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Menstrual cycle effects on amygdala reactivity to emotional stimulation in premenstrual dysphoric disorder

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ABSTRACT

Premenstrual dysphoric disorder (PMDD) with luteal phase related anxiety and mood swings compromise quality of life in around 4% of reproductive women. While anxiety is related to amygdala function, prior studies on amygdala reactivity both in healthy controls and women with PMDD are inconsistent with respect to menstrual cycle effects. Here women with PMDD and healthy controls were exposed to emotional faces during the mid-follicular and late luteal phase, and mean blood-oxygen-level dependence (BOLD) signal changes in the amygdala were determined with functional magnetic resonance imaging (fMRI). Women with PMDD had enhanced bilateral amygdala reactivity in the follicular phase in comparison with healthy controls, but there was no difference between groups during the luteal phase. In contrast, healthy controls displayed higher left amygdala reactivity in the luteal than in their follicular phase. However, among women with PMDD follicular phase progesterone serum concentrations were positively correlated with bilateral amygdala reactivity while depression scores were positively correlated with right amygdala reactivity in the luteal phase. In addition, women with PMDD and high scores on trait anxiety had increased right amygdala reactivity in the luteal as compared to the follicular phase. Finally, amygdala reactivity was more prone to habituation in women with PMDD, as they had enhanced amygdala reactivity in comparison with controls at the first, but not the second scanning session. Thus, while the study failed to indicate increased luteal phase amygdala reactivity in women with PMDD, our findings suggest that anxiety proneness and progesterone levels modulate menstrual cycle related amygdala reactivity in women with PMDD.

Introduction

Premenstrual dysphoric disorder (PMDD), characterized by recurrent luteal phase-associated mood and anxiety symptoms, affects 3–5% of women of reproductive age (Sveindottir and Backstrom, 2000). Symptoms occur only during ovulatory menstrual cycles in the presence of a corpus luteum (Sundstrom et al., 1999) and disappear within a few days after menstrual onset (Halbreich et al., 2007). The symptom cyclicity as well as symptom induction by exogenous estradiol and/or progesterone administration suggests an etiological role for the ovarian hormones (Segebladh et al., 2009).

Several lines of reasoning predict enhanced amygdala reactivity in women with PMDD. First, PMDD is classified as a mood and anxiety disorder in DSM IV and enhanced amygdala reactivity is a characteristic feature of other anxiety disorders (Fredrikson and Furmark, 2003; Fredrikson et al., 1995; Lorberbaum et al., 2004; Straube et al., 2006). Also, women with PMDD display higher startle response than healthy women (Bannbers et al., 2011; Kask et al., 2008) and the neural pathways mediating enhanced startle responses involve medial temporal lobe areas including the amygdala (Pissiota et al., 2003).

The amygdala, as all parts of the limbic system, is rich in both estradiol and progesterone receptors (McEwen, 1988; Osterlund et al., 2000a, b). Both ovarian hormones are accumulated in the brain (Bixo et al., 1986), and a human post mortem study indicated that the highest brain levels of progesterone are, in fact, found in the amygdala (Bixo et al., 1997). However, imaging studies on amygdala reactivity throughout the menstrual cycle are thus far not consistent: Increased amygdala reactivity to emotional stimuli has been found in the follicular as well as the luteal phase, and is reported to correlate both positively and negatively with progesterone (Andreano and Cahill, 2010; Derntl et al., 2008; Ossewaarde et al., 2010; van Wingen et al., 2008). Previous studies indicate an increased prevalence of anxious personality traits in women with PMDD (Critchlow et al., 2001; Freeman et al., 1995; Gingnell et al., 2010). In analogy with the enhanced amygdala reactivity found in patients with anxiety disorders (Fredrikson and Furmark, 2003; Fredrikson et al., 1995; Lorberbaum et al., 2004; Straube et al., 2006) and in healthy

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controls with anxiety-related personality traits (Etkin et al., 2004), it might be argued that an increased amygdala reactivity should characterize women with PMDD and high levels of trait anxiety.

The aims of this study were to test if women with PMDD display increased amygdala reactivity in the luteal as compared to their follicular phase and if reactivity is higher in women with PMDD than in controls during the luteal phase. A secondary aim was to evaluate the influence of trait anxiety levels and ovarian steroid serum concentrations on amygdala reactivity. Further studies on ovarian steroid interactions with amygdala reactivity might be of relevance not only for women with PMDD but may also aid in clarifying the relationship between ovarian steroid hormones and the increased prevalence of anxiety and depressive disorders among women in reproductive ages.

Method

Subjects

Eighteen women with PMDD and 16 asymptomatic controls 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. During the study, one woman with PMDD and one healthy control dropped out after the first scanning session due to personal reasons. Three participants were later excluded because of excessive movement during fMRI-acquisition (peaks of more than 3 mm in the x/y/z-axes or more than two degrees of head rotation). The final sample thus consisted of 15 healthy controls and 14 women with PMDD. There were no significant differences in behavioral and or demographic data between excluded and remaining participants.

Participating patients met the criteria for PMDD diagnosis, defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, 1994). The PMDD diagnosis was based on daily, prospective symptom ratings on the Cyclicity Diagnoser (CD) scale during two cycles prior to inclusion (Sundstrom et al., 1999). Patients were considered to have PMDD if they had a clinically relevant 100% increase in at least five of nine negative mood symptoms during seven premenstrual days as compared to seven mid-follicular days, associated with a clinically significant social and occupational impairment. Details on diagnostic procedures have been described previously (Gingnell et al., 2010).

The asymptomatic controls were physically healthy women with regular menstrual cycles and no history of premenstrual dysphoric symptoms. In addition, they displayed no significant premenstrual dysphoric symptoms in daily prospective ratings on the CD-scale.

Exclusion criteria for all participants included pregnancy, breastfeeding, treatment with hormonal compounds or psychotropic drugs, or presence of any ongoing psychiatric disorder. Absence of psychiatric disorders was confirmed using a structured psychiatric interview, the Swedish version of Mini International Neuropsychiatry Interview (M.I.N.I.), based on DSM-IV and ICD-10 (Sheehan et al., 1998). Furthermore, subjects with pacemakers, cardiac defibrillators, aneurysm clips, cochlear implants or other implant that use magnets, batteries or wires were excluded.

All subjects filled out the self-rated version of the Montgomery–Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Asberg, 1979) both in the follicular and luteal phase. The MADRS-S scores reflect depressive symptoms during the past three days on a scale ranging from 0 to 54. During the follicular phase the trait version of the Spielberger State-Trait Anxiety Inventory (STAI-T) (Hodgues and Spielberger, 1969), which measures trait anxiety on a scale ranging from 20 to 80, was administered. One of the women with PMDD did not fill out the STAI-T, otherwise all participants completed this inventory.

All subjects gave written consent to participate and the study procedures were approved by the Ethical Review Board of Uppsala, Sweden.

Study design

FMRI sessions were performed twice for each participant, once in the mid-follicular phase (6–12 days after the onset of menstrual bleeding) and once in the late luteal phase. The luteal phase scanning sessions were scheduled according to a positive luteinizing hormone assay (Clearplan, Unipath, Bedford, UK) to coincide with the late luteal phase (postovulatory days 8–13). The luteal phase intervals were chosen to correspond with maximum severity of mood symptoms rather than peak progesterone levels. Monitoring of the luteal phase was confirmed by progesterone serum concentrations and records on the onset of the next menstrual bleeding. To counterbalance test order effects across the menstrual cycle, half of the subjects had their first scanning session scheduled in the follicular phase, whereas the remaining subjects started in the luteal phase.

MR imaging

MR imaging was performed using a 3T whole body scanner (Achieva 3T X Philips scanner Philips Medical Systems, Best, The Netherlands) equipped with an 8 channel head coil. An anatomical T_1-weighted reference data set to a voxel size of $0.8 \times 1.0 \times 2.0$ mm^3 and 60 slices was acquired at the beginning of each scanning session. During stimulus presentation BOLD imaging was performed using a single shot EPI sequence with parameters TE/TR 35/3000 ms, flip angle 90°, acquisition matrix 76×77, acquired voxel size $3.0 \times 3.0 \times 3.0$ mm^3 and 30 slices.

Subjects were lying facing upwards in the scanner with the head lightly fixated with Velcro strips. During scanning, visual stimuli were presented through goggles mounted on the head coil (VisualSystem, NordicNeuroLab, Bergen, Norway). The stimulus paradigm was implemented using the commercial software package E-prime (Psychology Software Tools, Sharpsburg, PA, USA). In order to synchronize the paradigm and the MR-scanner, trigger pulses from the scanner were fed to the paradigm controlling PC through SyncBox (NordicNeuroLab, Bergen, Norway).

Emotional paradigm

An emotion processing task based on Hariri and co-workers was used, which consistently has been shown to engage the amygdala (Hariri et al., 2002).

The task consisted of three faces or shapes ordered as a triangle pointing upwards. Faces included both angry and afraid Ekman-faces while shapes included vertical or horizontal elipses. The target face or shape was displayed at the top and subjects were instructed to compare the target face/shape with the two images below and decide which one displayed the same emotion/orientation as the target image. Subjects responded by pressing a button with the left or right index finger. Face and shape trials were presented in blocks of 6 in which all images were presented for 4 s, interspaced with a fixation cross (2 s for the sensorimotor control tasks and randomly selected 2, 4 or 6 s for the emotion task). The expressed emotion or spatial orientation of the target face and shape, respectively, varied from trial to trial and each emotion block had an equal mix of target and non-target emotions as well as sex of the actors. Subject accuracy and reaction time were registered for each trial.

Hormonal assays

Progesterone and estradiol serum concentrations were measured before each scanning session and analyzed by competitive immunometry electrochemistry luminescence detection at the Department of Clinical Chemistry, Uppsala University hospital. The samples were run on a Roche Cobas e601 with Cobas Elecsys estradiol and progesterone reagent kits respectively (Roche Diagnostics, Bromma, Sweden). For progesterone the measurement interval was 0.1–191 nmol/l and for estradiol