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Research paper

A pilot investigation of differential neuroendocrine associations with fronto-limbic activation during semantically-cued list learning in mood disorders

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ABSTRACT

Background: : Decreased volume and disrupted function in neural structures essential for memory formation (e.g. medial temporal lobe and prefrontal cortex) are common among individuals with depression. Hypothalamic-pituitary-axis function, as reflected by measurement of cortisol levels, is linked to neural activity during memory encoding in healthy people. However, it is not as well understood whether cortisol is associated with alterations in fronto-temporal recruitment during memory encoding in depression.

Methods: : In this pilot study, we evaluated associations between cortisol and neural activation during memory encoding in 62 adults (18–65 years) with mood disorders (MD; n = 39, 66.7% female), including major depression (n = 28) and bipolar I disorder (n = 11), and healthy controls (HC; n = 23, 43.5% female). Participants provided salivary cortisol samples before and after completing a semantically-cued list-learning task during 3-Tesla fMRI. Links between pre-scan cortisol (and cortisol change) and activation during encoding were evaluated using block and event-related models.

Results: : Overall, pre-scan cortisol level was positively associated with greater engagement of fronto-limbic activation during the encoding block. However, in MD, pre-scan cortisol was associated with attenuated activation during encoding in medial frontal, superior and middle temporal gyri, insula, lingual gyrus, and claustrum relative to HCs. Cortisol-related attenuation of activation in MD was also observed during encoding of words subsequently recalled in the ventral anterior cingulate, hypothalamus, and middle temporal gyrus. By and large, cortisol change (pre/post scan) predicted the same pattern of findings in both block and event-related contrasts.

Limitations: : Although analyses accounted for variations in scanner time of day, circadian alterations in cortisol may have introduced variability into the results.

Conclusions: : Pre-scan cortisol may selectively interfere with recruitment of important fronto-temporal memory circuitry in mood disorders. The inverted associations between cortisol and neural function in MD relative to HC also elucidate potentially unique pathophysiological markers of mood disorders.

1. Introduction

Mood disorders (MD), such as major depressive disorder (MDD) and bipolar disorder (BD) are characterized by objective impairments in episodic memory of moderate effect sizes; these include tests of verbal list learning, recall, and working memory (Ahern and Semkovska, 2017; Langenecker et al., 2010). The neural basis for learning and memory decrements may relate to significant overlap between brain regions recruited for encoding and retrieval and the neural alterations characteristic of depression (Okon-Singer et al., 2015). Fundamentally,

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encoding and recall are thought to rely upon the integrity of the Papez Circuit (Papez, 1937), including the hippocampus, fornix, parahippocampal gyrus, mammillary bodies, insula, and cingulate gyrus. Because successful encoding and retrieval additionally rely on intact attention, working memory, and executive functioning, memory processes are also understood to draw upon fronto-parietal networks (Kizilirmak et al., 2015; Luckmann et al., 2014). Indeed, hippocampal and frontal lobe volumes are inversely linked to memory performance in MDD (Ajilore et al., 2015; Cao et al., 2016; Engvig et al., 2014; Jayaweera et al., 2016; Marano et al., 2015; Turner et al., 2012). Increasingly, functional MRI (fMRI) has also revealed alterations in limbic, fronto-parietal, and fronto-subcortical circuitry during verbal memory tasks (Kassel et al., 2016; Kelley et al., 2013; Miskowiak et al., 2016; Oertel-Knochel et al., 2013; Rao et al., 2016; Weisenbach et al., 2014).

Hypothalamic-pituitary-adrenal (HPA)-axis function represents a possible pathway in the development of alterations in neural structures and circuitry supporting encoding and subsequent recall in mood disorders (Tsigos and Chrousos, 2002). The HPA-axis has a central role in regulating many homeostatic systems in the body, in large part through secretion of corticosteroid hormones from the adrenal glands (Bifulco et al., 2000; Lupien et al., 2009a). In humans, cortisol exerts its effects on cognitive, emotional, and metabolic processes by binding to glucocorticoid receptors (GR) diffusely located throughout cerebral structures (Parker et al., 2003) and mineralocorticoid (MR) receptors predominantly located in limbic structures (Funder, 2005). Cortisol has a preferential impact in the hippocampus, amygdala, and prefrontal cortex where GR and MR receptors are co-localized (Bao et al., 2008; Lupien et al., 2009b). Continuous hyper-activation of the HPA-axis has been associated with dendritic retraction, neuronal death, and suppressed neurogenesis in these areas, thereby increasing susceptibility to a variety of mental and physical health conditions (Magarinos et al., 1996; Sapolsky, 1994, 2000). Indeed, hyperactivity of the HPA-axis has been found in several case control studies of MDD and BD reflected by high basal cortisol levels, an altered diurnal rhythm, decreased escape from dexamethasone suppression, and exaggerated responses in the combined dexamethasone-CRH challenge test (Barden, 2004; Kamali et al., 2012; Stokes, 1995; Watson et al., 2006). However, there is a degree of variability in these findings, as low basal cortisol has also been associated with depression (Maripuu et al., 2014, 2017; Wardenaar et al., 2011).

There is also significant variability with respect to whether cortisol relates to improved versus impaired learning and recall (Shields et al., 2017) and increased or decreased activation of the Papez circuit during encoding and recall (van Stegeren, 2009). Variability in the effects of cortisol on memory encoding and consolidation, specifically, are especially pronounced in depression (de Quervain et al., 2009; Finsterwald and Alberini, 2014; Wolf, 2009), with both enhancing (Kukolja et al., 2008; Pruessner et al., 2007) and impairing (Elzinga et al., 2005; van Stegeren, 2009) effects reported. Moreover, emotional state at the time of glucocorticoid elevations also alters cortisol effects on neural function and subsequent recall (de Kloet et al., 1999; Joels and Krugers, 2007; Okuda et al., 2004; Roozendaal et al., 2006). Additionally, variability might relate to the methodological challenges of isolating memory functions from executive organizational strategies or the possible influence of immediate rehearsal, which facilitates memory consolidation (Schallmo et al., 2015a). Thus, the integration of fMRI with measurement of cortisol and encoding with limited reliance on executive function in mood disorders, may provide increased clarity regarding role of the HPA-axis in the integrity of encoding circuitry and pathophysiology of mood disorders (Peters et al., 2016b; Weldon et al., 2015a).

The aim of the present pilot study was to evaluate associations between blood-oxygen-level dependent (BOLD) activation during encoding and pre-scan cortisol among healthy individuals and those with active mood disorders. Critically, the present study extends previous work by measuring how levels of endogenous cortisol prior to fMRI might relate to functional activation patterns and memory task performance. Specifically, we use the Semantic Learning Task (Schallmo et al., 2015), which employs a Brown-Peterson paradigm to minimize rehearsal of recent words. This method diminishes the contributions of individual variability in working memory to overall memory recall, thereby isolating encoding processes. The task also includes semantic organizational cues (e.g. semantic clustering) for both encoding and recall to minimize the influence of executive functioning resources on performance. Finally, we compare patterns of activation between healthy individuals and those with a mood disorder to dissociate global and disease-specific associations between cortisol and memory circuitry. As endocrine alterations are associated with both unipolar depression and bipolar disorder (Barden, 2004; Kamali et al., 2012; Stokes, 1995; Watson et al., 2006), the inclusion of both diagnoses was intentional - leveraging individual differences to better understand how neuroendocrine function may contribute to cognitive sequalae across the full range of mood dysfunction. This approach is directly in line with the Research Domain Criteria (RDoC) initative to better delineate the shared and overlapping, rather than distinct, neurobiological features of psychiatric constructs.

Given the evidence for HPA hyperactivity in mood disorders, and the preferential impact of cortisol on brain regions dense in GR and MR receptors, we hypothesized that higher pre-scan cortisol levels would predict decreased activity in frontal and medial temporal regions that often characterizes encoding among MD individuals (Kassel et al., 2016; Weisenbach et al., 2014). We were specifically interested in the effects of pre-scan cortisol because fMRI scans have been shown to evoke an anticipatory stress response (that is present before but normalizes after the scan) in both depressed (Peters et al., 2011) and healthy (Weldon et al., 2015) individuals. In contrast, consistent with prior healthy control (HC) findings (van Stegeren, 2009), we expected that neural activation in HCs would remain robust to variations in pre-scan cortisol. Exploratory analyses evaluated whether these neural alterations were associated with change in cortisol before/after scanning and subsequent memory recall performance.

2. Methods and materials

2.1. Participants

Adults aged 18–65 (M = 38.84, SD = 16.21) years with a mood disorder (MD: MDD [n = 28] or BD I disorder [BD; n = 11]) and healthy comparisons without a mood disorder (HC; n = 23) were recruited for one of three studies; a study of emotion processing in HC (Langenecker et al., 2012), an investigation of emotion processing in MDD and HC (Briceno et al., 2013) and a study of emotion processing in BD I and HC (Ryan et al., 2015). At the time of enrollment and scanning, MD participants were in a depressed state or in partial-remission from a major depressive episode and currently reporting at least two residual depressive symptoms. All MD participants had a mimimum score of 10 on the Hamilton Depression Rating Scale [HDRS; (Hamilton, 1960a)] and partial remission was defined as an HDRS between 10–13. Based on these criteria, n = 15 of 39 MD participants were in partial remission. Suicidality was assessed via the HDRS and the Structured Clinical Interview for DSM-IV [SCID-I; (First, 1995)]; participants with passive suicidality were not excluded, but participants were excluded for acute plan with intent.

The research was conducted at the University of Michigan and participants were recruited de novo from the surrounding community, and consented in accordance with Institutional Review Board approval. Participants were excluded for any medical disorder (including hypertension or diabetes) or recent infection, medication use to treat physical conditions (including hormonal contraceptives or menopausal hormone therapy and antibiotics), use of tobacco products, current alcohol or substance use disorder, history of head injury or neurological