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Neural substrates of emotional conflict with anxiety in major depressive disorder: Findings from the Establishing Moderators and biosignatures of Antidepressant Response in Clinical Care (EMBARC) randomized controlled trial

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ABSTRACT

Background: The brain circuitry of depression and anxiety/fear is well-established, involving regions such as the limbic system and prefrontal cortex. We expand prior literature by examining the extent to which four discrete factors of anxiety (immediate state anxiety, physiological/panic, neuroticism/worry, and agitation/restlessness) among depressed outpatients are associated with differential responses during reactivity to and regulation of emotional conflict.

Methods: A total of 172 subjects diagnosed with major depressive disorder underwent functional magnetic resonance imaging while performing an Emotional Stroop Task. Two main contrasts were examined using whole brain voxel wise analyses: emotional reactivity and emotion regulation. We also evaluated the association of these contrasts with the four aforementioned anxiety factors.

Results: During emotional reactivity, participants with higher immediate state anxiety showed potentiated activation in the rolandic operculum and insula, while individuals with higher levels of physiological/panic demonstrated decreased activation in the posterior cingulate. No significant results emerged for any of the four factors on emotion regulation. When re-analyzing these statistically-significant brain regions through analyses of a subsample with (n = 92) and without (n = 80) a current anxiety disorder, no significant associations occurred among those without an anxiety disorder. Among those with an anxiety disorder, results were similar to the full sample, except the posterior cingulate was associated with the neuroticism/worry factor.

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Conclusions: Divergent patterns of task-related brain activation across four discrete anxiety factors could be used to inform treatment decisions and target specific aspects of anxiety that involve intrinsic processing to attenuate overactive responses to emotional stimuli.

Clinical Trial Information: The EMBARC study (NCT01407094); https://clinicaltrials.gov/ct2/show/NCT01407094.

1. Introduction

Depression and anxiety are comorbid, common psychiatric disorders (Kessler et al., 2005), and anxiety symptoms - but not comorbid anxiety disorders - alongside depression are associated with worse depression treatment and remission outcomes (Fava et al., 2008; Saveanu et al., 2015). Depressive symptom reduction and remission rates are similar in participants with the anxiety distress subtype of major depressive disorders versus those with other subtypes (Arnow et al., 2015). Comorbid depression and anxiety also impair emotion regulation. Specifically, during emotional conflict regulation (an established task whereby participants must regulate receiving two consecutive trials of stimuli in which emotion words superimposed on facial emotional expressions do not match), patients with depression and comorbid anxiety perform more poorly than those with depression only, and such performance is related to brain function differences in the ventral cingulate and amygdala (Etkin and Schatzberg, 2011). However, anxiety presentation in depression is heterogeneous, and may present as one or multiple comorbid anxiety disorders, an anxious distress specifier, or elevated anxiety symptoms without a formal anxiety disorder; accordingly, delineating neural correlates associated with each distinct pattern of presentation could be important to parse the heterogeneity of MDD and ultimately inform treatment decisions. It is also vital to understand how anxiety *symptoms* – not just comorbid anxiety disorder *diagnoses* – impact the treatment of and patient functioning with MDD, especially given the National Institute of Mental Health's Research Domain Criteria (Cuthbert, 2015; Insel et al., 2010; Morris and Cuthbert, 2012) emphasis on dimensional constructs implicated cross-diagnostically. In addition, the anxious distress specifier for major depressive disorder – characterized by an increased likelihood of, but not requiring, a comorbid anxiety disorder – is both valid and common (Zimmerman et al., 2019), and has been associated with worse antidepressant treatment side effect profiles and poorer treatment outcomes (Gaspersz et al., 2017). Thus, improving our understanding of which aspects of brain and behavioral abnormalities are related to different facets of anxiety/fear circuitry within major depression could improve our ability to match patients with appropriate treatments (Krishnan and Nestler, 2008; Ressler and Mayberg, 2007).

Beyond major depression, the anxiety/fear circuitry has also been independently well-established and involves brain regions including prelimbic/limbic regions (e.g., amygdala, anterior cingulate, hippocampus, thalamus, and hypothalamus) and the prefrontal cortex (Duval et al., 2015; Etkin, 2010; Shin and Liberzon, 2010; Tovote et al., 2015). Furthermore, anxiety is associated with disruptions in amygdala functional connectivity and activity during emotional processing (Etkin, 2010; Etkin and Schatzberg, 2011; Etkin and Wager, 2007). Unfortunately, despite the clinically observed heterogeneity of anxiety, a key limitation is that prior research has analyzed anxiety as a single construct, typically either as a diagnostic criterion or self-report questionnaire score. It is currently unknown how different types or factors of anxiety relate to brain and behavioral functioning among individuals with MDD; filling this gap is a key aim of the current project.

Recent research has identified four unique anxiety factors that characterize a sample of depressed outpatients: immediate state anxiety, physiological/panic, neuroticism/worry, and agitation/restlessness (Trombello et al., 2018). Specifically, neuroticism/worry was associated with impaired performance on an executive (cognitive control) task, such that patients with greater neuroticism/worry responded faster, but with less accuracy, to incongruent trials, negatively impacting task performance. Conversely, panic was associated with slower task response times. These results raise the possibility that response inhibition is linked to a specific component of anxiety and reinforce the notion that anxiety is a multifactorial construct (Trombello et al., 2018).

In the present study, we extend this research by considering whether anxiety factors within an unmedicated MDD sample are associated with differences in brain activation during a neuroimaging task of emotion reactivity and regulation, with the aim of linking discrete biomarkers with specific components of anxiety. Specifically, we hypothesize that the four anxiety factors of immediate state anxiety, physiological/panic anxiety, neuroticism/worry, and agitation/restlessness will be associated with brain activation during an emotion conflict fMRI task. These specific fMRI tasks are vital to be studied, given long-standing findings on emotion dysregulation in depression and anxiety (Hofmann et al., 2012; Joormann and Siemer, 2014). Due to this work's exploratory nature, we did not have specific predictions about which components will be implicated. Nonetheless, such differential results would further demonstrate that anxiety is multifaceted – not unidimensional – in accordance with Research Domain Criteria that associate specific neural circuits with specific behaviors (Cuthbert, 2015; Insel et al., 2010; Morris and Cuthbert, 2012). Furthermore, understanding the extent to which discrete brain regions are involved in specific components of depression and anxiety may also assist with treatment selection, optimization, and personalization (Mayberg, 2003; Phillips et al., 2015).

2. Materials and methods

2.1. Participants

A total of 296 subjects with recurrent or chronic single episode major depressive disorder (MDD) or dysthymia per the Structured Clinical Interview for DSM-IV-TR (SCID-I; First et al., 2002) were recruited and randomized in the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study. EMBARC was a 16-week double-blinded placebo-controlled trial of sertraline (first eight weeks), and bupropion for sertraline (or sertraline for placebo) non-responders during the second eight weeks. The 17-item Hamilton Rating Scale for Depression was used as the primary outcome to measure the clinical severity of patients.

Key inclusion criteria were participants aged 18–65, with chronic or recurrent MDD with first MDD onset before age 30, and self-report Quick Inventory of Depressive Symptomatology (Rush et al., 2003) score $\geq$14 at both screening and randomization visits. Key exclusion criteria included failure to respond to a prior antidepressant trial within the current episode, current pregnancy, lifetime psychosis or bipolar disorder, substance dependence in the past six months and abuse in the past two months, unstable psychiatric or general medical conditions requiring hospitalization or contraindicating study medication, and clinically significant laboratory abnormalities. Full inclusion/exclusion criteria can be found in the EMBARC rationale and design paper (Trivedi et al., 2016). Furthermore, conditions including a history of epilepsy, metal in the body, and other medical conditions were contraindications to neuroimaging. Of the 296 correctly randomized MDD subjects (3 were excluded from analyses because they were randomized but did not in fact meet criteria, while 10 were treated with citalopram during the brief initial duration in time that citalopram and not sertraline was the study drug), some were subsequently excluded due to missing behavioral or MRI data (n = 36), poor behavioral performance (<70% accuracy, n = 32), excessive motion (>4 mm, n = 24), and poor MRI data quality (n =

32). Therefore, fMRI analyses were performed on 172 MDD participants; see CONSORT diagram (Fig. 1). Conducting VBA/whole-brain analysis requires substantial quality control with frequent data loss to ensure such stringency (McGrath et al., 2013), explaining the sample size reduction from prior EMBARC research using a region-of-interest approach (Greenberg et al., 2015). All participants completed self-report measures and a task-based functional MRI (fMRI) scan at baseline. The study was approved by the IRB committee at each of the four sites [UT Southwestern Medical Center (UTSW), Massachusetts General Hospital (MGH), Columbia University (CU), University of Michigan (UM)], and all participants signed written informed consent before completing any study procedures.

2.2. Behavioral measures

2.2.1. Anxiety factors

The anxiety factors were derived from the following self-report scales: 12 items from the neuroticism subscale of the NEO Five Factor Inventory–3 (McCrae and Costa, 2010); four items that assess anxiety and two items that assess panic from the Concise Associated Symptoms Tracking Scale (Trivedi et al., 2011); ten items from the Anxious Arousal subscale of a 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (Wardenaar et al., 2010); one item from the General Distress subscale ("I worried about a lot of things") with face-validity for anxiety; and 20 items from the state version of the Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1983). These factors were derived through exploratory principal components factor analysis with orthogonal varimax rotation and items with loadings of 0.35 or greater for a factor were summed to form the factor score. This computation followed identical principles outlined in prior EMBARC research (Trombello et al., 2018) that determined four discrete anxiety factors – immediate state anxiety, physiological/panic, neuroticism/worry, and agitation/restlessness – that characterized depressed outpatients. Reliability and validity of these four factors, more elaborate definitions of these factors, and factor loadings can be found in the original publication (Trombello et al., 2018).

2.2.2. Emotion conflict regulation task

The study followed prior methods for the Emotional Conflict Regulation Task (Etkin and Schatzberg, 2011; Etkin and Wager, 2007). Briefly, participants saw emotional faces (fearful or happy), presented pseudo randomly. Each face had an emotional word imposed on it, either *FEAR* or *HAPPY,* resulting in an emotional Stroop. For each emotional face-word pair presented, participants made one of two responses based on the face's emotional expression: (1) "fear" when they judged the face to be fearful, or (2) "happy" when they judged the face to be happy. As in prior work (Etkin and Schatzberg, 2011), emotional reactivity was operationalized by considering trials when an emotional pair did not match (i.e., face-word pair are always incongruent) subtracted from instances where they did match (congruent). Emotional

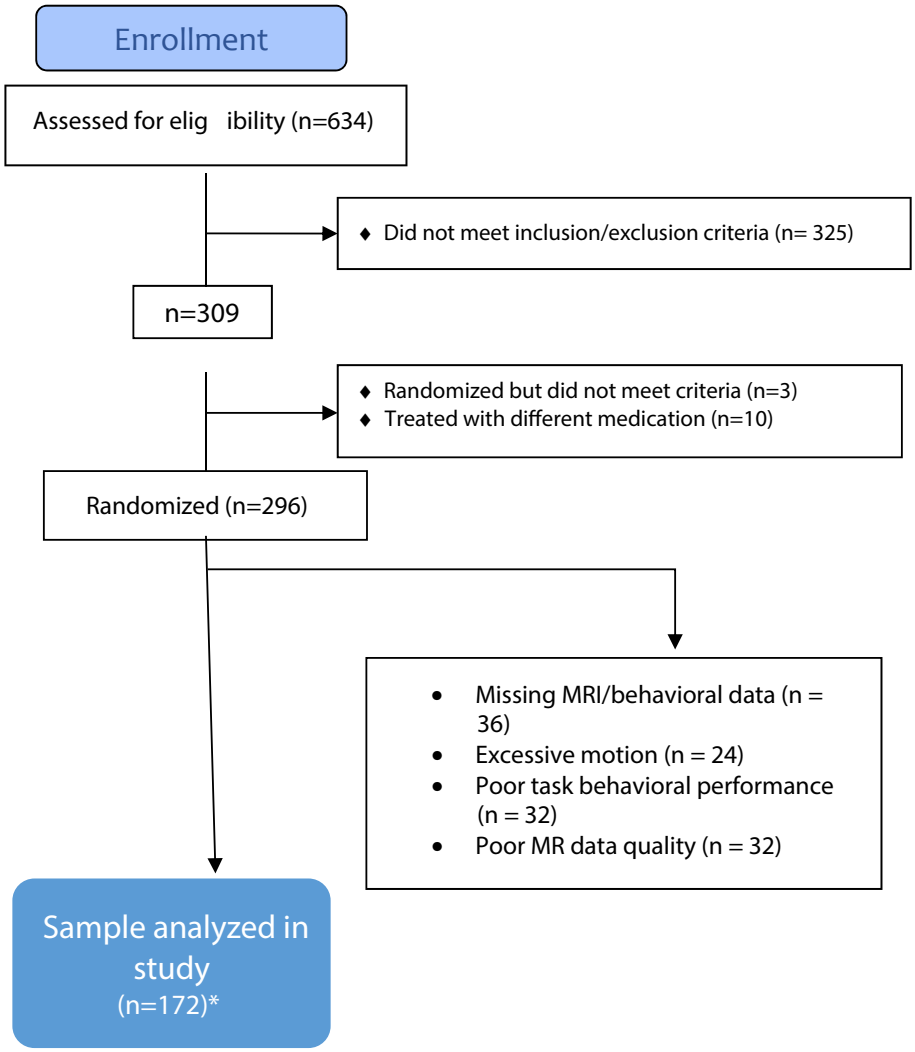

Fig. 1. CONSORT diagram.

regulation was operationalized by considering incongruent pairs presented immediately after another incongruent pair (i.e., two consecutive incongruent pairings between emotion face and emotion word) subtracted from cases when an incongruent pairing was presented after a congruent pair, whereby emotional processing to control reactivity to emotional conflict is continued in order to judge the facial expression while disregarding the word. A minimum level of task accuracy (>70%) was set to ensure modeling task-relevant brain activation.

2.2.3. MRI acquisition

Magnetic resonance neuroimaging data were collected at four different sites, all using 3 T scanners: CU (General Electric), MGH (Siemens), UM (Philips), and UTSW (Philips). T1-weighted structural and task-based fMRI were acquired in the same session. The acquisition parameters were similar across sites (see Supplemental Table 1). All scans were collected before participants received their first study medication dose.

2.2.4. MRI data analyses

Data were preprocessed using FSL tools (Woolrich et al., 2009). Affine transformation of functional to structural images using boundary-based registration was performed. Functional images were aligned to the middle volume of the run. Global signal corresponding to segmented white matter and CSF was regressed out of motion-corrected functional images, which were isotropically smoothed with a 6 mm full-width half max. Participants with a root mean square absolute movement >4 mm across the mean of the squared maximum displacements in each of the six estimated translational and rotational motion parameters for each functional run were excluded from further analysis for quality control. In line with prior literature (Etkin et al., 2006; Fonzo et al., 2017), the a priori contrasts of interest were Incongruent vs. Congruent trials (Inc-Con; emotional conflict reactivity) and Post-incongruent Incongruent trials vs. Post-congruent Incongruent trials (iI-cI; an established measure of regulation of conflict reactivity).

In order to assess the relationship between the anxiety factors and brain activation, whole-brain, voxel-wise multiple regression analyses were performed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). Each participant's contrast maps of interest (Inc-Con and iI-cI) were regressed against their anxiety factor scores (immediate state anxiety, physiological/panic anxiety, neuroticism/worry, restlessness/agitation). Each regression was performed against each factor separately. All analyses were controlled for age, sex, site, handedness, and signal-to-noise ratio. As the standard criterion for analysis, statistical maps were generated with activations identified within a whole brain binary mask (excluding cerebellum) at a voxel-wise uncorrected threshold of $p < .001$ and whole-brain corrections for multiple comparisons using SPM-based random field theory approaches for significance, cluster extent at familywise error rate p[cFWE]<0.05 and topological false discovery rate p[FDR]<0.05. Following prior research (Meng et al., 1992), pairwise comparisons of correlated coefficients [$p < .0083$ (two-tailed test) after Bonferroni correction for 6 pairwise comparisons] were then conducted to determine if results for one factor with one brain region were statistically different from those of the other three factors.

Finally, we employed post-hoc, exploratory analyses to determine if the regression results among the full MDD sample would replicate when differentiating between those with and without anxiety disorders. We conducted the regression analyses using the same statistically-significant regions and sum of items for each factor and repeated this process for all participants (n = 92) with any anxiety disorder (current GAD, panic disorder, agoraphobia, social phobia, OCD or PTSD) as determined by the SCID-I and those (n = 80) with no anxiety disorder. The region activations along with age, gender, handedness, and site were used as post-hoc predictors of each anxiety factor separately.

3. Results

3.1. Demographics and descriptive statistics

The 172 participants were predominantly female (72.1%), with a mean age of 35.8 years (SD = 12.6). These participants had baseline depressive symptoms in the moderate-to-severe range. See Table 1 for additional demographic information. Comparing the 172 participants included in the analysis to the 124 participants excluded, we found significant differences for sex (72.1% female for those included and 56.4% female for those excluded, p = .005), and race (69.8% White, 14.5% Black, 15.7% Other for those included vs 58.9% White, 26.6% Black, and 15.7% Other for those excluded, p = .034). Thus, those excluded were more likely to be male and Black than those included.

3.2. MDD anxiety factors associations with BOLD signal change

When considering the contrast probing emotional conflict reactivity, multiple regression analyses revealed positive associations between the immediate state anxiety factor and fMRI activations within the left rolandic operculum and insula (BA13), $p < .05$ for both FWE and FDR corrected analyses (Fig. 2). Follow-up analyses indicated that the association between these brain regions and the immediate state anxiety factor was statistically significantly different from the physiological/panic factor ($p < .0001$).

When analyzing the psychological/panic factor, multiple regression analyses indicated decreased activations in the left posterior cingulum (BA 31), $p < .001$ for both FWE and FDR corrections during the emotional reactivity task. Meng tests indicated that the correlation involving the physiological/panic factor was significantly different from the immediate state anxiety factor ($p < .0001$). In addition, using FWE-corrected results, there was a nonsignificant trend (p = .051) for the association between the right angular gyrus (BA 39) activation and higher levels of physiological/panic anxiety (Fig. 3). Additional analyses determined that only the pairwise comparison between the physiological/panic factor and the immediate state anxiety factor was statistically significant (p = .0009). Significant results can be found in Table 2.

Regressions of the emotional reactivity contrast maps against the neuroticism/worry and the agitation/restlessness factors did not reveal any significant results after correction for multiple comparisons.

Table 1
Demographic and descriptive characteristics (n = 172).

Variable	Frequency (Mean)	Percent (SD)
Gender		
Male	48	27.91%
Female	124	72.09%
Marital Status		
Single	101	59.06%
Married	40	23.39%
Divorced	25	14.62%
Separated	3	1.75%
Widowed	1	0.58%
Partnered	1	0.58%
Hispanic or Latino Origin		
No	139	80.81%
Yes	33	19.19%
Race		
White	120	69.77%
Black or African-American	25	14.53%
Asian	15	8.72%
American Indian or Alaska Native	1	0.58%
Other	11	6.40%
Depressive Symptoms		
Clinician-rated $HRSD_{17}$	18.8	4.4
Self-report $QIDS_{16}$	18.0	2.7

Note. $HRSD_{17}$ = Hamilton Rating Scale for Depression; $QIDS_{16}$ = Quick Inventory of Depressive Symptomatology.

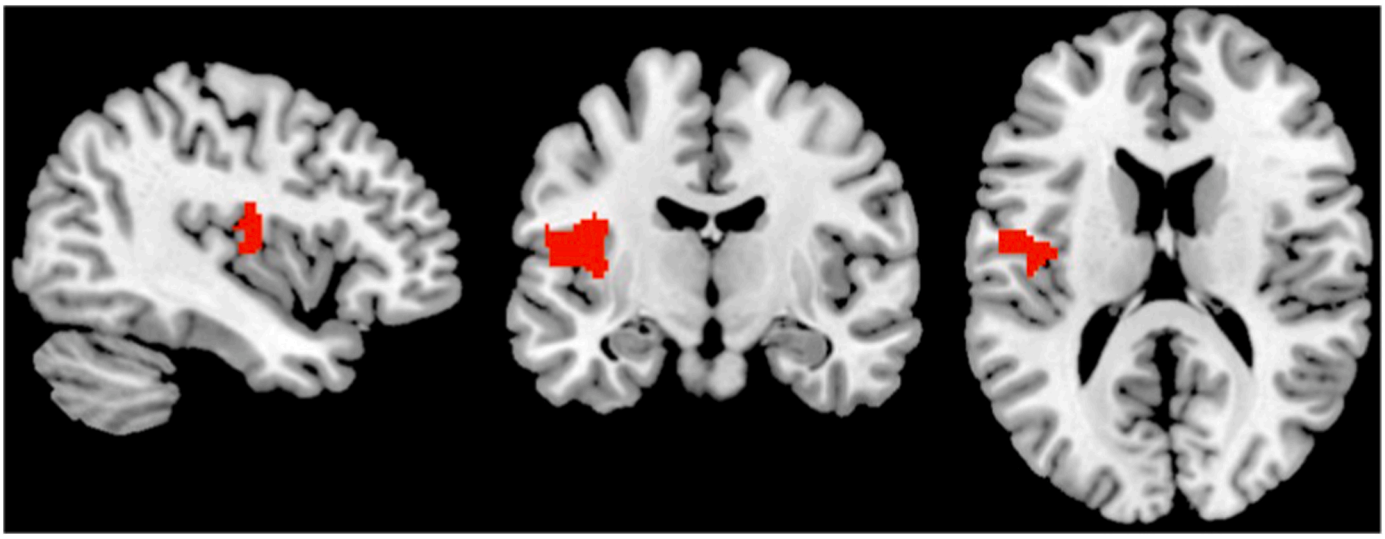

Fig. 2. Regions of significant positive correlations are seen between anxiety factor 1 (immediate state anxiety) and activation within the left insula and rolandic operculum for the emotional reactivity contrast. Activation maps have been thresholded at p[FWE<0.05].

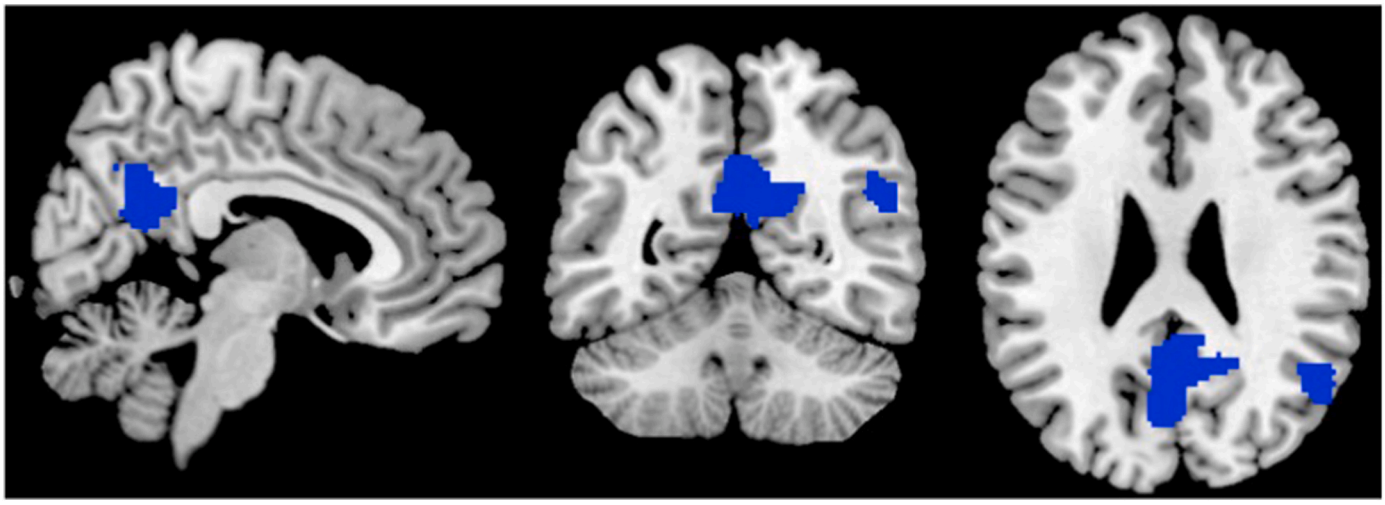

Fig. 3. Regions of significant negative correlations are seen between anxiety factor 2 (physiological/panic) and activation within bilateral posterior cingulate (extending to bilateral precuneus), and the right angular gyrus for the emotional reactivity contrast. Activation maps have been thresholded at p[FWE<0.05].

Table 2
Regions of significant 1) positive correlation between fMRI activation during emotional reactivity and Factor 1 (Immediate State Anxiety), N = 172, and 2) negative correlation between fMRI activation during emotional reactivity and Factor 2 (Physiological/Panic), N = 171.

Activation maxima (Clusters) Inset: Secondary activation maxima within the cluster	Brodmann Area (BA)	Peak *T*	MNI Coordinates (x, y, z)	Number of Voxels	*p*[cFWE]	*p*[FDR]	*p*[uncorr]
Factor 1 – Immediate State Anxiety							
Left Rolandic Operculum	13	4.4	−50, −6, 14	314	0.011	0.037	0.002
Left Rolandic Operculum							
Left Insula							
Factor 2 – Physiological/Panic							
Left Posterior Cingulum	31	4.3	0, −54, 30	1053	0.000	0.000	0.000
Right Precuneus	39	4.7	50, −60, 24	210	0.051	0.156	0.009
Left Cuneus							
Right Angular Gyrus							

Furthermore, no significant clusters of activations were found for emotional conflict regulation.

When further decomposing these analyses to those with and without formal anxiety disorders, none of the previously significant regions of interest were significantly associated with any of the anxiety factors among the group without any anxiety disorder. Among the group with any anxiety disorder, activation in the left rolandic operculum was significantly associated with the neuroticism/worry factor (p = .020), while activation in the left posterior cingulum was significantly associated with the physiological/panic factor (p = .047). Taken together,

these results demonstrate that associations between activation in specific brain regions and anxiety factors occur only among those with a formal anxiety disorder.

4. Discussion

In a sample of depressed outpatients we found, we believe for the first time, that baseline levels of immediate state anxiety and physiological/panic manifestations of anxiety were significantly associated with differential neural activation during reactivity to – but not regulation of – emotion conflict. Importantly, highlighting further specificity, neither neuroticism/worry nor agitation/restlessness was associated with task-related activation among the full sample, although the neuroticism/worry factor was associated with brain activation when analyzing only those with a current anxiety disorder. All analyses were independent of the other anxiety factors, allowing us to test unique effects of each factor beyond common severity. Moreover, relations between brain activation and significant anxiety factors were statistically different from those involving the other factors, further highlighting dissociations.

These results extend prior findings with this sample (Trombello et al., 2018) that indicated the physiological/panic and neuroticism/worry factors were significantly associated with behavioral differences during a non-emotional conflict task (Flanker Interference Task). Although our prior analyses did not examine neuroimaging data and used a purely non-emotional behavior task, it is noteworthy that both tasks involved processing conflict between incongruent stimuli. Furthermore, the current emotional conflict task can be used to probe corticolimbic regions (Etkin et al., 2006), while the Flanker task involves cognitive control and response inhibition, which more directly target the prefrontal cortex. It is therefore unsurprising that different cognitive and neuroimaging tasks with discrete brain circuitry targets would demonstrate dissimilar associations with various facets of anxiety; in fact, this result is consistent with RDoC, which focuses on dimensional constructs that cut across DSM diagnoses and are linked to distinct neural circuitries. An interesting commonality across the current and our prior study (Trombello et al., 2018) is that the physiological/panic factor was associated with distinct association with neural and behavioral patterns in interference tasks.

Specifically, in the prior study, greater physiological/panic was associated with slower reaction time, while in the current study, greater physiological/panic was associated with lower activation of areas in the posterior cingulate cortex and the angular gyrus during reactivity to emotion conflict. The posterior cingulate, a key default mode network hub, has been linked to internally focused attention and implicated in other intrinsic control processes (Leech and Sharp, 2014). Similarly, the angular gyrus, a division of the inferior parietal lobule, has been implicated in default-mode-related processes and also task-positive functions (Fox et al., 2005) such as emotion and attention processes. These regions are important for task-specific modulation, such that the posterior cingulate should be deactivated during task-related challenges, while the angular gyrus, depending on function, should be activated. Emotional interference in task-processing can negatively impact this interplay (Di Plinio et al., 2018). Both regions are lower in the current study for the physiological/panic factor, suggesting resting-state activity is more reactive (deactivated), and task-directed activity is less reactive for those with greater physiological anxiety. We posit that increased physiological arousal may disrupt the interplay between internally (resting-state) versus externally directed (task-directed) information.

The involvement of immediate/state anxiety in regions within the insula during the emotion conflict task is noteworthy. The insula has been previously implicated in emotional tasks that also require cognition, emotion recall, and emotion evaluation, especially for distressing or danger-signaling emotions (Phan et al., 2002). It is also noteworthy that the neuroticism/worry factor, which was associated with response time and accuracy in processing non-emotional conflicting information (Trombello et al., 2018), was not implicated in the current analyses probing activation during reactivity and regulation of emotional conflicting stimuli. This is surprising, given the association of neuroticism, negative affectivity, and trait anxiety, and that neuroticism is a tendency to experience aversive emotions (Watson and Clark, 1984). While individuals high in neuroticism responded more quickly and less accurately to incongruent, non-emotional material (Trombello et al., 2018), differential brain activation patterns with this factor were not observed during an emotion conflict task. Power issues, including sample size, may also partially explain these null findings, as well as differences in what was tested (i.e., behavioral performance versus brain activation).

Despite some key differences, across both analyses, agitation/restlessness was not associated with performance during a non-emotional conflict task (Trombello et al., 2018) or brain activation during an emotion conflict task. Furthermore, the fact that some factors – but not all – were associated with statistically significant brain activation patterns indicates that anxiety is not unidimensional but is instead composed of multiple cognitive and physiological components with differential effects on brain and behavior. These results confirm that reactivity to emotional conflict occurred in expected brain regions implicated in emotion processing. Results also differentiate brain regions that are and are not involved in emotional reactivity and regulation, and further suggest the need for targeted interventions on these specific brain regions. Psychotherapy for anxiety has primarily relied on cognitive-behavior therapy (Kaczkurkin and Foa, 2015), with modifications for exposure procedures (i.e., interceptive exposures for panic, imaginal exposures for generalized anxiety disorder), and our results suggest that interventions such as CBT that involve the limbic system and default mode network (Li et al., 2018; Shpaner et al., 2014) may be important for anxiety treatment.

Our results also indicated that immediate state, physiological/panic anxiety, and neuroticism/worry were implicated in reactivity of emotion conflict but not regulation of this conflict; in fact, null results for emotion conflict regulation were uniform across all anxiety factors and among those with and without an anxiety disorder diagnosis. These results diverge from prior reports using the same task in this sample (Fonzo et al., 2019), which indicated how emotion conflict regulation was associated with worse sertraline treatment outcomes, although it should be noted that the current project did not consider treatment prediction. Our results also contrast with prior work on impairment in emotion conflict regulation in other samples/settings, such as comorbid GAD/MDD (Etkin and Schatzberg, 2011), GAD (Etkin et al., 2010), and PTSD (Marusak et al., 2015), as our sample of participants did not show the same deficit in regulating conflict. There are several explanations for these findings. First, emotion conflict reactivity is likely a faster process than emotion regulation, which requires sustained identification after an emotionally incongruent trial. It is therefore logical that immediate/state anxiety would be implicated in the fast conflict reactivity process but relatively unrelated to the slower regulation process. Physiological/panic anxiety also seems implicated for the same reason – it is a fast process that represents immediate awareness of physiological sensations that develop very quickly, and it is therefore likely to impact a fast but not a slower cognitive process.

It is also likely that the effects of co-morbid anxiety were dispersed among the factors, decreasing our ability to observe blunted regulation consistent with prior work. Our eligibility exclusion of a primary anxiety disorder may have also prevented such significant findings, but this would be an important area for future research. Nonetheless, we utilized post-hoc analyses to test significant associations between brain region activation and anxiety factors among those with a current anxiety disorder, and our results mostly confirmed the findings of the full sample, although these analyses implicated the neuroticism/worry factor. Furthermore, we demonstrated that brain region activation and anxiety factor associations were not present among those without a current anxiety disorder.

The present findings need to be interpreted cautiously in light of limitations. These include the exclusion of participants with a primary anxiety disorder, differences in race and sex between included and excluded participants which may affect the interpretation of study results, and the fact that only participants with chronic or recurrent MDD or dysthymia were included, limiting external validity. Furthermore, continuous scores on anxiety factors are not the same as diagnoses or cutoff points, so these findings may be challenging to implement in clinical practice. Finally, the sample was predominantly female, indicating that the results may be less generalizable to men.

5. Conclusions

In summary, our results extend prior research with purely behavioral tasks across four anxiety factors (Trombello et al., 2018) to indicate that regions involving the limbic system were involved in reactivity of emotion conflict for participants with higher immediate state anxiety and lower physiological/panic anxiety. Our results further suggest that anxiety is multifaceted and differentially impacts task performance of emotion conflict reactivity, with some (immediate state, physiological/panic anxiety, neuroticism/worry), but not other (agitation/restlessness) factors implicated.

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Author statement

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Declaration of competing interest

Dr. Joseph Trombello currently owns stock in Merck and is a paid consultant for Alto Neuroscience. **Dr. Crystal Cooper, Dr. Cherise Chin Fatt, Bruce Grannemann, Taryn Mayes, Uma Yezhuvath**, **Sina Aslan, Dr. Christian Webb, Dr. Amit Etkin, and Dr. Ramin Parsey** do not report any personal, financial or professional relationships or conflicting interests. **Dr. Thomas Carmody** is a consultant for Alkermes, Inc. **Dr. Manish Jha** has received contract research grants from Acadia Pharmaceuticals and Janssen Research & Development, educational grant to serve as Section Editor of the Psychiatry & Behavioral Health Learning Network, consultant fees from Eleusis Therapeutics US, Inc, Janssen Global Services, and Guidepoint Global, and honoraria from North American Center for Continuing Medical Education and Global Medical Education. **Dr. Tracy Greer** has received research funding from NARSAD and contracted research support from Janssen Research & Development, LLC. She has received honoraria and/or consultant fees from H. Lundbeck A/S and Takeda Pharmaceuticals International, Inc. Over the past 3 years, **Dr. Diego Pizzagalli** has received consulting fees from Albright Stonebridge Group, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals, as well as one honorarium from Alkermes. In addition, he has received stock options from BlackThorn Therapeutics and research support from National Institute of Mental Health, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. **Dr. Daniel Dillon** has been an advisor/consultant for Pfizer Inc., on activities unrelated to the current project. **Dr. Patrick McGrath** has received funding from the National Institute of Mental Health, New York State Department of Mental Hygiene, Research Foundation for Mental Hygiene (New York State), Forest Research Laboratories, Sunovion Pharmaceuticals, and Naurex Pharmaceuticals (now Allergan). In the past three years, **Dr. Myrna Weissman** received funding from the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Sackler Foundation, the Templeton Foundation; and receives royalties from the Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems. **Dr. Maurizio Fava** has received research support from Abbott Laboratories; Acadia Pharmaceuticals; Alkermes, Inc.; American Cyanamid;Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; AXSOME Therapeutics; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon; Cerecor; Clintara, LLC; Covance; Covidien; Eli Lilly and Company;EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; Ganeden Biotech, Inc.; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM);National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); Neuralstem, Inc.; NeuroRx; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates., Inc.; Pharmavite® LLC; PharmoRx Therapeutics; Photothera; Reckitt Benckiser; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Takeda Pharmaceuticals;Tal Medical; VistaGen); Wyeth-Ayerst Laboratories; he has served as advisor or consultant to Abbott Laboratories; Acadia; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc.; Biogen; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; Cerecor; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest

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