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Neurobiological Signatures of Anxiety and Depression in Resting-State Functional Magnetic Resonance Imaging

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ABSTRACT

BACKGROUND: There is increasing interest in using neurobiological measures to inform psychiatric nosology. It is unclear at the present time whether anxiety and depression are neurobiologically distinct or similar processes. It is also unknown if the best way to examine these disorders neurobiologically is by contrasting categorical definitions or by examining symptom dimensions.

METHODS: A cross-sectional neuroimaging study was conducted of patients with generalized anxiety disorder (GAD), major depressive disorder (MDD), comorbid GAD and MDD (GAD/MDD), or neither GAD nor MDD (control subjects). There were 90 participants, all medication-free (17 GAD, 12 MDD, 23 GAD/MDD, and 38 control subjects). Diagnosis/category and dimensions/symptoms were assessed to determine the best fit for neurobiological data. Symptoms included general distress, common to anxiety and depression, and anxiety-specific (anxious arousal) or depression-specific (anhedonia) symptoms. Low-frequency (.008–.1 Hz) signal amplitude and functional connectivity analyses of resting-state functional magnetic resonance imaging data focused on a priori cortical and subcortical regions of interest.

RESULTS: Support was found for effects of diagnosis above and beyond effects related to symptom levels as well as for effects of symptom levels above and beyond effects of diagnostic categories. The specific dimensional factors of general distress and anxious arousal as well as a diagnosis of MDD explained unique proportions of variance in signal amplitude or functional connectivity.

CONCLUSIONS: Using resting-state functional magnetic resonance imaging, our data show that a single conceptual model alone (i.e., categorical diagnoses or symptom dimensions) provides an incomplete mapping of psychopathology to neurobiology. Instead, the data support an additive model that best captures abnormal neural patterns in patients with anxiety and depression.

Keywords: Anhedonia, Anxiety, Depression, fMRI, Neuroimaging, Resting state

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A key issue for understanding the pathophysiology of mental illness as well as its nosology is the need to determine how symptoms relate to abnormal brain processes (i.e., putative mechanisms) (1). This issue is particularly salient for mood and anxiety disorders because comorbidity between disorders is the normative clinical course (2,3). One view that treats anxiety and depression as reflecting the same core process is supported by concordance studies indicating a shared genetic diathesis between generalized anxiety disorder (GAD) and major depressive disorder (MDD) (4,5). Symptom-based evidence also suggests a general class of "anxious-misery" disorders including GAD and MDD (6–8). However, these disorders can be differentiated with respect to illness predictors and symptoms (3,9–11). Comparisons between GAD and MDD indicate greater emotion intensity and goal motivation in GAD and lower positive affect in MDD, among other factors (10).

Not only is it unclear to what degree GAD and MDD are similar or different as disorders, but also it is unclear whether categorical definitions of GAD and MDD best capture abnormalities. Many authors have argued for understanding anxiety and depression as a set of distinct and overlapping dimensions of dysfunction (12,13). One of the most well-known models (13–15) proposes a tripartite organization: a shared general factor (general negative affect or distress) and two specific factors—anxious arousal (more central to anxiety) and low positive affect or anhedonia (more central to depression).

Complicating a clearer understanding of the neurobiology of anxiety and depressive disorders is the fact that few studies directly compare patients across these diagnostic groups (16–18). In a more recent study, we found that only patients with GAD (with or without MDD) showed a behavioral deficit in emotion regulation; this was not present for patients with MDD only (19). This deficit reflected an abnormality in cingulate-amygdala circuitry normally required for this task (20) as well as a unique (compensatory) pattern of activation in patients with MDD only. In a study of anxious and depressed adolescents, Beesdo *et al.* (21) found both common and disorder-specific

abnormalities in amygdala activation during emotional face processing. All patients had greater amygdala activation to fear faces when focused on their own emotions, but facial affect interactions divided patients into complex patterns during passive viewing.

Broadly comparing anxiety and depression, it may be advantageous to examine task-independent brain activity, allowing assessment across brain regions that may not be involved in a particular task. A powerful tool for doing so is resting-state functional magnetic resonance imaging (fMRI), in which intrinsic activity and connectivity of brain circuitry can be examined across many brain systems and regions (22). Separate resting-state studies of patients with GAD and patients with MDD have implicated abnormalities in many structures, including amygdala, hippocampus, ventral striatum, insula, dorsal and subgenual anterior cingulate (ACC), and dorsolateral and medial prefrontal cortices (DLPFC, mPFC) (23–32). It is still unclear how these brain areas covary in patients as a function of pathophysiology. Analyses of the relationship between anxiety symptoms in healthy subjects and resting-state brain activity have demonstrated effects in many of these same regions (33–35). However, to our knowledge, anxiety and depression have never been directly compared using task-independent resting-state methods, and categorical and dimensional conceptualizations have not been evaluated in a single cohort.

In this study, we sought to answer the following three questions: 1) Are neural signatures of anxiety and depression consistent with their being common or distinct neurobiological processes? 2) What are the relative contributions of categorical and dimensional formulations of anxiety and depression on neural processes? 3) Which brain regions are most strongly related to anxiety and depression? We analyzed models of combined categorical and dimensional factors according to the amplitude of the low-frequency resting-state signal within each region as well as functional connectivity between regions, measured as time series correlations between region pairs. All participants were medication-free when scanned.

To ensure a comprehensive categorical analysis, we recruited participants with a diagnosis of GAD, with a diagnosis of MDD, with both diagnoses, or with neither diagnosis. Because these three groups overlapped by symptom profiles, we were similarly able to conduct dimensional analyses. For the categorical analyses, separate predictors corresponding to a diagnosis of GAD or MDD allowed us to examine disorder-specific effects, whereas a single predictor corresponding to either diagnosis tested for a general patient deficit relative to controls. By having partially overlapping patient groups and modeling diagnoses together, we allowed for the possibility that abnormalities in one diagnostic group (e.g., MDD) could be best explained by its frequent comorbid diagnosis (e.g., GAD) or the possibility that individual diagnoses could explain independent neural abnormalities even after accounting for the presence of the other diagnosis. For dimensional analyses, we used the Mood and Anxiety Symptom Questionnaire (36), developed to assess the common symptom domain of general distress elevated across anxiety and depressive disorders, and specific domains of anxious arousal and anhedonia in accordance with the dimensional tripartite model of anxiety and depression. Three separate models were run for each metric (signal amplitude and functional connectivity): individual categorical and dimensional models were first run to establish possible relationships between these factors and brain measures. Next, to understand further the primacy of either categorical or dimensional measures for explaining variability in brain measures, we combined categorical and dimensional measures in a simultaneous regression. This strategy allowed for uncovering additive or overlapping predictors across categories and dimensions depending on which measures were the strongest predictors and which explained unique brain variability after accounting for the other factors.

METHODS AND MATERIALS

Participants

After providing informed consent, 90 subjects participated in this study; these subjects largely overlapped with the subjects reported in our articles on task-based fMRI (19,23,37). Current-episode DSM-IV–based psychiatric diagnoses (38) were determined with the Mini International Neuropsychiatric Interview (39,40). Participants included 38 healthy control subjects, 17 subjects with a primary diagnosis of GAD and no MDD, 12 subjects with a primary diagnosis of MDD and no GAD, and 23 subjects with both diagnoses (see Table S1 in Supplement 1 for other comorbidities). Exclusion criteria were the presence of substance abuse or posttraumatic stress disorder; a history of a neurologic disorder or severe mental illness (psychosis or bipolar); a history of head trauma or loss of consciousness; claustrophobia; or regular use of benzodiazepines, opiates, or thyroid medications. All control subjects were free of current or past Axis I conditions or psychiatric medications. No patient took a benzodiazepine within 48 hours of the scan, and all patients were free of antidepressant medication for >6 weeks.

fMRI Data Acquisition and Processing

Neuroimaging data were acquired on a 3-Tesla GE Signa scanner (GE Healthcare, Milwaukee, Wisconsin) using a custom-built eight-channel head coil. Functional data were acquired in 29 axial slices (4.0-mm thickness, .5-mm gap) across the whole brain using a T2*-weighted gradient echo spiral (in/out) sequence (repetition time = 2 sec; echo time = 30 msec; flip angle = 80°; 1 interleaf; field of view = 22 cm; 64 × 64 matrix; 236 volumes) (41). Instructions for the 8-min resting-state scan asked participants to keep still, keep their eyes closed, and let their mind wander. An automated high-order shim for spiral acquisitions was used before acquiring fMRI data (42). A high-resolution T1-weighted three-dimensional inversion recovery spoiled gradient recoil anatomic scan (inversion time = 300 msec; repetition time = 8 msec; echo time = 3.6 msec; flip angle = 15°; field of view = 22 cm; 124 coronal plane slices; matrix = 256 × 192; 2 excitations; acquired resolution = 1.5 mm × 0.9 mm × 1.1 mm) was acquired in the same session as fMRI data.

Physiologic variability recorded in respiration and heart rate pulse oximetry was used for fMRI data correction as an initial preprocessing step (image based using acquisition timing relative to phases of cardiac and respiratory cycles) (43). Motion (middle volume reference; 12 degrees of freedom affine, FSL FLIRT [FMRIB Linear Image Registration Tool, University of