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Research paper

Neural - hormonal responses to negative affective stimuli: Impact of dysphoric mood and sex

K. Mareckova[a,b], L. Holsen[a], R. Admon[c], S. Whitfield-Gabrieli[d], L.J. Seidman[e], S.L. Buka[f], A. Klibanski[g], J.M. Goldstein[a,h,*]

[a] Connors Center for Women's Health and Gender Biology, Department of Medicine, Brigham and Women's Hospital; Department of Psychiatry, Harvard Medical School (HMS), Boston, MA, USA
[b] CEITEC, Masaryk University, Brno, Czechia
[c] McLean Hospital, Department of Psychiatry, HMS, Boston, MA, USA
[d] Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA
[e] Beth Israel Deaconess Medical Center, Division of Public Psychiatry, Massachusetts Mental Health Center; Department of Psychiatry, HMS, Boston, MA, USA
[f] Department of Community Health, Brown University, Providence, RI, USA
[g] Massachusetts General Hospital, Department of Medicine, Neuroendocrine Unit; HMS, Department of Medicine, Boston, MA, USA
[h] Departments of Psychiatry and Medicine, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Background: Maladaptive responses to negative affective stimuli are pervasive, including clinically ill and healthy people, and men and women respond differently at neural and hormonal levels. Inspired by the Research Domain Criteria initiative, we used a transdiagnostic approach to investigate the impact of sex and dysphoric mood on neural-hormonal responses to negative affective stimuli.

Methods: Participants included 99 individuals with major depressive disorder, psychosis and healthy controls. Functional magnetic resonance imaging (fMRI) was complemented with real-time acquisition of hypothalamo-pituitary-adrenal (HPA) and -gonadal (HPG) hormones. fMRI data were analyzed in SPM8 and task-related connectivity was assessed using generalized psychophysiological interaction.

Results: Across all participants, elevated cortisol response predicted lower brain activity in orbitofrontal cortex and hypothalamus-amygdala connectivity. In those with worse dysphoric mood, elevated cortisol response predicted lower activity in hypothalamus and hippocampus. In women, elevated cortisol response was associated with lower activity in medial prefrontal cortex and low hypothalamo-hippocampal connectivity. In women with high dysphoric mood, elevated cortisol response was associated with low hypothalamo–hippocampal connectivity. There were no interactions with diagnosis or medication.

Limitations: There was limited power to correct for multiple comparisons across total number of ROIs and connectivity targets; cortisol responses were relatively low.

Conclusions: We conclude that the pathophysiology in neural-hormonal responses to negative affective stimuli is shared across healthy and clinical populations and varies as a function of sex and dysphoric mood. Our findings may contribute to the development of hormonal adjunctive therapeutics that are sex-dependent, underscoring the importance of one's sex to precision medicine.

Introduction

Maladaptive responses to negative affective stimuli are pervasive across healthy and ill populations, and men and women respond differently at the neural and hormonal levels. This is not surprising given that brain regions that regulate responses to negative affective stimuli, subsequently referred to as “stress response”, are highly sexually dimorphic (Tobet et al., 1993, 2009; Filipek et al., 1994; Giedd et al., 1996; Goldstein et al., 2001), regulate the hypothalamic pituitary adrenal and gonadal (HPA and HPG) axes (Keverne, 1988; Tobet and Hanna, 1997; Östlund et al., 2003; Swaab, 2004; Bao et al., 2005), arousal (Keverne, 1988; McEwen and Magarinos, 1997; Price, 1999) and mood (Mareckova et al., 2016). Brain regions include: periaqueductal gray (PAG), hypothalamus (HYPO), amygdala (AMYG), hippocampus (HIPP), and medial and orbital prefrontal cortices (mPFC, OFC) (see Mareckova et al. (2016)), areas of the brain that have been found

* Correspondence to: Connor's Center, Brigham and Women's Hospital, One Brigham Circle, 3rd flr. 1620 Tremont Street, Boston, MA 02120, USA.
E-mail address: jill_goldstein@hms.harvard.edu (J.M. Goldstein).

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to be abnormal structurally and functionally across a number of psychiatric disorders.

Understanding the physiology and the impact of sex on the regulation of responses to negative affective stimuli may provide clues to the development of therapeutics that may be shared across disorders. In fact, the NIMH Research Domain Criteria (RDoC; Insel et al., 2010) initiative argues that it is critical to identify neurobiologic signatures at the level of genes, brain circuits, and physiology associated with behavioral traits that are shared across broadly defined diagnostic categories (Van Os and Kapur, 2009). Consistent with this approach, we aimed to identify neural and hormonal responses to negative affective stimuli across individuals with varying levels of dysphoric mood, regardless of their diagnosis (major depressive disorder, bipolar disorder, schizophrenia), and the sex differences therein (Pariante and Lightman, 2008; Holsen et al., 2013; Dedovic and Ngiam, 2015; Colich et al., 2015; Mocking et al., 2015; Pruessner et al., 2013; Goldstein et al., 2010b and 2015; Belvederi Murri et al., 2016).

Neural responses to stress are defined by their associated physiology. That is, stress triggers secretion of corticotropin-releasing hormone (CRH) by the hypothalamic paraventricular nucleus (PVN), which in turn triggers release of adrenocorticotropin hormone (ACTH) from the anterior pituitary, and ultimately release of cortisol from the adrenal cortex (Tsigos and Chrousos, 2002; Goldstein et al., 2014). The PVN, located in anterior hypothalamus, is considered the key relay center for HPA axis function (Herman et al., 1996; Goldstein et al., 2007; Tobet et al., 2013; Evanson and Herman, 2015; Laryea et al., 2015). It receives negative feedback from stress circuitry regions with high densities of glucocorticoid receptors, particularly from hippocampus, and, to a lesser extent, from amygdala and medial and orbital prefrontal cortices (mPFC, OFC) (De Kloet et al., 1998; Myers et al., 2012). Cortisol is the most direct measure of "stress hormone physiology" related to HPA axis functioning (Dickerson and Kemeny, 2004; Bozovic et al., 2013), and it provides a stimulus for negative feedback that attenuates activity of the PVN through limbic (hippocampal) and mPFC areas (Herman et al., 2005). Behavioral studies reported a positive relationship between negative affect trait and cortisol response (Mendonca-De-Souza et al., 2007; Quiring et al. (2009). Functional MRI (fMRI) studies showed that increased cortisol response predicted blood oxygen level dependent (BOLD) signal activity in limbic and frontal regions (Thomason et al., 2011; Collip and Nicolson, 2011; Holsen et al., 2013; Goldstein et al., 2014), modulating neural circuits related to affect and cognition (Henckens et al., 2010; Holsen et al., 2011).

The current study investigated the coupling between neural and hormonal physiology during a mild visual stress task with negative valence/high arousal and neutral valence/low arousal images adapted from the International Affective Picture System (IAPS; Lang et al., 2008) for this fMRI paradigm (Goldstein et al., 2005). The ability of this task to evoke BOLD responses in the neural circuitry associated with arousal and negative affect has been demonstrated in multiple studies of ours over the last 11 years in healthy populations and distinct psychiatric disorders (i.e., Goldstein et al., 2005; and 2010a, 2010b; Holsen et al., 2011, 2012, 2013; Jacobs et al., 2015), and recently, we demonstrated shared brain activity responses in the regions listed above across healthy and ill populations in the same sample as reported here (Mareckova et al., 2016). The ability of this task to elicit HPA response has been demonstrated by Admon et al. (2015) and Holsen et al. (2013).

Brain activity in response to negative affective stimuli in these regions has also been reported by others using passive viewing of negative valence/high arousal stimuli (van Stegeren et al., 2007; Cunningham-Bussel et al., 2009; Root et al., 2009) or other stress-related paradigms, including psychosocial stressors such as mental arithmetic task with continuous negative feedback on task performance (Wang et al., 2007; Pruessner et al., 2008). Activity in these regions has been associated with physiologic responses, including cortisol response (e.g. Urry et al., 2006; Liberzon et al., 2007; Kern et al., 2008; Cunningham-Bussel et al., 2009; Veer et al., 2012; Holsen et al., 2013) and loss of parasympathetic cardiac tone (Holsen et al., 2012). This is consistent with other studies linking hypercortisolemia (Collip and Nicolson, 2011) and autonomic arousal (Wik and Wiesel, 1991; Lane and Wager, 2009) with response to negative affective stimuli. Further, exogenous administration of cortisol has been significantly associated with decreased activation of the AMYG and HIPP during rest (Lovallo et al., 2010).

Substantial data support sex differences in neural and physiologic responses to stress in healthy (Kudielka and Kirschbaum, 2005; Goldstein et al., 2010a) and clinical populations with psychiatric disorders associated with this circuitry, such as major depressive disorder (MDD) and schizophrenia. Women are at significantly higher risk for mood disorders (Kendler, 2006; Kessler, 2003; Goldstein et al., 2014; Seney and Sibille, 2014) and demonstrate greater arousal to aversive cues (Lane et al., 1997; Lang et al., 1998; Bradley et al., 2001; Caseras et al., 2007) than men (although this varies in healthy women by timing of menstrual cycle). Sex differences may be related to the fact that the brain regions implicated in stress response and HPA axis function include some of the most sexually dimorphic nuclei in the brain (Tobet et al., 1993, 2009; Filipek et al., 1994; Giedd et al., 1996; Goldstein et al., 2001). While women have significantly larger hippocampal volumes, relative to cerebrum size (Filipek, 1994; Giedd, 1996; Goldstein, 2001), men have relatively larger volumes of the amygdala (Giedd, 1996; Goldstein, 2001), many of the hypothalamic nuclei (Swaab and Fliers, 1985), paracingulate gyrus (Goldstein, 2001; Paus, 1996), and mPFC (Goldstein, 2001). These regions are also dense in sex steroid receptors (McEwen, 1981; Keverne, 1988; Östlund et al., 2003; Bao et al., 2005).

Sex differences in stress response and the prevalence of psychiatric disorders have also been linked to dysregulation of HPG function. Human studies have found deficits in gonadal function in MDD (Goldstein et al., 2014; Rubinow and Schmidt, 1996; Harlow et al., 2003; Jacobs et al., 2015), including androgens (Rubinow and Schmidt, 1996; Schweiger et al., 1999; Seidman et al., 2001; Weiner et al., 2004), estradiol (Young et al., 2000; Holsen et al., 2011; Jacobs et al., 2015; Harlow et al., 2003), and progesterone (Schiller et al., 2014). HPA (e.g., hypercortisolemia) and HPG (hypogonadal) deficits have also characterized people with psychotic disorders, such as schizophrenia and bipolar disorder (Collip et al., 2011; Walker and Diforio, 1997; Walder et al., 2000; Seeman and Lang et al., 1990; Canuso et al., 2000; Kulkarni et al., 2001).

This study builds on the fMRI findigns of Mareckova et al. (2016) and extends them by studying the coupled hormonal responses acquired *in real time* during the functional imaging. Based on the substantial body of functional imaging work relating endocrine function with mood regulation (e.g. Goldstein et al., 2010a; Root et al., 2009; Pruessner et al., 2008; Wang et al., 2007; Stark et al., 2006; Goldstein et al., 2005; Andreano and Cahill, 2010; Protopopescu et al., 2005; Amin et al., 2006) and reports on abnormal HPA axis functioning (Carroll et al., 1976, Carroll and Mendels, 1976) and response to stress (Burke et al., 2005), we hypothesized that sex and dysphoric mood symptomatology would be associated with deficits in neural-hormonal response to negative affect. We predicted that women would demonstrate stronger coupling between neural and cortisol responses to negative affective stimuli than men and that these sex differences would be further modulated by the levels of androgens in men and estradiol in women. We also predicted that the coupling of neural and cortisol responses would increase as a function of worsening mood. These hypotheses were explored initially in the context of BOLD response and additionaly in the context of connectivity between hypothalamus, the key relay station for HPA axis function, and the other ROIs defined in Mareckova et al. (2016). Findings will contribute to elucidating the neural and physiologic mechanisms regulating stress and mood responses and the impact of sex.