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Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle

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Summary Although ovarian hormones are thought to have a potential role in the well-known sex difference in mood and anxiety disorders, the mechanisms through which ovarian hormone changes contribute to stress regulation are not well understood. One mechanism by which ovarian hormones might impact mood regulation is by mediating the effect of psychosocial stress, which often precedes depressive episodes and may have mood consequences that are particularly relevant in women. In the current study, brain activity and mood response to psychosocial stress was examined in healthy, normally cycling women at either the high or low estradiol phase of the menstrual cycle. Twenty eight women were exposed to the Montreal Imaging Stress Task (MIST), with brain activity determined through functional magnetic resonance imaging, and behavioral response assessed with subjective mood and stress measures. Brain activity responses to psychosocial stress differed between women in the low versus high estrogen phase of the menstrual cycle: women with high estradiol levels showed significantly less deactivation in limbic regions during psychosocial stress compared to women with low estradiol levels. Additionally, women with higher estradiol levels also had less subjective distress in response to the MIST than women with lower estradiol levels. The results of this study suggest that, in normally cycling premenopausal women, high estradiol levels attenuate the brain activation changes and negative mood response to psychosocial stress. Normal ovarian hormone fluctuations may alter the impact of psychosocially stressful events by presenting periods of increased

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vulnerability to psychosocial stress during low estradiol phases of the menstrual cycle. This menstrual cycle—related fluctuation in stress vulnerability may be relevant to the greater risk for affective disorder or post-traumatic stress disorder in women.

1. Introduction

The sex difference in affective and stress-related disease rates (2 to 3 times greater incidence and prevalence of major depression in women compared to men (Bromet et al., 2011; Kessler et al., 2005)) emerges at puberty and remains until menopause (Kessler et al., 1994). The stress exposure model of depression suggests that MDD is the result of a vulnerability to depression, combined with the trigger of stressful life events (Hankin et al., 2007; Liu and Alloy, 2010). Accordingly, psychosocial stressors are among the top reported antecedents to depression episodes (Frank et al., 1994; Kendler et al., 1999; Kendler et al., 2000), and dysregulation of the hypothalamic—pituitary—adrenal (HPA) axis response is a consistent finding in major depression (Burke et al., 2005; Lupien et al., 2009). Psychosocial stress may be especially important in the etiology of mood disorders in women as the depressogenic effects of life stressors are reportedly greater in women than men (Mezulis et al., 2010), even when there is no difference in the number of stressful life events or in the subjective perception of these events (Korszun, 2009). Although this finding is consistent and has been replicated by studies across the globe (Bromet et al., 2011), the reasons for the sex difference in incidence and prevalence of mood and anxiety disorders are not well understood. The cortisol response to stress shows consistent sex differences (Vamvakopoulos, 1995), and changes across the menstrual cycle, decreasing during the late follicular phase when circulating estrogen is high (Kirschbaum et al., 1999). Women are more likely than men to show variations in HPA function in response to stressors (Weiss et al., 1999) and during depressive episodes (Korszun, 2009). These differences in stress system response likely contribute to mood disorder risk in women (Weiss et al., 1999), and may be modulated by ovarian hormone fluctuations across the menstrual cycle (Kajantie, 2006; Roca et al., 2005). The role of corticosteroids in stress response and regulation is well known, however the effects of gonadal steroids (e.g. estradiol) — which may be specifically important in women — are less well characterized.

The concurrence of increased major depression disorder (MDD) and post-traumatic stress disorder (PTSD) risk in women during the reproductive period of life suggests that the cyclic fluctuation of ovarian hormones during this period may contribute to the risk for psychopathology. Understanding the role of ovarian hormones in emotional processing and mood regulation in women may provide important insight into the mechanisms underlying the stress response and potentially the increased incidence of MDD and PTSD in women.

Ovarian hormones may modulate the effects of stress on mood. Brain areas that are central to mood regulation (including the amygdala and hippocampus) show some of the largest densities of estrogen receptors in the human brain (Merchenthaler et al., 2004; Ostlund et al., 2003); interestingly, those areas are also very rich in cortisol receptors. Estrogen may modulate the activity of these areas; large community and clinic based studies indicate that negative mood complaints (Davydov et al., 2005; Gonda et al., 2008) (even in healthy women) and suicidal behavior (Baca-Garcia et al., 2004; Saunders and Hawton, 2006) increase in women during low estrogen phases of the menstrual cycle. Brain activity related to processing negative emotional information is also modulated by changing estradiol levels across the menstrual cycle (Goldstein et al., 2005; Merz et al., 2012), suggesting that estrogen may alter the mood response to negative information, making this information more or less salient to cognitive processes and subsequently mood states.

Although there is strong evidence that estrogen modulates the response to negatively valenced stimuli, such as negative images (Andreano and Cahill, 2010; Goldstein et al., 2005), the effect of estrogen on the response to psychosocial stress is less well understood. Animal models suggest that female rodents do not gain the same beneficial effect of acute stress on hippocampally-mediated or prefrontal tasks as male animals, and that high estrogen levels enhance the negative effects of stress in these areas (Shansky et al., 2004; Shors and Leuner, 2003). In contrast studies in ovariectomized female rats indicate that estrogen replacement increases resilience to stress in earned helplessness models and support hippocampal plasticity (Bredemann and McMahon, 2014; Smith et al., 2010). The modulation of stress effects on brain activity and function remain unclear and likely depend on the type of stress and measure of function (Shansky, 2009). The effects of estradiol on the cognitive consequences or brain activity in women have not been widely investigated. Previous studies have generally compared stress response in women during the early follicular phase and mid luteal phase. However, this approach precludes examining the effects of estradiol separately from progesterone (Kirschbaum et al., 1992; Kirschbaum et al., 1999). Additionally, few of these studies have included subjective mood measures, and the measurement of stress response solely through free circulating (salivary) cortisol is complicated by menstrual effects on cortisol binding globulin and adrenocorticotropic hormone sensitivity. Psychosocial stress differs from processing emotional information in a number of ways — stress includes elements of self-esteem, uncontrollability, and personal threat. Further, studies using performance — based stressors provide evidence that there is a sex difference in the endocrine (cortisol) response to this type of stress, and that cycling ovarian hormones may modulate this response in women (Kirschbaum et al., 1992; Kirschbaum et al., 1999). Social-evaluative threat is one element of psychosocial stress that may be especially salient for women, and has face validity for the real life stressors women experience and that contribute to mood disorder risk (Kendler et al.,