Commentary

Biological Psychiatry

Brain Connectivity Reflects Mental and Physical States in Generalized Anxiety Disorder

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Since Rene Descartes proposed that the mind and body are distinct interacting entities, the mind–body relationship has fueled intense philosophical inquiry and scientific study. Modern neuroscience and physiology have since demonstrated that mind–body interactions occur via complex feedback mechanisms on various levels. However, our understanding of the mind–body relationship still falls short of a unified conceptualization, particularly in the area of mental illness. Consider generalized anxiety disorder (GAD), a highly impairing condition identified by core symptoms segregated into these two very distinct domains: chronic, pervasive worry and difficulty concentrating (the mind); and feeling restless/on edge, easily fatigued, and experiencing muscle tension (the body). Cartesian mind–body dualism continues to influence the field of psychiatry, where attempts to conceptualize a disorder such as GAD emphasize the distinctiveness of the two. Worry is thought to defend against future stressor-induced physiological reactivity, and this reactivity reduction is thought to reinforce the propensity for the mind to engage in worry (1). Although studies have probed how worry engages brain circuitry in GAD, none have examined how brain circuitry mediates the interface between the pathological worry and alterations in peripheral physiology that characterize the disorder.

In this issue, Makovac *et al.* (2) address this question by examining the relationship between heart rate variability (HRV) and amygdala connectivity at rest and following the induction of perseverative dysphoric cognition (rumination or worry). HRV is of particular relevance to GAD given that 1) it is an indicator of parasympathetic modulatory capacity, i.e., how well one can inhibit a tonic cardiac input for sympathetic activation; 2) it serves as an autonomic marker of worry states; and 3) HRV is chronically decreased in GAD (3). The amygdala is a core neural substrate for GAD (4) and is crucial to the detection of salient emotional stimuli, the engagement of physiological fight-or-flight readiness, and the subjective experience of fear (5). Prior work in GAD has demonstrated that the amygdala displays highly variable patterns of connectivity abnormalities at rest—both increased (6) and decreased (7) connectivity with prefrontal regions, important for cognitive control and emotion regulation, and both increased (7) and decreased (6) connectivity with paralimbic substrates, e.g., the insula and anterior cingulate cortex, important for awareness of one's physiological state and how this fits into the context of one's experience. Thus, understanding how patterns of amygdala connectivity with these targets change from rest to induction of perseverative dysphoric cognition and how these changes relate to changes in peripheral physiology are both of key importance in understanding the neurocircuitry underlying the mind–body manifestations of GAD.

Makovac *et al.* (2) acquired resting-state functional magnetic resonance imaging on 19 individuals with GAD and 21 matched healthy comparison participants before and after the induction of perseverative cognition. Participants were asked to recall a past episode that made them sad, anxious, or stressed or to think about a future situation that worries them, and they gave ratings regarding how distracted they were by external stimuli, internal stimuli, and worry/rumination before and after. Measures of HR and HRV were collected throughout.

Consistent with prior findings (3), individuals with GAD displayed elevated HR and decreased HRV prior to the induction, indicating deficient parasympathetic modulation of cardiac tone in the absence of any induced affect. Moreover, they displayed a breakdown in connectivity between the right amygdala and the right dorsal cingulate and prefrontal cortex, consistent with prior findings of deficient fronto-amygdalar resting state connectivity in GAD (7). Prior to and across induction, GAD individuals reported greater levels of rumination/worry and being more distracted. Induction increased HR across both groups and decreased distraction from external stimuli, indicating the expected drive toward internal focus on dysphoric cognition. There was no differential effect of the induction in the GAD group on rumination/worry, distraction, or change in cardiac measures (though the GAD group trended toward having a greater HRV reduction). Importantly, there was no main effect of induction on HRV, which unfortunately renders the physiological significance of the manipulation challenging to interpret.

Fronto-amygdalar connectivity patterns reversed between groups following the induction, albeit at trend-level significance, such that individuals with GAD showed an increase in the connectivity between these regions (which were low at baseline) whereas healthy participants showed a decrease in connectivity. This crossover effect is challenging to interpret, as there were disorder-related fronto-amygdalar connectivity differences both pre- and postinduction. It does, however, suggest a mismatch between normative patterns of connectivity and those in GAD participants at rest, regardless of the affective context. Thus, contrary to expectations for an amplified effect of the induction on relationships between fronto-amygdalar connectivity and HRV in GAD, these findings illustrate a notable physiological and experiential invariance in GAD participants to an induced change in the affective context despite shifts in fronto-amygdalar connectivity.

The relevance of physiological and neural abnormalities in GAD prior to the induction is further illustrated in findings for

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preinduction connectivity predicting change in postinduction HRV and self-reported worry/rumination. The authors interpret relationships between brain connectivity and change in perseverative cognition and HRV as reflecting effects of the induction. However, an important caveat to consider is that this finding may also reflect preinduction relationships between neural and physiological measures, which were not reported or controlled for.

Regardless, this study provides important insight into how mind–body alterations in GAD are reflected in brain connectivity. Most generally, these findings remind us that dysfunction in the brain, physiology, and subjective experience of individuals with psychopathology is far generalized beyond the contexts, behaviors, or perceptual triggers that we conceptualize to be relevant to the clinical presentation—in this case, worry and rumination. Disorder-related alterations can be as prominent, if not more so, during an unconstrained resting state as during symptom provocation, as we see here. More specifically, these findings implicate a functional disconnect between the amygdala, a key structure underlying the attribution of salience to a perceptual stimulus (5) and the dorsal cingulate. The dorsal cingulate has been repeatedly implicated in sympathetic activation, covariation with HR acceleration, and other peripheral cardiac measures of elevated arousal (8), and the connectivity breakdown observed here is informative in the context of elevated HR and decreased HRV. One interpretation the authors offered was that this reflected a breakdown in prefrontal control of the amygdala-mediated anxiety state, but other interpretations are also plausible. Perhaps it is just as likely that this disconnect reflects a tonic elevation in dorsal cingulate activity at rest (consistent with numerous observations for positive relationships between elevated sympathetic cardiac activity and dorsal cingulate cortex recruitment) (8) or a combination of exaggerated dorsal cingulate–driven top-down control of the internal milieu alternating with exaggerated amygdala-driven exteroceptively oriented fear and arousal. The amygdala has also been related to cardiac measures of sympathetic arousal, but more typically in contexts that involve the presentation of perceptual stimuli (9) as opposed to those involving internally generated affective states such as perseverative cognition. Thus, future mechanism-focused work will be needed to bring clarity to these possible explanations.

From a clinical theoretical and treatment development perspective, these findings highlight the possibility that the cognitive and physiological alterations in GAD reflect an imbalance between the imposition of top-down control on the internal affective milieu and openness toward experiencing bottom-up reactivity to the affective shifts in the environment. Although worry was originally conceptualized as a form of emotional avoidance in GAD (1), more recent evidence indicates worry actually induces a mild, prolonged state of negative affect, which is theorized to attenuate the magnitude of affective shift, i.e., emotional contrast, from an unexpected or surprising negative emotion induction (e.g., worrying about losing one's job induces a negative emotional state that is closer to the emotional state experienced when actually losing one's job) (10). Therefore, it is reasonable to theorize that the fronto-amygdalar and amygdalo-insular connectivity abnormalities so frequently observed in GAD at rest reflect the varying configurations of this imbalance between a stimulus-independent prolonged cognitive vigilance and a stimulus-dependent exaggerated physiological reactivity. Indeed, the pathological neural and physiological alterations observed in GAD when reacting to an emotional stimulus (4) and at rest (6,7) suggest a two-pronged approach toward treatment—increasing resting parasympathetic modulation of physiological state via relaxation training, acceptance, and mindful awareness of interoceptive states, and sympathetic activation via exposure exercises targeted at emotional contrast avoidance, i.e., inducing an unexpected, high-magnitude change in affective state from highly relaxed to highly aroused (10). The combination of both approaches may yield the most effective treatment package for GAD—specifically, increasing an individual's tolerance, acceptability, and capability of dynamically shifting across a wide range of mind–body states while preventing the affective constriction reflected in chronically dysphoric mind states and tonically elevated bodily arousal.

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