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The many faces of anxiety-neurobiological correlates of anxiety phenotypes

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ABSTRACT

Anxiety is an all-inclusive concept incorporating somatic symptoms (palpitations, dizziness, dyspnea), emotional and cognitive elements (negative affect, fear, worry, rumination) and behavioral components (e.g., avoidance). The aim of this study was to examine the specific neural correlates associated with anxiety phenotypes (worry, rumination, somatic anxiety) and negative affect (neuroticism). Twenty-nine anxious participants and 30 healthy controls were included in the study. We analyzed seed-based intrinsic connectivity and used correlation maps in a multivariable regression model to describe the specific effect of each anxiety phenotype independently of the effects of age and the other measures of anxiety. Worry severity was uniquely correlated with increased intrinsic connectivity between right anterior insula (RAI) and the precuneus. Global and somatic anxiety were associated with the limbic and paralimbic structures (increased connectivity between the amygdala, PVN, and hippocampus), while neuroticism was correlated with increased connectivity between limbic and prefrontal structures. Rumination severity did not correlate significantly with any measures of functional connectivity once we controlled for other clinical measures of anxiety. Measures of worry, global anxiety, somatic anxiety, and neuroticism have distinct 'neural signatures'. These results advocate for a fine-grain approach when analyzing the neural substrates of clinical samples with various anxiety disorders.

1. Introduction

Anxiety is an all inclusive concept incorporating somatic symptoms (e.g., palpitations, dizziness, dyspnea), emotional and cognitive elements (e.g., negative affect, fear, worry, and rumination) and behavioral components (e.g., avoidance) (Zebb and Beck, 1998). Additionally, personality traits such as neuroticism are highly comorbid with anxiety disorders (Clark et al., 1994; Hettema et al., 2004, 2006). All of these phenotypes have been the object of extensive research and have been characterized by constructs such as defensive reactivity (Lueken et al., 2013), intolerance of uncertainty (Krain et al., 2008; Simmons et al., 2008), anticipatory apprehension (Nitschke et al., 2009), emotional reactivity (Goldin et al., 2009), emotion regulation (Campbell-Sills et al., 2010), and interoceptive sensitivity (Domschke et al., 2010). Multiple studies have described several neuroimaging features of anxiety (for review see, Etkin and Wager, 2007; Hilbert et al., 2014). Most of these studies have focused on specific disorders, such as specific phobia, panic disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and social phobia. Some of the neurobiological findings implicate structures involved in heightened fear response, especially hyperactivation in the amygdala and insula in specific phobia, PTSD and social anxiety (Etkin and Wager, 2007). PTSD has been additionally linked to hypoactivity in the thalamus, the dorsal and rostral cingulate as well as the ventro- and dorsomedial prefrontal cortex (Etkin and Wager, 2007). GAD has been associated with a more polymorphic pattern, including heightened amygdala response to anticipatory threat (Nitschke et al., 2009), increased amygdala–dorsolateral prefrontal connectivity (Etkin et al., 2009), and greater insula–orbitofrontal connectivity during induction of worry (Andreescu et al., 2014a).

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The neurobiological landscape shaped by these studies offers, however, a limited view on specific anxiety phenotypes. Following the RDoC perspective to isolate core neurobiological processes linked to psychopathology, we propose in this study to identify the neural markers related to specific anxiety phenotypes such as worry, rumination, and somatic anxiety. In order to analyze the neural basis of these psychopathological components, we have used specific psychometric scales or homogenous factors extracted from well-validated psychometric scales.

In this study, we examine the functional connectivity markers correlated with three different anxiety phenotypes: worry, somatic anxiety, and rumination. We also include the total HARS as an omnibus measure of global anxiety. Additionally, we include neuroticism in the model in order to isolate the effects of personality traits. We included the neuroticism subscale from the Five Factor Inventory (FFI-N) given the well-described association between neuroticism and anxiety (Clark et al., 1994), including worry (Hale et al., 2010; Watson et al., 1994). A recent neuroimaging study (Servaas et al., 2014) examined the neural correlates of worry in association with neuroticism and found an association between neuroticism and decreased activation in the retrosplenial and visual cortex during worry induction.

In order to examine the functional connectivity correlates of anxious phenotypes, we focused on two neural networks frequently involved in anxious psychopathology, namely the Default Mode Network (DMN) and the Salience Network (SN). The DMN is an organized functional network of several brain regions: posterior cingulate cortex (PCC), medial prefrontal cortex, inferior parietal lobule, and medial temporal regions (Raichle et al., 2001). This network shows a high level of functional connectivity at rest, and its activity consistently decreases during performance of active tasks such as goal directed cognition and task engagement (Buckner et al., 2008; Raichle et al., 2001). Changes in the DMN intrinsic connectivity have been reported in social phobia and generalized anxiety (Andreescu et al., 2014b; Ding et al., 2011; Gentili et al., 2009; Liao et al., 2010; Zhao et al., 2007). The SN, comprised of the anterior insula, dorsal anterior cingulate cortex (ACC), amygdala, ventral tegmental area, and the ventromedial nucleus of the thalamus, is involved in monitoring the salience of interoceptive and external events (Craig, 2009; Menon and Uddin, 2010). Abnormal SN connectivity has been implicated in anxiety disorders as the neural basis for pathologically enhanced salience detection (Andreescu et al., 2014a; Pannekoek et al., 2012a, b; Paulus and Stein, 2006). We explored the functional connectivity of the SN using two seeds: the right anterior insula (RAI) and the left amygdala.

We also explored the functional connectivity of three additional regions-of-interest (ROI) frequently cited in the neurobiological literature of anxiety: the ventral hippocampus, implicated in emotion generation and regulation (Adhikari, 2014; Bishop, 2007; Chen and Etkin, 2013; Davis and Whalen, 2001), the bed nucleus of stria terminalis (BNST), which is considered a key brain ROI for generalized anxiety (Davis, 1998, 1999; Davis et al., 2010; Walker et al., 2009) and stress regulation (Crane et al., 2003), and the paraventricular nucleus (PVN), which is critical for both neuroendocrine and autonomic stress regulation (Flandreau et al., 2012; Pego et al., 2010).

We hypothesize that each anxiety phenotype has a different neural signature, but that all overlap partially with the neural signatures of global anxiety and neuroticism. More specifically, we hypothesized that (1) the worry phenotype will be correlated mainly with RAI and BNST connectivity (Andreescu et al., 2015; Walker et al., 2009), (2) the somatic and global anxiety will be correlated mainly with functional connectivity of the limbic/paralimbic structures (amygdala, PVN, ventral hippocampus (Bishop, 2007; Etkin and Wager, 2007)), (3) the rumination phenotype will correlate with PCC connectivity (Berman et al., 2011), and (4) the neuroticism phenotype will have a more diffuse signature, including correlations with PCC, RAI as well as limbic/paralimbic structures (Feinstein et al., 2006; Stein et al., 2007; Adelstein et al., 2011; Aghajani et al., 2013).

2. Method

2.1. Participants

The data were collected from two studies conducted at the University of Pittsburgh: "Structural and functional neuroanatomy of late-life GAD" and "A pilot fMRI study of emotion modulation in midlife anxiety." Subjects were recruited from direct advertisement through flyers, local radio and bus ads, as well as from two research registries affiliated with the University of Pittsburgh: The Advanced Center for Intervention and Services Research in Late-Life Mood Disorders (ACISR) registry and the Clinical and Translational Science Institute (CTSI) registry.

This study included participants diagnosed with GAD, as well as non-anxious participants. The primary inclusion criteria for the anxiety participants was a principal diagnosis of GAD for at least six months according to the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) and a score of 17 or higher on the HARS (Hamilton, 1959) at the time of scanning. Patients with other anxiety disorders were included if GAD was the principal diagnosis (based on severity and duration), as were patients with a past history of alcohol or substance abuse that was in full remission for at least three months. Lifetime comorbid unipolar depression was allowed if GAD was the primary diagnosis (based on duration), but subjects with current Major Depressive Disorder at the time of scanning were excluded.

Other exclusion criteria were lifetime psychosis or bipolar disorder, a diagnosis of dementia, a Mini Mental State Examination score less than 24, increased suicide risk (e.g., current ideation), medical instability according to reviews of medical chart data, ongoing psychotherapy, and current antidepressant or anxiolytic use. All subjects were psychotropic-free at the time of scanning, and they underwent a wash out period of two weeks if previously on an antidepressant (six weeks if on fluoxetine). Participants were allowed to receive non-psychotropic medications. Non-anxious participants had no history of psychiatric disorders. Both studies were approved by the University of Pittsburgh Institutional Review Board.

2.2. Clinical measures

Participants were assessed using the Hamilton Anxiety Rating Scale (HARS), the self-report Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990), the Response Style Questionnaire-Rumination Subscale RSQ-RS (Treynor et al., 2003) and the Five Factor Inventory (FFI)-Neuroticism subscale (FFI-N)(Costa, 1992).

The Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) is one of the most popular scales to measure the severity of anxiety symptoms. The 14-item assessment measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety-physical complaints related to anxiety, such as cardiovascular symptoms (e.g., palpitations, chest pain), respiratory symptoms (e.g., choking feelings, sighing, dyspnea) gastrointestinal symptoms (e.g., swallowing difficulties, burning sensations, nausea), genitourinary symptoms (e.g., urgency, premature ejaculation, etc.). While largely used as a measure of global anxiety (Clark and Donovan, 1994), the HARS has been criticized for its lack of specificity especially with regard to the somatic symptoms (Maier et al., 1988). HARS factor analysis (Serretti et al., 1999) identified