Psychiatry Research: Neuroimaging 339 (2024) 111791

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Transdiagnostic symptom of depression and anxiety associated with reduced gray matter volume in prefrontal cortex

Anna C. Cichocki [a,*], Richard E. Zinbarg [a,b], Michelle G. Craske [c], Iris K.-Y. Chat [a], Katherine S. Young [c], Susan Y. Bookheimer [c], Robin Nusslock [a]

[a] Department of Psychology, Northwestern University, Swift Hall, 2029 Sheridan Road, Evanston IL 60208, United States
[b] The Family Institute at Northwestern University, Evanston, IL, United States
[c] Department of Psychology, University of California Los Angeles, Los Angeles, CA, United States

ARTICLE INFO

Keywords:
Depression
Major depressive disorder
Anxiety
Structural MRI
Dimensional models
Symptoms
Tri-level model

ABSTRACT

Dimensional models of psychopathology may provide insight into mechanisms underlying comorbid depression and anxiety and improve specificity and sensitivity of neuroanatomical findings. The present study is the first to examine neural structure alterations using the empirically derived Tri-level Model. Depression and anxiety symptoms of 269 young adults were assessed using the Tri-level Model dimensions: General Distress (transdiagnostic depression and anxiety symptoms), Anhedonia-Apprehension (relatively specific depression symptoms), and Fears (specific anxiety symptoms). Using structural MRI, gray matter volumes were extracted for emotion generation (amygdala, nucleus accumbens) and regulation (orbitofrontal, ventrolateral, and dorsolateral prefrontal cortex) regions, often implicated in depression and anxiety. Each Tri-level symptom was regressed onto each region of interest, separately, adjusting for relevant covariates. General Distress was significantly associated with smaller gray matter volumes in bilateral orbitofrontal cortex and ventrolateral prefrontal cortex, independent of Anhedonia-Apprehension and Fears symptom dimensions. These results suggests that prefrontal alterations are associated with transdiagnostic dysphoric mood common across depression and anxiety, rather than unique symptoms of these disorders. Additionally, no regions of interest were associated with Anhedonia-Apprehension or Fears, highlighting the importance of studying transdiagnostic features of depression and anxiety. This has implications for understanding mechanisms of and interventions for depression and anxiety.

1. Introduction

Major depressive disorder (MDD) and anxiety disorders are among the most prevalent and debilitating psychiatric disorders in the U.S. (Kessler et al., 2005; World Health Organization, 2017). MDD and anxiety disorders are highly comorbid (Fava and Kendler, 2000; Lamers et al., 2011). However, most research measures clinical constructs using the Diagnostic Statistical Manual of Mental Disorders (DSM), which uses a categorical model and assumes each disorder is distinct and separate. This classification method may limit insights into the nature of mental illness. As a result, initiatives such as the Research Domain Criteria (RDoC) framework and Hierarchical Taxonomy Of Psychopathology (HiTOP), have focused their efforts on data driven constructs and dimensional measures of psychopathology. The present study extends previous structural neuroimaging literature by examining gray mater volume of emotion generation and regulation regions using dimensional symptoms of depression and anxiety from the Tri-level Model (Prenoveau et al., 2010). These regions have been previously implicated in the depression and anxiety literature.

1.1. Emotion generation and depression and anxiety

The amygdala and nucleus accumbens (NAcc) are two brain regions involved in emotion generation, which is the facilitation of emotional processes and accompanying physiological processes. The amygdala is implicated in threat processing and mediates defensive emotional, behavioral, and physiological states (Hur et al., 2019). Although depression and anxiety are associated with elevated amygdala activation, the structural neuroimaging literature is more inconsistent (Hamilton et al., 2008). Many studies have shown an association between depression and smaller amygdala gray matter volume (Bora et al., 2012; Sacher et al., 2012), though others have shown enlarged (Anand and

* Corresponding author.
E-mail address: anna.cichocki@u.northwestern.edu (A.C. Cichocki).

https://doi.org/10.1016/j.pscychresns.2024.111791

Available online 10 February 2024

Shekhar, 2006; Frodl et al., 2002; Lange and Irle, 2004) or unchanged (Campbell et al., 2004; MacMaster et al., 2008) volumetric alterations. Anxiety has been associated with larger amygdala gray matter volumes (De Bellis et al., 2000; Hur et al., 2019; Schienle et al., 2011; Suor et al., 2020), though not always (e.g., Blackmon et al., 2011; Hayano et al., 2009; Warnell et al., 2018). How anxiety is defined and measured may contribute to these inconsistencies, in that larger amygdala volume is associated with generalized anxiety disorder (De Bellis et al., 2000; Schienle et al., 2011) and social anxiety (Suor et al., 2020), contrasted with smaller amygdala volume associated with panic disorder (Hayano et al., 2009), obsessive-compulsive disorder (Anand and Shekhar, 2006), and trait anxiety (Warnell et al., 2018). Inconsistencies in the neural structure literature may also reflect variability in the distribution of depression and anxiety symptoms not captured in categorical DSM diagnoses. For example, differences in amygdala structure may be driven in part by the common dysphoric mood and negative emotionality seen in depression and anxiety (Hur et al., 2019; Shackman et al., 2016).

The nucleus accumbens (NAcc) is a sub-component of the ventral striatum that mediates motivation, reward, emotion processing, and reward-related behaviors (Harvey et al., 2007; O'Doherty, 2004). Reward functioning in the NAcc is blunted in depression Forbes et al. (2009) and implicated in anxiety (Guyer et al., 2012). Anatomically, smaller volume of the NAcc is associated with depression symptoms (Auerbach et al., 2017; Phillips, 2003; Wacker et al., 2009) and anxiety disorders (Anand and Shekhar, 2006; Hilbert et al., 2015), though a large portion of research did not support an association between depression or anxiety and alterations in NAcc structure (e.g., Besteher et al., 2020; Kempton et al., 2011). Some research suggests that smaller NAcc volumes may reflect reward-related dysfunction, impacting brain function and symptom presentation across internalizing disorders.

1.2. Emotion regulation and depression and anxiety

Emotion regulation is the process of implementing conscious or non-conscious processes to modulate the trajectory of an emotion (Phillips et al., 2008). The ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC) have distinct roles from the orbitofrontal cortex (OFC) in regulating behaviors and emotion processing via structural connections to subcortical emotion generation regions (Phillips et al., 2008). Specifically, the VLPFC and DLPFC are involved in voluntary, purposeful emotion regulation processes, while the OFC is involved in automatic emotion regulation processes (Phillips et al., 2008). Some suggest that the OFC may mediate connections between the VLPFC and DLPFC regions and subcortical regions (Phillips et al., 2008).

Depression and anxiety are characterized by disordered emotion regulation (Amstadter, 2008; Cisler et al., 2010; Joormann and Stanton, 2016). In particular, depression and anxiety are associated with the use of maladaptive strategies and reduced ability to use effective strategies for emotion regulation (Cisler et al., 2010; Joormann and Stanton, 2016). This can include rumination, emotion suppression, experiential avoidance, emotional non-acceptance, negative reactivity to emotions and less use of reappraisal (Amstadter, 2008; Cisler et al., 2010; Joormann and Stanton, 2016). These regulatory strategies can maintain or increase depression and anxiety symptoms (Amstadter, 2008; Joormann and Stanton, 2016).

Anatomical differences in emotion regulation regions are associated with depression and anxiety. Depression is commonly characterized by reduced gray matter volume in the prefrontal cortex (Anand and Shekhar, 2006; Phillips, 2003), including in the OFC (Anand and Shekhar, 2006; Bremner et al., 2002; Koolschijn et al., 2009; Webb et al., 2014), DLPFC (Chang et al., 2011; Li et al., 2010), and VLPFC (Lener et al., 2016; Salvadore et al., 2011). Anxiety is also associated with reduced prefrontal cortex gray matter volume (Syal et al., 2012), particularly in the OFC (Anand and Shekhar, 2006; Blackmon et al., 2011; Zhao et al., 2017). Anxiety disorders are sometimes associated with smaller DLPFC (Fonzo et al., 2016; Hilbert et al., 2015) and VLPFC (Auday & Pérez-Edgar, 2019) gray matter volume, though often show non-significant results (Mohlman et al., 2009; Schienle et al., 2011; Zhao et al., 2017). In sum, prefrontal alterations seem to be a common feature of both depression and anxiety and may be a mechanism that underlies the transdiagnostic emotion regulation dysfunction seen in depression and anxiety.

1.3. Need for and implementation of dimensional models of psychopathology

Most research on the pathophysiology of depression and anxiety focuses on DSM classification, however there are some limitations to the DSM that may play a role in the inconsistent results presented thus far (see Nikolaidis et al., 2022). First, categorical classification uses arbitrary cut off points for assignment of a psychiatric disorder, which does not reflect the continuous nature of psychological functioning and many forms of psychopathology (Haslam et al., 2012). Second, continuous measures of psychopathology outperform discrete measures in terms of reliability and validity (Markon et al., 2011). Third, psychiatric disorders are highly comorbid, particularly depression and anxiety (Kessler et al., 2005; Krueger and Markon, 2006; Rush et al., 2005), such that separation of discrete disorders may limit scientific research and applicability of interventions. Fourth, there is heterogeneity within and across DSM diagnoses, in that the clinical presentation for a disorder can vary widely, but also overlap with symptoms of different disorders (Allsopp et al., 2019). Further, phenomenology as defined by behavioral systems does not discretely map onto biology. Examples of this include common brain abnormalities across multiple illnesses (Krueger, 1999), overlapping genetic influences (Kendler, 1992), multiple etiological pathways leading to similar clinical manifestations (Kendler, 2019), and the effectiveness of the same treatments for multiple diagnoses (e.g. SSRIs; Barlow et al., 2017; Vaswani et al., 2003).

As a solution to these limitations, there has been a large push in the field to use dimensional analyses as additional models of psychopathology. These models could lead to a shift in how psychopathology is studied, classified, and treated (Michelini et al., 2021). Importantly, preliminary research shows that dimensional models have greater sensitivity and stronger associations to neural variables, compared to diagnoses (Kircanski et al., 2017; Michelini et al., 2021; Nikolaidis et al., 2022; Reininghaus et al., 2019).

The dimensional model we employ in the present study is the Tri-level Model, an empirically-derived, hierarchical structure underlying symptoms of unipolar mood and anxiety disorders (see Fig. 1 for model structure; Prenoveau et al., 2010). A broad, transdiagnostic factor, termed General Distress, is characterized by shared features of depression and anxiety, including distress, negative emotionality, and dysphoric mood. Then there are two intermediate level factors: (a) Fears is loaded on by anxiety specific symptoms, such as interoceptive-agoraphobic fears, social fears, and fears of specific stimuli, and (b) Anhedonia-Apprehension (previously termed Anxious-Misery) is loaded on by relatively specific depression symptoms of anhedonia and hopelessness. The Fears factor is significantly related to social phobia, specific phobia, and obsessive-compulsive disorder (Prenoveau et al., 2010). The Anhedonia-Apprehension factor is significantly related to major depression, social phobia, and generalized-anxiety disorder (Prenoveau et al., 2010). Though the model also defines narrower factors, these were not used in the current analyses due to our specific interest in transdiagnostic and disorder differences, rather than specific disorder subtypes. Additionally, we were concerned about having enough power to detect associations at the narrow factor level. This model has been independently replicated and published on by our group (Naragon-Gainey et al., 2016; Prenoveau et al., 2010; Williams et al., 2021; Young et al., 2021; Zinbarg et al., 2022). The Tri-level Model is empirically driven and has never been examined in the context of structural brain data. We chose to use the Tri-level Model because it gives us the unique opportunity to study

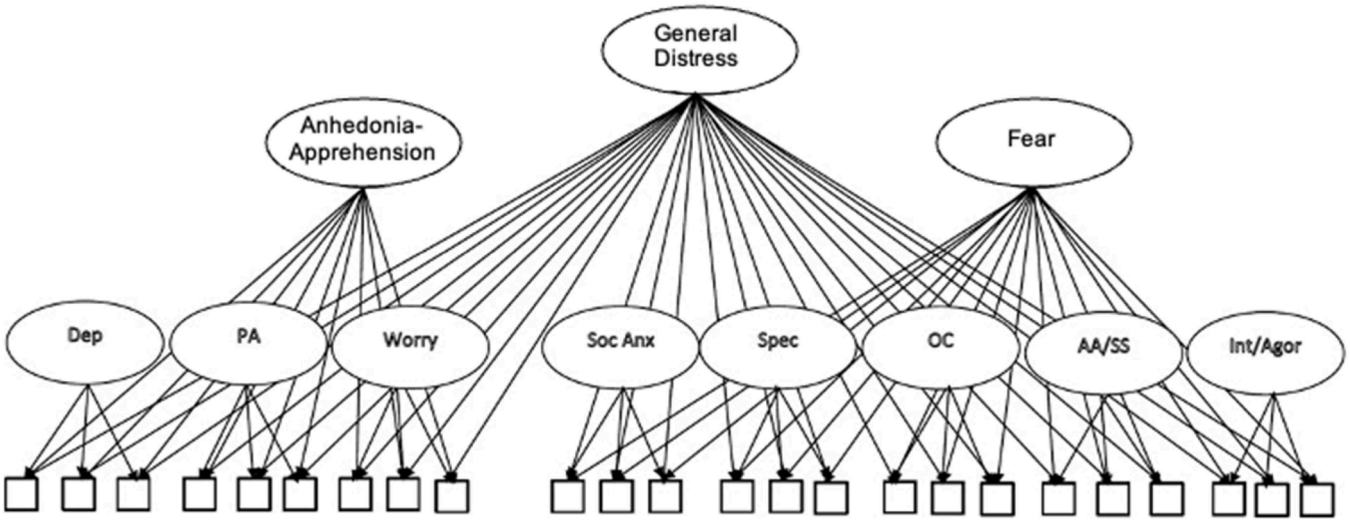

Fig. 1. Structural specification for the initial (baseline) tri-level model. Note that items are not labeled and not all items are shown for the sake of presentational clarity. Dep = depression, PA = positive affect, Soc Anx = social anxiety, Spec = specific fears, OC = obsessive-compulsive symptoms, AA/SS = anxious arousal/somatic sensations, Int/Agor = interoceptive/agoraphobic fears. All factors are uncorrelated. Figure adapted from Naragon-Gainey et al. (2016).

transdiagnostic features as well as those that are more disorder specific, which is not possible using DSM diagnosis.

For context, the Tri-level Model is similar to the Internalizing spectrum of the HiTOP model (Kotov et al., 2017). Both models have a hierarchical structure and utilize dimensional symptoms of psychopathology, though the Internalizing spectrum of HiTOP is embedded in a larger higher order model. Specific dimensions, namely, the HiTOP Internalizing spectrum, Fear subfactor, and Distress subfactor largely overlap with General Distress, Fears, and Anhedonia-Apprehension, respectively (Kotov et al., 2017; Naragon-Gainey et al., 2016; Prenoveau et al., 2010). There are a few minor differences between the two models. First, the Tri-level Model methodologically relies on self-report indicators to this point, which is not yet a component of the HiTOP model which relies on diagnostic data to this point. Second, the HiTOP Internalizing spectrum includes additional forms of internalizing symptoms (e.g., sexual problems, eating problems) not found in the Tri-level Model. However, despite these differences, they are highly similar constructs, and we expect the Tri-level Model to largely generalize to the HiTOP Internalizing spectrum dimensions.

1.4. Current study

In the present study, we investigate structural metrics of emotion generation- and regulation-related neural regions and Tri-level Model symptom dimensions in young adults. We focused on young adulthood as it is an important time in regards to (1) neurodevelopmental change, particularly in prefrontal cortical regions, which are the last to develop (Powers and Casey, 2015; Shaw et al., 2011), and (2) the emergence of psychopathology, in that the peak of onset for depression and anxiety disorders is during adolescence and young adulthood (Paus et al., 2008).

Though other work has explored the neural correlates of transdiagnostic and comorbid depression and anxiety (see review Sindermann et al., 2021), this is the first study to explore the association between brain structure and the Tri-level Model. This work has the potential to provide insight into the association between the structure of specific brain regions and specific dimensional symptoms of depression and anxiety. We expected alterations in gray matter volumes of emotion generation regions, the amygdala and NAcc, to be negatively associated with the General Distress symptom dimension based on the literature linking these regions to negative emotionality and dysphoric mood. We predicted that volumetric alterations in the amygdala and NAcc would also be associated with Fears and Anhedonia-Apprehension symptom dimensions, respectively. This is based on literature linking the amygdala to anxiety and NAcc to depression both functionally and structurally. Lastly, we expected that emotion regulation regions (OFC, VLPFC, DLPFC) would be negatively associated with the General Distress, Anhedonia-Apprehension, and Fears symptom dimensions, due to this association being mostly consistent across the depression and anxiety literature. We tested these predictions using linear regression analyses and significant results were followed up with specificity analyses by adjusting for the other Tri-level Model symptom dimensions.

2. Methods

2.1. Participants

Participants were recruited at University of California, Los Angeles and Northwestern University for the Brain, Motivation, and Personality Development (BrainMAPD) study investigating the relationship between threat and reward neurocircuitry and risk for depression and anxiety in late adolescence and early adulthood. We enrolled 272 young adults (183 female, mean age 19.15 years, SD = 0.52) in the study from a larger sample of 2461 screened individuals. Participants were recruited based on reward sensitivity using the Behavioral Activation Scale (BAS) and threat sensitivity using the trait Neuroticism scale from the Eysenck Personality Questionnaire-Neuroticism (EPQ-N). Institution IRB approval at both sites and participant written, informed consent was obtained for all procedures. See supplement for additional details on recruitment and study exclusion criteria.

Three participants were excluded based on excessive motion during their MRI scan and poor FreeSurfer segmentation, resulting in a total sample of 269. For OFC specific analyses, additional participants were removed due to FreeSurfer parcellation errors, resulting in a subsample of 241 individuals for those specific analyses. This method was used to maximize the total sample size for all other analyses. See Table 1 for participant characteristics.

2.2. Tri-level symptom assessment and factor analysis

To implement the Tri-level Model, participants completed a symptom assessment consisting of specific, a priori defined items from seven self-report measures of depression and anxiety (Naragon-Gainey et al., 2016; Prenoveau et al., 2010): Albany Panic and Phobia Questionnaire

Table 1
Sample Demographics and variables of interest.

	All (n = 269)	OFC analysis (n = 241)
Age [mean (s.d.)]	19.15 (0.52)	19.17 (0.52)
Sex (F/M/O)	181/87/1	161/79/1
Scan Site (UCLA/NU)	124/145	114/127
Psychotropic Medication Use (%)	7.7%	8.3%
Sample Race/Ethnicity (%)		
White/Caucasian (Non-Hispanic)	33%	34%
Black/African American	9%	7%
Hispanic	19%	20%
Asian	28%	29%
Native American	1%	1%
Pacific Islander	0%	0%
Multiracial	8%	8%

F=female, *M*=male, *O*=other; NU=Northwestern University, UCLA=University of California Los Angeles.

(Rapee et al., 1994), Fear Survey Schedule-II (Geer, 1965), Penn State Worry Questionnaire (Meyer et al., 1990), Self-Consciousness subscale of the Social Phobia Scale (SPS; Mattick and Clarke, 1998; Zinbarg and Barlow, 1996), Obsessive Compulsive-Inventory Revised (Foa et al., 2002), Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995, 1995), and Inventory to Diagnose Depression (Zimmerman and Coryell, 1987). Using the present study data, others have shown goodness of fit of the Tri-level Model in using these specific self-report items through confirmatory factor analyses (for details see Zinbarg et al., 2022). Factor score estimates from this model were saved and used to represent symptom dimensions of a broad factor, General Distress, and two intermediary factors of Anhedonia-Apprehension and Fears. Only broad and intermediate factors of the Tri-level Model were used in analyses due to interest in transdiagnostic and disorder specific measures of depression and anxiety symptoms, rather than subtypes or narrower factors of these disorders.

2.3. MRI acquisition and analysis

Structural images were acquired at UCLA and Northwestern University using a Siemens Prisma 3.0 Tesla scanners with 64-channel head coils. High resolution structural images were collected using a magnetized prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence using 0.8 mm isotropic voxels, TR/TE/flip angle=2300 ms/2.99 ms/7°, FOV=256 mm^2, 208 slices. Gray matter volume estimates were extracted using FreeSurfer automatic recon-all segmentation and parcellation (http://surfer.nmr.mgh.harvard.edu/; (Fischl et al., 2002). All segmentations were visually inspected for processing and segmentation/parcellation errors, consistent with Raamana et al. (2020), see supplement for details. Due to significant errors in the FreeSurfer parcellation of the OFC, additional subjects were removed from those specific analyses by removing their OFC data from the dataset. FreeSurfer parcellation and segmentation was not manually edited due to the lack of benefit of this time-intensive process (Ross et al., 2021). Scans determined to be unusable were removed from analyses moving forward (full sample due to motion n = 3, plus OFC-specific unusable n = 28).

We restricted current analyses to gray matter volume measures, rather than cortical thickness or surface area measures, based on its common use and robust findings in the depression and anxiety literature. Only one metric was selected for analysis to minimize the number of tests, due to concerns of type I error rate inflation from multiple comparisons. Gray matter volume preforms similarly to other metrics (Schwarz et al., 2016) and therefore is an optimal metric for the purposes of the present study.

Bilateral gray matter volumes for NAcc, amygdala, VLPFC, DLPFC, and OFC regions-of-interest (ROIs) were then extracted for analyses. See supplement for ROI details. Other ROIs commonly studied in the literature, such as hippocampus and anterior cingulate cortex, were not the focus of these analyses examining emotion generation and regulation specifically. See Fig. 2 for segmentations and parcellations from a representative participant. Estimates of total intracranial volume, which we used as a covariate in our analyses, was also obtained using FreeSurfer.

2.4. Analytic approach

Using R, we separately regressed each Tri-level Model dimensional symptom factor (General Distress, Anhedonia-Apprehension, Fears) onto the gray matter volume for each ROI, separately. If these initial statistical tests were significant, a subsequent linear regression analysis was preformed additionally adjusting for the other two Tri-level symptom factor scores to investigate specificity of findings. For the OFC only, any significant analyses using the subsample were rerun using the full study sample to test for sensitivity and confirm findings were not specific to the subsample. This was done by adding back in the raw OFC volume data from the analysis dataset for the participants with unusable OFC parcellation as defined by the quality checks. We adjusted for psychotropic medication use at the time of the scan because these affect gray matter volume and were associated with higher Tri-level factor scores (p<.01). Additionally, we adjusted for racial and ethnic identity given their possible association with emotion regulation (Weiss et al., 2022) and self-report symptom ratings (Dunlop et al., 2020; Kalibatseva and Leong, 2018), which is particularly relevant for our diverse sample (i.e., high proportion of Hispanic and Asian participants). We coded racial and ethnic identity as follows: 0=Non-Hispanic White, 1=Asian, 2=Black, 3= Native American, 4=Pacific Islander, 5=Multiracial, 6=Hispanic White. We also adjusted for scan site (e.g. UCLA, Northwestern), total intracranial volume, age, and sex in all analyses.

2.5. Demographic characteristics

Demographic participant characteristics are presented in Table 1. Linear regression, two sample t-tests, and ANOVAs were used to examine demographic differences across each of the three Tri-level symptom dimensions. The Tri-level factor scores did not correlate with age (p's>0.1) or racial and ethnic identity (p's>0.1) and did not differ by scan site (p's>0.1). Females had significantly higher Fears factor scores than males, t(269,1)=−2.01, p=.045, which is consistent with known sex differences in anxiety prevalence (Bekker and van Mens-Verhulst, 2007). There were no significant sex differences for General Distress nor Anhedonia-Apprehension factor scores (p's>0.1). Intracranial volume was negatively associated with Fears, F(270,1)=8.36, p=.004, and General Distress, F(270,1)=4.57, p=.03, but not Anhedonia-Apprehension (p>.1). This was somewhat expected due to the strong association between intracranial volume and sex, along with sex differences associated with anxiety and these dimensions (Ruigrok et al., 2014). Psychotropic medication use was associated with higher General Distress factor scores t(270,1)=−2.67, p=.008, but not Fears nor Anhedonia-Apprehension (p's>0.1), consistent with the expected relationship between General Distress and severity of symptoms.

3. Results

3.1. Emotion generation gray matter volumes

There were no significant correlations between gray matter volumes of the amygdala nor NAcc and any of the Tri-level Model symptom factor scores (General Distress, Anhedonia-Apprehension, Fears), adjusting for all covariates (all p's>0.05).

3.2. Emotion regulation gray matter volumes

Smaller gray matter volume in the bilateral OFC (sr^2=0.022,

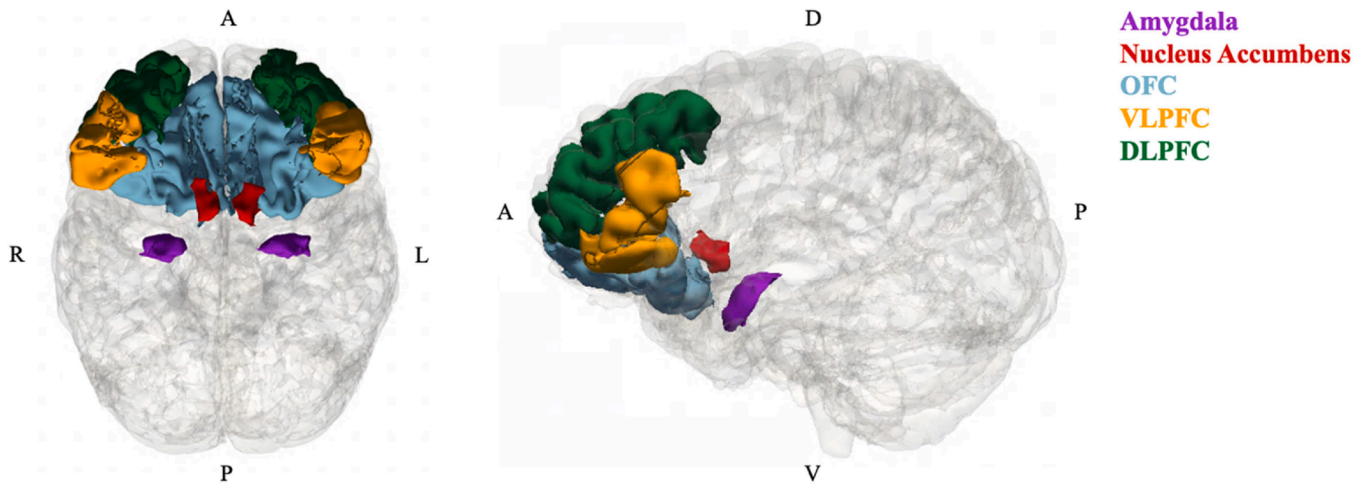

Fig. 2. Gray matter segmentation and parcellation of the 5 regions of interest. All gray matter volume and total intracranial estimates were extracted in individual brain space. Structures visualized here are from a representative participant, displayed from a (**left**) inferior and (**right**) sagittal perspective. OFC = orbitofrontal cortex; VLPFC = Ventrolateral Prefrontal Cortex; DLPFC = Dorsolateral prefrontal cortex; *A* = anterior; *P* = posterior; *R* = right; *L* = left; *D* = dorsal; *V* = ventral.

B=−0.211, 95% CI [−0.388, −0.034], t_{233}=−2.34, *p*=.020; Fig. 3) and bilateral VLPFC (sr^2=0.017, *B*= −0.163, 95% CI [−0.311, −0.016], t_{261}=−2.18, *p*=.030; Fig. 4) were each significantly associated with higher General Distress factor scores, adjusting for all covariates. To examine the specificity of these findings, we reran these significant analyses with the addition of Anhedonia-Apprehension and Fears factor scores as covariates. These associations remained significant, and barely diminished (e.g., by less than 10%), such that smaller bilateral OFC (sr^2=0.018, *B*= −0.191, 95% CI [−0.372, −0.016], t_{231}=−2.15, *p*=.032) and VLPFC (sr^2=0.014, *B*= −0.150, 95% CI [−0.297, −0.003], t_{259}=−2.00, *p*=.046) gray matter volumes are associated with higher General Distress factor scores when adjusting for all covariates as well as Anhedonia-Apprehension and Fears. A follow up analysis also showed a negative correlation between the bilateral OFC and General Distress factor scores using the full study sample, adjusting for all covariates (sr^2=0.016, *B*= −0.177, 95% CI [−0.339, −0.015], t_{261}=−2.15, *p*=.033). Additionally, 86% of the association between gray matter volume in the bilateral DLPFC and General Distress factor scores remained when adjusting for all covariates, albeit the association only approached conventional levels of statistical significance (sr^2=0.013, *B*= −0.153, 95% CI [−0.312, 0.006], t_{261}=−1.90, *p*=.059). The gray matter volumes in all bilateral ROIs were not significantly associated with Anhedonia-Apprehension or Fears factor scores (all *p*'s > 0.1). To minimize type I error, we limited the number of statistical tests by using a small set of a priori ROIs, bilateral variables for each ROI, and only one neuroanatomical metric (gray matter volume).

4. Discussion

Reliance on diagnostic categorization of depression and anxiety may contribute to gaps and inconsistencies in neuroanatomical research, which dimensional models, such as the Tri-level Model, aim to rectify. The present study addresses this gap as the first to investigate the relationships between Tri-level Model symptom dimensions and gray matter volumes of emotion generation and regulation regions. As expected, smaller gray matter volumes of emotion regulation regions (OFC and VLPFC) were associated with the General Distress symptom dimension. Following specificity analyses, this relationship remained significant showing smaller gray matter volume in the OFC and VLPFC are specific to the General Distress symptom dimension, independent of

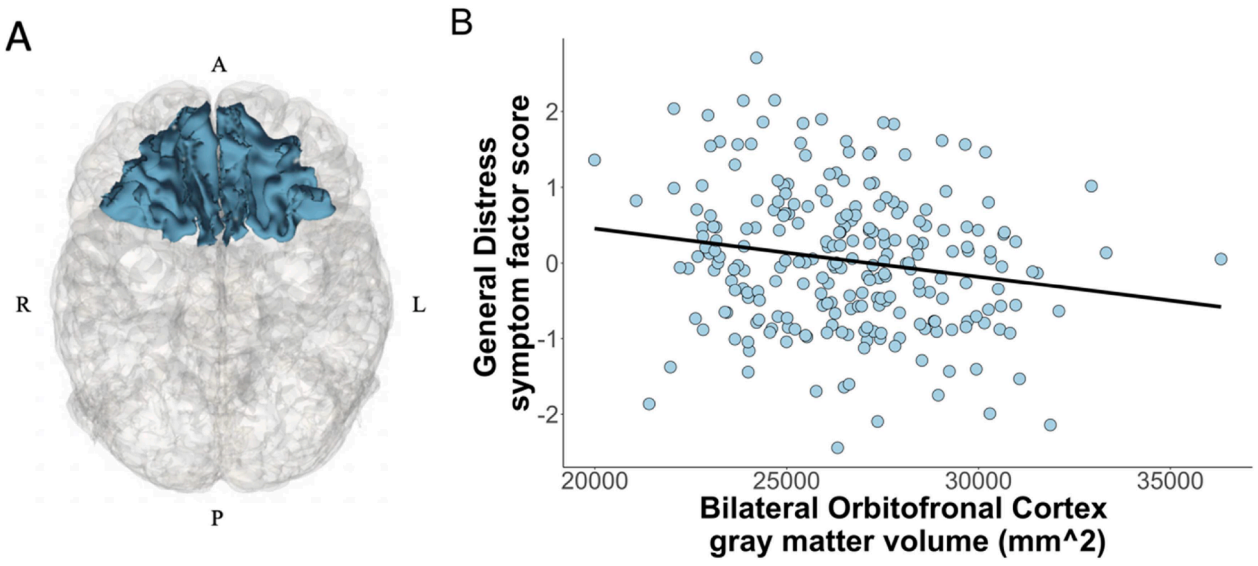

Fig. 3. A. Visualization of the OFC region of interest from an inferior view of a representative participant. **B**. Reduced gray matter volume of the bilateral OFC significantly predicts higher General Distress symptom factor scores. OFC = orbitofrontal cortex; *A* = anterior; *P* = posterior; *R* = right; *L* = left.

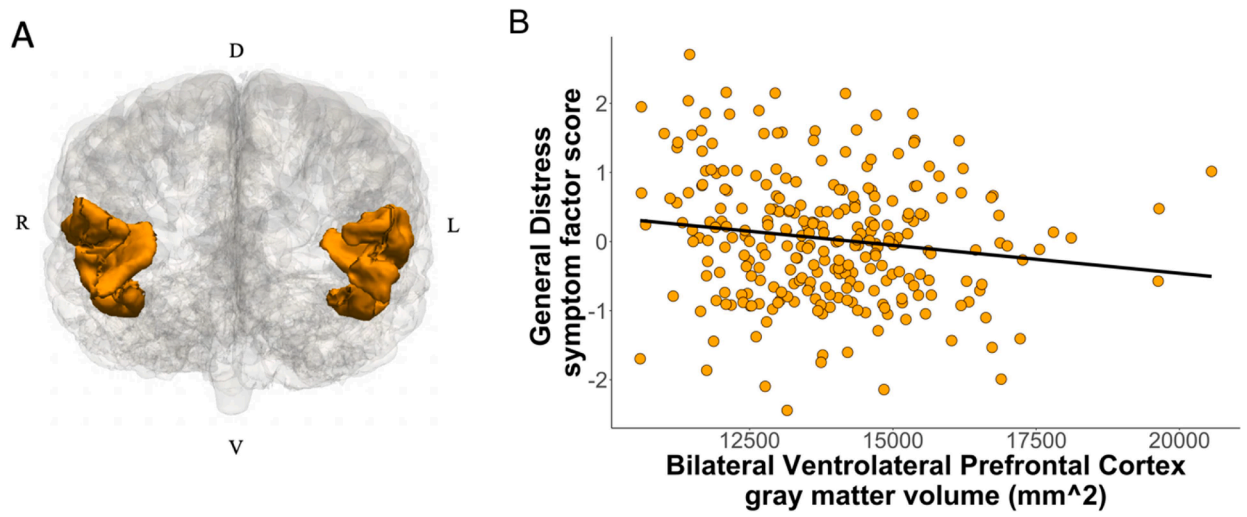

Fig. 4. **A**. Visualization of the VLPFC region of interest from a coronal view of a representative participant. **B**. Reduced gray matter volume of the bilateral VLPFC significantly predicts higher General Distress symptom factor scores. VLPFC = ventrolateral prefrontal cortex; *D* = dorsal; *V* = ventral; *R* = right; *L* = left.

Anhedonia-Apprehension and Fears symptom dimensions. We unexpectedly did not find any significant associations between any Tri-level symptom dimension and DLPFC, amygdala, or NAcc gray matter volume. These findings are unlikely attributable to age, sex, racial and ethnic identity, scan site, intracranial volume, and psychotropic medication use, as we adjusted for these variables in all analyses.

Our findings specifically highlight structural alterations in emotion regulation regions as a pathway of General Distress, independent of Anhedonia-Apprehension and Fears. The commonality of deficits in emotion regulation across depression and anxiety may explain why this association was seen only for the General Distress symptom dimension, and not Anhedonia-Apprehension or Fears symptom dimensions. Together, these findings are an extension of prior research that shows that alterations in the PFC are associated with depression and anxiety symptoms (Besteher et al., 2020). We, however, show that it is likely the shared distress, dysphoric mood, and negative emotionality features present in depression and anxiety that may account for these brain structure alterations.

Emotion regulation may affect the relationship between emotion reactivity and depression and anxiety symptoms (Cisler et al., 2010; Joormann and Stanton, 2016), possibly via increased bottom-up reactivity in emotion generation regions (e.g. amygdala, NAcc), and attenuated top-down regulatory influence of emotion regulations regions on emotion generation regions (Disner et al., 2011). The OFC, involved in automatic emotion regulation, also plays a role in mediating the influence of more lateral regions in voluntary emotion regulation onto emotion generation regions (Phillips et al., 2008). Smaller OFC volumes may reflect less or dysfunctional communication between the lateral prefrontal regulatory regions and emotion generation limbic regions. Smaller OFC volumes may also directly impact emotion generation, in offering less regulatory control of the hyperactive subcortical regions. For example, smaller OFC volume may increase negative emotionality via less regulatory control of the many connections from the OFC to the amygdala, particularly since there are fewer connections from the lateral PFC regions to the amygdala (Phillips et al., 2008).

We also showed that General Distress was associated with alterations in those lateral regions, the VLPFC specifically, which likely impacts voluntary emotion regulation. Smaller VLPFC, volumes may reflect less use of adaptive and greater use of maladaptive emotion regulation strategies associated with depression and anxiety. Together, these structural alterations may lead to prolonged failure to regulate emotional reactivity, which puts individuals more at risk for developing depression and anxiety disorders (Amstadter, 2008; Powers and Casey, 2015). Importantly, the prefrontal deficits were not associated with all symptoms of depression and anxiety, but rather one transdiagnostic symptom, General Distress. This set of results suggests that alterations in emotion regulation regions may be a mechanism impacting transdiagnostic features of distress and dysphoric mood, which are core to depression and anxiety.

Emotion regulation regions (e.g. OFC and VLPFC) could be a target for intervention, including psychotherapeutic, pharmacological, or transcranial magnetic stimulation (TMS), to improve depression and anxiety symptoms (Cisler et al., 2010; de Wit et al., 2015; Joormann and Stanton, 2016; Månsson et al., 2016; Shackman et al., 2016). Not only are these regions good candidates for TMS, but TMS used upon lateral emotion regulation regions have been shown to improve emotion regulation abilities in OCD (de Wit et al., 2015). Our findings suggest that interventions that act upon emotion regulation regions may specifically improve dysphoric mood and negative emotionality symptoms common across depression and anxiety. These results contribute to our understanding of mechanisms of emotion regulation in depression and anxiety and can inform the development of improved prevention and treatment strategies.

Failing to support our hypotheses, none of the emotion regulation regions of interests were significantly associated with Anhedonia-Apprehension or Fears symptom dimensions. Based on the depression and anxiety literature (e.g. Anand and Shekhar, 2006), we expected smaller volumes to be associated with these disorder specific symptom dimensions. However, our findings suggest that it may be the common dysphoric mood driving these associations in the literature, rather than the unique symptoms of depression and anxiety. This is supported by our finding that General Distress was associated with smaller OFC and VLPFC gray matter volumes independent of Anhedonia-Apprehension and Fears. Therefore, it is possible we would not see a relationship between emotion regulation regions and Anhedonia-Apprehension or Fears symptom dimensions if the transdiagnostic dysphoric mood accounts for these neural alterations. This further highlights the importance of this transdiagnostic features of depression and anxiety. Future research is needed to explore and better test this relationship.

Our results also did not detect significant associations between structural alterations of emotion generation regions and any Tri-level Model symptom dimension. We may need a larger sample size to detect these associations. The unexpected lack of significant association between the amygdala and the General Distress symptom dimension may be explained by other research utilizing the HiTOP model, which shows internalizing symptoms of fear disorders, rather than distress disorders, are more strongly associated with threat reactions, and thus the amygdala (Gorka et al., 2017). However, we also did not detect an

association between amygdala volume and the Fears symptom dimension, contrary to the anxiety literature. It is important to study this in future work based on the amygdala's established involvement in threat and fear processing (Hur et al., 2019). We also did not find any significant correlations between volume of the NAcc and any Tri-level Model symptom dimension, which was relatively unsurprising based on many non-significant findings in the literature (e.g. Besteher et al., 2020; Kempton et al., 2011). Additionally, the NAcc is a difficult region to study due to its small size and limitations of FreeSurfer segmentation approaches (Khan et al., 2008).

As noted, HiTOP is another dimensional model of psychopathology used in the literature. Though there are some differences, there are many similarities between the model employed in the present study and HiTOP Internalizing spectrum. Accordingly, we do not see our results as being limited to the Tri-level Model and may be applicable to similar dimensional models. Specifically, we would expect the present General Distress findings to generalize to the HiTOP Internalizing spectrum dimension. Future research should test this hypothesis.

Few studies investigate neuroanatomical differences associated with comorbid depression and anxiety (see Sindermann et al., 2021 for a review). The current findings add to this literature by documenting the association between emotion regulation brain structures and a dimensional and transdiagnostic symptom (i.e., General Distress). Future work would benefit from the more frequent use of transdiagnostic measures to better elucidate the neural similarities of clinical disorders. Future studies should also directly compare the sensitivity of diagnosis and dimensional measures of psychopathology, which was not in the scope of the present study.

4.1. Study limitations and future directions

The present study should be considered in the context of its limitations. First, the study utilized a community sample with oversampling for variability on neuroticism and reward sensitivity, however this is not equivalent to a clinical sample. The study may lack severe forms of psychopathology, therefore we may find stronger associations in samples with greater variability in the clinical range (as suggested by Sackett and Yang, 2000). Second, the Tri-level Model symptom dimensions in the present study rely solely on self-report. The reliance on self-reporting may affect the accuracy of emotion and emotion regulation data as we are skeptical of people's ability to validly report on their ability to regulate emotion (e.g. Lewis et al., 2010). Third, the present study may not have adequate power to detect small associations, which may contribute to our limited number of significant findings. More studies utilizing the Tri-level Model with different and/or larger samples could improve upon these limitations. Lastly, the cross-sectional nature of the data limits our understanding of the influence of neuroanatomical alterations on symptoms over time. Future work using longitudinal studies would help to inform these effects on symptom progression and their underlying mechanisms. Additionally, it is important to investigate these associations across different developmental periods since neural correlates of dimensional symptoms may change across development (Michelini et al., 2021; Tseng et al., 2019).

5. Conclusion

The present study was the first to use the Tri-level Model to investigate neuroanatomical differences and similarities of depression and anxiety. We focused on emotion generation (amygdala, NAcc) and regulation (OFC, VLPFC, DLPFC) regions implicated in depression and anxiety. We provide preliminary evidence for gray matter volume alterations in emotion regulation regions associated with the General Distress symptom dimension. Specifically, we found that smaller bilateral OFC and VLPFC gray matter volume is associated with greater elevation in the transdiagnostic General Distress symptom dimension, independent of Anhedonia-Apprehension and Fears symptom dimensions. These expected negative relationships are consistent with diagnostically defined depression and anxiety research. No other significant relationships were found. Based on the results, emotion regulations regions, particularly the OFC and VLPFC, may be central to the distress, dysphoric mood, and negative emotionality symptoms that are common across depression and anxiety, rather than unique symptoms of these disorders. This research highlights not only the importance of studying dimensional models of psychopathology, but also the importance of transdiagnostic symptoms of depression and anxiety, often overlooked in the literature.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (NIMH; R01 MH100117; R01 MH123473) and the National Institute of Drug Abuse (NIDA; P50 DA051361).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2024.111791">doi:.

References

Allsopp, K., Read, J., Corcoran, R., Kinderman, P., 2019. Heterogeneity in psychiatric diagnostic classification. Psychiatry Res. 279, 15–22. https://doi.org/10.1016/j.psychres.2019.07.005.

Amstadter, A., 2008. Emotion regulation and anxiety disorders. J. Anxiety. Disord. 22 (2), 211–221. https://doi.org/10.1016/j.janxdis.2007.02.004.

Anand, A., Shekhar, A., 2006. Brain imaging studies in mood and anxiety disorders: special emphasis on the amygdala. Ann. N. Y. Acad. Sci. 985 (1), 370–388. https://doi.org/10.1111/j.1749-6632.2003.tb07095.x.

Auerbach, R.P., Pisoni, A., Bondy, E., Kumar, P., Stewart, J.G., Yendiki, A., Pizzagalli, D. A., 2017. Neuroanatomical prediction of anhedonia in adolescents. Neuropsychopharmacology 42 (10), 2087–2095. https://doi.org/10.1038/npp.2017.28.

Barlow, D.H., Farchione, T.J., Bullis, J.R., Gallagher, M.W., Murray-Latin, H., Sauer-Zavala, S., Bentley, K.H., Thompson-Hollands, J., Conklin, L.R., Boswell, J.F., Ametaj, A., Carl, J.R., Boettcher, H.T., Cassiello-Robbins, C., 2017. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: a randomized clinical trial. JAMa Psychiatry 74 (9), 875. https://doi.org/10.1001/jamapsychiatry.2017.2164.

Bekker, M.H.J., van Mens-Verhulst, J., 2007. Anxiety disorders: sex differences in prevalence, degree, and background, but gender-neutral treatment. Gend. Med. 4, S178–S193. https://doi.org/10.1016/S1550-8579(07)80057-X.

Besteher, B., Gaser, C., Nenadić, I., 2020. Brain structure and subclinical symptoms: a dimensional perspective of psychopathology in the depression and anxiety spectrum. Neuropsychobiology 79 (4–5), 270–283. https://doi.org/10.1159/000501024.

Blackmon, K., Barr, W.B., Carlson, C., Devinsky, O., DuBois, J., Pogash, D., Quinn, B.T., Kuzniecky, R., Halgren, E., Thesen, T., 2011. Structural evidence for involvement of a left amygdala-orbitofrontal network in subclinical anxiety. Psychiatry Res. 194 (3), 296–303. https://doi.org/10.1016/j.pscychresns.2011.05.007.

Bora, E., Fornito, A., Pantelis, C., Yücel, M., 2012. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J. Affect. Disord. 138 (1–2), 9–18. https://doi.org/10.1016/j.jad.2011.03.049.

Bremner, J.D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., Staib, L.H., Charney, D.S., 2002. Reduced volume of orbitofrontal cortex in major depression. Biol. Psychiatry 51 (4), 273–279. https://doi.org/10.1016/S0006-3223(01)01336-1.

Campbell, S., Marriott, M., Nahmias, C., MacQueen, G.M., 2004. Lower Hippocampal volume in patients suffering from depression: a meta-analysis. Am. J. Psychiatry 161 (4), 598–607. https://doi.org/10.1176/appi.ajp.161.4.598.

Chang, C.C., Yu, S.C., McQuoid, D.R., Messer, D.F., Taylor, W.D., Singh, K., Boyd, B.D., Krishnan, K.R.R., MacFall, J.R., Steffens, D.C., Payne, M.E., 2011. Reduction of

dorsolateral prefrontal cortex gray matter in late-life depression. Psychiatry Res. 193 (1), 1–6. https://doi.org/10.1016/j.pscychresns.2011.01.003.
Cisler, J.M., Olatunji, B.O., Feldner, M.T., Forsyth, J.P., 2010. Emotion regulation and the anxiety disorders: an integrative review. J. Psychopathol. Behav. Assess. 32 (1), 68–82. https://doi.org/10.1007/s10862-009-9161-1.
De Bellis, M.D., Casey, B.J., Dahl, R.E., Birmaher, B., Williamson, D.E., Thomas, K.M., Axelson, D.A., Frustaci, K., Boring, A.M., Hall, J., Ryan, N.D., 2000. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol. Psychiatry 48 (1), 51–57. https://doi.org/10.1016/S0006-3223(00)00835-0.
de Wit, S.J., van der Werf, Y.D., Mataix-Cols, D., Trujillo, J.P., van Oppen, P., Veltman, D. J., van den Heuvel, O.A, 2015. Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder. Psychol. Med. 45 (14), 3059–3073. https://doi.org/10.1017/S0033291715001026.
Disner, S.G., Beevers, C.G., Haigh, E.A.P., Beck, A.T., 2011. Neural mechanisms of the cognitive model of depression. Nature Rev. Neurosci. 12 (8), 467–477. https://doi.org/10.1038/nrn3027.
Dunlop, B.W., Still, S., LoParo, D., Aponte-Rivera, V., Johnson, B.N., Schneider, R.L., Nemeroff, C.B., Mayberg, H.S., Craighead, W.E., 2020. Somatic symptoms in treatment-naïve Hispanic and non-Hispanic patients with major depression. Depress. Anxiety. 37 (2), 156–165. https://doi.org/10.1002/da.22984.
Fava, M., Kendler, K.S., 2000. Major depressive disorder. Neuron 28 (2), 335–341. https://doi.org/10.1016/S0896-6273(00)00112-4.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation. Neuron 33 (3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X.
Foa, E.B., Huppert, J.D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., Salkovskis, P.M., 2002. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol. Assess. 14 (4), 485–496. https://doi.org/10.1037/1040-3590.14.4.485.
Fonzo, G.A., Ramsawh, H.J., Flagan, T.M., Simmons, A.N., Sullivan, S.G., Allard, C.B., Paulus, M.P., Stein, M.B., 2016. Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. Psychol. Med. 46 (5), 1037–1054. https://doi.org/10.1017/S0033291715002603.
Forbes, E.E., Hariri, A.R., Martin, S.L., Silk, J.S., Moyles, D.L., Fisher, P.M., Brown, S.M., Ryan, N.D., Birmaher, B., Axelson, D.A., Dahl, R.E., 2009. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am. J. Psychiatry 166 (1), 64–73. https://doi.org/10.1176/appi.ajp.2008.07081336.
Frodl, T., Meisenzahl, E., Zetzsche, T., Bottlender, R., Born, C., Groll, C., Jäger, M., Leinsinger, G., Hahn, K., Möller, H.J., 2002. Enlargement of the amygdala in patients with a first episode of major depression. Biol. Psychiatry 51 (9), 708–714. https://doi.org/10.1016/S0006-3223(01)01359-2.
Geer, J.H., 1965. The development of a scale to measure fear. Behav. Res. Ther. 3 (1), 45–53. https://doi.org/10.1016/0005-7967(65)90040-9.
Gorka, S.M., Lieberman, L., Shankman, S.A., Phan, K.L., 2017. Startle potentiation to uncertain threat as a psychophysiological indicator of fear-based psychopathology: an examination across multiple internalizing disorders. J. Abnorm. Psychol. 126 (1), 8–18. https://doi.org/10.1037/abn0000233.
Guyer, A.E., Choate, V.R., Detloff, A., Benson, B., Nelson, E.E., Perez-Edgar, K., Fox, N.A., Pine, D.S., Ernst, M., 2012. Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. Am. J. Psychiatry 169 (2), 205–212. https://doi.org/10.1176/appi.ajp.2011.11010006.
Hamilton, J.P., Siemer, M., Gotlib, I.H., 2008. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol. Psychiatry 13 (11), 993–1000. https://doi.org/10.1038/mp.2008.57.
Harvey, P.O., Pruessner, J., Czechowska, Y., Lepage, M., 2007. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol. Psychiatry 12 (8), 767–775. https://doi.org/10.1038/sj.mp.4002021.
Haslam, N., Holland, E., Kuppens, P., 2012. Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. Psychol. Med. 42 (5), 903–920. https://doi.org/10.1017/S0033291711001966.
Hayano, F., Nakamura, M., Asami, T., Uehara, K., Yoshida, T., Roppongi, T., Otsuka, T., Inoue, T., Hirayasu, Y., 2009. Smaller amygdala is associated with anxiety in patients with panic disorder: smaller amygdala and anxiety in PD. Psychiatry Clin. Neurosci. 63 (3), 266–276. https://doi.org/10.1111/j.1440-1819.2009.01960.x.
Hilbert, K., Pine, D.S., Muehlhan, M., Lueken, U., Steudte-Schmiedgen, S., Beesdo-Baum, K., 2015. Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization. Psychiatry Res. 234 (3), 314–320. https://doi.org/10.1016/j.pscychresns.2015.10.009.
Hur, J., Stockbridge, M.D., Fox, A.S., Shackman, A.J., 2019. Dispositional negativity, cognition, and anxiety disorders: an integrative translational neuroscience framework. In: Progress in Brain Research, 247. Elsevier, pp. 375–436. https://doi.org/10.1016/bs.pbr.2019.03.012.
Joormann, J., Stanton, C.H., 2016. Examining emotion regulation in depression: a review and future directions. Behav. Res. Ther. 86, 35–49. https://doi.org/10.1016/j.brat.2016.07.007.
Kalibatseva, Z., Leong, F.T.L., 2018. Cultural factors, depressive and somatic symptoms among Chinese American and European American College students. J. Cross. Cult. Psychol. 49 (10), 1556–1572. https://doi.org/10.1177/0022022118803181.
Kempton, M.J., Salvador, Z., Munafò, M.R., Geddes, J.R., Simmons, A., Frangou, S., Williams, S.C.R., 2011. Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Arch. Gen. Psychiatry 68 (7), 675. https://doi.org/10.1001/archgenpsychiatry.2011.60.
Kendler, K.S., 1992. Major depression and generalized anxiety disorder: same genes, (partly) different environments? Arch. Gen. Psychiatry 49 (9), 716. https://doi.org/10.1001/archpsyc.1992.01820090044008.
Kendler, K.S., 2019. From many to one to many—the search for causes of psychiatric illness. JAMa Psychiatry 76 (10), 1085. https://doi.org/10.1001/jamapsychiatry.2019.1200.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62 (6), 593. https://doi.org/10.1001/archpsyc.62.6.593.
Khan, A.R., Wang, L., Beg, M.F., 2008. FreeSurfer-initiated fully-automated subcortical brain segmentation in MRI using Large Deformation Diffeomorphic Metric Mapping. Neuroimage 41 (3), 735–746. https://doi.org/10.1016/j.neuroimage.2008.03.024.
Kircanski, K., LeMoult, J., Ordaz, S., Gotlib, I.H., 2017. Investigating the nature of co-occurring depression and anxiety: comparing diagnostic and dimensional research approaches. J. Affect. Disord. 216, 123–135. https://doi.org/10.1016/j.jad.2016.08.006.
Koolschijn, P.C.M.P., van Haren, N.E.M., Lensvelt-Mulders, G.J.L.M., Hulshoff Pol, H.E., Kahn, R.S., 2009. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum. Brain Mapp. 30 (11), 3719–3735. https://doi.org/10.1002/hbm.20801.
Kotov, R., Krueger, R.F., Watson, D., Achenbach, T.M., Althoff, R.R., Bagby, R.M., Brown, T.A., Carpenter, W.T., Caspi, A., Clark, L.A., Eaton, N.R., Forbes, M.K., Forbush, K.T., Goldberg, D., Hasin, D., Hyman, S.E., Ivanova, M.Y., Lynam, D.R., Markon, K., Zimmerman, M., 2017. The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J. Abnorm. Psychol. 126 (4), 454–477. https://doi.org/10.1037/abn0000258.
Krueger, R.F., 1999. The structure of common mental disorders. Arch. Gen. Psychiatry 56 (10), 921. https://doi.org/10.1001/archpsyc.56.10.921.
Krueger, R.F., Markon, K.E., 2006. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu. Rev. Clin. Psychol. 2 (1), 111–133. https://doi.org/10.1146/annurev.clinpsy.2.022305.095213.
Lamers, F., van Oppen, P., Comijs, H.C., Smit, J.H., Spinhoven, P., van Balkom, A.J.L.M., Nolen, W.A., Zitman, F.G., Beekman, A.T.F., Penninx, B.W.J.H., 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). J. Clin. Psychiatry 72 (03), 341–348. https://doi.org/10.4088/JCP.10m06176blu.
Lange, C., Irle, E., 2004. Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. Psychol. Med. 34 (6), 1059–1064. https://doi.org/10.1017/S0033291703001806.
Lener, M.S., Kundu, P., Wong, E., Dewilde, K.E., Tang, C.Y., Balchandani, P., Murrough, J.W., 2016. Cortical abnormalities and association with symptom dimensions across the depressive spectrum. J. Affect. Disord. 190, 529–536. https://doi.org/10.1016/j.jad.2015.10.027.
Lewis, A.R., Zinbarg, R.E., Durbin, C.E., 2010. Advances, problems, and challenges in the study of emotion regulation: a commentary. J. Psychopathol. Behav. Assess. 32 (1), 83–91. https://doi.org/10.1007/s10862-009-9170-0.
Li, C.T., Lin, C.P., Chou, K.H., Chen, I.Y., Hsieh, J.C., Wu, C.L., Lin, W.C., Su, T.P., 2010. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. Neuroimage 50 (1), 347–356. https://doi.org/10.1016/j.neuroimage.2009.11.021.
MacMaster, F.P., Mirza, Y., Szeszko, P.R., Kmiecik, L.E., Easter, P.C., Taormina, S.P., Lynch, M., Rose, M., Moore, G.J., Rosenberg, D.R., 2008. Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol. Psychiatry 63 (4), 385–390. https://doi.org/10.1016/j.biopsych.2007.05.005.
Månsson, K.N.T., Salami, A., Frick, A., Carlbring, P., Andersson, G., Furmark, T., Boraxbekk, C.J., 2016. Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder. Transl. Psychiatry 6 (2), e727. https://doi.org/10.1038/tp.2015.218. –e727.
Markon, K.E., Chmielewski, M., Miller, C.J., 2011. The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. Psychol. Bull. 137 (5), 856–879. https://doi.org/10.1037/a0023678.
Mattick, R.P., Clarke, J.C, 1998. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety11Editor's note: this article was written before the development of some contemporary measures of social phobia, such as the Social Phobia and Anxiety Inventory (Turner et al., 1989). We have invited this article for publication because of the growing interest in the scales described therein. S.T. Behav. Res. Ther. 36 (4), 455–470. https://doi.org/10.1016/S0005-7967(97)10031-6.
Meyer, T.J., Miller, M.L., Metzger, R.L., Borkovec, T.D., 1990. Development and validation of the penn state worry questionnaire. Behav. Res. Ther. 28 (6), 487–495. https://doi.org/10.1016/0005-7967(90)90135-6.
Michelini, G., Palumbo, I.M., DeYoung, C.G., Latzman, R.D., Kotov, R., 2021. Linking RDoC and HiTOP: a new interface for advancing psychiatric nosology and neuroscience. Clin. Psychol. Rev. 86, 102025 https://doi.org/10.1016/j.cpr.2021.102025.
Mohlman, J., Price, R.B., Eldreth, D.A., Chazin, D., Glover, D.M., Kates, W.R., 2009. The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder. Psychiatry Res. 173 (2), 121–127. https://doi.org/10.1016/j.pscychresns.2008.09.010.
Naragon-Gainey, K., Prenoveau, J.M., Brown, T.A., Zinbarg, R.E., 2016. A comparison and integration of structural models of depression and anxiety in a clinical sample: support for and validation of the tri-level model. J. Abnorm. Psychol. 125 (7), 853–867. https://doi.org/10.1037/abn0000197.

Nikolaidis, A., Chen, A.A., He, X., Shinohara, R., Vogelstein, J., Milham, M., Shou, H., 2022. *Suboptimal phenotypic reliability impedes reproducible human neuroscience* [Preprint]. Neuroscience. https://doi.org/10.1101/2022.07.22.501193.

O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr. Opin. Neurobiol. 14 (6), 769–776. https://doi.org/10.1016/j.conb.2004.10.016.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nature Rev. Neurosci. 9 (12), 947–957. https://doi.org/10.1038/nrn2513.

Phillips, M.L., 2003. Understanding the neurobiology of emotion perception: implications for psychiatry. British J. Psychiatry 182 (3), 190–192. https://doi.org/10.1192/bjp.182.3.190.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13 (9), 833–857. https://doi.org/10.1038/mp.2008.65.

Powers, A., Casey, B.J., 2015. The adolescent brain and the emergence and peak of psychopathology. J. Infant Child Adolesc. Psychother. 14 (1), 3–15. https://doi.org/10.1080/15289168.2015.1004889.

Prenoveau, J.M., Zinbarg, R.E., Craske, M.G., Mineka, S., Griffith, J.W., Epstein, A.M., 2010. Testing a hierarchical model of anxiety and depression in adolescents: a tri-level model. J. Anxiety. Disord. 24 (3), 334–344. https://doi.org/10.1016/j.janxdis.2010.01.006.

Raamana, P.R., Theyers, A., Selliah, T., Bhati, P., Arnott, S.R., Hassel, S., Nanayakkara, N.D., Scott, C.J.M., Harris, J., Zamyadi, M., Lam, R.W., Milev, R., Müller, D.J., Rotzinger, S., Frey, B.N., Kennedy, S.H., Black, S.E., Lang, A., Masellis, M., Strother, S.C., 2020. *Visual QC protocol for freesurfer cortical parcellations from anatomical MRI* [Preprint]. Neuroscience. https://doi.org/10.1101/2020.09.07.286807.

Rapee, R.M., Craske, M.G., Barlow, D.H., 1994. Assessment instrument for panic disorder that includes fear of sensation-producing activities: the albany panic and phobia questionnaire: panic and Phobia Questionnaire. Anxiety 1 (3), 114–122. https://doi.org/10.1002/anxi.3070010303.

Reininghaus, U., Böhnke, J.R., Chavez-Baldini, U., Gibbons, R., Ivleva, E., Clementz, B. A., Pearlson, G.D., Keshavan, M.S., Sweeney, J.A., Tamminga, C.A., 2019. Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). World Psychiatry 18 (1), 67–76. https://doi.org/10.1002/wps.20607.

Ross, M.C., Dvorak, D., Sartin-Tarm, A., Botsford, C., Cogswell, I., Hoffstetter, A., Putnam, O., Schomaker, C., Smith, P., Stalsberg, A., Wang, Y., Xiong, M., Cisler, J.M., 2021. Gray matter volume correlates of adolescent posttraumatic stress disorder: a comparison of manual intervention and automated segmentation in FreeSurfer. Psychiatry Res. 313, 111297 https://doi.org/10.1016/j.pscychresns.2021.111297.

Ruigrok, A.N.V., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39, 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004.

Rush, A.J., Zimmerman, M., Wisniewski, S.R., Fava, M., Hollon, S.D., Warden, D., Biggs, M.M., Shores-Wilson, K., Shelton, R.C., Luther, J.F., Thomas, B., Trivedi, M.H., 2005. Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. J. Affect. Disord. 87 (1), 43–55. https://doi.org/10.1016/j.jad.2005.03.005.

Sacher, J., Neumann, J., Fünfstück, T., Soliman, A., Villringer, A., Schroeter, M.L., 2012. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J. Affect. Disord. 140 (2), 142–148. https://doi.org/10.1016/j.jad.2011.08.001.

Sackett, P.R., Yang, H., 2000. Correction for range restriction: an expanded typology. J. Appl. Psychol. 85 (1), 112–118. https://doi.org/10.1037/0021-9010.85.1.112.

Salvadore, G., Nugent, A.C., Lemaitre, H., Luckenbaugh, D.A., Tinsley, R., Cannon, D.M., Neumeister, A., Zarate, C.A., Drevets, W.C., 2011. Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. Neuroimage 54 (4), 2643–2651. https://doi.org/10.1016/j.neuroimage.2010.11.011.

Schienle, A., Ebner, F., Schäfer, A., 2011. Localized gray matter volume abnormalities in generalized anxiety disorder. Eur. Arch. Psychiatry Clin. Neurosci. 261 (4), 303–307. https://doi.org/10.1007/s00406-010-0147-5.

Schwarz, C.G., Gunter, J.L., Wiste, H.J., Przybelski, S.A., Weigand, S.D., Ward, C.P., Senjem, M.L., Vemuri, P., Murray, M.E., Dickson, D.W., Parisi, J.E., Kantarci, K., Weiner, M.W., Petersen, R.C., Jack, C.R., 2016. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. NeuroImage 11, 802–812. https://doi.org/10.1016/j.nicl.2016.05.017.

Shackman, A.J., Tromp, D.P.M., Stockbridge, M.D., Kaplan, C.M., Tillman, R.M., Fox, A. S., 2016. Dispositional negativity: an integrative psychological and neurobiological perspective. Psychol. Bull. 142 (12), 1275–1314. https://doi.org/10.1037/bul0000073.

Shaw, P., Gilliam, M., Liverpool, M., Weddle, C., Malek, M., Sharp, W., Greenstein, D., Evans, A., Rapoport, J., Giedd, J., 2011. Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. Am. J. Psychiatry 168 (2), 143–151. https://doi.org/10.1176/appi.ajp.2010.10030385.

Sindermann, L., Redlich, R., Opel, N., Böhnlein, J., Dannlowski, U., Leehr, E.J., 2021. Systematic transdiagnostic review of magnetic-resonance imaging results: depression, anxiety disorders and their co-occurrence. J. Psychiatr. Res. 142, 226–239. https://doi.org/10.1016/j.jpsychires.2021.07.022.

Suor, J.H., Jimmy, J., Monk, C.S., Phan, K.L., Burkhouse, K.L., 2020. Parsing differences in amygdala volume among individuals with and without social and generalized anxiety disorders across the lifespan. J. Psychiatr. Res. 128, 83–89. https://doi.org/10.1016/j.jpsychires.2020.05.027.

Syal, S., Hattingh, C.J., Fouché, J.P., Spottiswoode, B., Carey, P.D., Lochner, C., Stein, D. J., 2012. Grey matter abnormalities in social anxiety disorder: a pilot study. Metab. Brain Dis. 27 (3), 299–309. https://doi.org/10.1007/s11011-012-9299-5.

Tseng, W.L., Deveney, C.M., Stoddard, J., Kircanski, K., Frackman, A.E., Yi, J.Y., Hsu, D., Moroney, E., Machlin, L., Donahue, L., Roule, A., Perhamus, G., Reynolds, R.C., Roberson-Nay, R., Hettema, J.M., Towbin, K.E., Stringaris, A., Pine, D.S., Brotman, M.A., Leibenluft, E., 2019. Brain mechanisms of attention orienting following frustration: associations with irritability and age in youths. Am. J. Psychiatry 176 (1), 67–76. https://doi.org/10.1176/appi.ajp.2018.18040491.

Vaswani, M., Linda, F.K., Ramesh, S., 2003. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Progr. Neuro-Psychopharmacol. Biol. Psychiatry 27 (1), 85–102. https://doi.org/10.1016/S0278-5846(02)00338-X.

Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 46 (1), 327–337. https://doi.org/10.1016/j.neuroimage.2009.01.058.

Warnell, K.R., Pecukonis, M., Redcay, E., 2018. Developmental relations between amygdala volume and anxiety traits: effects of informant, sex, and age. Dev. Psychopathol. 30 (4), 1503–1515. https://doi.org/10.1017/S0954579417001626.

Watson, D., Clark, L.A., Weber, K., Assenheimer, J.S., Strauss, M.E., McCormick, R.A., 1995a. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. J. Abnorm. Psychol. 104 (1), 15–25. https://doi.org/10.1037/0021-843X.104.1.15.

Watson, D., Weber, K., Assenheimer, J.S., Clark, L.A., Strauss, M.E., McCormick, R.A., 1995b. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J. Abnorm. Psychol. 104 (1), 3–14. https://doi.org/10.1037//0021-843x.104.1.3.

Webb, C.A., Weber, M., Mundy, E.A., Killgore, W.D.S., 2014. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: a voxel-based morphometric analysis. Psychol. Med. 44 (13), 2833–2843. https://doi.org/10.1017/S0033291714000348.

Weiss, N.H., Thomas, E.D., Schick, M.R., Reyes, M.E., Contractor, A.A., 2022. Racial and ethnic differences in emotion regulation: a systematic review. J. Clin. Psychol. 78 (5), 785–808. https://doi.org/10.1002/jclp.23284.

Williams, A.L., Craske, M.G., Mineka, S., Zinbarg, R.E., 2021. Neuroticism and the longitudinal trajectories of anxiety and depressive symptoms in older adolescents. J. Abnorm. Psychol. 130 (2), 126–140. https://doi.org/10.1037/abn0000638.

World Health Organization, 2017. Depression Fact Sheet. WHO, Genewa, Switzerland. http://www.who.int/news-room/fact-sheets/detail/depression.

Young, K.S., Bookheimer, S.Y., Nusslock, R., Zinbarg, R.E., Damme, K.S.F., Chat, I.K.-Y., Kelley, N.J., Vinograd, M., Perez, M., Chen, K., Cohen, A.E., Craske, M.G, 2021. Dysregulation of threat neurociruitry during fear extinction: the role of anhedonia. Neuropsychopharmacology 46 (9), 1650–1657. https://doi.org/10.1038/s41386-021-01003-8.

Zhao, Y., Chen, L., Zhang, W., Xiao, Y., Shah, C., Zhu, H., Yuan, M., Sun, H., Yue, Q., Jia, Z., Zhang, W., Kuang, W., Gong, Q., Lui, S., 2017. Gray matter abnormalities in non-comorbid medication-naive patients with major depressive disorder or social anxiety disorder. EBioMedicine 21, 228–235. https://doi.org/10.1016/j.ebiom.2017.06.013.

Zimmerman, M., Coryell, W., 1987. The Inventory to Diagnose Depression (IDD): a self-report scale to diagnose major depressive disorder. J. Consult. Clin. Psychol. 55 (1), 55–59. https://doi.org/10.1037/0022-006X.55.1.55.

Zinbarg, R.E., Barlow, D.H., 1996. Structure of anxiety and the anxiety disorders: a hierarchical model. J. Abnorm. Psychol. 105 (2), 181–193. https://doi.org/10.1037//0021-843x.105.2.181.

Zinbarg, R.E., Williams, A.L., Mineka, S., 2022. A current learning theory approach to the etiology and course of anxiety and related disorders. Annu Rev. Clin. Psychol. 18 (1), 233–258. https://doi.org/10.1146/annurev-clinpsy-072220-021010.