [PubMed: 25020268]

Morawetz C, Bode S, Baudewig J, & Heekeren HR (2016). Effective amygdala-prefrontal connectivity predicts individual differences in successful emotion regulation. Social Cognitive and Affective Neuroscience, nsw169 10.1093/scan/nsw169

Morin A, & Hamper B (2012). Self-reflection and the inner voice: activation of the left inferior frontal gyrus during perceptual and conceptual self-referential thinking. The Open Neuroimaging Journal, 6(1). Retrieved from http://benthamopen.com/FULLTEXT/TONIJ-6-78

Nakao T, Sanematsu H, Yoshiura T, Togao O, Murayama K, Tomita M, Kanba S (2011). fMRI of patients with social anxiety disorder during a social situation task. Neuroscience Research, 69(1), 67–72. 10.1016/j.neures.2010.09.008 [PubMed: 20888872]

Nozari N, & Thompson-Schill SL (2016). Left Ventrolateral Prefrontal Cortex in Processing of Words and Sentences In Neurobiology of Language (pp. 569–584). Elsevier 10.1016/B978-0-12-407794-2.00046-8

Ochsner KN, Bunge SA, Gross JJ, & Gabrieli JDE (2002). Rethinking Feelings: An fMRI Study of the Cognitive Regulation of Emotion. Journal of Cognitive Neuroscience, 15(8), 1215–1229.

Ochsner KN, Silvers JA, & Buhle JT (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion: Functional imaging studies of emotion regulation. Annals of the New York Academy of Sciences, 1251(1), E1–E24. 10.1111/j.1749-6632.2012.06751.x [PubMed: 23025352]

O'Reilly JX, Woolrich MW, Behrens TEJ, Smith SM, & Johansen-Berg H (2012). Tools of the trade: psychophysiological interactions and functional connectivity. Social Cognitive and Affective Neuroscience, 7(5), 604–609. 10.1093/scan/nss055 [PubMed: 22569188]

Palm ME, Elliott R, McKie S, Deakin JFW, & Anderson IM (2011). Attenuated responses to emotional expressions in women with generalized anxiety disorder. Psychological Medicine, 41(05), 1009–1018. 10.1017/S0033291710001455 [PubMed: 20716396]

Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, & Hichwa RD (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. American Journal of Psychiatry, 156(10), 1618–1629. [PubMed: 10518175]

Parker JG, Zalusky EJ, & Kirbas C (2014). Functional MRI mapping of visual function and selective attention for performance assessment and presurgical planning using conjunctive visual search. Brain and Behavior, 4(2), 227–237. 10.1002/brb3.213 [PubMed: 24683515]

Paschke LM, Dörfel D, Steimke R, Trempler I, Magrabi A, Ludwig VU, Walter H (2016). Individual differences in self-reported self-control predict successful emotion regulation. Social Cognitive and Affective Neuroscience, 11(8), 1193–1204. 10.1093/scan/nsw036 [PubMed: 27013102]

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, & Tancer ME (2005). Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biological Psychiatry, 57(3), 210–219. 10.1016/j.biopsych.2004.10.030 [PubMed: 15691521]

Picó-Pérez M, Radua J, Steward T, Menchón JM, & Soriano-Mas C (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in

Neuro-Psychopharmacology and Biological Psychiatry, 79, 96–104. 10.1016/j.pnpbp.2017.06.001 [PubMed: 28579400]

Quirk GJ, & Gehlert DR (2003). Inhibition of the amygdala: key to pathological states? Annals of the New York Academy of Sciences, 985, 263–272. [PubMed: 12724164]

Rabinak CA, Angstadt M, Lyons M, Mori S, Milad MR, Liberzon I, & Luan Phan K (2014). Cannabinoid modulation of prefrontal–limbic activation during fear extinction learning and recall in humans. Neurobiology of Learning and Memory, 113, 125–134. 10.1016/j.nlm.2013.09.009 [PubMed: 24055595]

Schaefer SM, Jackson DC, Davidson RJ, Aguirre GK, Kimberg DY, & Thompson-Schill SL (2002). Modulation of amygdalar activity by the conscious regulation of negative emotion. Journal of Cognitive Neuroscience, 14(6), 913–921. [PubMed: 12191458]

Shapero BG, Abramson LY, & Alloy LB (2016). Emotional Reactivity and Internalizing Symptoms: Moderating Role of Emotion Regulation. Cognitive Therapy and Research, 40(3), 328–340. 10.1007/s10608-015-9722-4 [PubMed: 27231404]

Shenhav A, Botvinick MM, & Cohen JD (2013). The Expected Value of Control: An Integrative Theory of Anterior Cingulate Cortex Function. Neuron, 79(2), 217–240. 10.1016/j.neuron.2013.07.007 [PubMed: 23889930]

Sripada C, Angstadt M, Kessler D, Phan KL, Liberzon I, Evans GW, Swain JE (2014). Volitional regulation of emotions produces distributed alterations in connectivity between visual, attention control, and default networks. NeuroImage, 89, 110–121. 10.1016/j.neuroimage.2013.11.006 [PubMed: 24246489]

Strawn JR, Bitter SM, Weber WA, Chu W-J, Whitsel RM, Adler C, DelBello MP (2012). NEUROCIRCUITRY OF GENERALIZED ANXIETY DISORDER IN ADOLESCENTS: A PILOT FUNCTIONAL NEUROIMAGING AND FUNCTIONAL CONNECTIVITY STUDY: Research Article: Pediatric GAD Physiology. Depression and Anxiety, 29(11), 939–947. 10.1002/da.21961 [PubMed: 22628125]

Townsend JD, Eberhart NK, Bookheimer SY, Eisenberger NI, Foland-Ross LC, Cook IA, Altshuler LL (2010). fMRI activation in the amygdala and the orbitofrontal cortex in unmedicated subjects with major depressive disorder. Psychiatry Research: Neuroimaging, 183(3), 209–217. 10.1016/j.pscychresns.2010.06.001

Tripp JC, McDevitt-Murphy ME, Avery ML, & Bracken KL (2015). PTSD Symptoms, Emotion Dysregulation, and Alcohol-Related Consequences Among College Students With a Trauma History. Journal of Dual Diagnosis, 11(2), 107–117. 10.1080/15504263.2015.1025013 [PubMed: 25793550]

Tull MT, Bardeen JR, DiLillo D, Messman-Moore T, & Gratz KL (2015). A prospective investigation of emotion dysregulation as a moderator of the relation between posttraumatic stress symptoms and substance use severity. Journal of Anxiety Disorders, 29, 52–60. 10.1016/j.janxdis.2014.11.003 [PubMed: 25483275]

Urry HL (2006). Amygdala and Ventromedial Prefrontal Cortex Are Inversely Coupled during Regulation of Negative Affect and Predict the Diurnal Pattern of Cortisol Secretion among Older Adults. Journal of Neuroscience, 26(16), 4415–4425. 10.1523/JNEUROSCI.3215-05.2006 [PubMed: 16624961]

van Tol M-J, Demenescu LR, van der Wee NJA, Kortekaas R, Marjan MA, N., Boer JAD, Veltman DJ (2012). Functional Magnetic Resonance Imaging Correlates of Emotional Word Encoding and Recognition in Depression and Anxiety Disorders. Biological Psychiatry, 71(7), 593–602. 10.1016/j.biopsych.2011.11.016 [PubMed: 22206877]

Wager TD, Davidson ML, Hughes BL, Lindquist MA, & Ochsner KN (2008). Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation. Neuron, 59(6), 1037–1050. 10.1016/j.neuron.2008.09.006 [PubMed: 18817740]

Wang H-Y, Zhang X-X, Si C-P, Xu Y, Liu Q, Bian H-T, Yan Z-R (2018). Prefrontoparietal dysfunction during emotion regulation in anxiety disorder: a meta-analysis of functional magnetic resonance imaging studies. Neuropsychiatric Disease and Treatment, *Volume* 14, 1183–1198. 10.2147/NDT.S165677 [PubMed: 29785110]

Watson D, O'Hara MW, Simms LJ, Kotov R, Chmielewski M, McDade-Montez EA, Stuart S (2007). Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychological Assessment, 19(3), 253–268. 10.1037/1040-3590.19.3.253 [PubMed: 17845118]

Whalen PJ, Johnstone T, Somerville LH, Nitschke JB, Polis S, Alexander AL, Kalin NH (2008). A Functional Magnetic Resonance Imaging Predictor of Treatment Response to Venlafaxine in Generalized Anxiety Disorder. Biological Psychiatry, 63(9), 858–863. 10.1016/j.biopsych.2007.08.019 [PubMed: 17964548]

Yamagishi T, Takagishi H, Fermin A de SR, Kanai R, Li Y, & Matsumoto Y (2016). Cortical thickness of the dorsolateral prefrontal cortex predicts strategic choices in economic games. Proceedings of the National Academy of Sciences, 113(20), 5582–5587.

Zbozinek TD, Rose RD, Wolitzky-Taylor KB, Sherbourne C, Sullivan G, Stein MB, Craske MG (2012). DIAGNOSTIC OVERLAP OF GENERALIZED ANXIETY DISORDER AND MAJOR DEPRESSIVE DISORDER IN A PRIMARY CARE SAMPLE: Research Article: GAD and MDD Diagnostic Overlap. Depression and Anxiety, 29(12), 1065–1071. 10.1002/da.22026 [PubMed: 23184657]

Zilverstand A, Parvaz MA, & Goldstein RZ (2016). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. NeuroImage. 10.1016/j.neuroimage.2016.06.009

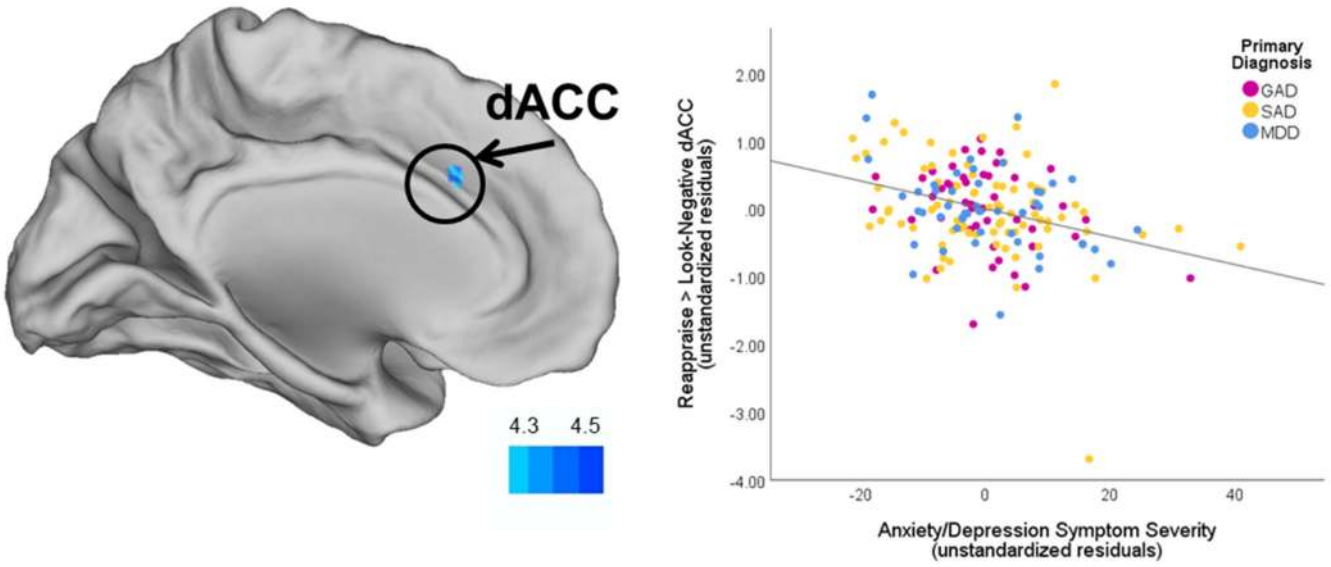

Figure 1.

Spatial location of negative relationship with summation of symptom severity across Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) scores with dorsal anterior cingulate cortex (dACC [peak MNI coordinate: −8, 24, 30]) during Reappraise > Look-Negative.

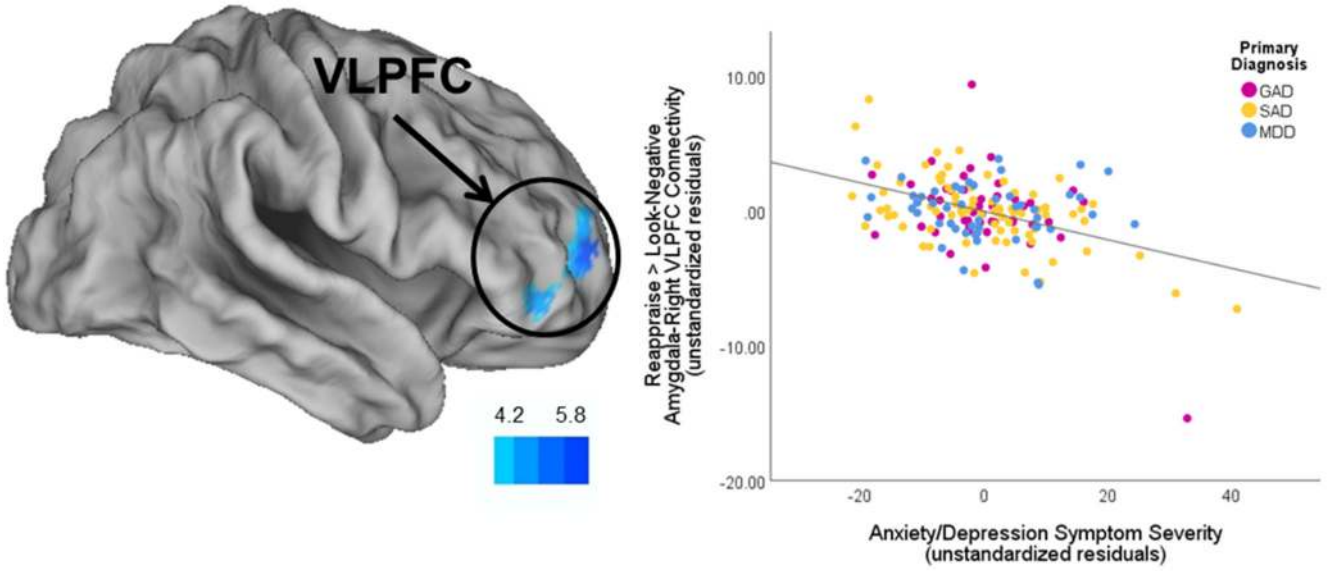

Figure 2.

Spatial location of negative relationship with summation of symptom severity across Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) scores with amygdala-right ventrolateral prefrontal cortex (VLPFC) connectivity (peak MNI coordinate: 30, 60, 2).

Table 1.

Sample Demographics

	GAD (*n* = 47)	SAD (*n* = 78)	MDD (*n* = 49)		
	M (SD)	***M (SD)***	***M (SD)***	***test statistic***	***p***
Age	27.79 (7.35)	24.91 (6.46)	25.49 (8.46)	2.35	0.10
Years of Education	16.72 (3.50)	15.41 (2.47)	15.06 (2.50)	4.85	0.01
HAM-A	15.02 (6.09)	13.86 (7.78)	18.55 (7.23)	6.52	<0.01
HAM-D	10.30 (3.61)	8.60 (5.00)	15.31 (4.80)	32.51	<0.001
	n (%)	*n (%)*	*n (%)*	*test statistic*	*p*
Gender (Female)	29 (61.70%)	55 (70.51%)	39 (79.59%)	3.71	0.16
Race				12.18	0.27
Caucasian	33 (70.21%)	48 (61.54%)	31 (63.27%)		
African-American	3 (6.38%)	5 (6.41%)	8 (16.33%)		
Asian or Pacific Islander	6 (12.77%)	15 (19.23%)	9 (18.37%)		
Native American	2 (4.26%)	1 (1.28%)	0 (0%)		
More than one race	2 (4.26%)	8 (10.26%)	1 (2.04%)		
Other or unknown	1 (2.13%)	1 (1.28%)	0 (0%)		
Ethnicity (Hispanic)	7 (14.89%)	20 (25.64%)	12 (24.49%)	2.12	0.35
Comorbidity				49.93	<0.001
AD	21 (44.68%)	23 (29.49%)	26 (53.06%)		
AD, MDD	9 (19.15%)	16 (20.52%)	-		
AD, PTSD	0 (0%)	1 (1.28%)	9 (18.37%)		
AD, MDD, PTSD	1 (2.13%)	0 (0%)	-		
MDD	3 (6.38%)	13 (16.67%)	-		
MDD, Substance Abuse	0 (0%)	2 (2.56%)	-		
PTSD	1 (2.13%)	0 (0%)	1 (2.04%)		
None	12 (25.53%)	23 (29.49%)	13 (26.53%)		

Note. HC=healthy control; PT=patient; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; GAD=generalized anxiety disorder; SAD=social anxiety disorder; MDD=major depressive disorder; AD=anxiety disorder; PTSD=posttraumatic stress disorder. Group comparisons were performed using Analysis of Variance (ANOVA), except for gender, race, ethnicity, and comorbidity, which was calculated using Pearson chi-square.