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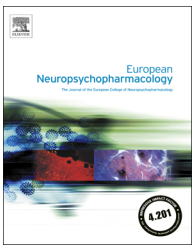

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Premenstrual dysphoric disorder and prefrontal reactivity during anticipation of emotional stimuli

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Abstract
Premenstrual disorder (PMDD) affects around 5% of women in childbearing ages. An increased sensitivity in emotion processing areas of the brain to variations in ovarian steroid levels has been suggested as part of the pathophysiology in PMDD, but prior neuroimaging studies of emotion processing are yet inconclusive. Previous behavioral studies of women with PMDD have, however, reported enhanced luteal phase startle responsivity during emotional anticipation. Here we used functional magnetic resonance imaging (fMRI) to investigate central neural circuitry activity during anticipation of, and exposure to, emotional stimuli across the menstrual cycle in women with and without PMDD. As compared to healthy controls, women with PMDD displayed significantly enhanced reactivity in the prefrontal cortex during anticipation of, but not exposure to, negative emotional stimuli during the luteal phase. In PMDD patients, BOLD reactivity during anticipation or viewing of negative emotional stimuli was not dependent on absolute levels of estradiol or progesterone. However, progesterone levels were positively correlated with emotion-induced reactivity in the dorsolateral prefrontal cortex to positive emotional stimuli. These findings suggest that cortical emotional circuitry reactivity

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood oxygenation level dependent; CD-scale, cyclicty diagnoser scale; dlPFC, dorsolateral prefrontal cortex; DICOM, digital imaging and communications in medicine; DSM, diagnostic and statistical module of mental disorders; fMRI, functional magnetic resonance imaging; HC, healthy control; IAPS, international affective pictures system; IFG, inferior frontal gyrus; k, cluster size; M.I.N.I., mini international neuropsychiatric interview; MNI, montreal neurological institute; MR, magnetic resonance imaging; NIfTI, neuroimaging informatics technology initiative; OFC, orbitofrontal cortex; PMDD, premenstrual dysphoric disorder; ROI, regions of interest; SPM, statistical parametric mapping; T, tesla; TE, echo time; TR, time of repetition

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during anticipation is altered in PMDD during the luteal phase, which might be part of the pathophysiology behind the emotional symptoms or lack of emotional control reported by women with PMDD.

1. Introduction

Premenstrual dysphoric disorder (PMDD) affects 4–6% of women in childbearing ages (Sveindóttir and Bäckström, 2000). Core PMDD symptoms are mainly affective and include depressed mood, irritability, emotional lability and anxiety. As PMDD symptoms appear only during the luteal phase of the menstrual cycle (Helbreich et al., 2003), disappear during anovulatory menstrual cycles (Wyatt et al., 2004) and are reinstated with combined estradiol and progesterone administration (Segebladh, et al., 2009), ovarian steroids are etiologically implicated. In addition, women with PMDD display increased scores of anxiety-related personality traits (Freeman et al., 1995; Gingnell et al., 2010) and are more prone to experience panic attacks during exposure to anxiety-producing agents (Gorman et al., 2001; Harrison et al., 1989; Sandberg et al., 1993), indicating an increased vulnerability for anxiety in PMDD.

Anticipation shapes our experience of emotional events (Onoda et al., 2008; Sarinopoulus et al., 2010), and women with PMDD may be more susceptible to anticipatory modulation during the luteal phase. For instance, we have previously demonstrated that women with PMDD have increased luteal-phase potentiation of the acoustic startle response during emotional anticipation (Bannbers et al., 2011). Possibly, anticipation of emotional events may influence the experienced symptomatology during the premenstrual period.

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), are useful tools to gather further insight into CNS processing. Thus far only three fMRI studies in women with PMDD have been published, two using inhibition tasks with (Protopopescu et al., 2008) and without (Bannbers et al., 2011) emotional content and one study using an emotional task (Gingnell et al., 2012). The study by Protopopescu et al. (2008) reported increased emotion-induced amygdala reactivity during the luteal phase in women with PMDD, but prior results from our lab indicate that a luteal phase associated increase in amygdala reactivity is only found in individuals with high anxiety-proneness (Gingnell et al., 2012). Two structural studies using fMRI and PET also suggest that cerebellar volume and glucose consumption might be affected in women with PMDD (Rapkin et al., 2011, Berman et al., 2013). In addition, lower menstrual cycle variability in serotonin 5-HT_{1A} binding (Jovanovic et al., 2006) and altered cortical GABA levels have been reported in women with PMDD (Epperson et al., 2002). No previous brain imaging studies of anticipation processing have been conducted in PMDD patients.

Anticipation of emotional events is generally associated with activation of the prefrontal cortex (PFC), including medial and prefrontal parts of Brodmann areas (BA) 6, 8, 9, 10, and anterior cingulate cortex (ACC) (BA 24 and 32) (Bermpohl et al., 2006; Herwig et al., 2007; Ueda et al., 2003). Studies also suggest a role for the insula in emotional anticipation, at least in individuals with a predisposition for anxiety (Simmons et al., 2006) and in women with post traumatic stress disorder (PTSD) (Simmons et al., 2008). Furthermore, enhanced amygdala reactivity during exposure to anticipated negative emotional stimuli has been observed (Ueda et al., 2003).

Stimulus-induced emotional processing activates the amygdala, ACC and insula, forming a hypothesized emotion processing network (Davidsson et al., 2000) where also areas of the ventromedial and orbitofrontal cortex are involved (Fusar-poli et al., 2009; Pessoa and Adolphs, 2010;). Increases in amygdala reactivity during emotional processing are linked to negative affective states like anxiety (Etkin and Wager, 2007; Ressler and Mayberg, 2007). Across the menstrual cycle, amygdala reactivity has been reported to increase in the luteal phase of healthy women (Gingnell et al., 2012; Ossewaarde et al., 2010; Andreano and Cahill, 2010), while findings in women with PMDD are less conclusive (Protopopescu et al., 2008; Gingnell et al., 2012).

In the present study we used fMRI during an emotional anticipation task to study if brain reactivity during anticipation and emotional processing differ between women with PMDD and healthy controls and if menstrual cycle phase influences the group differences.

We hypothesized that women with PMDD would have increased anticipatory reactivity during the luteal phase, both in comparison with healthy controls and their own follicular phase anticipatory reactivity. As previous studies on anticipation and emotion processing demonstrate involvement of both prefrontal and subcortical areas, we hypothesized that the increase in reactivity during anticipation would be located in the orbitofrontal, medial and dorsolateral PFC (BA 6, 8, 9 and 10), ACC, insula and amygdala (Bermpohl et al., 2006; Davidsson et al., 2000; Herwig et al., 2007; Ueda et al., 2003; Simmons et al., 2008, 2006).

During exposure to emotional stimuli we predicted an increased reactivity in amygdala, ACC and insula as well as prefrontal areas (BA 6, 8, 9 and 10) in all participants (Fusar-poli et al., 2009; Pessoa and Adolphs, 2010; Etkin et al. 2011; Davidsson et al., 2000). However, as prior result of emotional stimuli across the menstrual cycle among women with PMDD are inconclusive (Protopopescu et al., 2008; Gingnell et al., 2012), we did not have a directional hypothesis about the difference between groups.

2. Experimental procedures

2.1. Participants

37 women with self experienced PMDD were recruited through newspaper advertisement and among women seeking help for premenstrual symptoms at the out-patient ward of the Department of Obstetrics and Gynecology, Uppsala University Hospital. Upon screening, seventeen women were excluded (no informed consent (n=12), ongoing treatment for PMDD or immediate request for treatment (n=3), or