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Acute cortisol reactivity attenuates engagement of fronto-parietal and striatal regions during emotion processing in negative mood disorders

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ABSTRACT

Objective: Depression and bipolar disorder (negative mood disorders, NMD) are associated with dysregulated hypothalamic-pituitary-adrenal (HPA)-axis function and disrupted emotion processing. The neural networks involved in attenuation of HPA-axis reactivity overlap with the circuitry involved in perception and modulation of emotion; however, direct links between these systems are understudied. This study investigated whether cortisol activity prior to undergoing fMRI was related to neural processing of emotional information in participants with NMD.

Methods: Forty-one adults (M_{age} = 40.33, *SD* = 15.57) with major depression (n = 29) or bipolar disorder (n = 12) and 23 healthy control comparisons (M_{age} = 36.43, *SD* = 17.33) provided salivary cortisol samples prior to completing a facial emotion perception test during 3-Tesla fMRI.

Results: Overall, pre-scan cortisol level was positively associated with greater engagement of the dorsal anterior cingulate (dACC), inferior parietal lobule, insula, putamen, precuneus, middle and medial frontal and postcentral gyri, posterior cingulate, and inferior temporal gyrus during emotion processing of all faces. NMD status moderated this effect; in NMD participants' pre-scan cortisol was associated with attenuated activation of the insula, postcentral gyrus, precuneus, and putamen for fearful faces and the medial frontal gyrus for angry faces relative to HCs. Cortisol-related attenuation of activation among NMD participants was also observed for facial identification in the dACC, putamen, middle temporal gyrus, precuneus, and caudate.

Conclusions: Across all participants, cortisol was associated with greater activation in several regions involved in the perception and control of emotion. However, cortisol responsivity was associated with hypoactivation of several of these regions in the NMD group, suggesting that HPA-axis activity may selectively interfere with the potentially adaptive recruitment of circuits supporting emotion perception, processing and/or regulation in mood disorders.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is the primary circuit of the neuroendocrine stress system and an essential route by which the brain influences many psychological processes, including emotion processing, emotion regulation, and cognitive functioning (Tsigos and Chrousos, 2002). Major depressive disor-

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der (MDD) and bipolar disorder (BP) are often characterized by increased activity of the HPA-axis (Kamali et al., 2012; Stokes, 1995; Watson et al., 2006), as well as deficits in emotion regulation (Joormann and Quinn, 2014) and cognitive processes involved in allocating attention and modulating affect (Murrough et al., 2011). A biobehavioral construct thought to cut across both MDD and BP is response to acute threat, which is directly relevant to the negative valence systems that are characteristic of these two disorders. Behaviorally, an acute threat response is frequently organized through emotion processing, which is supported, in part, at the neurobiological level by neuroendocrine response and the integrity of functional neural circuits. Thus, in line with the Research Domain Criteria (RDoC) initiative, it is valuable to move beyond operationalizing MDD and BP as independent constructs or homogenous disorders, and instead, leverage individual differences to better understand how neuroendocrine and neurofunctional systems contribute to the range of negative mood disorders (NMD) that are characterized by disrupted negative valence systems. By way of guiding hypotheses relevant to these constructs, the subsequent literature covered addresses 1) targets of the HPA-axis in the central nervous system (CNS), 2) functional role of brain-based endocrine targets in emotional salience, and 3) cognitive and emotional control, 4) existing neural correlates of disrupted HPA-axis functioning, and 5) how the study of neuroendocrine and functional systems can advance understanding of the pathophysiology of NMDs.

1.1. Targets of the HPA-axis in the central nervous system

Acute stress (Bifulco et al., 2000; Lupien et al., 2009), such as the presentation of a fearful stimulus, can trigger temporary activation of the HPA-axis; namely, secretion of corticotropin releasing hormone from the hypothalamus, release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, and increased secretion of cortisol from the adrenal cortex. Accumulation of stress exposures over time can disrupt the feedback pathways of the HPA-axis and down regulate glucocorticoid receptors (GR), resulting in hypercortisolemic disruptions that commonly characterize chronic NMDs (Parker et al., 2003). Further, some central tissues in the stress response system such as the hippocampus, express abundant mineralocorticoid receptors (MR), but are relatively deficient in enzymes that protect against cortisol binding, ultimately resulting in an aldosterone-cortisol imbalance (Funder, 2005). Importantly, elevated levels of cortisol can lead to cortical atrophy, perhaps through reduced dendritic arborization, with a preferential impact upon limbic system structures such as the hippocampus, amygdala, and medial and orbital prefrontal cortex, where densities of GR and MR are high (Bao et al., 2008; Lupien et al., 2009). Dysregulated HPA-axis function, therefore, may provide one possible mechanism for how disrupted neural structures and circuitry influence emotion processing and regulation in mood disorders.

1.2. Functional role of CNS endocrine targets

1.2.1. Emotional salience

Indeed, the networks (e.g., salience and emotion, default mode) with high GR/MR receptor densities overlap with cognitive and affective networks that process emotional experience among healthy individuals. Following fearful eliciting stimuli, increased activity in the hippocampus is understood to facilitate down-regulation of the HPA axis via inhibitory connections to the paraventricular nucleus of the hypothalamus (Jankord and Herman, 2008), resulting in an inverse association between hippocampal activation and cortisol secretion (Kern et al., 2008; Liu et al., 2012; Pruessner et al., 2008). Increased activation in both the amygdala and insula has been positively related to cortisol levels, suggesting that these regions, which underlie saliency, emotion, and attention, also participate in the recruitment and ongoing stimulation of the HPA axis (Langenecker et al., 2012). The sensitivity of these specific structures to negative emotional content is relevant to features of anxiety such as fear, threat detection, and avoidance (Etkin and Wager, 2007; Seeley et al., 2007).

Given the anatomical projections and functional connections of the insula to the amygdala (Banks et al., 2007), an extended salience and emotion network is presumed to serve broad functions in emotion perception, including mind–body integration of affective information and visceral and autonomic processing (Paulus and Stein, 2006; Zald, 2003). In addition, although neuroimaging stress literature has been historically dominated by focus on the amygdala and hippocampus as pivotal mediators of the stress response (Dedovic et al., 2009; McEwen, 2007; Phillips and LeDoux, 1992), fear evoking stimuli are also thought to alter motivational processes by increasing dopamine secretion in the brain's "reward system", supported primarily by striatal regions (Haber and Knutson, 2010; O'Doherty, 2004). Preclinical evidence indicates a robust role of the ventral (nucleus accumbens) and dorsal (caudate, putamen) striatum in reward and stress processing (Cabib and Puglisi-Allegra, 2012; Sesack and Grace, 2010). These findings are corroborated by human neuroimaging studies where engagement of striatal regions during reward processing (Knutson et al., 2008) and decision-making (Forbes et al., 2006) has been linked to affect regulation in response to stress (Forbes et al., 2009). Indeed, high cortisol response to psychosocial stress in healthy individuals has been shown to prevent reductions in sensitivity toward reward as evidenced by hyperactivity in the nucleus accumbens (Oei et al., 2014).

1.2.2. Cognitive and emotional control

The neural networks involved in cortisol modulation also share functions with the circuitry implicated in control and modulation of emotion. A frontal-subcortical problem-solving circuit operates in the "top down" regulation of cognitive and behavioral inhibition and guides the selection of actions based on reward expectations. This circuit, which is often referred to as the cognitive control network (CCN) (Bonelli and Cummings, 2007; Chudasama and Robbins, 2006; Seo et al., 2012), includes the anterior cingulate, inferior frontal gyrus, inferior parietal lobule, caudate, thalamus, globus pallidus, and putamen (Bonelli and Cummings, 2007; Chudasama and Robbins, 2006; Seo et al., 2012). Positive associations have been established between cortisol levels and activation within this network, such as in parietal, ventrolateral and dorsolateral prefrontal areas (Kern et al., 2008; Weerda et al., 2010). Left and right lateral PFC activation has been associated with increased and decreased cortisol reactivity to psychosocial stress, respectively (Kern et al., 2008; Sullivan and Gratton, 2002; Taylor et al., 2008; Wang et al., 2005), and activation of the medial PFC has been associated with decreased cortisol reactivity to stress (Kern et al., 2008). In addition, increased cortisol during emotion processing has been shown to engage the caudate while successfully directing attention away from negative content and towards positive affect (Dedovic et al., 2015). Given the functional connections between the PFC and limbic, parietal, and striatal structures that are important for the integration of emotion and cognition (Seeley et al., 2007), the CCN is likely active in the down-regulation of the stress response and might facilitate attenuation of cortisol levels (Amodio and Frith, 2006; Phelps, 2004; Urry et al., 2006; Veer et al., 2012).

1.3. Neural correlates of disrupted HPA-axis functioning

Although the fundamental and adaptive purpose of the HPA-axis is to mobilize resources for defense during acute stress and/or threat response, and subsequently for repair and healing (Susman, 2006), this biological response system can become dysregulated