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Extended Functional Connectivity of Convergent Structural Alterations Among Anxiety Disorders: A Meta-Analysis and Functional Connectivity Analysis

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EXTENDED FUNCTIONAL CONNECTIVITY OF CONVERGENT STRUCTURAL ALTERATIONS AMONG ANXIETY DISORDERS: A META-ANALYSIS AND FUNCTIONAL CONNECTIVITY ANALYSIS

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by

Brianna S. Pankey

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To: Dean Michael R. Heithaus
College of Arts, Science and Education

This dissertation, written by Brianna S. Pankey, and entitled Extended Functional Connectivity of Convergent Structural Alterations among Anxiety Disorders: A Meta-Analysis and Functional Connectivity Analysis, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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The dissertation of Brianna S. Pankey is approved.

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Vice President for Research and Economic Development
and Dean of the University Graduate School

Florida International University, 2021

DEDICATION

I dedicate this dissertation to my Dad, Kevin Pankey; no longer on earth, I kept a promise to and to my Mom, Odessa Pankey, and family. Anything is possible for all those a part of the African Diaspora out there with a dream to succeed.

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ABSTRACT OF THE DISSERTATION

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Professor Angela R. Laird, Major Professor

Anxiety-related disorders are some of the most pervasive mental health disorders affecting adult and youth populations. Despite growing evidence of the neurobiology associated with anxiety-related conditions, a consensus on the neurobiological mechanisms of anxiety-related disorders remains unclear. I first provide background literature on the reasoning behind this dissertation in Chapter 1. Chapter 2 conducted a neuroimaging meta-analysis on post-traumatic stress disorder to identify convergent structural and functional alterations associated with this anxiety-related disorder among adults. In Chapter 3**,** I conducted a neuroimaging meta-analysis to identify convergent structural alterations across a diverse grouping of anxiety-related disorders among adults, adolescents, and youth. Chapter 3 also includes a contrast analysis to examine the effects of clinical anxiety associated with brain structure between adults, adolescents, and youth. In Chapter 4, I conducted an extended functional connectivity analysis to characterize functional profiles of the regions of interests (ROIs) identified in Chapter 3. I provide concluding thoughts in Chapter 5. The

present collection of studies provides implications for understanding the neurobiology of anxiety-related disorders and brain-based approaches to treatment.

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CHAPTER 1. INTRODUCTION

Assessments of mental health among Americans reveal it is at the most concerning place it has ever been (Charara et al., 2016). Anxiety-related disorders are the most common, pervasive mental-health-related disorders among adults and adolescents (Kessler et al., 2005). A large body of neuroscience literature reveals brain-related alterations associated with neural, sociocultural, and environmental determinants of health and psychopathology. My long-term research goals are to examine how sociocultural and environmental factors relate to differences in brain structure and function in psychopathology. Achieving these goals requires a clear understanding of the neural correlates of psychopathology. Thus, my dissertation focuses on a series of quantitative neuroimaging meta-analyses to identify brain regions and networks associated with anxiety psychopathology. The following chapters synthesize research on anxiety-related disorders, and their relation to brain structure and function, at varying adult and youth developmental stages.

Rationale for Research

Anxiety-related disorders are the most prevalent mental health disorders among adults and youth in the US (Beesdo-Baum & Knappe, 2012; Cummings et al., 2014) with high comorbidity rates with mood disorders (Byers et al., 2010) and significant impairment of cognitive functioning (Kendall et al., 2010; Robinson et al., 2013), including memory and attention processes (Castaneda et al., 2008). Anxiety-related disorders contain symptom characteristics of excessive fear and worry that interfere with everyday life

(NIMH, 2018). Over the past few decades, advancements in noninvasive, neuroscientific techniques broadened a general understanding of associations between behavior, development, and health, including psychopathology. Structural magnetic resonance imaging (sMRI), a noninvasive imaging modality, utilizes strong magnetic fields to produce images of organs in the body (e.g., the brain) to measure brain structure (e.g., gray and white matter) (Lerch et al., 2017). A common data-analytic approach to sMRI data is voxel-based morphometry (VBM), a coordinate-based voxel-wise technique used to identify whole-brain structural differences (e.g., gray matter volume) between two groups (Ashburner & Friston, 2000). This technique allows for whole-brain analysis rather than region of interest (ROI) approaches to understand brain structure. Much heterogeneity exists in the VBM literature, likely due to small sample sizes and varying analytic pipelines. As a result, various statistical approaches have been developed to enable formal, quantitative meta-analyses of neuroimaging data. One such approach is anatomical likelihood estimation (ALE), which is commonly used to meta-analyze VBM studies (Eickhoff et al., 2012).

Functional magnetic resonance imaging (fMRI), on the other hand, measures neuronal activity associated with changes in blood flow via the blood oxygenation level dependent (BOLD) signal (Poldrack, 2012). A common analytic approach to fMRI data is to examine functional connectivity (FC), which measures the temporal correlations of BOLD signals across brain regions (Fingelkurts et al., 2005). FC is studied while participants are either at rest or completing a task. Together, the sMRI and fMRI modalities allow researchers to investigate associations between brain structure and function and psychopathology across various mental-health-related disorders.

Genetic, molecular, and systematic approaches collectivity provide insight into diagnosis and treatment associated with the neurobiology of anxiety-related disorders. The neuroimaging literature on anxiety-related disorders indicates altered structure and function of frontal-limbic circuitry related to fear conditioning (Critchley & Garfinkel, 2014; Shin & Liberzon, 2010) is associated with the development and maintenance of anxiety-related disorders. This circuitry typically encompasses the amygdala, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). However, integrating disruptions in emotion domains, such as emotion regulation processes, is associated with maintenance of anxiety-related disorders (Mennin, 2004). The association between emotion regulation strategies (e.g., emotion reappraisal) and altered function of the PFC, ACC, and amygdala is linked to fear expression (Cisler & Olatunji, 2012). Previous work suggests an association between atypical structural and functional circuitry of these frontal-limbic regions and various anxiety disorders among adults. Specifically, previous VBM evidence of the altered structure of the amygdala (Hayano et al., 2009), PFC (Etkin et al., 2011), and ACC (Asami et al., 2008; Kitayama et al., 2006) exists. However, a considerable concern across previous VBM meta-analytic findings among adults with clinical anxiety is the inconsistent reporting of patterns of structural gray matter (GM) increases or decreases within these frontal-limbic regions across various anxiety-related disorders (Cheng et al., 2015; O'Doherty et al., 2017; Radua et al., 2010; Shang et al., 2014; Wang et al., 2021). A consensus of the structural alterations and functional connectivity patterns among adults with clinical anxiety remains to be elucidated.

In addition, potential differences in the neurobiological correlates of anxiety between adults and youth with clinical anxiety may exist. Anxiety disorders often emerge

during childhood and adolescence (Murray et al., 2009); however, neuroimaging studies with pediatric and adolescent samples reveal broadly similar, but somewhat inconclusive, patterns of structural and functional alterations. A few neuroimaging studies found an association between larger amygdala volume and pediatric generalized anxiety disorder (GAD) (De Bellis et al., 2002; Milham et al., 2005), while other studies found decreased amygdala volume among adolescents (Mueller et al., 2013) and youth (Strawn et al., 2013). Other investigations observed increased gray matter volume (GMV) in PFC regions among adolescents with GAD or post-traumatic stress disorder (PTSD) (Carrion et al., 2009). However, a more extensive study with youth diagnosed with multiple, different anxiety disorders found decreased GM volume in the dorsolateral PFC (dlPFC) (Wehry et al., 2015). Previous VBM meta-analytic work among youth or adolescents with clinical anxiety revealed increased GMV in the dorsal ACC (dACC), ventrolateral and dorsolateral PFC (vlPFC; dlPFC), and striatum (Gold et al., 2016; Mueller et al., 2013; Strawn et al., 2015). Overall, there remains limited consensus across pediatric anxiety-related disorders. Hence, a comprehensive meta-analysis to identify the neurobiological mechanisms among youth with clinical anxiety is needed. Examining the neurobiological correlates of anxiety-related disorders in early life will contribute to understanding the etiology, maintenance, and treatment of anxiety-related disorders.

Presentation of Research Findings

To summarize, existing neuroscience research has not yet determined if a range of anxiety-related disorders are characterized as having unique or shared neurobiological mechanisms. Despite evidence of frontal-limbic circuitry associated with the maintenance

of anxiety, a consensus on structural alterations linked to clinical anxiety remains unclear. Further, how these structural alterations may differ between adult and youth remains inconclusive. Emergent meta-analytic techniques provide a way to assess the nuanced reporting of the neurobiology of anxiety-related disorders across the lifespan and examine connectivity patterns associated with structural alterations of clinical anxiety. The use of meta-analytic techniques may contribute new insight into a brain-based understanding of factors relevant to the nation's significant mental health crisis.

CHAPTER 2

EXTENDED FUNCTIONAL CONNECTIVITY OF CONVERGENT STRUCTURAL ALTERATIONS AMONG INDIVIDUALS WITH PTSD

ABSTRACT

Post-traumatic stress disorder (PTSD) is a debilitating disorder defined by the onset of intrusive, avoidant, negative cognitive or affective, and/or hyperarousal symptoms after witnessing or experiencing a traumatic event. Previous and voxel-based morphometry (VBM) studies provide insight into altered brain structure associated with PTSD but these studies reported heterogeneous findings and conflicting results. Here, I present a quantitative meta-analysis of 23 VBM studies examining structural alterations associated with PTSD. Using emergent meta-analytic techniques, I sought to first identify clusters of convergent structural alterations in PTSD using the anatomical likelihood estimation (ALE) approach. Next, I generated functional profiles of identified convergent structural regions utilizing resting-state functional connectivity (rsFC) and meta-analytic co-activation modeling (MACM) methods. Finally, I performed functional decoding to examine mental functions associated with our ALE, rsFC, and MACM brain characterizations. I observed convergent structural alterations in a single region located in the medial prefrontal cortex. The resultant rsFC and MACM maps identified functional connectivity across a widespread, whole-brain network that included frontoparietal and limbic regions. Consensus-based functional connectivity was observed in regions of the default mode and salience networks, which play a role in the tripartite model of psychopathology. Functional decoding revealed overlapping associations with attention, memory, and emotion processes. Taken together, these findings have important implications in understanding the neurobiological mechanisms associated with PTSD.

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a psychiatric disorder in which the onset of a multitude of symptoms develops after experiencing or witnessing a traumatic event, such as violence, accidents, or combat (Yehuda et al., 2015). Symptoms associated with PTSD are categorized into clusters according to the DSM 5: 1) intrusion/re-experiencing trauma, 2) avoidance, 3) negative cognition and mood, and 4) hyperarousal (Kirkpatrick & Heller, 2014; Pai et al., 2017). Roughly 70% of adults experience at least one traumatic event in their lifetime (Sidran Institute, 2018); however, not all individuals who experience a traumatic event develop PTSD symptoms. Individuals with PTSD may experience long-term debilitating effects, mentally, physically, and cognitively. In the United States, roughly 8 million adults suffer from PTSD every year (National Center for PTSD, 2019).

Current theories aim to understand the etiology of PTSD, including behavioral, cognitive, and social models. An original model of PTSD suggests that the persistence of PTSD symptoms is a consequence of processing a traumatic event as a current threat explained by exaggerated negative appraisal of the threat and poorer autobiographical memory function including contextualization of the trauma exposure (Ehlers & Clark, 2000). Though this cognitive model characterizes utilized previous DSM criteria on PTSD, it shows a unique characteristic of PTSD where the onset of symptoms occur as a result of an event that happened in the past. However, cognitive models of anxiety-related disorders differ in that the unique characteristic of these types of disorders is associated with negative appraisals to imminent threat. However, updated models of PTSD complement this original cognitive model by integration of emotion and social cognitive perspectives and the association between these domains and the manifestation of PTSD symptoms as a result of

trauma exposure (Ehlers & Clark, 2000; Maercker & Horn, 2013; Sharp et al., 2012). Despite progress in understanding the vulnerability, symptomatology, and trajectory of PTSD (Agaibi & Wilson, 2005; Kirkpatrick & Heller, 2014; Pitman et al., 2012), the underlying neurobiological determinants of PTSD are less clear. Substantial work has attempted to identify structural brain alterations observed among individuals with PTSD. Voxel-based morphometry (VBM) is a commonly used methodological approach for analyzing structural magnetic resonance imaging (MRI) data, allowing for quantitative comparisons statistical inferences between groups (e.g., differences in gray matter volume; GMV) to more clearly understand the structural alterations associated with psychopathology, such as PTSD. Prior meta-analytic work has collectively identified convergent gray matter reductions in the anterior cingulate cortex (ACC), hippocampus, medial prefrontal cortex (mPFC), amygdala, and insula (Bromis et al., 2018; Klaming et al., 2019; Kühn & Gallinat, 2013; Li et al., 2014; Meng et al., 2014).

While prior meta-analytic work has advanced the understanding of structural brain alterations among individuals with PTSD, results across these meta-analyses demonstrate substantial variability, where not all these regions are consistently listed across the literature. Given the substantial heterogeneity among previous meta-analytic work, it presents an opportunity to conduct an updated meta-analysis examining distinct or similar structural alterations between PTSD and trauma-exposed non-diagnosis individuals. In the present study, I conducted a series of meta-analyses to investigate the convergent structural alterations among individuals with PTSD compared to non-diagnosed trauma-exposed individuals and individuals without PTSD diagnosis or trauma exposure (healthy controls; HC). To this end, I first identified convergent regions of gray matter (GM)

reductions in PTSD vs. non-PTSD groups using anatomical likelihood estimation (ALE) (Eickhoff et al., 2009, 2012). Second, I identified the task-free and task-based functional connectivity patterns of convergent brain regions, thus providing multimodal functional connectivity profiles for each region. Lastly, I applied meta-analytic functional decoding methods to our consensus findings between task-free and task-based assessments to characterize the mental processes associated with the functional connectivity profiles. I expected the most profound GM reductions to be aligned with findings from previous meta-analytic literature (e.g. ACC, mPFC, amygdala, and insula). Due to inconsistencies in the meta-analytic literature about the structural alterations associated with trauma-exposed non-diagnosed individuals, I hypothesized for this group the most profound GM structural alterations in hippocampus, amygdala, and insula regions. A more comprehensive understanding of the neurobiological bases of PTSD is needed to delineate future pathways toward improved diagnosis, treatment, and prevention.

METHODS

Analysis Overview. I first conducted a literature search to identify studies reporting structural alterations comparing the following groups: individuals with PTSD, individuals who experienced trauma but were not diagnosed with PTSD, and individuals who did not report experiencing trauma nor have a PTSD diagnosis (HC). A coordinate-based meta-analysis was performed using the ALE algorithm to identify convergent brain regions showing GM structural alterations associated with PTSD. I then used multiple connectivity modeling approaches to comprehensively characterize the functional connectivity of these convergent regions. Specifically, rsFC and meta-analytic co-

activation modeling (MACM) assessments were applied to identify the functional profiles of structurally altered regions associated with PTSD. Lastly, I used the generalized correspondence latent dirichlet allocation (GC-LDA) functional decoding method to help guide interpretation of the consensus rsFC and MACM maps results. An overview of our methodological approach is provided in **Figure 1**.

Literature Search and Study Criteria. I conducted a comprehensive literature search to build a database of peer-reviewed MRI studies reporting structural alterations associated with PTSD from 2002-2020. In the first round of identifying studies, I examined previously published voxel-based morphometry meta-analysis papers on PTSD (Bromis et al., 2018; Klaming et al., 2019; Kühn & Gallinat, 2013; Li et al., 2014; Meng et al., 2014) and compiled a list of included studies. Next, I performed a *PubMed* search to identify additional peer-reviewed, structural MRI studies of interest using the search terms "morphometry + PTSD or trauma or gray matter". I utilized the same search terms to examine *Google Scholar* and *Web of Science* databases for any potential additional studies. The *PubMed* search aimed to identify any potential studies that were not included in the previously published meta-analyses. I then conducted a review of each identified publication to include the following study criteria: peer-reviewed MRI studies, reporting results among adult humans, written in the English language, focused on gray matter structural differences, and included original data (i.e., not a review). Subsequently, exclusion criteria were as follows: trauma or stressful life event studies not measuring PTSD, other non-voxel-based morphometry methods, post-treatment contrasts, longitudinal effects, papers reporting *a priori* regions of interest (ROIs), within-group

effects, null effects, overlapping samples to previous studies, and studies that did not report coordinate-based results.

Data-Analysis

Anatomical Likelihood Estimation. ALE is a voxel-based meta-analytic technique that identifies convergent coordinates (i.e., foci) across a set of neuroimaging studies. Foci are treated as 3D Gaussian distributions to address variability within and between studies. I used the coordinate-based ALE approach as implemented in NiMARE v.0.0.3 (*Neuroimaging Meta-Analysis Research Environment;* http://nimare.readthedocs.io), a Python library for neuroimaging meta-analysis. Reported coordinates in this meta-analysis were extracted from their original publication and transformed from Talairach to MNI space (Laird et al., 2010; Lancaster et al., 2007). Once transformed, statistical probability maps were created for each foci and combined to model the likelihood that a given voxel displayed a between-group structural difference for each study. Observed voxel-wise ALE scores characterized the most consistently reported foci across the whole brain. Significance testing and correction for multiple comparisons involved thresholding the voxel-wise ALE map using a cluster-forming threshold of $P < 0.001$. Then, a permutation procedure was performed in which a null distribution of maximum cluster sizes was generated from 10,000 iterations of replacing reported foci with randomly selected gray matter voxels, generating ALE maps from the randomized dataset, and identifying the maximum cluster size after thresholding at $P < 0.001$. The cluster-level FWE correction threshold was set at $P < 0.05$, meaning only those clusters from the original, thresholded ALE map were retained if their size was greater than the cluster size corresponding to the

95th-percentile from the null distribution. I applied the above ALE procedure to explore differences in convergent structural alterations between PTSD diagnosed individuals and a pooled control group (trauma exposed, non-diagnosed and HC). I next examined differences in convergent structural alterations among the trauma-exposed, non-diagnosed and PTSD groups. Lastly, I explored structural differences between the non-diagnosed, non-trauma exposed (HC) and PTSD groups.

Functional Profiles of Structurally Altered Regions Associated with PTSD. Next, I sought to identify the functional connectivity patterns associated with regions demonstrating structural alterations in PTSD. To this end, I investigated *task-free functional connectivity* utilizing a database of resting state fMRI data, as well as *task-based functional connectivity* using a meta-analytic database of co-activation results.

Task-free functional connectivity: Resting-state fMRI (rs-fMRI). Resting-state connectivity analyses typically identify voxels of the brain that demonstrate the highest temporal correlation with the average time series of a seed ROI and provide context about the underlying functional architecture of the brain. To derive robust rsFC maps for each ROI, I utilized the minimally pre-processed and denoised (or "cleaned") resting-state fMRI data provided by the Human Connectome Project's (Van Essen et al., 2013) Young Adult Study S1200 Data Release (March 1, 2017). On November 12, 2019, 150 randomly selected participants (28.7 ± 3.9 years) were downloaded via the HCP's Amazon Web Services (AWS) Simple Storage Solution (S3) repository. The randomly chosen participants included 77 females (30.3 ± 3.5 years) and 73 males (27.1 ± 3.7 years). A

difference in age between the two biological sex groups was significant but is consistent with the 1200 Subjects Data Release. Detailed acquisition and scanning parameters for HCP data can be found in consortium manuscripts (Smith et al., 2013; Uğurbil et al., 2013; Van Essen et al., 2012), but relevant scan parameters are briefly summarized here. Each participant underwent T1-weighted and T2-weighted structural acquisitions and four resting-state fMRI acquisitions. Structural images were collected at 0.7-mm isotropic resolution. Whole-brain EPI acquisitions were acquired on the 3T Siemens Connectome scanner: 32-channel head coil, TR = 720 msec, TE = 33.1 msec, in-plane FOV = 208 × 180 mm, 72 slices, 2.0 mm isotropic voxels, and multiband acceleration factor of 8 (Feinberg et al., 2010).

The S1200 data release contained minimally pre-processed and denoised data. The minimal pre-processing workflow is described by Glasser and colleagues (Glasser et al., 2016), but consists of typical imaging pre-processing techniques that leverage the high-quality data acquired by the HCP. First, T1- and T2-weighted images were aligned, bias field corrected, and registered to MNI space. Second, the functional fMRI pipeline removed spatial distortions, realigned volumes to compensate for subject motion, registered the fMRI data to structural volumes (in MNI space), reduced the bias field, normalized each functional acquisition to its corresponding global mean, and masked non-brain tissue. It is important to note that care was taken to minimize smoothing induced by interpolation and that no overt volume smoothing was performed.

The fMRI signal contains many sources of fluctuations, including artifactual and non-neuronal signals, that make identifying the underlying neuronal activity difficult. Using a combination of independent component analysis (ICA) and classification

techniques, HCP functional data were automatically denoised using FMRIB's ICA-based X-noiseifier (Salimi-Khorshidi et al., 2014). Briefly, ICA is performed on each functional dataset independently and characteristics of each component, such as spatial localization and power in high-frequencies, are evaluated by a classifier to determine if a given component is related to neuronal activity or artifact. The time-series corresponding to artifactual components are then regressed out of the data, providing a "cleaned", denoised dataset for further investigation.

Using the minimally pre-processed, denoised resting-state datasets for each participant, the "global signal" was removed using FSL's *fsl_glm* (Jenkinson et al., 2012) interface in NiPype (Gorgolewski et al., 2011). The "global signal", although controversial in the domain of resting-state analyses, was removed under the assertion that it performed better than other commonly used motion-correction strategies in removing motion-related artifacts in the HCP resting-state data (Burgess et al., 2016). The resulting data set was then smoothed with a FWHM kernel of 6-mm using FSL's *susaan* interface in NyPipe. For each participant, the average time series for each ROI was extracted and a whole-brain correlation map was calculated and averaged across runs for a single participant for every ROI. The average correlation maps for each participant were transformed to Z-scores using Fisher's r-to-z transformation. A group-level analysis was then performed to derive a rsFC map for each ROI using FSL's *randomise* interface (Winkler et al., 2014) in NiPype. Images were thresholded non-parametrically using GRF-theory-based maximum height thresholding with a (voxel FWE-corrected) significance threshold of $P < 0.001$ (Worsley, 2001), such that more spatially specific connectivity maps could be derived when using such a highly powered study (Woo et al., 2014).

Task-based functional connectivity: Meta-analytic co-activation modeling (MACM). Using reported coordinates from task-based fMRI studies, meta-analytic co-activation is a relatively new concept that identifies locations in the brain that are most likely to be co-activated with a given seed ROI across multiple task states. Thus, differing from rsFC, MACM provides context about neural recruitment during goal-oriented behaviors. I therefore aimed to integrate these two complementary modalities by supplementing the rsFC maps with MACM maps for each ROI. To do so, I relied on the Neurosynth database (Yarkoni et al., 2011), which archives published stereotactic coordinates from over 14,000 fMRI studies and 150,000 brain locations. Neurosynth relies on an automated coordinate extraction (ACE) tool to "scrape" each available fMRI study for reported coordinates. Due to the nature of this automated process, fMRI studies reporting results of multiple experimental contrasts as separate sets of coordinates are amalgamated into a single set of coordinates; in addition, "activation" and "de-activation" coordinates are not distinctly characterized. However, while this inherent noise may yield greater limitations in interpretation, the power over manually curated datasets outweighs the potential confounds of bi-directional or mixed-contrast effects.

To generate a MACM map for each ROI, I utilized NiMARE to search the Neurosynth database for all studies reporting a coordinate within the defined ROI mask. Neurosynth tools support using the multilevel kernel density analysis (MKDA) algorithm for performing meta-analyses based on a subset of studies, such as that proposed here. However, I opted to use the ALE algorithm as implemented in NiMARE due to its optimal performance in replicating image-based meta- and mega-analyses (Salimi-Khorshidi et al., 2009). The ALE algorithm requires sample size, or the number of subjects, that contribute

to a given experimental contrast to generate a smoothing kernel. However, Neurosynth is not able to capture sample size (which could also vary across experimental contrasts within a study). Thus, I utilized a smoothing kernel with a FWHM of 15-mm, which has been shown to yield results with strong correspondence with image-based meta- and mega-analyses (Salimi-Khorshidi et al., 2009). The ALE algorithm was applied to the set of studies reporting activation within the boundaries of each ROI. Once ALE maps were generated, as described above, for each ROI, voxel-FWE correction ($P < 0.001$) was performed to reflect the statistical thresholding approach used for rsFC maps.

Functional Decoding: Generalized Correspondence Latent Dirichlet Allocation (GC-LDA). I sought to infer what mental processes were most likely linked with brain regions identified in our ALE, MACM, and rsFC analyses. To do so, I utilized GC-LDA functional decoding methods applied to the resulting unthresholded ALE, rsFC, and MACM maps. This type of decoding provides a statistical approach to infer mental processes associated with neuroimaging spatial patterns. GC-LDA utilizes probabilistic Bayesian statistics that learns latent topics from a large database of papers (e.g., NeuroSynth) (Rubin et al., 2017). From the database, each topic found is treated as a probability distribution and creates a spatial distribution in MNI space across voxels from the maps entered into the decoding algorithm. The "topics" encompass terms and associated brain regions that co-occur in the literature from a literature database. I set the model to 200 topics (Rubin et al., 2016). I report the 10 terms corresponding to the highest weights associated with our ALE, rsFC, and MACM results.

RESULTS

Literature Search and Study Criteria. The literature search yielded a total of 85 articles using the above described search terms. Figure 2 provides a PRISMA diagram, which details the review and filtering of those 85 studies. In the first round of review, records (i.e., titles and abstracts) were screened to exclude 18 studies that corresponded to non-human or non-English studies, reviews, or studies reporting white matter differences or differences among children or adolescents. Then, I examined the full-text articles to assess additional study criteria; 44 additional studies were excluded as being not eligible for the current meta-analysis (see Figure 2).

The final set of included studies consisted of 23 publications. Within these publications, gray matter structural alterations were assessed by comparing whole-brain VBM results among individuals with and without PTSD, reported as 3D coordinates in MNI or Talairach space. Control comparison groups included individuals who had experienced trauma but did not develop PTSD and individuals who had not experienced trauma. Nineteen publications included trauma-exposed controls (TC), while ten publications included healthy, non-trauma-exposed controls (HC). Altogether, this set of 23 studies collectively examined 476 individuals with PTSD and 892 individuals without PTSD, which included 288 TC and 633 HC. With respect to the type of structural alterations observed, studies reported multiple different VBM metrics. Seventeen publications reported group differences in gray matter volume (GMV), seven publications reported differences in gray matter density (GMD), and one reported gray matter concentration (GMC). Collectively, I refer to all of these metrics as gray matter (GM) differences among individuals with and without PTSD. Additional details on the

demography of participant groups and study design are provided in Supplementary Table S1.

Within this final set of 23 publications, multiple contrasts of interest were reported. 25 contrasts reported *GM decreases* in PTSD vs non-PTSD for a total of 159 foci; this included 16 contrasts for PTSD vs. TC (82 foci) and 9 contrasts for PTSD vs. HC (77 foci). Conversely, 6 contrasts reported *GM increases* in PTSD vs. non-PTSD for a total of 20 foci, including 3 for PTSD (9 foci) vs. TC, 2 contrasts for PTSD vs. HC (9 foci) and 1 contrast for TC vs. HC (2 foci).

Anatomical Likelihood Estimation (ALE). Using NiMARE v.0.0.3, one ALE meta-analysis was performed to examine structural convergence across 25 contrasts of GM decreases among individuals with and without PTSD (i.e., pooled trauma-exposed and HC > PTSD). I was unable to assess the 6 contrasts of GM increases (i.e., PTSD > non-PTSD) given insufficient power (Eickhoff et al., 2016). With respect to GM decreases, I observed a single cluster of convergence located in the mPFC (x=0, y=46, z=10; BA32) (Figure 3; $P < 0.001$, FWE-corrected $P < 0.05$). Given these results, I performed additional ALE meta-analyses for the PTSD vs. TC and PTSD vs. HC contrasts (i.e., GM increases and decreases) to determine if the use of different comparison groups potentially contributed additional heterogeneity, limiting assessment of convergence. However, I observed null results for these additional contrasts as well, likely in part due to the underpowered samples (Eickhoff et al., 2016).

Functional Profiles of Structurally Altered Regions Associated with PTSD. I next investigated the functional connectivity of the mPFC cluster identified above showing convergent gray matter reductions among individuals with PTSD. To this end, I analyzed task-free rsFC and task-based MACM. First, I generated a rsFC map using the ALE-derived mPFC cluster as a seed region. The resultant rsFC map revealed rsFC with the superior frontal gyrus, medial frontal gyrus, inferior frontal gyrus, ACC, thalamus, posterior cingulate (PCC), superior temporal gyrus, medial temporal gyrus, precuneus, cuneus, and parahippocampus (Table 1). Next, to further examine functionally coupled regions with the mPFC seed, I generated a MACM map using the Neurosynth database which demonstrated task-based co-activations with a similar pattern as the rsFC map (Table 2). Figure 4 illustrates the rsFC (blue) and MACM (red) results, with overlapping regions, indicating a consensus between rsFC and MACM (pink), revealed in the ACC, medial prefrontal gyrus, middle temporal gyrus, insula, inferior parietal lobe, thalamus, precuneus, parahippocampus, insula and PCC regions (Table 3). This consensus pattern of regions suggests that PTSD-related gray matter loss in the mPFC may have implications for the optimal functioning of a widespread brain network.

Functional Decoding: Generalized Correspondence Latent Dirichlet Allocation (GC-LDA). Lastly, I performed functional decoding of the structural ALE, rsFC, and MACM maps to provide insight into the behavioral functions putatively associated with the observed functional connectivity patterns. Functional decoding was conducted using a GC-LDA analysis (Rubin et al., 2017). Because GC-LDA does not provide correlational or statistical rankings, the top 10 unique terms computed from the GC-LDA analysis were

taken into consideration separately for the structural ALE, rsFC, and MACM maps. The decoding terms with the top 10 weights from the GC-LDA analysis for the structural ALE map were: *visual, emotional, memory, novel, reward, motor, self, faces, learning,* and *face* (Table 4a). The decoding terms with the top 10 weights from the GC-LDA analysis for the rsFC map were: *default, default mode network, intrinsic, scale, self, person, reward, bias, judgements,* and *contexts*. (Table 4b). Topographically speaking, the rsFC results resembled regions of combined default mode (Greicius et al., 2003; Raichle, 2015) and salience networks (Menon & Uddin, 2010; Seeley et al., 2007), and the functional decoding outcomes suggested that the rsFC results were associated with reward and self-referential processes. Next, I examined MACM-based decoding results. The decoding terms with the top 10 weights from the GC-LDA analysis for the MACM map were: *visual, motor, emotional, memory, attention, auditory, reward, spatial, schizophrenia,* and *language*. (Table 4c). Topographically speaking, the MACM results also resembled regions of the default mode (Greicius et al., 2003; Raichle, 2015) and salience networks (Menon & Uddin, 2010; Seeley et al., 2007), and the functional decoding outcomes suggested, similar to the rsFC results, that the MACM results were associated with emotional and memory processes. Collectively, these functional decoding outcomes emphasize the functional roles of default mode, salience, and central executive networks, particularly with respect to self-referential and attentional processes.

DISCUSSION

The overall objective of this study was to investigate convergent alterations in brain structure among individuals with PTSD using emergent meta-analytic techniques. Further, I sought to extend the literature and assess potential functional consequences associated with observed structural alterations in PTSD by applying complementary rsFC and MACM analytic techniques. The current meta-analysis of 23 VBM studies evaluating GM structural alterations among PTSD versus non-PTSD groups identified a single node of convergent gray matter loss in the mPFC. GC-LDA-based functional decoding of this seed taken from the ALE analysis was linked to Neurosynth terms associated with emotion and social cognition domains: *visual, emotional, memory, novel, reward, motor, self, faces, learning,* and *face*. Follow-up ALE analyses exploring GM reductions in PTSD vs. HC (non-traumatized controls) and PTSD vs. TC (trauma-exposed controls not diagnosed with PTSD) yielded null findings likely due to insufficient power (Eickhoff et al., 2016). Subsequent analyses of the ALE-derived mPFC cluster were conducted to assess task-free (rsFC) and task-dependent (MACM) functional connectivity, identifying a consistent and widespread functional network implicated in PTSD. These results indicate that structural alterations in the mPFC among individuals with PTSD are likely linked to disruptions across a larger frontoparietal network that includes the medial, superior, and inferior frontal gyri, PCC, parahippocampal gyri, angular gyri, superior temporal gyrus, thalamus, caudate, and lentiform nucleus. Functional decoding of rsFC and MACM results indicates substantive term overlap with the mPFC ALE results, with additional network-related terms (e.g., *memory, emotion, social cognitive domains*).

Structural Alterations and Dysfunction in PTSD. Our current findings suggest the mPFC as the most convergent finding across VBM neuroimaging studies exploring the impact of PTSD on brain structure. Previous meta-analyses have identified consistent GM reductions in the ACC, hippocampus, mPFC, vmPFC, amygdala, parahippocampus and insula; however, not all of these regions were consistently observed across all meta-analyses (Bromis et al., 2018; Klaming et al., 2019; Kühn & Gallinat, 2013; Li et al., 2014; Meng et al., 2014). Beyond the mPFC, I did not observe additional convergent GM reductions, indicating that prior findings in these other regions were not replicated. Thus, there presents a difference in findings between previously meta-analytic work and the current study. Inconsistencies between the current findings and previous meta-analytic results could be due to greater conceptual and methodological differences, such as the scope of the research question exploring the neurobiology of PTSD, inclusion/exclusion of different comparison groups across studies, and the meta-analytic approach (e.g., effect size signed differential mapping, ALE, etc.). Importantly, it is likely that extensive heterogeneity in the PTSD literature, combined with varying meta-analytic inclusive/exclusion criteria, contributed to differences between our results and prior meta-analytic findings. Across the PTSD literature, there is a high degree of variability associated with participant trauma exposure, length of diagnosis of PTSD, medication use, and comorbidity. To our knowledge, the current meta-analysis of 25 contrasts represents the largest PTSD meta-analysis of structural findings to date. I observed that the mPFC is robustly associated with structural alterations in PTSD; however, it is important to consider how the mPFC is integrated within existing neurocircuitry models associated with PTSD symptomology.

Traditional neurocircuitry models of PTSD utilize a fear-conditioning framework, emphasizing hyperreactivity of the amygdala in response to fear-related stimuli and dysfunction between the mPFC and orbitofrontal cortex, as well as the hippocampus, in attention and top-down control during threat exposure (Rauch et al., 2006; Shin et al., 2006). However, limiting consideration of the psychopathology of PTSD to focus on a single brain region (i.e., the amygdala) emphasizes fear-related brain activity while minimizing brain circuitry implicated in the complex constellation of PTSD symptoms associated with response to trauma exposure, such as re-experiencing trauma, avoidance, negative mood, and numbing. These additional processes remain largely unexplained in original PTSD models. However, more recent neurocircuitry models build from this perspective, with increased emphasis on altered function of the mPFC, its role in contextualization, and how context processing is core to the constellation of PTSD symptoms (Liberzon & Abelson, 2016; Liberzon & Garfinkel, 2009). While our results indicated convergent structural alterations in the mPFC, I did not observe similar convergence in the amygdala or other regions that have been implicated in prior neurocircuitry models of PTSD (Hamner, 1999; Koenigs & Grafman, 2009; Rauch et al., 2006; Shin et al., 2006). However, our results are congruent with the expanded models of PTSD and I provide robust evidence in support of the mPFC as a critical node of hypofunction in PTSD neurocircuitry. Further, our functional decoding results (Table 4a) provide additional support for the contextualization models of PTSD. Taken together, reduced GM in the mPFC among individuals diagnosed with PTSD supports the premise that these structural alterations contribute to deficits in context processing and ultimately

play a dominant role in contributing to behaviors related to the constellation of symptoms in PTSD (Liberzon & Abelson, 2016; Liberzon & Garfinkel, 2009).

Functional Profiles of Structural Findings in PTSD: Support for the Tripartite Model of Psychopathology. rsFC and MACM analyses characterized mPFC functional connectivity extending across widespread, whole-brain networks engaging frontoparietal and limbic regions. These rsFC and MACM results, in conjunction with functional decoding outcomes, identified a functional connectivity profile suggesting spatial patterns associated with the default mode network (DMN) (Greicius et al., 2003; Raichle, 2015), the salience mode network (SN) (Menon & Uddin, 2010; Seeley et al., 2007), and the central executive network (CEN) (Dosenbach et al., 2007; Seeley et al., 2007). The DMN is a system of connected brain areas including the mPFC, PCC, inferior parietal, and temporal cortices that are often collectively observed as displaying anticorrelation with regions actively engaged during attention-demanding tasks. Areas of the DMN collectively contribute to mental processes associated with introspection and self-referential thought (Greicius et al., 2003; Liberzon & Shulman, 2001; Whitfield-Gabrieli & Ford, 2012). The SN consists of the dorsolateral ACC and bilateral insula, and is involved in saliency detection and attentional processes (Menon & Uddin, 2010; Seeley et al., 2007). Finally, the CEN often consists of the dorsolateral prefrontal and posterior parietal cortices and is typically involved in goal-directed behavior (Turner et al., 2019). These three networks are large-scale brain networks associated with neurobiological models of psychopathology(Goodkind et al., 2015; Menon, 2011a; Menon & Uddin, 2010). The application of the tripartite model to neurobiology models of psychiatric disorders define

dysfunction within and between connectivity of the DMN, SN, and CEN networks and relates to a broad range psychiatric disorders (Sha et al., 2019), including PTSD (Nicholson et al., 2020; Patel et al., 2012). In sum, the current meta-analysis identified a functional profile associated with network connectivity between the DMN, SN, and CEN in support of a network theory of PTSD (Akiki et al., 2017; Koch et al., 2016).

According to the tripartite model of brain function, the SN is thought to mediate activity between the DMN and CEN networks in order to orient to external stimuli or internal salient biological stimuli (Koch et al., 2016; Menon & Uddin, 2010; Sripada et al., 2012). Altered inter- and intra-network functional connectivity between the DMN, SN, and CEN exist in PTSD diagnosis (Koch et al., 2016). Specifically, seed-based resting state studies identified decreased connectivity *within* the DMN and SN, yet increased connectivity *between* these two networks among PTSD patients(Sripada et al., 2012; Tursich et al., 2015). Furthermore, other resting state studies on PTSD utilizing graph theory approaches (Lei et al., 2015) and independent component analysis (Y. Zhang et al., 2015) replicated weakened connectivity *within* the DMN, SN, and CEN, yet heightened connectivity *between* the DMN and SN (Holmes et al., 2018; Tursich et al., 2015). Taken together, this literature suggests deficits in top-down control over heightened responses to threatening stimuli and abnormal regulation of orienting attention to threatening stimuli (Koch et al., 2016; Lei et al., 2015; Sripada et al., 2012; Tursich et al., 2015; Zhang et al., 2015). Patterns from task-based studies reflect previous findings of weakened connectivity between the SN and DMN and heightened connectivity between the SN and CEN (Patel et al., 2012; Thome et al., 2014). In a study among individuals with recent trauma exposure, connectivity between the DMN, SN, and CEN was reported to be disrupted among

participants who developed PTSD vs. those who do not (Liu et al., 2017; Qin, 2012), providing evidence of differential functional connectivity between PTSD patients and traumatized non-diagnosed individuals. Network dysfunction associated with the DMN, SN, and CEN is also evident in task-based studies, including cues containing trauma stimuli (Rabellino et al., 2015), eye gaze (Thome et al., 2014), and a broad range of behavioral paradigms (Patel et al., 2012). Aberrant connectivity between and within the DMN, SN, and CEN has also been associated with PTSD symptoms, such that heightened connectivity and activity of the DMN was associated with depersonalization/derealization, while weakened connectivity and activity of the CEN was associated with hyperarousal and hypervigilance(Akiki et al., 2017). Additionally, weakened inter-network connectivity between the SN and DMN has been found to be positively correlated with Clinician Administered PTSD Scale (CAPS) scores that measure PTSD symptom severity (Sripada et al., 2012; Tursich et al., 2015). Moreover, Bluhm et al., (2009) found weakened connectivity in regions that typically comprise the DMN and task activity of the DMN to be correlated with measures of trait dissociation scores in PTSD patients. Thus, Bluhm et al., (2009) described a potential hypothesis that dissociative symptoms in PTSD could be related to alterations in the connectivity between the DMN and other brain regions related to cognition. In sum, the literature on abnormal brain function associated with PTSD points to a pattern of results suggesting that symptoms are related to aberrant connectivity within and between the DMN, SN, and CEN. In a recent review of the neuroimaging literature on PTSD, Lanius et al. (2015) summarized this work to reflect that dysfunction in the DMN is associated with an altered sense of self, dysfunction in the SN is associated with

hyperarousal and hypervigilance, and dysfunction in the CEN is associated with cognitive dysfunction, including memory and cognitive control deficits.

The results from the current meta-analysis provide a robust mPFC-centric model of PTSD that is aligned with the extant literature and compliments the tripartite model of psychopathology. The mPFC, a core region of the DMN (Greicius et al., 2003; Raichle, 2015), is often disrupted in individuals with PTSD (DiGangi et al., 2016; Rabellino et al., 2015). The results of the present meta-analysis suggest alterations in mPFC structure, and related function, may play a crucial role in the underlying neurobiology of PTSD. Dysfunction of the mPFC is thought to be associated with poorer regulation of contextualization of PTSD symptoms. Furthermore, our results are aligned with prior literature indicating weakened integration of the DMN and disrupted inter-network connectivity with the SN and CEN, representing aberrant dysfunction of these tripartite networks in the psychopathology of PTSD (Ross & Cisler, 2020). Most of the prior functional and structural work involved varying analytic approaches, examined heterogeneous populations, and utilized region of interest approaches or *a priori* hypotheses. The current application of advanced meta-analytic techniques allowed for a whole-brain assessment of structural alterations associated with PTSD and the associated functional profiles of the mPFC. Future work in PTSD should consider integrating network-based analytic approaches with an mPFC-centric tripartite model to investigate differences in neuropathology of PTSD subtypes (e.g., trauma experiences, duration of exposures), characterizing heterogeneous presentations of PTSD symptoms, and potential differences in the predispositions of PTSD between adults and youth.

Limitations. Our study is limited by several considerations. First, the present meta-analysis is limited by the small number of studies included. The studies that met the standards of inclusion for this study were considered to reduce instances of variance and consider reliability of study findings (inclusion and exclusion criteria are shown in Fig. 2). By considering the inclusion of trauma-exposed controls, healthy controls, and individuals with PTSD, the number of participants across each group was fairly unevenly distributed due to small sample sizes in the original studies. However, the current meta-analysis met the previously recommended standard of at least 20 experimental contrasts required to conduct a well-powered meta-analysis (Eickhoff et al., 2016). Second, much heterogeneity exists across the studies included in our meta-analysis. For example, many of the studies included diagnostic criteria for PTSD using different clinical measures and reported different instances of duration of PTSD (e.g., lifetime vs. first onset). Substantial variability was also present in the type of trauma and duration of exposure to trauma within the different groups for this study. Given these issues, I was unable to classify PTSD subtypes across the included studies and thus report results that relate to generalized PTSD. Furthermore, current DSM criteria categorizes PTSD as a trauma-related disorder. Future investigation containing current DSM criteria is needed. Many of the original studies were not able to clearly disentangle comorbidity of PTSD with other psychiatric disorders (e.g., depression, anxiety) or report instances of medication and drug abuse. Furthermore, studies relied on various neuroimaging acquisition and analysis methods, which likely introduced additional variability associated with methodological flexibility (Botvinik-Nezer et al., 2020; Carp, 2012). However, the goal of neuroimaging meta-analysis is to examine consensus despite such variability in the literature. With this in mind, I am confident that

the mPFC is a significant brain region linked to GM reductions in PTSD, as well as a robust node of the DMN that plays an important role in toggling between the DMN, SN, and CEN.

CONCLUSIONS

The present study utilized coordinate-based meta-analytic techniques to determine that structurally altered gray matter is consistently found in the mPFC among individuals with PTSD. Complementary analyses of rsFC and MACM functional connectivity provided new insight into how structural alterations of this region may have potential functional consequences. Our results indicated that decreases in mPFC gray matter may be linked to widespread functional systems that are implicated in behavioral deficits and cluster symptomatology of PTSD. Specifically, these consensus-based functional profiles emphasized neural regions associated with the tripartite model of psychiatric disorders where inter- and intra-network connectivity involving the DMN, SN, and CEN are core to PTSD dysfunction. Overall, these results may be important in providing a more comprehensive understanding of the neurobiological bases of PTSD, which is needed to understand the varying diagnosis, symptomatology, and treatment of PTSD, as well as enhanced targeting of treatment towards heterogeneous classification and symptom clusters of PTSD.

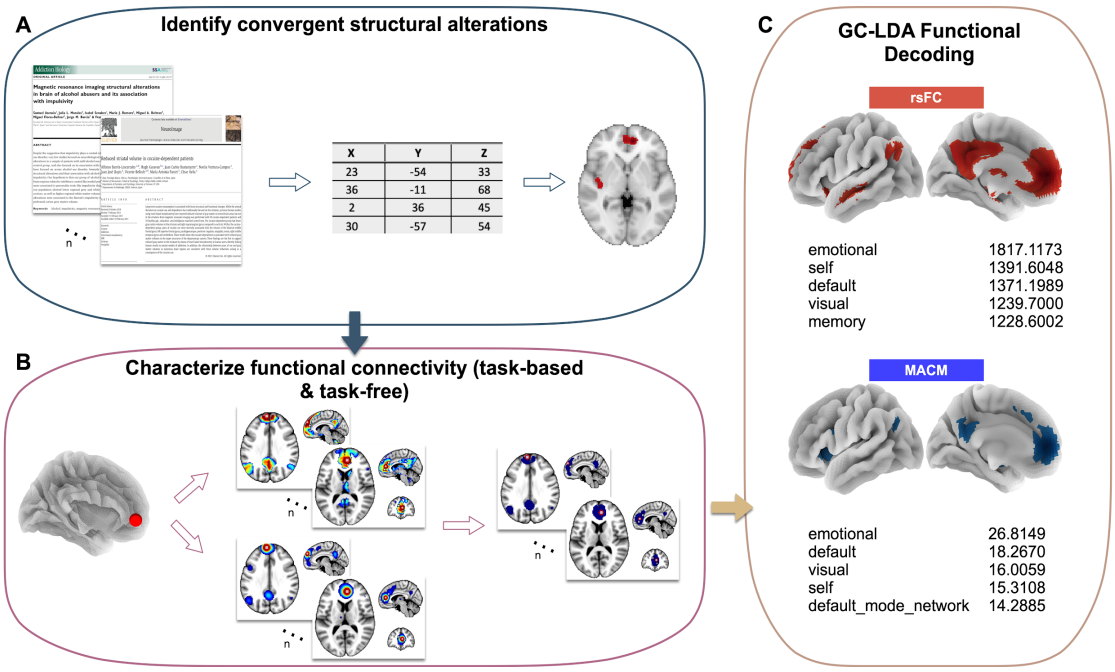


Figure 1. Analysis pipeline overview. We first conducted a literature search to extract structural coordinates and entered them into an ALE algorithm to identify convergent structural alterations in PTSD vs. non-PTSD groups. We next created task-free and task-based functional connectivity profiles of the convergent structural alterations. Last, we performed functional decoding analyses on the task-free and task-based functional profiles to make inferences about which mental functions were associated with our findings.

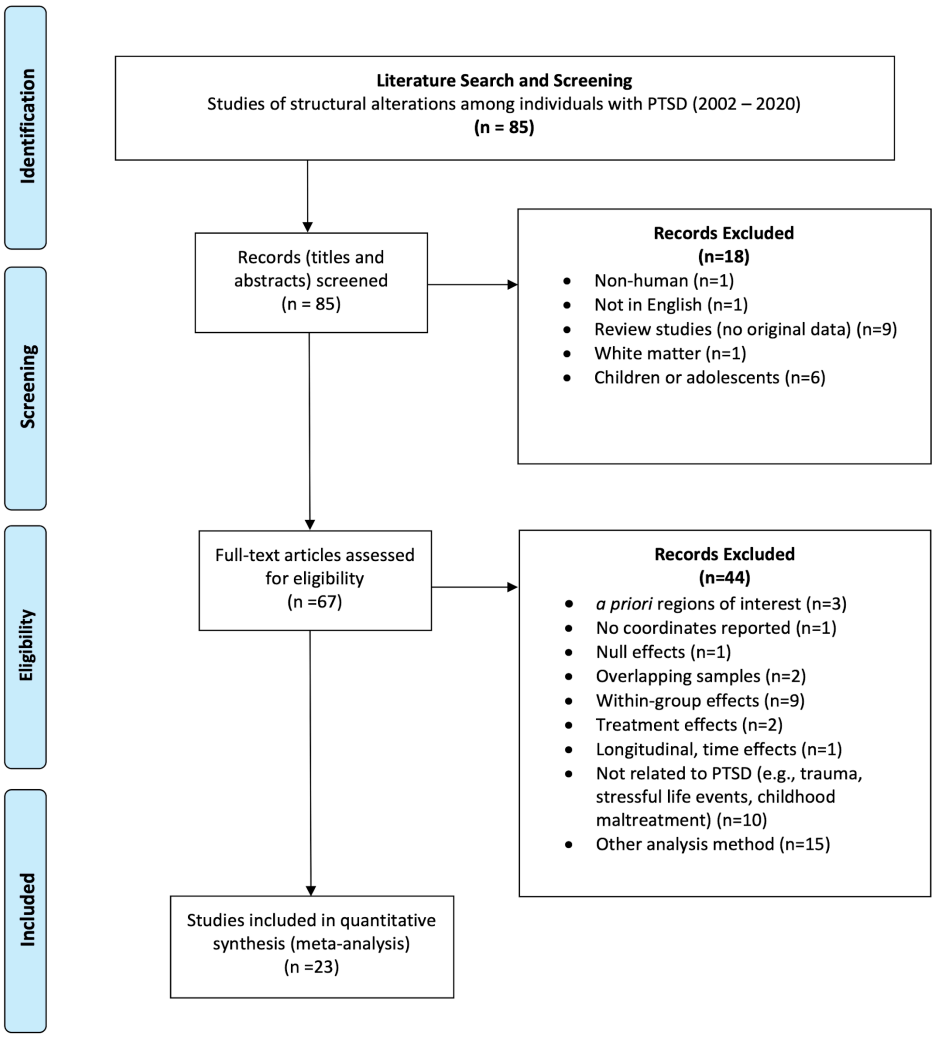


Figure 2. PRISMA diagram. PRISMA flow chart detailing the literature search and selection criteria of studies included in the meta-analysis.

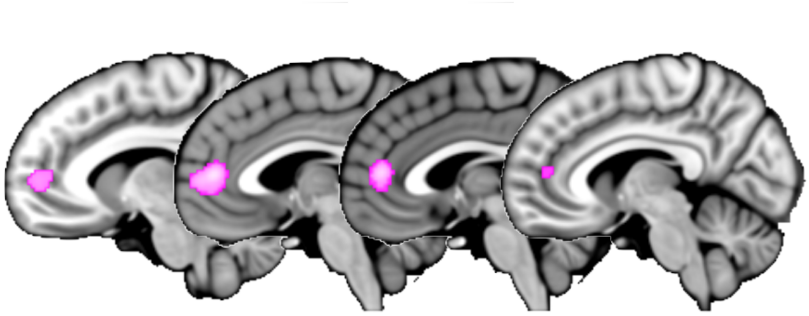
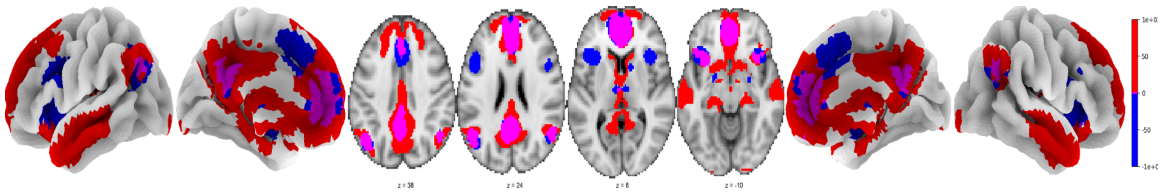


Figure 3. ALE results for non-PTSD > PTSD. Sagittal brain slices illustrating convergent structural alterations associated with PTSD as determined by an ALE meta-analysis of GM reductions (i.e., non-PTSD > PTSD). ALE results indicated convergence in the medial prefrontal cortex ($P < 0.001$, FWE-corrected $P < 0.05$).



<u>Figure 4.</u> Functional connectivity results. rsFC (blue) and MACM (red) results; common areas (pink) indicate consensus between connectivity approaches. Images are thresholded at voxel-wise FWE $P < 0.001$.

Cluster	Volume (mm^3)	Hemisphere	Label	x	y	z
1	7221032	R	Anterior Cingulate, BA32	4	44	10
		L	Inferior Frontal Gyrus, BA47	-30	14	-16
		R	Cingulate Gyrus, BA24	2	-18	36
		L	Anterior Cingulate, BA32	0	36	-6
		R	Posterior Cingulate, BA31	8	-52	24
		L	Cingulate Gyrus, BA31	-8	-54	26
			Midbrain	0	-20	-20
		R	Anterior Cingulate, BA24	4	28	16
		R	Inferior Frontal Gyrus, BA47	30	16	-16
		L	Precuneus, BA7	0	-70	34
		L	Caudate, Caudate Head	-4	12	-2
		R	Angular Gyrus, BA39	52	-64	36
		L	Inferior Parietal Lobule, BA39	-50	-64	40
		L	Posterior Cingulate, BA30	-6	-54	10
		L	Parahippocampal Gyrus, BA35	-22	-22	-14
		L	Superior Frontal Gyrus, BA8	-22	34	46
		L	Cingulate Gyrus, BA31	-4	-32	38
		R	Caudate, Caudate Head	10	18	-4
		L	Superior Frontal Gyrus, BA9	-20	48	34
		R	Cerebellar Tonsil	6	-50	-36

Table 1. Resting-state functional connectivity results. Coordinate locations of the rsFC results, including the volume, hemisphere, anatomical label, and MNI coordinates of local maxima. Negative x values indicate left hemisphere and positive x values indicate right hemisphere.

Cluster	Volume (mm^3)	Hemisphere	Label	x	y	z
1	47280	L	Medial Frontal Gyrus, BA10	-2	50	6
		L	Superior Frontal Gyrus, BA6	0	14	48
		R	Medial Frontal Gyrus, BA8	2	26	38
2	15112	L	Posterior Cingulate, BA31	-4	-54	26
3	10192	L	Extra-Nuclear, BA47	-34	20	-2
4	6984	R	Extra-Nuclear, BA47	36	22	-2
5	6616	L	Angular Gyrus, BA39	-46	-68	30
		L	Superior Parietal Lobule, BA7	-30	-62	46
6	3936	L	Inferior Frontal Gyrus, BA9	-46	10	28
7	3784	R	Superior Temporal Gyrus, BA39	52	-60	26
		R	Inferior Parietal Lobule, BA40	40	-52	44
8	1784	L	Parahippocampal Gyrus, Amygdala	-22	-8	-16
9	1592	R	Parahippocampal Gyrus, Amygdala	24	-6	-16
10	1392	R	Inferior Frontal Gyrus, BA9	46	10	28
11	696	R	Caudate, Caudate Head	12	10	2
12	424	L	Lentiform Nucleus	-12	8	-2
13	296	L	Thalamus, Medial Dorsal Nucleus	-6	-14	6
14	248	R	Thalamus, Medial Dorsal Nucleus	6	-14	6
15	32	L	Inferior Parietal Lobule, BA40	-42	-44	44
16	16	L	Inferior Temporal Gyrus, BA21	-56	-10	-16

Table 2: Meta-analytic co-activation results. Coordinate locations of the MACM results, including the volume, hemisphere, anatomical label, and MNI coordinates of local maxima. Negative x values indicate left hemisphere and positive x values indicate right hemisphere.

Cluster	Volume (mm^3)	Hemisphere	Label	x	y	z
1	35392	L	Medial Frontal Gyrus, BA10	-2	50	6
		R	Medial Frontal Gyrus, BA8	2	26	38
2	14832	L	Posterior Cingulate, BA31	-4	-54	26
3	5240	L	Angular Gyrus, BA39	-46	-68	30
4	2864	R	Superior Temporal Gyrus, BA39	52	-60	26
5	1936	L	Inferior Frontal Gyrus, BA47	-32	18	-6
6	688	R	Inferior Frontal Gyrus, BA47	38	20	-8
7	320	L	Parahippocampal Gyrus, BA28	-24	-16	-18
8	96	L	Lentiform Nucleus, Putamen	-12	10	-4
9		R	Caudate, Caudate Head	10	10	-2
10		L	Thalamus, Medial Dorsal Nucleus	-4	-14	6
11	32	R	Thalamus, Medial Dorsal Nucleus	6	-14	8
12	16	L	Parahippocampal Gyrus, BA34	-20	2	-12
13	8	R	Parahippocampal Gyrus, Hippocampus	26	-14	-20
14		R	Parahippocampal Gyrus, Hippocampus	26	-16	-16
15		L	Inferior Temporal Gyrus, BA21	-56	-10	-16
16		L	Parahippocampal Gyrus, BA28	-16	-4	-14

Table 3: Consensus functional connectivity between functional assessments. Coordinate locations of the consensus between rsFC and MACM results, including the volume, hemisphere, anatomical label, and MNI coordinates of local maxima. Negative x values indicate left hemisphere and positive x values indicate right hemisphere.

(a) ALE Meta-analysis			(b) Resting State Functional Connectivity (rsFC)			(c) Meta-Analytic Co-Activation Modeling (MACM)		
Term Rank	**Term**	**Weight**	**Term Rank**	**Term**	**Weight**	**Term Rank**	**Term**	**Weight**
1	visual	1.886	1	default	11.234	1	visual	5900.643
2	emotional	0.919	2	default mode network	9.225	2	motor	3839.578
3	memory	0.845	3	intrinsic	7.494	3	emotional	3665.765
4	novel	0.616	4	scale	6.236	4	memory	3476.688
5	reward	0.576	5	self	5.081	5	attention	2931.357
6	motor	0.521	6	person	4.977	6	auditory	2267.840
7	self	0.509	7	reward	4.780	7	reward	2107.441
8	faces	0.472	8	bias	4.568	8	spatial	2072.742
9	learning	0.467	9	judgements	4.279	9	schizophrenia	2070.157
10	face	0.450	10	contexts	4.271	10	language	2057.731

Table 4: Functional decoding results. Functional decoding results for (a) ALE structural meta-analysis, (b) rsFC, and (c) MACM results as described by Neurosynth terms. Rankings display weighted terms listed from highest (1) to lowest (10).

Author	Year	N Patient Group (M/F)	Patient Group Age (SD)	Type of trauma	N Non-Patient Group (M/F)	Non-Patient Group Mean (SD)	N Non-Diagnosed Trauma Exposed (M/F)	Non-diagnosed Mean Age	Contrast
Bossni	2017	19 (10/9)	40(9)	Multiple traumas	19 (15/4)	41(6)	x	x	HC > PTSD PTSD > HC
Cheng	2015	30 (21/9)	26.3(8.1)	Earthquake	30 (21/9)	26.2 (6.6)	x	x	HC > PTSD
Chen	2009	12 (4/8)	34.56(4.91)	Fire disaster			12 (4/8)	33.25 (5.27)	Trauma Exposed > PTSD
O'Dohetry	2017	25 (12/13)	34(8.4)	Multiple traumas	25 (12/13)	31.7(6.0)	25 (12/13)	36.4(8.1)	HCs > PTSD Trauma exposed > PTSD
Rocha-Rego	2012	16 (7/9)	43.3(5.78)	Multiple traumas	x	x	16 (7/9)	44.9 (6.60)	Trauma exposed > PTSD
Chao	2012	21 (21/0)	35.9(11.2)	Combat; military incident	x	x	20 (20/0)	35.2(13.1)	Trauma exposed > PTSD

Chen	2012	10 (10/0)	40.8(6.8)	Coal mine flood	20 (20/0)	37.6(7.0)	10 (10/0)	34.3(5.6)	HC > PTSD
Corbo	2005	14 (6/8)	33.36(12.06)	Motor incidents	14 (6/8)	33.29(12.31)	x	x	HC > PTSD
Eckhart	2011	20 (20/0)	36.2(7.7)	Refugee	13 (13/0)	29(7.2)	19 (19/0)	34.1(9.9)	HC > PTSD
Hakamata	2007	14 (0/14)	45.6(6.2)	Breast cancer	70 (0/70)	46.0(6.9)	100 (0/100)	47.1(5.7)	Trauma exposed > PTSD HC > PTSD
Herringa	2012	13 (11/2)	28.9(4.2)	Combat	x	x	15 (14/1)	30.1(6.3)	Trauma Exposed > PTSD
Kasi* Mention twin study in description	2008	PTSD pairs: 18 (18/0) Unexposed with PTSD pairs: 18 (18/0)	PTSD pairs: 52.8(3.4) Unexposed with PTSD pairs: 52.8(3.4)	Combat	x	x	Exposed no PTSD pairs: 23 (23/0) Unexposed no PTSD pairs: 23 (23/0)	Exposed no PTSD pairs: 51.8(2.3) Unexposed no PTSD pairs: 51.8(2.3)	Twins w/ PTSD > Trauma exposed twins
Li	2006	12(4/8)	34.56(4.91)	Fire disaster	x	x	12(4/8)	33.25(5.27)	Trauma Exposed > PTSD
Nardo	2010	21 (15/6)	41.7(9.1)	Person under train	x	x	22(16/6)	40.8(8.9)	Trauma exposed > PTSD

Sui	2010	11 (0/11)	25.55(4.01)	Assaulted at work Rape	12 (0/12)	26.42(3.45)	8 (0/8)	27.5(4.0)	HC > PTSD PTSD > HC Trauma exposed > PTSD PTSD > Trauma exposed
Tavanti	2012	25 (8/17)	38.16(10.90)	Multiple traumas	25 (8/17)	38.08(11.01)	x	x	HC > PTSD
Yamasue	2003	9 (5/4)	44.6(16)	Subway attack	x	x	16 (10/6)	44.4(14)	Trauma exposed > PTSD
Zhang	2011	10 (no gender info found)	40.8(6.83)	Coal mine disaster	x	x	10 (no gender info found)	34.30(5.37)	Trauma Exposed > PTSD
Flemingham	2009	21(no gender info found)	x	Motor vehicle accidents	x	x	17 (no gender info found)	x	Trauma Exposed > PTSD
Zhang	2018	35 (14/21)	50.86(6.62)	Assault Earthquake	x	x	36 (19/17)	48.22(6.75)	PTSD > Trauma exposed

Kroes	2011	24 (9/15)	35.9	Multiple traumas	x	x	Depression: 29 (8/21) Trauma Exposed: (9/16)	Depression: 33.4 Trauma Exposed: 32.45	Trauma exposed > PTSD Trauma exposed > PTSD + Depression
Niedtfield	2013	BPD and PTSD: 21 (0/21)	x	Physical or sexual abuse	60 (0/60)	28.5(7.49)	BPD Patients without PTSD: 32 (0/32)	x	BPD + PTSD > BPD - PTSD
Qi	2020	57 (17/40)	57.7(5.48)	Multiple traumas	x	x	163 (91/72)	58.87(5.53)	Trauma exposed > PTSD

Table S1. Demographic data of studies included in the PTSD meta-analysis.

* =Twin study
x = No data reported
Multiple traumas= Indicates studies containing more than two types of trauma

CHAPTER 3

IDENTIFYING CONVERGENT DEVELOPMENTAL DIFFERENCES ASSOCIATED WITH ANXIETY-RELATED DISORDERS: A VOXEL-BASED MORPHOMETRY META-ANALYSIS

ABSTRACT

Anxiety-related disorders are pervasive mental health disorders. However, inconsistencies exist across the voxel-based morphometry (VBM) literature investigating convergent structural alterations among adults, adolescents, and youth with clinical anxiety utilizing DSM diagnostic criteria. Here, I present a series of meta-analyses of 93 studies (70 containing adults with clinical anxiety; 23 containing youth with clinical anxiety) utilizing the anatomical likelihood estimation (ALE) approach to examine the convergent structural alterations among adults and youth with clinical anxiety. I observed convergent decreased gray matter (GM) alterations located in the left anterior cingulate cortex (ACC) and inferior frontal gyrus (IFG) among adults with clinical anxiety. I also observed convergent decreased GM in the left dorsolateral prefrontal cortex among youth with clinical anxiety. A contrast analysis confirmed statistically significant differences in the convergent structural brain correlates between adults and youth with clinical anxiety. The current results provide a consensus of the convergent structural alterations between adults and youth with clinical anxiety. The differences in brain structure associated with clinical anxiety between adults and youth has important implications for the structural brain correlates associated with clinical anxiety.

INTRODUCTION

According to the National Institute of Mental Health (NIMH), the defining characteristics of any anxiety disorder include excessive, chronic fear or worry that interferes with everyday life (NIMH, 2018). All anxiety-related conditions share similar symptoms of excessive worry, avoidance, and hyperarousal that affect the quality of life and worsen over time (Friedman et al., 2011). Anxiety-related disorders continue to remain one of the most pervasive mental-health-related disorders among adults and adolescents (Bandelow & Michaelis, 2015; Michael et al., 2007). Approximately 31.9% of youth between the ages of 13 through 18 will experience any anxiety disorder in their lifetime (NIMH, 2017). A similar percentage is among adults, where an estimated 31.9% of adults over the age of 18 will experience any anxiety-related disorder. Significant comorbidity exists between anxiety and depression among adults (Byers et al., 2010). Comorbidity rates between anxiety and depression are significantly higher among youth (Costello et al., 2003; Cummings et al., 2014; Garber & Weersing, 2010), and associated with an increased likelihood for functional impairment across social and cognitive domains (Kendall et al., 2010), suicidal risk (Norton et al., 2008), and development of other mental-health-related psychopathology (Freeman et al., 2002; Lopez et al., 2005). One standard diagnostic criteria for anxiety-related disorders is the DSM (Diagnostic and Statistical Manual of Mental Disorders) (Regier et al., 2013).

Previous structural neuroimaging studies showed GM alterations associated with post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) when these psychopathologies were considered anxiety-related disorders based on previous DSM criteria. Fewer studies examined the nuance between the GM alterations associated

with current versions of DSM criteria associated with anxiety-related disorders (e.g., social anxiety disorder [SAD], generalized anxiety disorder [GAD], panic disorder [PD], and agoraphobia). More recent meta-analytic work has attempted to address if distinct or dissimilar neural substrates exist across anxiety-related disorders (Cheng et al., 2015; Radua et al., 2010; Shang et al., 2014; Wang et al., 2021). Reports of gray matter volume (GMV) alterations associated with anxiety-related disorders in frontal, medial frontal, and cortical-limbic structures; however, a consensus of GM alterations varies across meta-analytic studies based on previous DSM criteria. Moreover, across prior meta-analytic results, included studies contain outdated DSM criteria and inconsistent reporting of the precise localization of GM alterations across frontal, medial frontal, and cortico-limbic structures. Thus, it remains unclear if anxiety-related disorders are distinct disorders associated with specific neural substrates or, instead, varying presentations associated with shared neuropathology (Goodkind et al., 2015).

Evidence of neuroanatomical correlates of clinical anxiety in childhood and adolescence. Anxiety-related disorders are common psychopathology affecting children and adolescents (Costello et al., 2003; Merikangas et al., 2010). The period between childhood and adolescence is a vulnerable time associated with significant brain structure and function alterations (Sharma et al., 2013; Uddin et al., 2011). This sensitive time increases the vulnerability of the development of secondary psychiatric psychopathology. Integration of stress models into examining the trajectory of cortical development showed a relation between environmental factors associated with the cortical development of psychopathology among youth and adolescents (Eiland & Romeo, 2013; Lupien et al., 2009). Increased GMV in cortico-striatal circuitry associated with pediatric OCD is

somewhat consistent with findings from the adult literature (Gonçalves et al., 2017; Pujol et al., 2004). However, meta-analytic work examining the widespread structural alterations utilizing whole-brain VBM approaches across the different pediatric anxiety-related disorders based on DSM diagnostic criteria is limited (Gold et al., 2016; Mueller et al., 2013; Strawn et al., 2015). Some meta-analytic work among youth populations across multiple anxiety disorders (GAD, social/specific phobias, and separation anxiety disorder) revealed increased GMV in the dorsal anterior cingulate cortex (dACC), the IFG, vlPFC, cuneus, and precuneus (Strawn et al., 2015). Similar problems from the literature on clinically anxious adults exist across literature about clinically anxious youth. In particular, variability across the prior meta-analytic work reveals inconsistent reporting of structural alterations across the whole brain and more broadly limited work on this topic. Limited sample sizes and strict inclusion criteria across the prior meta-analytic work pose a problem for low statistical power. Due to this, the generalizability of previous findings is limited and does not account for the effects of comorbidity or other sociocultural factors associated with pediatric anxiety. Thus, a consensus of the structural alterations associated with pediatric anxiety is unclear. Furthermore, if pediatric anxiety is associated with distinct or similar neurobiological substrates remains to be elucidated.

The relation between vulnerability to psychopathology and cortical development. The brain undergoes significant changes from childhood to adolescence, where brain development and function happen in a non-linear process (Giedd et al., 1999; Gogtay et al., 2004). Adolescence represents a period of dramatic neuroplasticity, meaning rapid developmental changes in brain structure, circuitry, function, and cognitive, behavioral, and psychosocial domains (Spear, 2000). The frontal lobe, parietal lobe,

temporal lobe, brain stem, cerebellum, and occipital lobe mature linearly during adolescence. In contrast, the PFC develops over time in a non-linear pattern from adolescence to adulthood (Sharma et al., 2013). Research on cortical development from childhood to adolescence showed the trajectory of white matter as a linear pattern of growth while the trajectory of cortical gray matter (including subcortical regions) an inverse "U" pattern (Blakemore & Choudhury, 2006; Giedd, 2004). The inverse "U" shape was associated with the rapid growth of overall GMV of the frontal, parietal, and temporal lobes in childhood and a steady decline of GMV of these regions into adolescence (Mills et al., 2016). Increased experience-dependent neuroplasticity, including rapid synaptic and myelination in the process of non-linear growth of cortical gray matter (Paus, 2005; Sharma et al., 2013), is thought to be associated with higher-order cognitive functions such as emotion regulation, executive functioning, and socio-environmental processing (MacMaster et al., 2016; Tamnes et al., 2017). Investigations of the interaction between sociocultural, environmental, and genetic factors on the trajectory of cortical development (Hartley & Lee, 2015; Sharma et al., 2013) found deviations from "typical" development patterns associated with psychopathology (Gogtay & Thompson, 2010; Meyer & Lee, 2019). Though adolescence is a period of rapid neurobiological changes, it is a period of vulnerability to psychopathology (Paus et al., 2008) associated with specific cortical deviations from "typical" development.

Anxiety has an early onset (Kessler et al., 2005) and is associated with neuropathology early in life. Abnormalities in structure and function specific to prefrontal and limbic structures exist among youth with clinical anxiety. On the other hand, prefrontal, parietal and cortico-limbic abnormalities exist among adults with clinical

anxiety. Investigating structural alterations among youth and how they differ from adults could provide knowledge of the brain-based cortical- deviations associated with clinical anxiety (Hirshfeld-Becker et al., 2008).

Rationale for the Present Research

Consensus regarding the structural alterations among adults and youth with clinical anxiety based on DSM criteria remains to be elucidated. In the present study, I sought to investigate: 1) what are the common structural alterations across multiple anxiety-related disorders defined by DSM criteria among adults; 2) what are the common structural alterations across multiple anxiety-related disorders among children and adolescents, and 3) if these structural alterations differ between adult and youth groups. I first used the anatomical likelihood estimation (ALE) technique to examine the convergent structural alterations associated with clinical anxiety and brain structure among adults and youth, respectively. I also utilized the ALE approach to conduct a contrast analysis to explore potential convergent or differential structural alterations between adults and youth with clinical anxiety. I hypothesized the most profound GM structural alterations among adults would be observed in prefrontal and frontal-cortical-striatal (e.g., striatum, inferior frontal gyrus, anterior cingulate cortex, and hippocampus) regions. I hypothesized that GM alterations among children and adolescents would be observed in the anterior cingulate cortex, vlPFC, mPFC, and amygdala. I hypothesized that developmental effects between adults and youth would be most profound in prefrontal, temporal, and parietal regions. These regions grow faster earlier in the developmental stages of cortical development and could be anxiety-related vulnerable regions associated with cortical development.

METHODS

Literature Search and Study Criteria. I conducted a comprehensive literature search to build a database of peer-reviewed MRI studies reporting structural alterations associated with any DSM-related anxiety diagnostic criteria related disorder among adults and youth from 2002-2020. In the first round of identifying studies to compile a list of included studies, I examined previously published voxel-based morphometry (VBM) meta-analysis papers on any anxiety-related disorder diagnosis with adult or youth samples. Next, I performed a *PubMed* search to identify additional peer-reviewed, structural MRI studies of interest using the search terms "morphometry + anxiety", "children + morphometry + anxiety", "adolescents + morphometry + anxiety". I utilized the same search terms to examine *Google Scholar* and *Web of Science* databases for any potential additional studies. Due to the small number of VBM studies reporting structural alterations among youth with clinical anxiety based on DSM criteria, I used the above search terms to identify and include studies on youth containing clinical anxiety measures. The *PubMed* search identified any potential studies that were not included in the previously published meta-analyses. I then conducted a review of each identified publication to include the following study criteria: peer-reviewed MRI studies utilizing clinical anxiety or DSM anxiety-related diagnosis criteria, reporting results among adult and youth humans, written in the English language, focused on whole brain grey matter structural differences, and included original data (i.e., not a review). Subsequently, exclusion criteria were as follows: trauma or stressful life event studies unrelated to clinical anxiety, other non-voxel-based morphometry methods, post-treatment contrasts, longitudinal effects, papers reporting *a priori* regions of interest (ROIs), subclinical samples, within-group effects, null effects,

subclinical samples, overlapping samples to previous studies, and studies that did not report coordinate-based results.

Anatomical Likelihood Estimation (ALE). ALE is a voxel-based meta-analytic technique that identifies convergent coordinates (i.e., foci) across a set of neuroimaging studies. Foci are treated as 3D Gaussian distributions to address variability within and between studies. I used the coordinate-based anatomical likelihood estimation (ALE) method as implemented in NiMARE v.0.0.3 (*Neuroimaging Meta-Analysis Research Environment;* http://nimare.readthedocs.io), a Python library for neuroimaging meta-analysis. Reported coordinates in this meta-analysis were extracted from their original publication and transformed from Talairach to MNI space (Laird et al., 2010; Lancaster et al., 2007). Once transformed, statistical probability maps were created for each foci and combined to model the likelihood that a given voxel displayed a between-group structural difference for each study. Observed voxel-wise ALE scores characterized the most consistently reported foci across the whole brain. Significance testing and correction for multiple comparisons involved thresholding the voxel-wise ALE map using a cluster-forming threshold of $P < 0.001$. Then, a permutation procedure was performed in which a null distribution of maximum cluster sizes was generated from 10,000 iterations of replacing reported foci with randomly selected gray matter voxels, generating ALE maps from the pseudo-ALE maps, and identifying the maximum cluster size after thresholding at $P < 0.001$. The cluster-level FWE correction threshold was set at $P < 0.05$, meaning only those clusters from the original, thresholded ALE map were retained if their size was greater than the cluster size corresponding to the 95th-percentile from the null distribution.

I applied the above ALE procedure to explore differences in convergent structural alterations between a pooled anxiety group (adults and youth with clinical anxiety) and pooled controls (adult and youth controls). I next meta-analyzed all decreased GM contrasts among adults with clinical anxiety compared to adult controls. I also meta-analyzed all increased GM contrasts among adults with clinical anxiety compared to adult controls. I then separately meta-analyzed all decreased GM contrasts and increased GM contrasts among youth with clinical anxiety compared to youth controls. I used the GingerALE function with ALE subtraction procedures (Eickhoff et al., 2011) to explore statistical differences in GM structural alterations between development groups. The first contrast analysis explored statistically different brain areas of decreased GM between adults and youth groups with clinical anxiety. The second contrast analysis explored statistically different brain regions of increased GM between adults and youth groups with clinical anxiety.

RESULTS

Literature Search and Study Criteria. The literature search yielded a total of 479 articles from *PubMed* using the above-described search terms. Figure 1 provides a PRISMA diagram, which details the review and filtering of the 479 studies included. In the first round of review, records (i.e., titles and abstracts), 258 studies met exclusion criteria of non-clinical anxiety studies, reviews, mega-analysis studies, meta-analysis studies, functional studies, and studies reporting white matter differences among the adult and youth samples of interest for the current study. Then, I examined the full-text articles to

assess additional study criteria; 128 additional studies were not eligible for the present meta-analysis (see Figure 1).

The final set of included studies consisted of 93 publications. Of the 93 publications, 70 studies contained adult-only samples, and 23 studies had youth (i.e., children and adolescent) only samples. These publications assessed gray matter structural alterations by comparing whole-brain VBM results among adults with any anxiety-related disorder and non-diagnosed adult controls, reported as 3D coordinates in MNI or Talairach space. The same criteria applied to studies containing youth with clinical anxiety and non-diagnosed youth. One control group included adults without an anxiety-related disorder based on DSM criteria. The other control group had youth without clinical anxiety based on DSM criteria or did not meet clinical anxiety measure criteria. Altogether, 70 studies collectively examined 1,878 adults with anxiety and 2,370 adults without anxiety. Twenty-three studies collectively examined 508 adolescents and youth with anxiety and 555 adolescents and youth without anxiety. Concerning the type of structural alterations observed, studies reported multiple, different VBM metrics. Seventy-five publications reported group differences in gray matter volume (GMV), nine publications reported differences in gray matter density (GMD), one publication reported gray matter concentration (GMC), eight studies reported GM but did not specify the metric. Collectively, I refer to all of these metrics as gray matter (GM) differences among individuals with and without any anxiety. Supplementary Table S2 provides additional details on the demography of developmental groups and the study design of the current study.

Anatomical Likelihood Estimation. The current meta-analytic work contains a series of ALE meta-analyses to assess convergence among adults and non-adult populations using NiMARE v.0.0.3. I examined the main effect of anxiety by meta-analyzing 84 contrasts of GM decreases (i.e., pooled controls > pooled anxiety groups) and 48 contrasts of GM increases (i.e., pooled anxiety groups > pooled controls) separately. For GM decreases, I observed a main effect of convergence located in the left anterior cingulate (x=0, y=46, z=8) (Figure 2; $P < 0.001$, FWE-corrected $P < 0.05$) in the pooled anxious group compared to the pooled controls. The meta-analyzed contrasts of GM increases among the pooled clinically anxious group compared to pooled controls produced null results. Ten studies contributed to these foci (Chen et al., 2009; Felmingham et al., 2009; Hou et al., 2013; Kasai et al., 2008; Kroes, 2011; Li et al., 2006; O'Doherty et al., 2017; Qi et al., 2020) where nine studies compared individuals with PTSD vs. traumatized or non-traumatized controls and one study compared individuals with OCD vs. controls. Additional information on the included studies is in Supplementary Table S2.

Adults with clinical anxiety. I examined the convergent structural alterations among adults with clinical anxiety by meta-analyzing 67 contrasts of GM reductions among adults with clinical anxiety (i.e., non-diagnosed adult controls > adults with clinical anxiety) and 24 contrasts of GM increases (i.e., adults with clinical anxiety > non-diagnosed adult controls) separately. For GM decreases among adults with clinical anxiety, I observed two clusters of convergence located in the left anterior cingulate cortex (ACC) (x=0, y=46, z=8) and left inferior frontal gyrus (IFG) (x=-36, y=24, z=-18) (Figure 3A; $P < 0.001$, FWE-corrected $P < 0.05$) among adults with clinical anxiety compared to adult controls. The meta-analyzed contrasts of GM increases among adults with clinical anxiety

produced null results. Ten studies contributed foci to the left ACC cluster (Chen et al., 2009; Felmingham et al., 2009; Hou et al., 2013; Kasai et al., 2008; Kopřivová et al., 2009; Kroes, 2011; Li et al., 2006; O'Doherty et al., 2017; Qi et al., 2020; Rocha-Rego et al., 2012). Nine studies examined GM alterations between individuals diagnosed with PTSD vs. controls or trauma-exposed controls, and two studies examined GM alterations between individuals diagnosed with OCD vs. controls. Five studies contributed foci to the left IFG cluster. Three studies examined GM alterations associated with PTSD diagnosis vs. trauma-exposed or non-traumatized controls, one study examining GM alterations associated with GAD diagnosis, and one study examined GM alterations associated with an OCD diagnosis. Additional information on the included studies is in Supplementary Table S2.

Youth with clinical anxiety. The youth population consisted of individuals below the age of eighteen. I examined convergent structural alterations among youth with clinical anxiety by meta-analyzing seventeen contrasts of GM reductions among youth with clinical anxiety (i.e., non-diagnosed youth > youth with clinical anxiety) and fourteen contrasts of GM increases separately (i.e., youth with clinical anxiety > non-diagnosed youth). With respect to GM decreases, I observed a single cluster of convergence located in the left dorsolateral prefrontal cortex (dlPFC) (x=-44, y=22, z=20) (Figure 3B; $P < 0.001$, FWE-corrected $P < 0.05$) among youth with clinical anxiety compared to youth controls. The meta-analyzed contrasts of GM increases produced null results. Four studies contributed foci to the left dlPFC cluster (Carmona et al., 2007; J. Chen et al., 2013; De Brito et al., 2013; Milham et al., 2005). Two studies compared youth with OCD diagnosis to controls, one study compared youth with varying anxiety-related disorder diagnoses based on DSM

criteria vs. controls, and one study compared maltreated non-adults (containing a clinical anxiety measure) vs. controls. Additional information on the individual studies included in the current meta-analysis is in Supplementary Table S2.

Development Group Effects. I conducted two contrast analyses to test if the convergent structural alterations between adults and youth with clinical anxiety differed statistically. The contrast ALE analysis examining GM decreases contrasts between developmental groups (i.e., GM increases adults with clinical anxiety > GM increases youth with clinical anxiety) revealed significant GM reductions in the left medial frontal gyrus including the left ACC among adults compared to non-adults (Figure 3C; $P < 0.001$, FWE-corrected $P < 0.05$). An additional contrast examining GM reductions among youth compared to adults did not reach significance. The contrast ALE analysis examining GM increases between adults and youth did not reach significance.

DISCUSSION

Convergent Structural Alterations Associated with Anxiety. I integrated 93 VBM studies to examine the main effect for the convergent structural alterations associated with clinical anxiety compared to non-diagnosed controls. The inclusion of structural MRI studies allowed for paradigm-free, coordinate-based comparisons of convergent structural alterations between a diverse grouping of anxiety-related disorders based on DSM criteria. I found one significant cluster of decreased GM in the left ACC among the pooled anxious group compared to the pooled controls. Meta-analyzed contrasts of GM increases produced null results. Eight studies compared individuals diagnosed with PTSD to non-traumatized controls or healthy controls, and one study examined individuals with OCD vs. controls.

Shared decreased GM in the left ACC across a diverse grouping of anxiety-related disorders could support the various presentations of multiple anxiety-related disorders with shared neural mechanisms in the pathogenesis of clinical anxiety (Goodkind et al., 2015).

One core symptom in any anxiety-related disorder diagnosis is chronic, crippling fear and worry that interferes with everyday life. Individuals with anxiety disorders tend to bias attention towards threat (Bar-Haim et al., 2007) and have greater emotional reactivity to negative input (Cisler et al., 2010). Previous fMRI studies differentiate subdivisions of the ACC associated with fear and threat-related circuitry (Shin & Liberzon, 2010) and behavioral processes such as emotion regulation, threat detection, and environment evaluation. The disrupted PFC-amygdala and ACC functional connectivity are associated with diminished capacities to regulate negative emotions and more distracted by negative stimuli (Goldin et al., 2009). Previous studies suggest disrupted engagement associated with emotion regulation and threat detection processes in GAD (Etkin et al., 2010) and SAD (Klumpp et al., 2012) diagnoses. Our results partially support previous literature of the ACC being a key node in the neurobiology of clinical anxiety. The current results show the left ACC as the most robust finding of structural alterations associated with the neurobiology of clinical anxiety based on DSM criteria. The GM reductions in this region show the most profound disturbances across a diverse grouping of anxiety-related disorders where these effects seem to be left-lateralized. The diminished structure could be associated with poor recruitment of this region, possibly correlating with deficits in emotion regulation and maintenance of chronic worry and fear interfering with everyday life function.

Meta-analytic evidence using older DSM criteria found reduced GM in the left ACC associated with posttraumatic stress disorder (PTSD) (Meng et al., 2014) though this finding is not consistent across individual VBM studies (Corbo et al., 2005; Thomaes et al., 2010). Furthermore, decreased GMV in the left ACC is associated with OCD (Nakaaki et al., 2014). More recently, decreased GMV of the right ACC is associated with SAD, GAD, PD, and specific phobia anxiety diagnosis (Shang et al., 2014). The mixed findings of decreased GM in the ACC, including laterality of these effects between the current and previous, work might be explained by the varying methodological methods (ALE vs. effect-size seed-based mapping). Also, heterogeneity in inclusion criteria, such as the low number of included studies across anxiety-related disorder groups based on current DSM criteria, inadequate sample sizes, and confounding factors like controlling for comorbid depression, medication use, or other mental-health related disorders could contribute to the differences between the current findings and previous findings.

Convergent Structural Alterations in Prefrontal Circuitry Among Adults with Clinical Anxiety. Seventy studies met inclusion criteria for the series of meta-analyses among adults with clinical anxiety. I meta-analyzed 67 contrasts of decreased GM and 24 contrasts of increased GM separately. I found two clusters of decreased GM in the left ACC and the left IFG in anxious adults vs. non-diagnosed adult controls. The meta-analyzed GM increases produced null results.

As mentioned above, the ACC is a crucial node associated with the neurobiology of clinical anxiety based on DSM criteria. Previous meta-analytic work showed decreased GMV in frontal, dorsomedial, and the anterior cingulate shared across OCD, PD, and PTSD

(Radua et al., 2010). However, Radua and colleagues found increased bilateral GMV in the caudate nucleus associated with OCD while PD and PTSD diagnosis had reduced GMV in the left lenticular nucleus. Other meta-analytic evidence showed reduced GMV associated with SAD, GAD, PD, and agoraphobia in the right ventral ACC and left IFG independent of comorbid depression (Shang et al., 2014).

Inconsistencies in laterality (right or left-centric) exist across the previous meta-analytic findings of the ACC structural alterations associated with adults with clinical anxiety. For example, decreased GMV reductions in the ventral ACC and left anterior cingulate are associated with GAD (Kolesar et al., 2019); however, decreased GMV in the right ACC is associated with PD, SAD, and GAD (Shang et al., 2014). This evidence collectively provides consideration of differences in the lateralization of structural brain correlates among adults with clinical anxiety. Thus, the current results show the structural alterations of the left ACC being the most robust region among adults with clinical anxiety. However, the specific subdivisions in the neuroanatomy of the ACC require further investigation.

Prior meta-analytic revealed structural GMV differences associated with PTSD, OCD, and SAD diagnoses in the left hypothalamus and left IFG compared to healthy controls (Cheng et al., 2015). Cheng and colleagues also found more profound structural GMV reductions in the frontal lobe, temporal lobe, and cerebellum in the PTSD group compared to OCD and SAD groups. They found no significant differences in GMV between SAD and OCD groups. The authors speculated after conducting posthoc analyses the significant differences between PTSD and all other patient groups significantly contributed to their main effect across all anxiety groups. Meta-analytic work comparing

SAD and PD diagnosis found reduced GMV in the right inferior frontal gyrus (IFG) specific to PD and reductions of GMV in the left striatum and thalamus specific to SAD (Wang et al., 2021). The current study's decreased GM in the left IFG aligns with previous meta-analytic findings of multiple anxiety-related disorders (Shang et al., 2014). The present results suggest the IFG as another robust region of structural alterations associated with clinical anxiety though inconsistencies in laterality and reports of decreased GM exist across the meta-analytic literature for this region (Picado et al., 2015, 2015; Picó-Pérez et al., 2020; Wang et al., 2021). The studies contributing to foci in the left ACC and the left IFG finding of the current study were studies that had PTSD, trauma-exposed, and OCD samples compared to controls. I speculate inconsistencies between the current work and previous work for the ACC and IFG regions among adults with clinical anxiety might be associated with the inclusion of studies containing previous DSM criteria (OCD and PTSD recategorized into different categories based on DSM 5 criteria) and heterogeneity of the broader literature. Furthermore, prior meta-analytic work contained a low number of included studies, inconsistent reporting of comorbid conditions such as depression, and inconsistent reporting of individual factors like medication or drug use. In sum, the current results suggested the left ACC and left IFG being the most robust regions of decreased GM associated with various groupings of anxiety-related disorders based on DSM diagnostic criteria.

Convergent Structural Alterations in Cognitive Control Circuitry among Youth with Clinical Anxiety. Twenty-three studies met inclusion criteria for the series of meta-analyses among youth with clinical anxiety. I meta-analyzed seventeen contrasts of

decreased GM and fourteen contrasts of increased GM separately. I found one cluster of decreased GM in the left dlPFC. The meta-analyzed contrasts of GM increases produced null results.

Meta-analytic evidence observed decreased GMV in the left orbital gyrus and posterior cingulate and increased GMV in the right precentral gyrus and precuneus associated with GAD (Strawn et al., 2013). Other meta-analytic evidence revealed decreased GMV in the dorsolateral (dlPFC) among adolescents with comorbid conditions and anxiety diagnoses (Wehry et al., 2015). Wehry and colleagues found the differences between diagnostic groups most profound in DSM criteria but not as defined when examining these effects with the research domain criteria or RDOC framework. Meta-analytic work examining widespread structural alterations utilizing whole-brain VBM approaches across different pediatric DSM criteria anxiety-related disorders among children and adolescents is limited (Gold et al., 2016; Mueller et al., 2013; Strawn et al., 2015). Across this limited literature, the anxiety triad hypothesis explained social anxiety disorder, separation anxiety disorder, and social phobia contain similar clinical courses (Beesdo-Baum & Knappe, 2012; Strawn et al., 2015). Another meta-analysis examined brain morphometry across bipolar disorder, disruptive mood dysregulation disorder (DMDD), attention deficit hyperactivity disorder (ADHD), and diverse grouping of anxiety disorders found increased GMV in the left dorsolateral PFC (dlPFC), right vlPFC, and right parahippocampal gyrus (Gold et al., 2016). Decreased amygdala and anterior hippocampus GMV and increased GMV in the striatum among youth with clinical anxiety versus controls (Mueller et al., 2013). Muller and colleagues explored the role of the brain-derived neurotrophic factor polymorphism (BDNF), where they found this gene modulated insula

and dorsal anterior (dACC) structure and function. Speculation of differences in findings between the current study and previous meta-analytic work could be due to variability across the literature such as inclusion criteria for youth with clinical anxiety, differences in controlling for comorbid depression and other mental health-related disorders, and use of different clinical anxiety measurement criteria. Furthermore, examining the structural alterations across updated DSM criteria for anxiety utilizing VBM studies needs further investigation.

Structural alterations to the dlPFC are well documented in the adult literature on PD (Wu et al., 2018) and SAD (Wang et al., 2018), where structural alterations of the dlPFC are more profound in females with PD (Asami et al., 2009). Across comorbid depression and anxiety, conditions are increased GMV in the right dlPFC (Shang et al., 2014). Shang and colleagues also found decreased GMV in the dlPFC in a pure anxiety diagnosis with no other comorbidities. However, the association between the dlFPC and neurobiology in pediatric anxiety is less clear. The dlPFC is part of neuropathological models of clinical anxiety and is associated with cognitive control and working memory functions (Balderston et al., 2017). Taken together, to our knowledge, this most extensive study exploring the convergent structural alterations among youth with clinical anxiety and the dlPFC as the most robust region of structural alterations associated with pediatric anxiety. The current results partially support our original hypothesis that prefrontal areas have robust structural alterations associated with pediatric anxiety. The structural deficits in the dlPFC might be an important mechanism associated with clinical anxiety among youth.

Structural Alterations of Regions Between Developmental Groups. To test if the results between groups differed statistically, I conducted two contrast analyses to examine significantly divergent GM alterations between adult and non-adult groups. The contrast analysis examining if GM decreases between the adult and youth groups were different revealed significant differences in the left medial frontal gyrus, including the left ACC and left IFG among adults with clinical anxiety compared to the youth. An additional contrast analysis produced null results for comparison of GM decreases among children compared to adults. The contrast analysis examining significant differences of increased GM between developmental groups produced null results. To our knowledge, this is the first study to utilize the ALE approach to investigate differences in the structural brain correlates between adults and youth with clinical anxiety. The current results provided evidence of structural alterations in the left ACC and left IFG most profound among adults with clinical anxiety.

The specific brain deficits associated with the vulnerability to anxiety psychopathology among adolescents are unclear and more defined in the adult literature (Xie et al., 2021). Gene and environment interactions moderate early-life anxiety symptoms (Domschke & Maron, 2013) and potentially are continually mentalized negatively over life. Previous work showed disorder-specific deviations from "typical" development across ADHD (Carrey et al., 2012; Shaw et al., 2007), schizophrenia (Douaud et al., 2009), and bipolar disorder (Bora, 2015; Roybal et al., 2012) psychopathologies. A recent model proposes differences between anxiety-related brain networks between adults and adolescents (Xie et al., 2021). The proposed model emphasizes in adolescence hypoactivation of emotion control-related systems, immature growth of fear-conditioning-

related neural circuitry, and hypersensitivity of reward and stress-related neural systems associated with anxiety. The current findings complement this proposed model of anxiety-related brain regions in adolescence. The altered structure of the dlPFC shows the most robust region associated with clinical anxiety among youth, where this region could be a distinct biomarker of clinical anxiety early in life (Wehry et al., 2015). The structural alterations in the left ACC and left IFG among adults with clinical anxiety might be associated with sustained cognitive control and emotional regulation processes over anxiety-related stimuli exposure. In sum, the current results complement the proposed model of Xie and colleagues (2021), where regions associated with emotion regulation could be a specific brain-based mechanism for the detection and treatment (e.g., cognitive reappraisal) of clinical anxiety among youth. It is important to note that our youth sample contained children and adolescents, so I could not examine differences between structural alterations between these two early-life stages due to the limited literature separating these two types of developmental stages. Furthermore, one study included childhood maltreatment (De Brito et al., 2013), where childhood maltreatment moderates frontal-limbic circuitry differently (Hart & Rubia, 2012).

Limitations. The intricate examination of GM structural alterations comparisons of clinical anxiety based on DSM criteria and between adults and youth utilizing the current meta-analytic methods bear limitations. The 93 studies included in the current meta-analysis were significantly heterogeneous regarding design, methodology, sample criteria, and controlling for covariates. I used liberal inclusion criteria meaning all patients (adults and youth samples) included in this meta-analysis were diagnosed with previous DSM

criteria. Furthermore, only 23 studies were eligible for our ALE and functional connectivity assessments of our youth group. Due to the limited number of studies meeting the inclusion criteria for the youth meta-analysis, we included studies containing measures of clinical anxiety. I pooled together the child and adolescent groups, thus limiting examining structural brain correlations between child and adolescent stages. Though many studies included PTSD and OCD when both were once considered anxiety-related disorders, the potential dimensional mediated effects of these disorders (e.g., trauma exposure or dimensions of OCD) were unclear. It also is unclear from the current results if comorbid conditions, medication use, and other socio-cultural factors (i.e., gender) explained for variability in the convergent alterations within and between our adult and youth samples. Future research is needed to properly account for covariates and potential lateralization contributions to interpretation of the association between clinical anxiety and brain structure among adults and youth.

CONCLUSIONS

This is the first study to compare GM structural alterations across the whole brain among adults and youth with clinical anxiety. Using the ALE neuroimaging meta-analysis approach, I found convergent decreased GM in the left ACC associated with the neurobiology of clinical anxiety. The differences between the structural alterations of the left ACC and left IFG among adults and left dlPFC among youth show altered structure of these regions associated with emotion-related circuitry. The structural brain correlates differed between adults and youth with clinical anxiety. The current results contribute a

more comprehensive understanding of the neurobiology of clinical anxiety and how its association with brain structure differs among adults and youth.

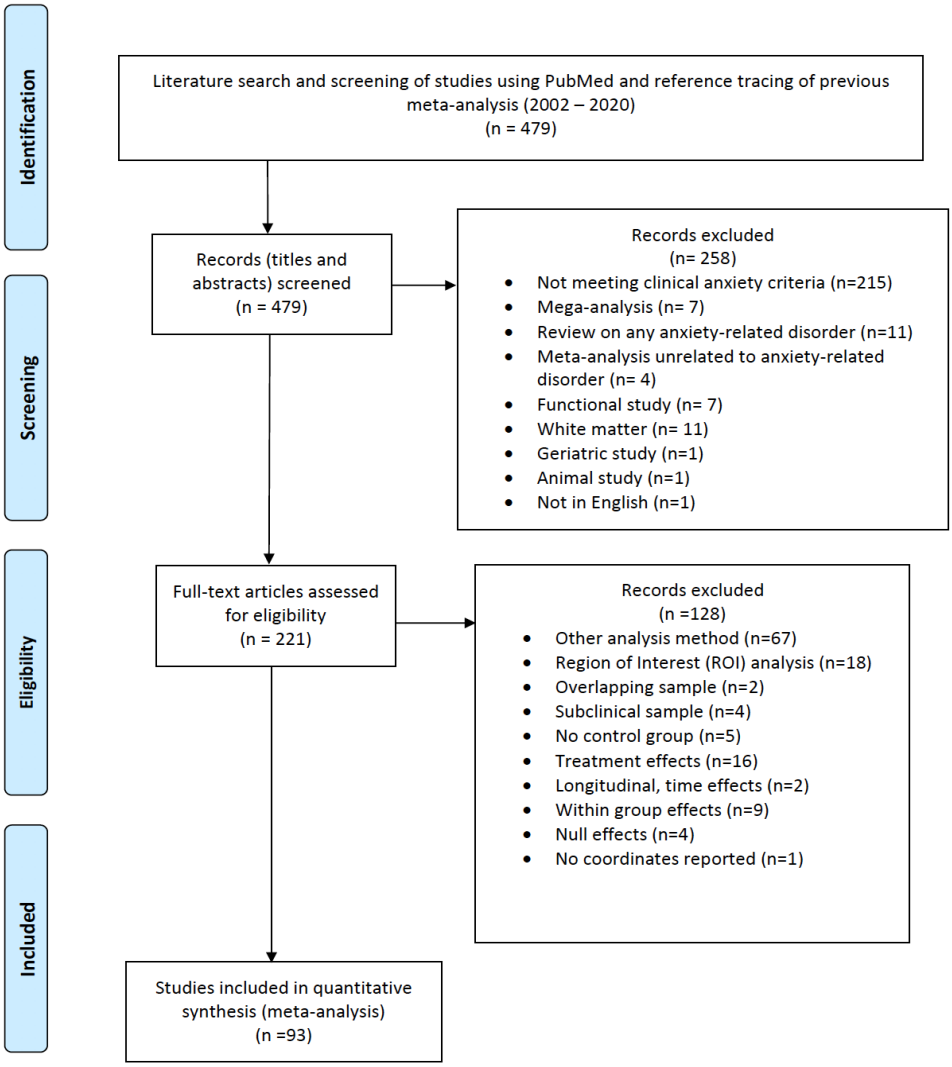
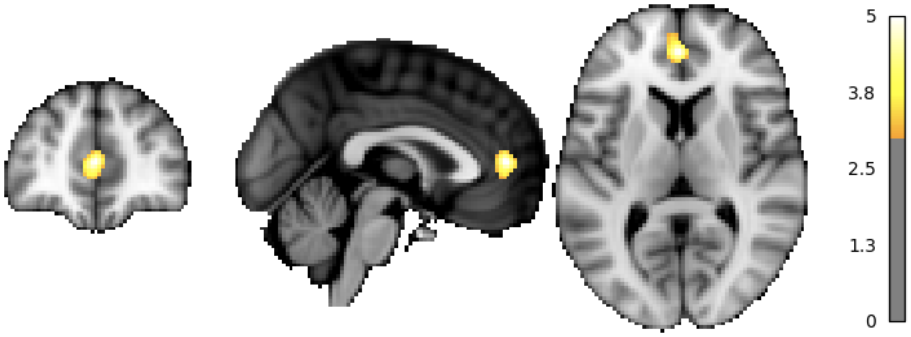


Figure 1. PRISMA diagram. PRISMA flow chart detailing the literature search and selection criteria of all studies included in the meta-analysis.



<u>Figure 2.</u> Main effects of ALE results for pooled controls > pooled anxious groups. Coronal, sagittal, and horizontal slices illustrating convergent structural alterations associated with anxiety as determined by a main effect ALE meta-analysis of GM reductions (i.e. All controls > Combined clinically anxious groups). ALE results indicated convergence in the medial prefrontal cortex ($P < 0.001$, FWE-corrected $P < 0.05$).

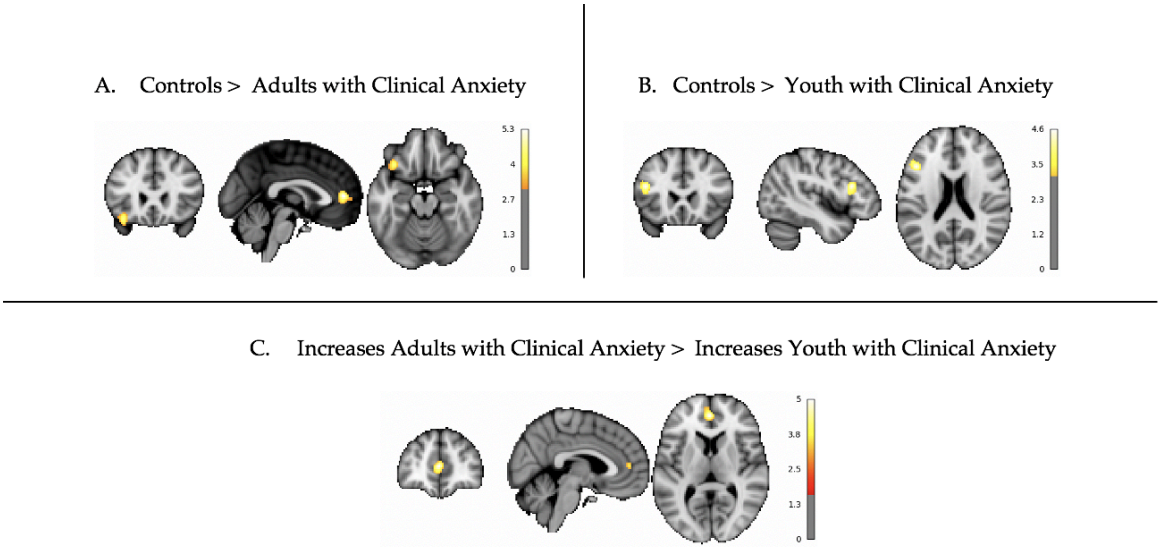


Figure 3. ALE meta-analysis results. Illustration of convergent GM structural reductions for **A)** adults with clinical anxiety compared to adult controls, **B)** youth with clinical anxiety compared to youth controls, **C)** contrast analysis of anxiety compared to controls: anxious adults vs. youth groups.

Author	Year	Anxiety-Related Disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Strawn et al., 2013	2013	GAD	15 (7M, 8F)	13(2)	28 (11M, 17F)	13(2)	GAD > HC HC > GAD
Whery et al., 2015	2015	GAD	Anxious depression patients AND comorbid anxiety disorder 12 (3M,9F)	Anxious depression patients: 14(3)	41 (14M, 27F)	13(2)	Anxious depression > HC MDD controls > Anxious depression
Liao et al., 2013	2013	GAD	Total GAD: 26 Childhood maltreatment (CM): n=14(7F, 7M) Without (WCM): n=12(6F, 6M)	CM: 17.0(0.20) WCM: 16.67(0.22) GAD Males: 16.77(0.73) GAD Females: 16.92(0.64)	Total GHC: 26 Childhood maltreatment (CM): n=14(6F, 6M) Without (WCM): n=13(6F, 7M)	CM: 16.58(0.22) WCM: 16.85(0.21) GAD Males: 16.92(0.86) GAD Females: 16.50(0.80)	GAD > HC
Liao et al. 2014	2014	GAD	26(13M/13F)		25(13M, 12F)		GAD > HC
Gilbert et al., 2008	2008	OCD	10 (6M,4F)	13.26(2.46)	Unaffected siblings (no OCD diagnosis): 10 (6M, 4F)	Unaffected siblings: 13.11(2.99) HC: 12.97(2.68)	OCD > Siblings (HC) HC > OCD

					Healthy controls (HC): 10 (6M, 4F)		
Strawn et al., 2015	2015	GAD, Social Phobia, SAD	38 (10M,28F)	14.4(3.0)	27 (12M,15F)	14.8(3.9)	AD > HC HC > AD
Milham et al., 2005	2005	Social Phobia, Separation Anxiety Disorder, GAD	17 (8M, 9F) social phobia=9, Separation anxiety disorder= 3 GAD=13.	12.9(2.3)	34(16M, 18F)	12.4(2.2)	HC > ANX
Carmona et al., 2007	2007	OCD	18 (13M, 5F)	12.86(2.76)	18(13M, 5F)	13.03(3.04)	HC > OCD
Szesko et al., 2008	2008	OCD	37 (14M, 23F)	13.0(2.7)	26 (9M, 17F)	13.0(2.6)	OCD > HC HC > OCD
Chen et al., 2013	2013	OCD	12 (6M,6F)	11.8(2.2)	8 (4M,4F)	11.7(2.7)	HC > OCD

Cabrera et al., 2019	2019	OCD	14 (10M,4F)	11.14(1.72)	14	11.14(1.72)	#OCD > HC
Cheng et al., 2016	2016	OCD	30 (18M,12F)	10.8(2.1)	30 (18M, 12F)	10.5(2.2)	OCD > HC HC > OCD
Lázaro et al., 2009	2009	OCD	15 (8M,7F)	13.7(2.5)	15 (8M, 7F)	14.3(2.5)	HC > OCD
Huyser et al., 2013	2013	OCD	29 (11M, 18F)	13.78(2.58)	29 (11M, 18F)	13.6(2.73)	OCD > HC
Mirabella et al., 2020	2020	OCD	N (total)=20 (15M, 5F) OCD n=9 (5M, 4F) Tourette's n=11 (10M, 1F)	Total mean age of entire sample: 10.9(2.3)	12 (9M, 3F)	10.5(1.1)	HC > OCD
Zarei et al., 2011	2011	OCD	26 (14M, 12F)	16.6(1.5)	26 (14M,12F)	16.5(1.4)	OCD > HC
De Brito et al., 2013	2013	Maltreatment and anxiety	maltreated: 18(11M, 7F)	12.01(1.38)	maltreated: 20 (10M,10F)	12.63(1.29)	Non-maltreated > maltreated Maltreated > Non-maltreated

Gold et al., 2016	2016	Bipolar disorder (BD), anxiety, ADHD, Disruptive Mood Dysregulation Disorder (DMDD)	BD= 20 (14M,6F) DMDD=52 (34M,18F) ADHD=20 (14M,6F) Anx=39 (20M,19F)	BD= 14.6(2.3) DMDD=13.6(2.8) ADHD=13.9(2.7) Anx=12.7(3.1)	53 (24M,29F)	13.8(2.5)	ANX > HC
Carrion et al., 2009	2009	PTSD	24(14M,10F)	11(2.24)	24 (14M,10F)	11(2.73)	PTSD > HC
Ahmed et al., 2012	2012	PTSD	21(11M,10F)	16.17(1.68)	32(15M,17F)	14.49(2.23)	non-PTSD (traumatized controls) > PTSD (diagnosed PTSD)
Kedding et al., 2015	2015	PTSD	27 (9M, 18F)	14.2(2.7)	27 (14M,13F)	13.6(3.0)	HC > PTSD
Brunner et al., 2010	2010	Borderline Personality Disorder(BPD); 4 subjects with anxiety disorder and clinical controls with anxiety disorder diagnosis	Borderline Personality Disorder (BPD) 20 (0M,20F) Clinical controls 20 (0M, 20F)	BPD: 16.7(1.6) Clinical controls: 16.0(1.3)	20 (0M, 20F)	16.8(1.2)	HC > BPD HC > Clinical controls

Table S2. Demographic data for studies on youth with clinical anxiety.

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Moon et al.	2014	GAD	22 (13M/9F)	37.0(10.7)	22 (13M/9F)	33.4(9.7)	HC > GAD
Kim et al.	2018	GAD	16 (10M/6F)	34.7(10.6)	16 (10M/6F)	32.5(7.3)	HC > GAD
Hilbert et al.,	2015	GAD	19 (3M, 16F)	33.47 (8.90)	24 (7M, 17F)	32.25 (9.33)	GAD > HC
Moon & Jeong	2016	GAD	20 (13M/7F)	36.9(11.3)	20 (13M/7F)	35.0(9.3)	HC > GAD
Makovac et al.,	2015	GAD	19 (3M, 16F)	30 (6.9)	19 (3M, 16F)	29.2(9.8)	HC > GAD
Meng et al.,	2013	SAD	20 (14M/6F)	21.80 (3.68)	19 (13M/6F)	21.58 (3.72)	HC > SAD
Talati et al.,	2013	SAD	Sample 1: SAD: 16 (3M/13F) PD: 16 (3M/13F)	Sample 1: 34.1 (6.7) Sample 2: 29.1 (8.9)	Sample 1: 20 (11M/9F) Sample 2: 17 (7F, 10M)	Sample 1: 31.4 (7.8) Sample 2: 31.3 (10.7)	Sample 1: SAD > HC HC > SAD Sample 2:

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
			Sample 2: 17 (5M, 11F)				SAD > HC (
Zhao et al.,	2017	SAD	24 (15M/9F)	24.5 (4.0)	41 (26M/15F)	27.1 (7.2)	HC > SAD
Liao et al., 2011	2011	SAD	18 (12M/6F)	22.67(3.77)	18 (13M/5F)	21.89(3.69)	HC > SAD SAD > HC
Kodancha et al., 2020	2020	OCD	35 (ratio male: female= 5:30)	33.3(6.4)	39 (ratio male: female= 12:27)	32.1(6.5)	HC > OCD
Tang et al., 2015	2015	OCD	26 (15M/11F)	25.5 (4.9)	32 (17M/15F)	26.2(5.1)	OCD > HC HC > OCD

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Yoo et al., 2008	2008	OCD	71 (47M/24F)	26.61(7.50)	71 (47M/24F)	26.68(6.09)	OCD > HC #HC > OCD OCD > HC HC > OCD
Valente et al., 2005	2005	OCD	19 (10M/9F)	32.7(8.8)	15 (7M/8F)	32.3(11.8)	OCD + MDD > HC HC > OCD + MDD
Gilbert et al., 2008	2008	OCD	25 (13M/12F)	37.5(10.7)	20 (9M/11F)	29.8(7.86)	OCD > HC HC > OCD
Togao et al., 2010	2010	OCD	23(9M/14F)	32.6(9.7)	26 (12M/14F)	31.3(7.3)	HC > OCD
Moreira et al., 2017	2017	OCD	40(13M/27F)	26.28(6.62)	40 (13M/27F)	26.45(5.39)	HC > OCD

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Okada et al., 2015	2015	OCD	37(14M/23F)	34.4(10.5)	37(14M/23F)	36.8(10.8)	HC > OCD OCD > HC
Spalletta et al., 2014	2014	OCD	20(12M/8F)	33.10(8.85)	20(12M/8F)	35.20(9.38)	OCD > HC
Koprivová et al., 2009	2009	OCD	14(5M/9F)	28.6(6.1)	15 (6M/9F)	28.7(6.5)	HC > OCD
Christian et al., 2008	2008	OCD	21 (15M/6F)	38.0(9.6)	21 (15M/6F)	38.9(9.8)	OCD > HC OCD (without MDD) > HC
Tang et al., 2013	2013	OCD	18 (11M/7F)	25.5(6.7)	26(15M/11F)	25.2(6.6)	OCD > HC HC > OCD

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Hou et al., 2013	2013	OCD	33 (18M/15F)	25.3(9.6)	33 (18M/15F)	25.0(9.1)	OCD > HC #HC > OCD
Matsumoto et al., 2010	2010	OCD	16(7M/9F)	32.8(7.5)	32 (14M/18F)	32.6(8.7)	HC > OCD
van den Heuvel et al., 2009	2009	OCD	55(16M/39F)	33.7(9.19)	50 (20M/30F)	31.4(7.64)	HC > OCD
Tan et al., 2013	2013	OCD	28(19M/9F)	25.35(7.24)	22(15M/7F)	27.88(8.02)	OCD > HC
Exner et al., 2012	2012	OCD	23 (9M,14F) (61% female)	31.3(9.3)	36(18M,18F) (61% female)	30.4(7.8)	HC > OCD OCD > HC

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Pujol et al., 2004	2004	OCD	72 (40M/32F)	29.8(10.5)	72 (40M/32F)	30.1(10.2)	HC > OCD OCD > HC
Kim et al., 2001	2001	OCD	25 (17M/8F)	27.4(7.0)	25 (17M/8F)	27.0(6.2)	OCD > HC HC > OCD
Gonçalves et al., 2017	2017	OCD	15 (11M/4F) Total N= 95(55M, 40F)	31.67(11.44)	15 (9M/6F)	30.07(8.22)	NCC > OCD OCD > NCC
Subirá et al., 2013	2013	OCD	Autogenous group: n=30 (20M, 10F) Reactive group: n=65(29M, 36F)	Total N: 33.85(9.33) Autogenous group: 32.23(9.05) Reactive group: 34.60(9.43)	95(55M, 40F)	33.92(10.53)	Reactive OCD > HC HC > autogenous OCD

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Kunas et al.,	2020	Panic Disorder (PD)	PD Smokers: 71 (26M,45F) PD Non-Smokers: 72(28M,44F)	PD Smokers: 34.13(10.7) PD Non-Smokers: 33.18(11.3)	HC Smokers: 62 (28M,34F) HC Non-Smokers: 116 (49M,67F)	HC Smokers: 31.23(9.5) HC Non-Smokers: 31.85(10.8)	HC > PD HC (Non-Smoking; NS) > PD (Non-Smoking; NS)
Yoo et al., 2005	2005	Panic Disorder (PD)	18 (9M, 9F)	33.3(7.1)	18 (11M, 7F)	32.0(5.8)	HC > PD
Protopopescu et al.,2006	2006	Panic Disorder (PD)	10 (4F, 6M)	35.5(9.7)	23 (12M, 11F)	28.7(7.5)	PD > HC HC > PD
Uchida et al., 2008	2008	Panic Disorder (PD)	19 (3M/16F) PD patients with MDD=5 PD patients w/out MDD= n=14	37.05(9.75)	20 (4M,16F)	36.45(9.93)	HC > PD PD > HC HC > PD without MDD PD without MDD > HC

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Massana et al., 2003	2003	Panic Disorder (PD)	18 (7M,11F)	3.68(11.3)	18 (8M, 10F)	36.7(8.8)	HC > PD PD > HC
Lai & Wu	2015	Panic Disorder (PD)	53 (25M, 28F)	43.28(10.11)	54 (25M,29F)	40.38(10.51)	HC > PD
Asami et al., 2009	2009	Panic Disorder (PD)	24 (9M/15F)	Males 33.4(9.1) Females 39.2(10.5)	24 (9M/15F)	Males 33.2(5.2) Females 39.3(10.8)	HC > PD
Lai & Wu	2012	Panic Disorder (PD)	30	47.03(10.63)	21	41.14(11.81)	HC > PD
Na et al., 2013	2013	Panic Disorder (PD)	Total N: 22 (13M,9F) PDA (with agoraphobia): 12 (5M,7F) PDW (without agoraphobia): 10 (8M, 2F)	43.08(9.63)	22 (11M,11F)	40.18(12.38)	HC > PDA HC > PD

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
Sobanski et al., 2010	2010	Panic Disorder (PD)	17 (8M/9F)	34.9(6.7)	17 (8M/9F)	33.1(6.2)	HC > PD (PD PD > HC HC> PD SAD > HC
Talati et al.,	2013	Panic Disorder (PD)	Sample 1: SAD: 16 (3M/13F) PD: 16 (3M/13F) Sample 2: SAD 17 (5M, 11F)	Sample 1: 34.1 (6.7) Sample 2: 29.1 (8.9)	Sample 1: 20 (11M/9F) Sample 2: 17 (7F, 10M)	Sample 1: 31.4 (7.8) Sample 2: 31.3 (10.7)	HC> SAD SAD > HC HC> SAD SAD > HC HC> SAD
Picado et al., 2015	2015	Panic Disorder (PD)	SCZ/ANX= 20(12M/8F) SCZ= 20(11M/9F) ANX= 20(5M/15F)	SCZ/ANX= 32.55(6.901) SCZ= 35.9(0.773) ANX= 30.90(6.639)	20 (12M/8F)	33.20(6.613)	ANX > CNTRL CTRL > ANX

Author	Year	Anxiety-related disorder	Patient Group N (M/F)	Patient Group: Age Range/Mean (SD)	Non-Patient Group: Healthy Controls (HCs) (M/F)	Non-Patient Group: Age Range/Mean (SD)	Contrasts
			ANX group: n= 10 with Panic Disorder (PD) n=10 with agoraphobia				
Lai et al., 2010	2010	Panic Disorder (PD)	16 (5M, 11F)	37.91(8.76)	15 (4M,11F)	34.30(9.87)	HC > MDD + PD
Hilbert et al., 2015	2015	Dental phobia (DP) Snake phobia (SP)	Total N= 59 SP= 26 (6M, 20F) DP= 37 (8M,25F)	SP: 22.91(4.69) DP: 25.27(5.17)	37 (9M,28F)	22.76(3.88)	SP + DP > HC SP > HC DP > HC
Picado et al., 2015	2015	Specific Phobia	See listing above	See listing above	20 (12M/8F)	33.20(6.613)	ANX > CNTRL CTRL > ANX

Table S3. Demographic data for studies on adults with clinical anxiety.
*PTSD studies from chapter 2 were included. Breakdown of PTSD studies in Table S1.

CHAPTER 4

EXPLORING FUNCTIONAL CONNECTIVITY ASSOCIATED WITH CLINICAL ANXIETY: AN EXTENDED META-ANALYTIC MODELING ANALYSIS

ABSTRACT

The neurobiology of anxiety-related disorders includes prefrontal and cortico-striatal circuits. However, functional patterns associated with clinical anxiety are not fully understood. Using regions of interest (ROIs) found in the previous chapter, we sought to explore an extended functional connectivity network associated with the convergent structurally altered regions linked to clinical anxiety. To do so, I generated functional profiles for the left ACC, IFG, and dlPFC utilizing resting-state functional connectivity (rsFC) and meta-analytic co-activation modeling (MACM) methods. I performed functional decoding to guide interpretations of the mental functions associated with each functional profile. The rsFC and MACM assessments showed functional connectivity patterns across a widespread, whole-brain network that included frontoparietal and limbic regions compromising the default mode network (DMN), salience network (SN), and central executive network (CEN). Functional decoding results suggested behavioral terms associated with self-referential thought, emotion, reward, attention, and language processes. The current results provide new insight into potential targets for brain-based intervention and treatment of clinical anxiety.

INTRODUCTION

Resting-state functional magnetic resonance imaging (rs-fMRI) provides a non-invasive approach to investigating the neurobiology associated with psychopathology. Across clinical studies, rs-fMRI allows for paradigm-free operation and strong reliability of examining functional connectivity patterns associated with clinical anxiety. Previous rs-fMRI studies on adults with clinical anxiety revealed altered functional connectivity patterns of the amygdala, prefrontal, and cortical-limbic structures (Etkin et al., 2010). Aberrant functional connectivity between the amygdala, precuneus, and superior frontal gyrus also exists among adolescents and young adults with clinical anxiety based on DSM diagnostic criteria (Toazza et al., 2016). Unique patterns of rs-fMRI showed increased functional connectivity between limbic structures and weakened connectivity between frontal and temporal regions in GAD diagnosis (Qiao et al., 2017), PTSD (Brown et al., 2014), OCD (Zhang et al., 2017), and panic disorder (PD) (Pannekoek et al., 2013). Overall, a consensus across the literature regarding the underlying functional neurobiology associated with clinical anxiety has not yet been achieved.

The psychopathology-related functional patterns between adults and youth remain to be elucidated. Functional investigations among children and adolescents revealed altered function between the amygdala, ACC, and prefrontal cortex (PFC) regions, mainly compromising threat-related circuitry (McClure et al., 2007; Wolf & Herringa, 2016). For example, among adolescents with GAD, hyperactivity of the amygdala and functional coupling with the ventrolateral prefrontal cortex (vlPFC) were associated with emotion probing paradigms (Maslowsky et al., 2010; Monk et al., 2008; Strawn et al., 2012). Reduced connectivity between these cortico-frontal-limbic regions was associated with

deficits in mentalization and emotion regulation in GAD (Monk et al., 2008; Strawn et al., 2012). Hyperreactivity of the amygdala is associated with separation anxiety disorder and social phobia (Guyer et al., 2008). However, functional investigations among adults contain additional regions encompassing emotion-related circuitry (Xie et al., 2021).

More recently, functional investigations utilize network-based approaches to understand the neurobiology associated with clinical anxiety. Specifically, OCD (Fan et al., 2017) and PTSD (Sripada et al., 2012) contain differential connectivity between the default mode network (DMN), salience network (SN), and central executive network (CEN). In contrast, PD and SAD were associated with DMN-specific altered functional connectivity patterns (Kim & Yoon, 2018). This suggests different anxiety disorders may be characterized by unique patterns of functional network dysfunction (Sylvester, 2012).

Rationale for the Present Research

Differences exist in the altered structure and function of the amygdala, ACC, and PFC associated with clinical anxiety. Importantly, these regions associated with clinical anxiety are core nodes of the DMN, SN, and CEN. The connection between how the structural alterations associated with clinical anxiety may be linked to altered functional connectivity patterns remain to be elucidated. I sought to examine widespread extended functional connectivity of the convergent structural alterations associated with clinical anxiety utilizing resting-state functional connectivity (rsFC) and meta-analytic co-activation modeling (MACM) assessments. I performed functional decoding methods to characterize the association between behavior and the extended functional connectivity of clinical anxiety. I used the left IFG, ACC, and dlPFC previously identified from chapter 3

containing significant structural alterations among adults and youth with clinical anxiety, respectively, as our regions of interest for the extended functional connectivity analysis.

METHOD

Functional Profiles of Structurally Altered Regions Associated with Clinical Anxiety.

I sought to identify the functional connectivity patterns associated with regions demonstrating structural alterations in clinical anxiety. To this end, I investigated *task-free functional connectivity* utilizing a database of resting state fMRI data, as well as *task-based functional connectivity* using a meta-analytic database of co-activation results.

Task-free functional connectivity: Resting-state fMRI (rs-fMRI).

Resting-state connectivity analyses typically identify voxels of the brain that demonstrate the highest temporal correlation with the average time series of a seed ROI and provide context about the underlying functional architecture of the brain. To derive robust rsFC maps for each ROI, I utilized the minimally pre-processed and denoised (or "cleaned") resting-state fMRI data provided by the Human Connectome Project's (Van Essen et al., 2013b) Young Adult Study S1200 Data Release (March 1, 2017). On November 12, 2019, 150 randomly selected participants (28.7 ± 3.9 years) were downloaded via the HCP's Amazon Web Services (AWS) Simple Storage Solution (S3) repository. The randomly chosen participants included 77 females (30.3 ± 3.5 years) and 73 males (27.1 ± 3.7 years). A difference in age between the two biological sex groups was significant but is consistent with the 1200 Subjects Data Release. Detailed acquisition and scanning parameters for HCP data can be found in consortium manuscripts (Smith et al., 2013; Uğurbil et al., 2013; Van Essen et al., 2012), but relevant scan parameters are briefly summarized here. Each

participant underwent T1-weighted and T2-weighted structural acquisitions and four resting-state fMRI acquisitions. Structural images were collected at 0.7-mm isotropic resolution. Whole-brain EPI acquisitions were acquired on the 3T Siemens Connectome scanner: 32-channel head coil, TR = 720 msec, TE = 33.1 msec, in-plane FOV = 208 × 180 mm, 72 slices, 2.0 mm isotropic voxels, and multiband acceleration factor of 8 (Feinberg et al., 2010).

The S1200 data release contained minimally pre-processed and denoised data. The minimal pre-processing workflow is described by Glasser and colleagues (Glasser et al., 2016), but consists of typical imaging pre-processing techniques that leverage the high-quality data acquired by the HCP. First, T1- and T2-weighted images were aligned, bias field corrected, and registered to MNI space. Second, the functional fMRI pipeline removed spatial distortions, realigned volumes to compensate for subject motion, registered the fMRI data to structural volumes (in MNI space), reduced the bias field, normalized each functional acquisition to its corresponding global mean, and masked non-brain tissue. It is important to note that care was taken to minimize smoothing induced by interpolation and that no overt volume smoothing was performed.

The fMRI signal contains many sources of fluctuations, including artifactual and non-neuronal signals, that make identifying the underlying neuronal activity difficult. Using a combination of independent component analysis (ICA) and classification techniques, HCP functional data were automatically denoised using FMRIB's ICA-based X-noiseifier (Salimi-Khorshidi et al., 2014). Briefly, ICA is performed on each functional dataset independently and characteristics of each component, such as spatial localization and power in high-frequencies, are evaluated by a classifier to determine if a given

component is related to neuronal activity or artifact. The time-series corresponding to artifactual components are then regressed out of the data, providing a "cleaned", denoised dataset for further investigation.

Using the minimally pre-processed, denoised resting-state datasets for each participant, the "global signal" was removed using FSL's *fsl_glm* (Jenkinson et al., 2012) interface in NiPype (Gorgolewski et al., 2011). The "global signal", although controversial in the domain of resting-state analyses, was removed under the assertion that it performed better than other commonly used motion-correction strategies in removing motion-related artifacts in the HCP resting-state data (Burgess et al., 2016). The resulting data set was then smoothed with a FWHM kernel of 6-mm using FSL's *susaan* interface in NyPipe. For each participant, the average time series for each ROI was extracted and a whole-brain correlation map was calculated and averaged across runs for a single participant for every ROI. The average correlation maps for each participant were transformed to Z-scores using Fisher's r-to-z transformation. A group-level analysis was then performed to derive a rsFC map for each ROI using FSL's *randomise* interface (Winkler et al., 2014) in NiPype. Images were thresholded non-parametrically using GRF-theory-based maximum height thresholding with a (voxel FWE-corrected) significance threshold of $P < 0.001$ (Worsley, 2001), such that more spatially specific connectivity maps could be derived when using such a highly powered study (Woo et al., 2014).

Task-based functional connectivity: Meta-analytic co-activation modeling (MACM). Using reported coordinates from task-based fMRI studies, meta-analytic co-activation is a relatively new concept that identifies locations in the brain that are most likely to be co-activated with a given seed ROI across multiple task states. Thus, differing

from rsFC, MACM provides context about neural recruitment during goal-oriented behaviors. I therefore aimed to integrate these two complementary modalities by supplementing the rsFC maps with MACM maps for each ROI. To do so, I relied on the Neurosynth database (Yarkoni et al., 2011), which archives published stereotactic coordinates from over 14,000 fMRI studies and 150,000 brain locations. Neurosynth relies on an automated coordinate extraction (ACE) tool to "scrape" each available fMRI study for reported coordinates. Due to the nature of this automated process, fMRI studies reporting results of multiple experimental contrasts as separate sets of coordinates are amalgamated into a single set of coordinates; in addition, "activation" and "de-activation" coordinates are not distinctly characterized. However, while this inherent noise may yield greater limitations in interpretation, the power over manually curated datasets outweighs the potential confounds of bi-directional or mixed-contrast effects.

To generate a MACM map for each ROI, I utilized NiMARE to search the Neurosynth database for all studies reporting a coordinate within the defined ROI mask. Neurosynth tools support using the multilevel kernel density analysis (MKDA) algorithm for performing meta-analyses based on a subset of studies, such as that proposed here. However, I opted to use the ALE algorithm as implemented in NiMARE due to its optimal performance in replicating image-based meta- and mega-analyses (Salimi-Khorshidi et al., 2009). The ALE algorithm requires sample size, or the number of subjects, that contribute to a given experimental contrast to generate a smoothing kernel. However, Neurosynth is not able to capture sample size (which could also vary across experimental contrasts within a study). Thus, I utilized a smoothing kernel with a FWHM of 15-mm, which has been shown to yield results with strong correspondence with image-based meta- and mega-

analyses [Salimi-Khorshidi et al., 2009]. The ALE algorithm was applied to the set of studies reporting activation within the boundaries of each ROI. Once ALE maps were generated, as described above, for each ROI, voxel-FWE correction ($P < 0.001$) was performed to reflect the statistical thresholding approach used for rsFC maps.

Functional Decoding: Generalized Correspondence Latent Dirichlet Allocation (GC-LDA). I sought to infer what mental processes were most likely linked with brain regions identified in our ALE, MACM, and rsFC analyses. To do so, I utilized GC-LDA functional decoding methods applied to the resulting unthresholded ALE, rsFC, and MACM maps. This type of decoding provides a statistical approach to infer mental processes associated with neuroimaging spatial patterns. GC-LDA utilizes probabilistic Bayesian statistics that learns latent topics from a large database of papers (e.g., NeuroSynth) (Rubin et al., 2017). From the database, each topic found is treated as a probability distribution and creates a spatial distribution in MNI space across voxels from the maps entered into the decoding algorithm. The "topics" encompass terms and associated brain regions that co-occur in the literature from a literature database. I set our model to 200 topics (Rubin et al., 2016). I report the 10 terms corresponding to the highest weights associated with our ALE, rsFC, and MACM results.

RESULTS

I investigated the extend functional connectivity of the left IFG, ACC, and dlPFC identified previously in chapter 3. I generated rsFC, MACM, and consensus maps between the rsFC and MACM assessments for each ROI. To decipher mental associations with each

functional profile based on our ROIs, I conducted functional decoding procedures on each functional profile to form a word cloud of the terms most correlated with each functional profile. The following sections detail the results for each ROI.

Left ACC. The resultant rsFC patterns of the left ACC seed revealed bilaterally connectivity to the frontal gyrus including superior and medial regions, the cingulate gyrus, the temporal gyrus, the posterior cingulate, thalamus, parahippocampus, hypothalamus, fusiform gyrus and insula (Figure 1, first row). The MACM assessments revealed similar patterns of co-activation as the rsFC map (Figure 1, second row). Conjunction analysis of the rsFC and MACM assessments revealed extended functional connectivity of the left ACC bilaterally to the medial frontal gyrus (MFG) and the ACC (Figure 1, last row). The consensus pattern of regions demonstrate anxiety-related gray matter loss in the left ACC may have potentially significant consequences across a widespread brain network related to task-free and task-dependent functional connectivity in clinical anxiety.

The word cloud shows the top terms most associated with functional connectivity patterns of the conjunction analysis results (Figure 2). The larger appearance of text of the terms in the word cloud indicate stronger associations with the functional profile of the left ACC. Decoded terms included the terms *referential*, *default mode*, *self*, *valence*, *default*, *salience network*, and *reward*.

Left IFG. The resultant rsFC assessments of the left IFG revealed bilateral connectivity to the frontal gyrus and temporal gyrus including medial and superior regions, the caudate, parahippocampus, amygdala, hippocampus, subcallosal gyrus and the right IFG (Figure 3, first row). The MACM assessments revealed similar patterns of functional connectivity as the rsFC map (Figure 3, second row). Conjunction analyses across the

MACM and rsFC maps were computed to examine consensus task-free and task-based functional connectivity of the left IFG seed (Figure 3, last row). Conjunction analysis of rsFC and MACM assessments showed extended functional connectivity of the left IFG bilaterally to the middle frontal gyrus, parahippocampus, and the left IFG. The consensus pattern of regions demonstrate anxiety-related gray matter loss in the left IFG may have potentially significant consequences across a widespread brain network associated with clinical anxiety.

The word cloud shows the top terms most associated with functional connectivity patterns of the conjunction analysis results of the left IFG. Decoded terms associated with the consensus functional assessments of the left IFG included the terms *word*, *syntactic*, *sentences*, *semantic*, *pictures*, *emotional*, and *retrieval* (Figure 4).

Left dlPFC. The resultant rsFC assessments of the left IFG revealed bilateral connectivity to the superior frontal gyrus, precuneus, ACC, and left fusiform gyrus, medial frontal gyrus, precentral gyrus, post central gyrus and inferior parietal lobe (Figure 6, first row). The MACM assessments showed similar patterns of connectivity with the left dlPFC seed (Figure 6, second row). Conjunction analysis of rsFC and MACM assessments showed extended functional connectivity of the left dlPFC to the left dlPFC and middle frontal gyrus (Figure 6, third row). The consensus pattern of regions demonstrate anxiety-related gray matter loss in the left dlPFC may have potentially significant consequences across a widespread brain network associated with clinical anxiety.

The word cloud shows the top terms most associated with functional connectivity patterns of the conjunction analysis results of the left dlPFC. Decoded terms associated

with the consensus functional assessments of the left IFG included the terms *word*, *language*, *phonological*, *lexical*, *tasks*, *demands*, and *reading* (Figure 6).

DISCUSSION

I investigated extended functional connectivity of the left ACC, IFG, and dlPFC found in the previous chapter associated with clinical anxiety. I then used functional decoding techniques to characterize the functional profiles of each region analyzed.

Left ACC. Topographically speaking**,** the observed task-dependent and task-free functional connectivity patterns (FC) of the left ACC resembled regions of the default mode (DMN) (Greicius et al., 2003; Raichle, 2015) and salience (SN) (Menon & Uddin, 2010; Seeley et al., 2007) networks. Decoded terms associated with the extended functional connectivity patterns of the left ACC included terms such as *self-referential*, *default mode*, *salience network*, and *reward*. The DMN often encompasses a functional system of brain regions including medial prefrontal, anterior cingulate, posterior cingulate, inferior parietal and temporal cortices (Raichle, 2015; Raichle et al., 2001). During active, cognitive states, the DMN displays anticorrelated activity (Dosenbach et al., 2007; Raichle et al., 2001). Previous investigations reveal an association between regions encompassing the DMN are and introspection, self-referential thought, and autobiographical memory processes (Greicius et al., 2003; Whitfield-Gabrieli & Ford, 2012). The DMN also mediates retrieval and manipulation of past experiences for the future (Buckner et al., 2008; Greicius et al., 2003; Raichle & Snyder, 2007). The SN often encompasses the dorsolateral ACC, anterior insula, amygdala and ventral striatum (Menon, 2015) and functionally connected to limbic structures. Previous investigations evidence an association between SN function with The

salience detection, orientating self to stimuli, and attentional processes (Menon & Uddin, 2010; Seeley et al., 2007). Altered connectivity between the DMN, SN and central executive (CEN) networks is associated with a tripartite model of psychopathology (Broyd et al., 2009; Menon, 2011; Menon & Uddin, 2010). The tripartite model of psychopathology supports the notion that the SN takes the "driver's seat" over the DMN and CEN (Koch et al., 2016; Sripada et al., 2012) by identifying relevant internal or external stimuli and mediating DMN and CEN activity to sustain goal-driven behavior (Koch et al., 2016; Menon & Uddin, 2010; Seeley et al., 2007). A recent rs-FMRI meta-analysis suggest altered network dysfunction both within and between the DMN and the CEN associated with anxiety-related disorders (Xu et al., 2019).

Activity of the ACC is associated with emotion regulation and attention processes (Stevens, 2011). Resting-state fMRI investigations of the subdivisions of the ACC associated with aberrant functional connectivity in anxiety psychopathology (Brown et al., 2014; Kennis et al., 2015; Pannekoek et al., 2013) including GAD, SAD (Clauss et al., 2014; Prater et al., 2013), and other anxiety-related disorders based on previous DSM criteria (Zhao et al., 2007). Extended functional connectivity of the left ACC compliment the tripartite model of psychopathology (Menon, 2011) since the left ACC as a key node of the DMN. Consistent reports across the literature of altered connectivity of the DMN and SN consistent in both task-free and emotional-based paradigms across PTSD, OCD, and PD (MacNamara et al., 2016). Taken together disputed emotion regulation and attention processes contain brain-based network targets associated with clinical anxiety.

Left IFG. Topographically speaking**,** the observed task-dependent and task-free FC of the left IFG resembled regions of the SN network. Decoded terms associated with the

extended functional connectivity patterns of the left ACC included terms such as *semantic*, *emotional*, and *retrieving*. A combined VBM and resting state neuroimaging study found reduced GMV in the precentral gyrus and superior frontal gyrus ROIs showed aberrant FC between the IFG and superior temporal gyrus associated with SAD (Ma et al., 2019). During fear regulation tasks anxious individuals have "altered functional connectivity between the IFG and the vmPFC (Cha et al., 2016). Cha and colleagues speculated the IFG provided evaluation processes of the stimulus and informed prefrontal regions in cognitive control processes over amygdala responses associated with fear exposure. Therapeutic mechanisms such as cognitive behavioral therapy (CBT) have been found to reduce activation of the IFG in PD patients over course of treatment (Kircher et al., 2013).

In sum, the current FC results support a general pattern of extended functional connectivity associated with aberrant intrinsic network connectivity of the SN function associated with clinical anxiety (Xu et al., 2019). Anterior functional connectivity of the DMN is associated with self-referential and emotion processing where this FC pattern is positively correlated with anxiety and depression symptoms (Coutinho et al., 2016).. Taken together, the altered structure of the left ACC and left IFG show extended functional connectivity patterns encompassing DMN and SN networks. The extended functional connectivity patterns of the left ACC and left IFG could mean warped self-referential thought and poorer ability of emotional and attentional processes disrupted among individuals with clinical anxiety.

Left dlPFC. Topographically speaking**,** the observed task-dependent and task-free FC of the left IFG resembled regions of the CEN. Decoded terms associated with the extended functional connectivity patterns of the left dlPFC included terms such as

language, *working memory, phonological*, and *syntactic*. The CEN network commonly encompasses the dlPFC and lateral parietal regions (Habas et al., 2009). Activity of the CEN maintain and manipulate information, working memory, decision-making, and problem solving (Menon, 2011; Turner et al., 2019) and is most active during demanding cognitive and emotional tasks (Turner et al., 2019). Unique to CEN function is its lack of functional coupling with limbic, hypothalamus, and midbrain regions (Menon, 2015).

Attentional bias to threat is found among youth with clinical anxiety (Abend et al., 2018) and poorer executive functioning (Mogg et al., 2015). Hypofunction of the dlPFC associated with extinction of fear and error processing among youth and adolescents with clinical anxiety (Fitzgerald et al., 2013; Ganella et al., 2018). Network approaches to brain maturation indicate positive connectivity between the DMN, SN, and CEN in childhood and a shift to negative connectivity into adulthood (Chai et al., 2014; Jaeger et al., 2012). A meta-analysis and systematic review examining differences in DMN functional connectivity in healthy individuals by factors such as age and sex found patterns of DMN functional connectivity similar to neural cortical development of an inverted "U" shape pattern (Mak et al., 2017). A longitudinal study examining DMN connectivity across lifespan in GAD diagnosis found a great effect of anxiety on DMN connectivity in older adults vs. younger individuals (Andreescu et al., 2014). Andreescu and colleagues also found the duration of GAD diagnosis and symptom severity worsened DMN activity across lifespan.

Taken together, the current results support convergent structural alterations of the left associated with clinical anxiety show large spread altered CEN connectivity. The dlPFC being a node of the CEN and associated with poorer ability to regulate goal-directed

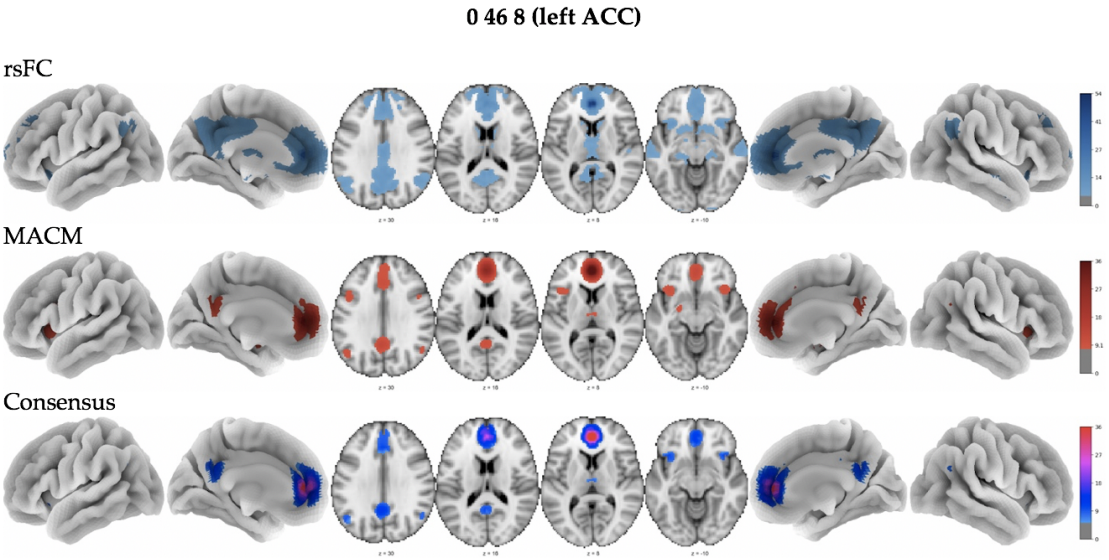
behavior might be associated altered control over DMN and SN. Slowed development of the PFC and its aberrant functional connectivity of the dlPFC in early life could be associated with an inability to process abstract concepts thus producing difficulties in eliciting or expressing anxiety symptoms and rumination behaviors (Borders, 2020).

Decoded patterns of the left dlPFC FC included language processes. Thus, our original findings of structural alterations of the dlPFC in the previous chapter among clinically anxious youth and adolescent groups might borderline regions pertaining to speech and language. Since brain regions related to higher order cognitive processes mature later (MacMaster et al., 2016; Tamnes et al., 2017), the ability to express and process psychopathology symptoms might not be fully developed. Emerging functional work indicates potential differences in functional connectivity patterns among pre-adolescence stages (Lees et al., 2021). Future investigations of this is needed.

Limitations. While this study builds on the findings from the previous chapter, there are some limitations. Though the results support extended functional profiles of clinical anxiety, I was unable to control for comorbidity of other mental-health related disorders and factors, such as medication and genetics. The rsFC and MACM assessments involved use of a specific dataset that could pose limitations in interpretations of the current functional results. Furthermore, functional decoding techniques were limited to studies archived in the Neurosynth database for the current analysis. From this work I was unable to make inferences about how the extended functional connectivity patterns of clinical anxiety may differ between adults and youth with clinical anxiety.

CONCLUSIONS

The current results extended prior work on clinical anxiety by examining the extended functional connectivity associated the convergent structural brain correlates associated with clinical anxiety. An extended network of clinical anxiety encompassing the left ACC, IFG, and dlPFC might be associated with larger intrinsic network neurobiology of anxiety. Aberrant connectivity between the DMN, SN, and CEN show disrupted emotion regulation and attentional biases among individuals with clinical anxiety and compliment the tripartite model of psychopathology. The current results provide implications for the psychophysiology associated with clinical anxiety at individual and network levels of dysfunction and advance work on potential targets for neural-based treatments of clinical anxiety.



<u>Figure 1.</u> Functional connectivity patterns of the left ACC seed. First row: rsFC results (blue). Second row: MACM results (red). Row three: Consensus between rsFC and MACM approaches (pink). Images are thresholded at voxel-wise FWE $P < 0.001$.

Figure 2. Functional decoding results of the left ACC seed. Functional decoding results from the unthresholded MACM map associated with *Neurosynth* terms. Words in larger font indicate stronger associations with the functional profile of the left ACC.

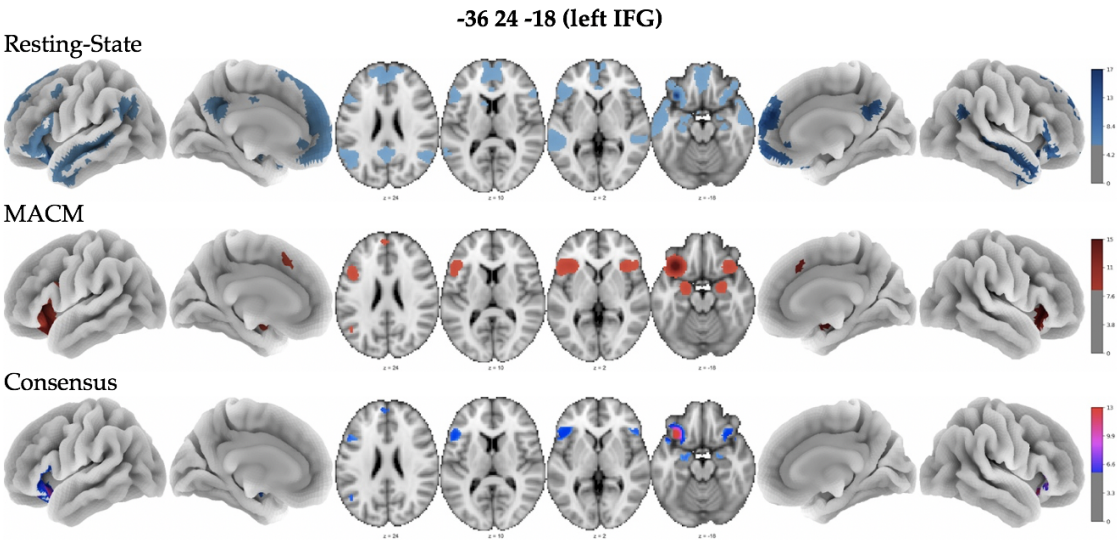


Figure 3. Functional connectivity patterns of the left IFG seed. First row: rsFC results (blue). Second row: MACM results (red). Row three: Consensus between rsFC and MACM approaches (pink). Images are thresholded at voxel-wise FWE $P < 0.001$.

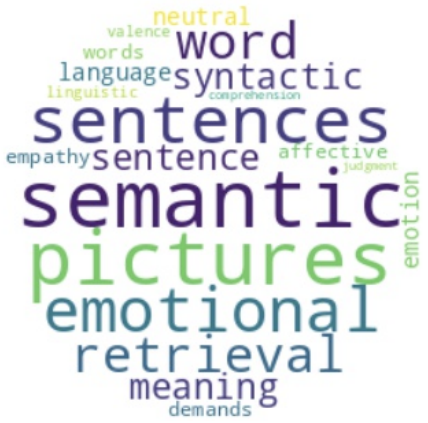


Figure 4. Functional decoding results of the left IFG seed. Functional decoding results from the unthresholded MACM map described by Neurosynth terms. Words in larger font indicate stronger associations with the functional profile of the left IFG.

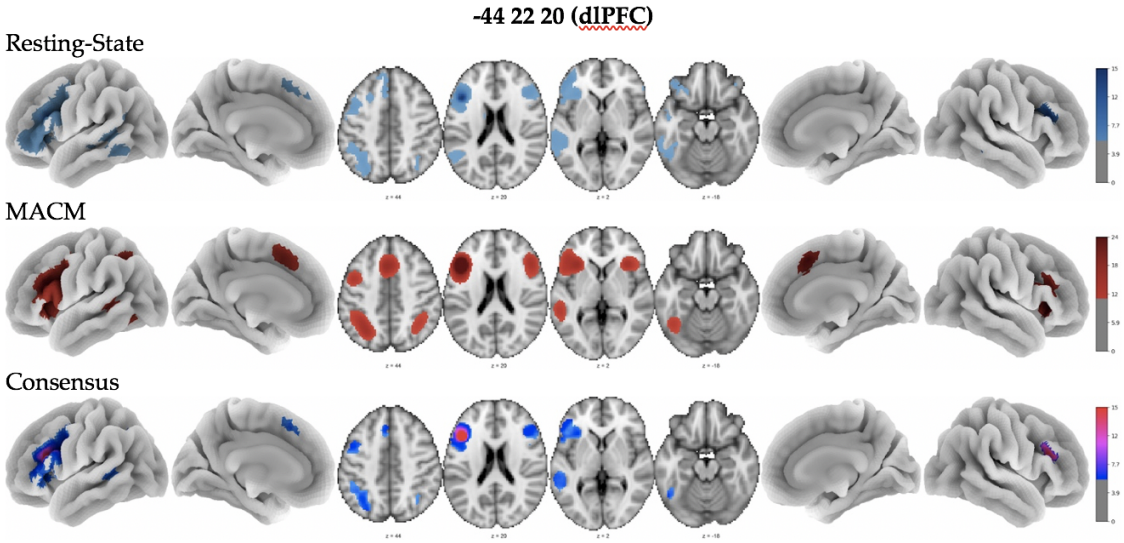


Figure 5. Functional connectivity patterns of the dlPFC seed. First row: rsFC results (blue). Second row: MACM results (red). Row three: Consensus between rsFC and MACM approaches (pink). Images are thresholded at voxel-wise FWE $P < 0.001$.

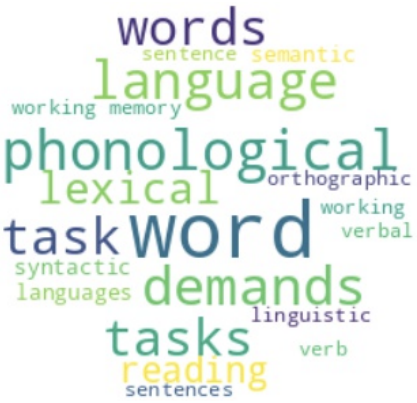


Figure 6. Functional decoding results of the left dlPFC seed. Functional decoding results from the unthresholded MACM map described by Neurosynth terms. Words in larger font indicate stronger associations with the functional profile of the dlPFC.

CHAPTER 5. CONCLUSION

This dissertation utilized structural MRI data associated with a diverse grouping of anxiety-related disorders to conduct a series of coordinate-based meta-analyses examining convergent structural alterations of anxiety. I investigated the functional connectivity patterns of these structural alterations between adult and youth groups. I utilized functional decoding techniques to characterize behavioral associations of the structural alterations between adults and youth with clinical anxiety. The work in this dissertation provides a unique meta-analytic approach to understanding the functional connectivity patterns of the convergent structural alterations associated with clinical anxiety.

Chapter 2 found the mPFC as the most robust region of convergent decreased GM in PTSD; no regions of convergent decreased GM were found. Complementary rsFC and MACM assessments utilizing the mPFC region provided insight into widespread aberrant functional connectivity between the DMN, SN, and CEN. The mental characterization of these networks included altered self-referential behavior and contextualization of symptoms associated with PTSD. Chapter 3 more broadly examined structural differences among adults and youth with clinical anxiety. The ACC and IFG regions were observed to be the most robust regions of convergent decreased GM among adults with clinical anxiety. The dlPFC was observed to be the most robust region of convergent decreased GM associated with clinical anxiety among youth. Exploratory contrast analysis in Chapter 3 confirmed these differences in GM structural alterations between adults and youth statistically significant. Chapter 4 delineated the extended functional connectivity of these structurally altered ROIs and suggested functional profiles of widespread connectivity

overlapped with the DMN, SN, and CEN. Functional decoding of the three ROIs returned behavioral terms related to self-referential, language, and emotional processes.

In sum, the current dissertation expanded on prior meta-analytic work by utilizing emergent meta-analytic techniques to provide a more comprehensive understanding of the functional connectivity patterns associated with the convergent structural alterations associated with clinical anxiety among adults and youth. Because clinical anxiety is thought to be characterized by multiple brain circuits and networks (Shin & Liberzon, 2010), I identified extended functional connectivity of the mPFC, left ACC, left IFG, closely corresponded with the DMN, SN, and CEN. Functional decoding of the functional profiles provided mental characteristics associated with self-referential, emotion, language, and executive function processes. Our findings support disrupted emotional regulation and cognitive control processes related to with the maintenance and anxiety psychopathology. The current results complement the tripartite model of psychopathology (Menon, 2011; Whitfield-Gabrieli & Ford, 2012) and provide new insight into potiential brain-based targets and treatment of anxiety-related disorders. The current dissertation provides a meta-analytic approach to disentangling the nuanced complexity of the neurobiology associated with anxiety-related conditions.

Future Considerations

The current dissertation addresses the neurobiology of anxiety-related disorders between adults and youth. Though many individual studies included this meta-analytic study contained previous DSM criteria of anxiety-related disorders, it synthesizes the previous work by confirming the structural alterations associated with clinical anxiety and

the functional connectivity of these structural brain correlations. An emerging treatment approach is transcranial direct current stimulation (tDCS). This technique is a non-invasive brain stimulation method that modulates neural activity during the completion of cognitive tasks (Nitsche et al., 2008). More recent investigations of the application of tDCS on frontal regions reduced attentional bias to threat among individuals with anxiety (de Lima et al., 2019; Heeren et al., 2017). However, future investigations of the effectiveness of tDCS are needed. The current work could provide brain-based mechanisms of focus for tDCS treatment to clinical anxiety.

This dissertation addressed short-term research goals by examining the neural correlates of psychopathology through a series of neuroimaging meta-analyses on anxiety-related disorders. However, the long-term research goals are to examine how sociocultural and environmental factors relate to differences in brain structure and function in psychopathology. I could not account for sociocultural and environmental factors in the current meta-analytic work due to inconsistencies in collecting of these measures across studies. Future work is still needed to address how these results may generalize to larger, population-based samples.

The predominance of western, educated, industrialized, rich, and democratic (WEIRD) samples throughout the scientific literature extend broadly into psychological science (Henrich et al., 2010). These likely skews models of human behavior, such as reasoning and perception, and in models for health research. The United States compromises less than 5% of the world's population (Arnett, 2008); however, American samples used in research are not demographically representative of the ethnic diversity in the country (Rad et al., 2018). Though 13.4% of the US population is Black or African

American, many Black and African Americans are not adequately represented in health and neuroscience research (Weinberger et al., 2020). The generalizability of health and neuroscience models of health might be skewed, particularly for Black, African American, and other minority communities.

Decades of work prove significant health disadvantages exist among Black and African Americans (Mays et al., 2007). Initiatives towards more inclusive samples in neuroscience, such as the African American Neuroscience Research Initiative (https://aaneurosciencesearch.com/) exist; however, Black and African Americans continue to face barriers such as distrust (Corbie-Smith et al., 2002), accessibility to healthcare (Copeland, 2005), and knowledge about research participation (Shavers et al., 2000). The barriers are also currently reflected in the COVID-19 pandemic (CDC, 2020). Systemic racism contributes to the disadvantages and adverse health outcomes among Black and African Americans (Harrell et al., 2011; Paradies et al., 2015). Race itself is not the reason for health inequities. Instead, racism causes significant distress among Black and African Americans (Thompson, 2002) and may thus be associated with negative health outcomes and societal inequities among this community. Race itself is not the reason for health inequities. Rather, racism causes significant distress among Black and African Americans (Thompson, 2002) and may thus be associated with harmful health outcomes and societal inequities among this community. These particular issues contribute to more prominent systemic barriers for the inclusion of Black and African Americans and representation of this population in neuroscience and health research (Branson et al., 2007).

The use of race and identity in America in clinical research is an ongoing, complicated debate. On the one hand, race has no biological basis (Foster, 2009), while on

the other hand, demographic data such as sex, age, and socioeconomic status (SES) are essential considerations in clinical research (Burchard et al., 2003). Access to affordable health services, working life conditions, and structural conflict are examples of the social determinants of health (WHO, 2021). The lack of measuring social determinants of health is extremely sparse or missing from neuroscience research, which ultimately is contributing to the larger, field-wide issues related to generalizability in clinical research. Focusing efforts on recruiting more racially diverse samples would provide an opportunity to advance research that reflects the ongoing growth of diversity in the US. Though racism influences health inequities among Black and African Americans, the inclusion and recruitment of participants from this background could help disentangle how systemic racism contributes to the health and mental health inequities plaguing the Black and African American community. In sum, the inclusion of social determinants of health in neuroscience research provides the potential to improve generalizability in models of health and mental health and advance the field in new ways in an ever-changing society.

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Pankey, B., Rose, S., Farhangi, S. (May 2019**).** *A Possible Barrier Affecting STEM Women of Color: The Intersectionality of International Men Faculty*. Poster presented at the annual NSF INCLUDES Symposium: Advancing Latinas in STEM Academic Careers, South Padre Island, TX.

Forscher, P. S., Taylor, V. J., Cavagnaro, D., Lewis, N. A., Jr., Buchanan, E. M., Moshontz, H., … Musser, E., Pankey, B., …Chartier, C. R. (2019, July 17). Stereotype Threat in Black College Students Across Many Operationalizations. https://doi.org/10.31234/osf.io/6hju9

Pankey, B., Melanie Stollstorff, Bethany C. Reeb-Sutherland (May, 2018). *Genetic underpinnings to race bias: the interaction between the serotonin transporter gene and race/ethnicity*. Poster presented at the annual Association for Psychological Science, San Francisco, CA.

Osibogun, O., & Pankey, B. (2017). Racial residential segregation and Poor health. *American Journal of Public Health, 107*(9), 1. doi:http://dx.doi.org/10.2105/AJPH.2017.303968