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Alterations in Amygdala-Prefrontal Functional Connectivity Account for Excessive Worry and Autonomic Dysregulation in Generalized Anxiety Disorder

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ABSTRACT

BACKGROUND: Generalized anxiety disorder (GAD) is characterized by the core symptom of uncontrollable worry. Functional magnetic resonance imaging studies link this symptom to aberrant functional connectivity between the amygdala and prefrontal cortex. Patients with GAD also display a characteristic pattern of autonomic dysregulation. Although frontolimbic circuitry is implicated in the regulation of autonomic arousal, no previous study to our knowledge combined functional magnetic resonance imaging with peripheral physiologic monitoring in these patients to test the hypothesis that core symptoms of worry and autonomic dysregulation in GAD arise from a shared underlying neural mechanism.

METHODS: We used resting-state functional magnetic resonance imaging and the measurement of parasympathetic autonomic function (heart rate variability) in 19 patients with GAD and 21 control subjects to define neural correlates of autonomic and cognitive responses before and after induction of perseverative cognition. Seed-based analyses were conducted to quantify brain changes in functional connectivity with the right and left amygdala.

RESULTS: Before induction, patients showed relatively lower connectivity between the right amygdala and right superior frontal gyrus, right paracingulate/anterior cingulate cortex, and right supramarginal gyrus than control subjects. After induction, such connectivity patterns increased in patients with GAD and decreased in control subjects, and these changes tracked increases in state perseverative cognition. Moreover, decreases in functional connectivity between the left amygdala and subgenual cingulate cortex and between the right amygdala and caudate nucleus predicted the magnitude of reduction in heart rate variability after induction.

CONCLUSIONS: Our results link functional brain mechanisms underlying worry and rumination to autonomic dyscontrol, highlighting overlapping neural substrates associated with cognitive and autonomic responses to the induction of perseverative cognitions in patients with GAD.

Keywords: Amygdala, Functional connectivity, Functional magnetic resonance imaging, Generalized anxiety disorder, Heart rate variability, Perseverative cognition

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Excessive and uncontrollable worry is an established central feature in the definition of generalized anxiety disorder (GAD). Importantly, worry has to be accompanied by symptoms of negative affect and tension and perceived by the individual as "difficult to control" according to DSM-5. The high prevalence of GAD creates a massive economic burden (1,2), yet its core symptom remains poorly characterized from a neurobiological perspective. The "spontaneous" nature of intrusive thoughts suggests that the neurobiological processes underpinning worry may be better examined over periods of free thinking rather than during behavioral engagement with an external task. Therefore, resting-state neuroimaging would be a useful tool for examining dysfunctional neural circuitry in GAD.

The few published functional connectivity studies of GAD focus largely on the amygdala and associated networks, following evidence for the central contribution of the amygdala to fear and threat processing (3). Resting-state neuroimaging studies support the view that perturbed amygdala-prefrontal connectivity underlies the core features of GAD (4). Decreased connectivity between the amygdala and lateral prefrontal cortex (PFC) was reported in adults (5) and adolescents with GAD (6,7). More recently, aberrant amygdala connectivity with ventromedial PFC and insula was noted in youths with anxiety disorders (8). Amygdala-based connectivity is found to be negatively correlated with anxiety rating scores (9,10).

Taken together, these findings point to a neural basis for emotion regulation deficits in GAD, centered on reduced

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functional connectivity within this major frontolimbic pathway. Conversely, effective emotion regulation and anxiety control are predicted by efficient communication between the amygdala and PFC. For example, the positive reappraisal of negative emotional material strengthens connectivity between the amygdala and medial prefrontal regions, with self-reported effectiveness of emotion regulation correlating positively with the degree of functional coupling (11). Moreover, effective emotion regulation evokes a selective increase in connectivity of the amygdala with ventromedial PFC and dorsolateral PFC (12).

Emotion dysregulation in GAD is expressed through poor prefrontal control of worrisome thoughts and chronic failure to downregulate autonomic arousal (13). Medial prefrontal cortices and amygdala are implicated in states of autonomic arousal during mental and emotional stress. These states are characterized by shifts in parasympathetic to sympathetic balance in which baroreflex suppression manifests as increased heart rate (HR) and blood pressure and decreased heart rate variability (HRV) (14,15).

Decreased HRV is a notable autonomic signature of worry states (16,17). However, to our knowledge, no detailed characterization of functional brain processes linking worry to measured changes in autonomic arousal has been conducted in patients with GAD. We combined resting-state functional magnetic resonance imaging (fMRI) with concurrent autonomic measurement, focusing on HRV as a measure of vagally mediated parasympathetic change. The simultaneous assessment of cognitive and physiologic correlates of GAD is particularly relevant in light of a previous study associating self-reported experience of worry and autonomic arousal with distinct patterns of neural connectivity (18).

We used a seed-based approach to analyze our resting-state fMRI data, first to validate earlier findings of decreased amygdala-prefrontal connectivity in patients with GAD compared with healthy control (HC) subjects and second to test the hypothesis that a behavioral induction of perseverative cognition (i.e., worry or rumination) will alter (uncouple) amygdala-prefrontal connectivity. To our knowledge, only one study (focusing on elderly patients) compared the consequences of a worry induction on neural connectivity patterns in GAD (19). The induction may place participants in a task-based state; therefore, our use of the term "resting state," motivated by the absence of direct instructions, should be considered with this caveat in mind.

In line with a dimensional view of psychopathology, we hypothesized that the induction will change the pattern of connectivity in HC subjects to the pattern more typically associated with patients with GAD and that such changes will reflect the dispositional tendencies (trait measures) of individuals to engage in perseverative cognition. We anticipated that resting-state amygdala connectivity reflects ongoing state measures of core GAD symptoms. Drawing on the theoretical model that the PFC downregulates amygdala responses to (real or perceived) threat, we hypothesized that aberrant resting amygdala-PFC would predict increases in self-reported state worry.

Similarly, given the involvement of PFC regions and amygdala in autonomic control (14,15,20–24) and notably in HRV (25), we tested the relationship between amygdala connectivity and changes in HRV in response to the induction. The HRV is a positive marker for emotion regulation (26) and is diminished during maladaptive emotion regulation processes, including worry (27,28). We hypothesized that changes in amygdala-PFC caused by the induction of perseverative cognition would correlate with reductions in HRV evoked by the same induction. We expected these relationships to be amplified in patients with GAD compared with HC subjects (29).

METHODS AND MATERIALS

Participants

All participants provided written informed consent. The study was approved by the National Research Ethics Service with local approval of the Brighton and Sussex Medical School Research Governance and Ethics Committee. After excluding one participant who did not complete the full experiment, the sample comprised 19 patients (17 women, 2 men; mean age, 29.58 ± 6.93 years) who met diagnostic criteria for GAD and 21 HC subjects (18 women, 3 men; mean age, 28.67 ± 9.45 years) (Supplement).

Procedure

The Structured Clinical Interview for DSM-IV was administered by a trained postdoctoral fellow (FM) to patients and HC subjects to confirm or exclude the diagnosis of GAD. To assess comorbid disorders, participants were asked if they currently or previously had a diagnosis of any other psychiatric disorder or had ever been treated by their general practitioner for symptoms other than anxiety. None of the participants had a formal diagnosis of comorbid major depressive disorder. Participants completed a series of online questionnaires on sociodemographic and dispositional traits. Participants were subsequently familiarized with the neuroimaging environment, were connected to the physiologic recording equipment, and underwent the MRI protocol.

Questionnaires

All participants completed a set of questions assessing sociodemographic and lifestyle information (nicotine, alcohol, and caffeine consumption; physical activity). To assess physical activity, participants were asked to report the type and amount (hours/week) of exercise they regularly did and how active they considered themselves compared with others of the same age and sex. Based on their responses, their perceived physical fitness was classified as low, medium, or high. Dispositional measures of 1) stress-reactive rumination (Stress-Reactive Rumination Scale [SRRS]) (30), 2) depressive rumination (Ruminative Response Scale) (31), and 3) worry (Penn State Worry Questionnaire [PSWQ]) (32) were also obtained.

Experimental Design

In the MRI scanner, participants underwent a series of four 5-minute resting-state periods, each followed by a 6-minute easy visuomotor tracking task (described elsewhere) (C. Ottaviani, Ph.D., unpublished data, 2015). During resting-state periods, participants were instructed to rest with their eyes open without thinking of anything and not falling asleep.