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Neuroimaging Evidence of Cerebellar Involvement in Premenstrual Dysphoric Disorder

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Abstract

Background—Premenstrual dysphoric disorder (PMDD) is a debilitating cyclic disorder that is characterized by affective symptoms, including irritability, depression, and anxiety which arise in the luteal phase of the menstrual cycle and resolve soon after the onset of menses. Despite a prevalence of up to 8% in women of reproductive age, few studies have investigated the brain mechanisms that underlie this disorder.

Methods—We used positron emission tomography with [¹⁸F] fluorodeoxyglucose and self-report questionnaires to assess cerebral glucose metabolism and mood in 12 women with PMDD and 12 healthy comparison subjects in the follicular and late luteal phases of the menstrual cycle. The primary biological endpoint was incorporated regional cerebral radioactivity (scaled to the global mean) as an index of glucose metabolism. Relationships between regional brain activity and mood ratings were assessed. Blood samples were taken before each session for assay of plasma estradiol and progesterone concentrations.

Results—There were no group differences in hormone levels in either the follicular or late luteal phase, but the groups differed in the effect of menstrual phase on cerebellar activity. Women with PMDD, but not comparison subjects, showed an increase in cerebellar activity (particularly in the right cerebellar vermis) from the follicular phase to the late luteal phase ($p = 0.003$). In the PMDD group, this increase in cerebellar activity was correlated with worsening of mood ($p = 0.018$).

Conclusions—These findings suggest that the midline cerebellar nuclei, which have been implicated in other mood disorders, also contribute to negative mood in PMDD.

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Keywords

premenstrual dysphoric disorder; premenstrual syndrome; positron emission tomography; fluorodeoxyglucose; cerebellum; neuroimaging

Introduction

PMDD is a psychoneuroendocrine disorder, and its symptoms are triggered by ovulation (1). It is estimated that 5-8 % of reproductive women suffer from PMDD, with decreases in the quality of life that are nearly comparable to parallel measures associated with major depressive disorder (2,3). Affective symptoms that are characteristic of PMDD include irritability/anger, depression, mood swings, anxiety/tension, feeling “out of control,” difficulty concentrating, and fatigue (4). Differences in concentrations of ovarian sex steroids between women with PMDD and asymptomatic women do not explain the symptoms (5,6). The symptoms of PMDD are not unique to the syndrome, but are distinguished by their appearance in the luteal phase of the menstrual cycle, reaching a zenith within the week prior to menses, and with resolution by day 7 of the subsequent follicular phase. PMDD does not share common biological markers or an identical profile of therapeutic responses to medications or psychotherapy with depressive and anxiety disorders (7).

Neuroimaging studies of the hormonally mediated changes in women with PMDD can provide valuable information about the underlying neurophysiological abnormalities in this disorder. Prior imaging studies of PMDD have focused on GABAergic and serotonergic systems (8-10). A protein magnetic resonance spectroscopy study showed increased cortical γ -aminobutyric acid (GABA) concentrations in the luteal phase of women with PMDD when compared to the asymptomatic follicular phase, whereas healthy women exhibited opposite findings (8). The authors concluded that an abnormality in GABA_A receptor functioning could reduce the sensitivity of the GABA system to the effects of GABA agonists, including neuroactive steroids such as the pregnane metabolites. Diminished progesterone-mediated GABAergic inhibition was also suggested when transcranial magnetic stimulation was applied to the motor cortex of women with PMS in a separate study (9). Positron emission tomography (PET) with a radioligand for 5-HT_{1A} receptors revealed that the increment in receptor binding in the dorsal raphe nuclei between the follicular and the luteal phase scans was significantly smaller in women with PMDD, as compared to healthy control women (10).

Protopopescu et al. (2008) used fMRI to study neural response to a cognitive Go/NoGo task designed to provoke negative emotion in women with PMDD (11). In response to negative vs. neutral words, control subjects showed more activity during the late luteal as compared to the follicular phase in the anterior-medial orbitofrontal cortex (OFC), but less activity in the lateral OFC, insula and posterior cingulate cortex. In contrast, PMDD subjects showed more activity in the amygdala during the late luteal as compared to the follicular phase, but less orbitofrontal cortex activity (11). The authors attributed these findings to diminished “top-down” modulation of the limbic system by the OFC in women with PMDD (11). During the luteal phase as compared with the follicular phase, PMDD subjects were also less able than control subjects to inhibit incorrect responses, particularly when exposed to words with negative emotional valence. Their performance on this probe of frontal lobe dysfunction was consistent with diminished impulse control in women with PMDD during the premenstrual phase.

We wanted to map functional brain abnormalities associated with negative mood states in PMDD in the absence of explicit provocation. Because the affective symptoms of PMDD change profoundly across the phases of the menstrual cycle, we used positron emission tomography (PET) with [^{18}F] fluorodeoxyglucose during an affectively neutral vigilance task to assess regional cerebral metabolism across the menstrual cycle in women with PMDD and healthy control subjects, and explored the relationship of symptom change to local metabolic change.

Materials and Methods

General Experimental Design

As described below, two groups of women were tested (prospectively screened women with PMDD and comparison subjects) in both the follicular and the late luteal phases of the menstrual cycle. In each phase, PET scans with FDG measured regional relative cerebral glucose metabolism as an index of regional brain function, and self-report measures of mood were recorded. The groups were compared on phase-related changes in relative cerebral glucose metabolism and mood.

Participants

All participants were healthy, English-speaking, right-handed females, 18 to 40 years of age, with regular menstrual cycles of 24 – 32 days. Participants were recruited through local newspaper advertisements and fliers. Those who responded to the advertisement were initially screened over the telephone and scheduled for an on-site visit to determine eligibility for the study and obtain written informed consent. Eligibility was assessed using medical history and physical examination, including a brief neurological examination, and a handedness inventory (12). Psychiatric evaluation was performed using the Mini International Neuropsychiatric Interview for DSM IV, English version 5.0 (MINI.) (13). Volunteers with a current or past history of any major Axis 1 psychiatric disorder in the DSM-IV or the ICD-10, including substance use disorders or alcohol abuse or dependence, were excluded. Subjects were also excluded if they used any prescription medications, including hormones, oral or injectable contraceptives, herbal treatments for the premenstrual syndrome, other psychoactive medications or recreational drugs, with the exception of less than weekly use of either ethanol or marijuana. Additional exclusion criteria were contraindications to MRI scanning, such as implanted ferromagnetic devices, pacemakers, or claustrophobia.

Self report measures

At the first visit, all prospective participants were given two copies of the Daily Record of Severity of Problems (DSRP) (14) for completion every night over the two months before the initial PET scan. This instrument requires rating of the following symptoms: 1) avoidance of social activity/impaired relationships, 2) decreased interest in activities, 3) feeling bloated, edema, weight gain, 4) feeling depressed, sad, or hopeless, 5) anxiety/jitteriness, 6) mood swings, 7) irritability, anger, or impatience, 8) increased appetite, overeating, or food cravings, 9) fatigue, weakness, or low energy, 10) headache, 11) breast pain, 12) difficulty concentrating, 13) insomnia and 14), reduction of productivity or inefficiency at work, school, or home. Participants rated the severity of their symptoms on a scale of 1-6. In addition to the medical history and the MINI, the Beck Depression Inventory (BDI) (15) was completed once on cycle days 9-12 of the first qualifying month, to rule out follicular phase symptoms of depression in both groups.

Prospective PMDD symptom assessment and PMDD inclusion and exclusion criteria

The DRSP ratings for the two qualifying months and the follicular phase BDI from the first qualifying month were assessed to confirm the diagnosis of PMDD and to ensure that the control subjects were asymptomatic throughout the follicular and late luteal phases. To qualify further, all subjects (PMDD and control) were required have individual DRSP scores ≤ 2 during the follicular phase (days 8-12). Control subjects were excluded if they had any DRSP mood symptoms scored > 2 during the late luteal phase. Prospective participants with PMDD were required to have a minimum of three mood symptom scores with an average rating ≥ 3 during the 5 days of the late luteal phase prior to menses, and to have an increase of at least 100% in the severity ratings of the mood symptoms from the follicular to late luteal phase. Per DSM IV criteria, PMDD subjects were required to have a total of at least five moderate to severe premenstrual symptoms, including one or more severe “core” DSM IV PMDD mood symptoms. Core mood symptoms assessed by the DRSP include: feeling depressed, sad, or hopeless; anxiety/jitteriness; mood swings; and irritability, anger, or impatience. For the PMDD group, premenstrual symptoms were required to produce subjective impairment in relationships or daily activities on two or more of the days of the late luteal phase. Impairment was based on achieving a score ≥ 3 on item #13 (avoidance of social activity/impaired relationships) or on #14 (reduction of productivity or inefficiency at work, school, or home) of DRSP. Participants in both groups were required to have BDI scores < 8 in the follicular phase.

PET and MRI Imaging

Participants continued to complete the DSRP nightly until the second PET scan was performed. Participants were also given a urinary LH assay kit to evaluate morning urine specimens during the mid-cycle in order to identify the day of ovulation for timing of the late luteal phase PET scanning session.

Each subject participated in two FDG-PET scanning sessions to assess regional relative cerebral glucose metabolism. The PET sessions were counterbalanced for menstrual phase order and were scheduled once during the asymptomatic follicular phase, on days 8-12 and once in the symptomatic late luteal phase, on days 24-28 of an idealized 28 day cycle. For the scan in the follicular phase, day 1 was the first day of menstrual bleeding. For the late luteal scan, the session was scheduled 10 – 14 days after the urinary LH surge. The luteal scan was rescheduled if the subject began her period before the scan. Subjects were asked to avoid using any medications, vitamins, aspirin, recreational drugs, nicotine or alcohol during the 12 h before assessment. Subjects were instructed to avoid vigorous exercise on the morning of any PET scan.

A urine sample was collected for a pregnancy test prior to each scanning session. At least, 1 h before each PET scan, phlebotomy was performed to collect 7 ml of blood for measurement of plasma estradiol and progesterone concentrations.

A volumetric MRI scan (1.5 T, Siemens Sonata) was acquired in a separate session, within a month of each of the 2 PET scans, and the data were used for co-registration with the PET scans in order to enhance anatomical definition. A high-resolution, sagittal T1-weighted, 3D volumetric scan was acquired using a whole-brain MPRAGE sequence (repetition time/echo time = 25/11 ms, number of excitations = 1, slice thickness = 1.2 mm contiguous, in-plane resolution = $1 \times 1 \text{ mm}^2$, runtime = 10 min).

PET images were acquired with a Siemens ECAT EXACT HR+ (CTI, Knoxville, TN) in 63 planes with a 15.5-cm field of view (FOV) in 3D mode, as described previously (16). A 3-min ^{68}Ge transmission scan verified proper positioning and a 20-min ^{68}Ge transmission scan provided data for attenuation correction. After the transmission scan, the participant was

removed from the gantry and seated to perform an auditory continuous performance task (CPT) (version 2.26; Sunrise Systems, Pembroke, Mass) that was administered to provide a consistent cognitive condition across all participants. The task required listening to a 35-minute tape of pure tones (inter-stimulus interval = 2 sec) presented to the left ear. Eighty percent of the tones had a lower pitch and twenty percent had a higher pitch. Participants were instructed that most of the sounds would be “low clicks” but that they should press a button with their right thumb every time they heard a much higher “beep.”

Approximately five min after the CPT was started, FDG (≤ 5 mCi, ≤ 185 MBq) was administered as an intravenous bolus. After 30 min of performing the CPT, subjects were repositioned in the scanner and brain images were acquired for 30 min (six 5-min frames), beginning 50 min after FDG injection. The brain images were reconstructed using the measured attenuation correction.

Data Analysis

PMDD symptoms

For the time period prior to and while undergoing the two PET scans, mean values for each of the DRSP symptoms were calculated for each subject for five days in the follicular phase (days 8-12 of the menstrual cycle) and five days in the late luteal phase (the five days prior to menses). Multivariate analysis of variance (MANOVA) was used to assess group differences between participants with PMDD and control subjects in DRSP symptom change scores from the follicular to late luteal phase of the menstrual cycle with significance threshold 0.05. After obtaining a significant omnibus MANOVA test statistic, univariate F-tests were used to examine the effect of the specific dependent variables that contributed to the overall effect.

In order to test for correlation of changes in brain activity with changes in mood, a composite mood summary score was created by summing the ratings from the DRSP on the day of the PET scan for the core mood symptoms of depression, anxiety, mood swings, and irritability. The difference between PMDD and control participants in the change in the composite mood score from follicular to luteal phase was assessed with a two tailed t-test using an alpha of 0.05.

PET and MRI imaging

As a surrogate index for regional relative cerebral glucose metabolism, we used decay-corrected, raw counts of radioactivity, scaled to the global mean of each scan. Analyses were performed using Statistical Parametric Mapping software (SPM5 <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). Each PET image was co-registered to the corresponding MRI data. The MR images were used to normalize each participant's PET data through linear and nonlinear transformations that warped the images into a standard coordinate system developed at the Montreal Neurological Institute (MNI space). Finally, the data were smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm³. The primary brain image analysis utilized a group (PMDD, Control) by menstrual cycle phase (follicular, late luteal) analysis of variance (ANOVA) to construct statistical parametric maps of the t-statistics. The relationship between change in relative glucose metabolism between menstrual phases and the composite mood symptom score was assessed using a separate covariate analysis. In both analyses, only voxels that exceeded a significance threshold of $p < 0.005$ within a cluster consisting of more than 100 contiguous voxels were considered. To correct for multiple comparisons, a cluster was considered significant by the criterion of spatial extent only if the probability of obtaining a cluster that large or larger was less than 0.05 after correction for the whole brain search volume of 173,047 voxels.

Results

Twelve symptomatic women with PMDD and twelve comparison women (control group) with only minimal physical and psychological premenstrual symptoms completed the study. Age was not significantly different between PMDD (mean age = 30.8 ± 6.2 yr) and control (mean age 29.6 ± 6.2) groups. There were also no significant group differences in mean estradiol or progesterone levels in either the follicular or late luteal phases and no significant correlations between plasma hormone levels and individual symptom ratings (Table 1). There was a significant difference comparing the follicular and late luteal phase mean progesterone levels in both the PMDD ($p < .01$) and healthy control ($p < .043$) groups, but not in the mean estradiol levels.

DRSP Symptoms

MANOVA showed significant group differences in change scores between PMDD and control participants ($p < .0001$). Descriptive statistics for each of the DRSP symptoms are presented in Table 2. Subsequent univariate tests indicated that PMDD subjects had significantly higher scores in the luteal phase compared to the follicular phase in all DRSP symptoms ($p < .05$) with the exception of insomnia ($p = .093$); whereas control subjects did not differ significantly between the follicular and luteal phase in any of the DRSP symptoms. There also was a significant group difference in the summary mood change score from follicular to luteal phase, with a greater change in the PMDD group ($p < .0001$) (Table 2).

Cerebral glucose metabolism

For each significant cluster, we present the cluster size and corresponding volume-corrected spatial-extent probability in Table 3. We also note the coordinates and value of the t statistic for the voxel of maximum effect. There were no significant main effects of menstrual phase. A Group $\times$ Phase interaction ($p = 0.010$) indicated that the PMDD and control groups differed in the effect of menstrual phase on activity in a large cluster comprising 972 voxels covering much of the right cerebellar vermis (Table 3^a) (Figure 1, top row).

Examination of menstrual cycle effects in the individual groups indicated that the interaction reflected an increase in cerebellar activity from the follicular to the late luteal phase in PMDD but not control women (Figure 1, middle row). This effect was significant ($p = 0.003$) for a cluster of 1213 voxels centered in the vermis (Table 3^b). Of four additional clusters containing >100 voxels, the three largest (238, 212 and 131 voxels) were also in the cerebellum.

The assessment of covariation between changes in mood and in relative glucose metabolism across the menstrual cycle phases in PMDD women indicated that the increase in activity from the follicular to the late luteal phase in a cerebellar cluster of 849 voxels was correlated with worsening of mood ($p = 0.018$) (Table 3^c). This effect had essentially the same location in the vermis depicted in the upper rows of Figure 1 (Figure 1, bottom row). Three of five additional clusters containing >100 voxels (458, 303 and 224 voxels), including the largest two clusters, were also in the cerebellum. Covariation between changes in mood and cerebral glucose metabolism could not be assessed in the comparison group due to insufficient change in mood scores between scans.

Discussion

Prospectively screened women with PMDD showed a greater increase in cerebellar activity from the follicular phase to the symptomatic late luteal phase, compared with a group of asymptomatic control women. The effect was localized primarily to the midline vermis and

fastigial cerebellar nuclei. These structures have been previously described as the “limbic” cerebellum (17-19). Our finding is consistent with previous reports of elevated glucose metabolism in the midline cerebellum and vermis in unipolar and bipolar depressed patients (20-22), and adds to the literature that indicates a role of the cerebellum in a wide range of behaviors involving emotion, pain, and executive functions (19,23).

The cerebellum is rich in GABA_A receptors containing both δ and α subunits (24,25), and GABAergic neurotransmission is thought to take part in the pathophysiology of PMDD and premenstrual syndrome (PMS) (1,26,27). This is in part based on findings that genetically altered mice with disruption of the δ subunit exhibit more seizures and weaker behavioral responses to neuroactive steroids such as progesterone metabolites, as compared to wild type mice (28). In the luteal phase, women with PMS/PMDD are less sensitive to the modulatory effects of neurosteroids and benzodiazepines (29,30) suggesting that GABA_A receptor expression and function may change across the menstrual cycle (31).

The neuroactive steroid, allopregnanolone, a ring A-reduced metabolite of progesterone, is produced in high concentrations by the ovary and brain during the luteal phase of the menstrual cycle (32). Allopregnanolone and other pregnane-derived neuroactive steroids are potent allosteric modulators of GABA_A receptors (32-37). Fluctuating levels of these progesterone-derived neuroactive steroids alter the composition and function of the GABA_A receptors and thereby may influence emotional and affective behaviors during the luteal phase (31,38-40).

In fact, largely on the basis of animal studies, has it been proposed that women with PMDD have deficiencies in mechanisms regulating the cycling of GABA_A subunits (31,37-43). Chronic treatment of rats with progesterone, at doses that model the exposure and withdrawal from progesterone that characterize the luteal phase, increases anxiogenic behavior and reduces sensitivity to the sedative effects of benzodiazepines. These effects parallel an increase in the $\alpha 4$ subunit of the GABA_A receptor (38,44), which confers insensitivity to neurosteroids and co-localizes with the δ subunit of the GABA_A receptor, particularly in cerebellar granule cells (45). It has also been proposed that a deficiency in mechanisms regulating cycling of δ GABA_A receptors may underlie the anxiety and decreased behavioral inhibition associated with PMDD (37,40-42). Our finding of increased cerebellar activity from the follicular to the late luteal phase in women with PMDD may reflect an alteration in GABA_A receptor composition in the cerebellum, consistent with reports of diminished sensitivity to the inhibitory effects of neuroactive steroids during the late luteal phase in this disorder.

There was a significant difference in both PMDD and healthy control groups in progesterone levels between the follicular and late luteal phases, but there was no between phase difference in estradiol levels in either group. As the subjects were scanned between days 8 and 12 of the follicular phase before the mid-cycle rise in estradiol, the estradiol levels were similar in the follicular and luteal phases. The finding of a phase-related difference in progesterone but not in estradiol levels also supports the potential relationship between progesterone, likely via the progesterone metabolite ALLO, and glucose metabolism in the cerebellum.

In an fMRI study, women with PMDD had a premenstrual increase in amygdala activity and decrease in activation of the medial orbitofrontal cortex when they were exposed to emotionally negative words during a go/no-go task (11). Although our PET results did not show effects on glucose metabolism in the amygdala and frontal cortex, we did not perform a challenge study with emotionally negative stimuli. In addition, fMRI has the time resolution to show changes over a few seconds that would not be resolved by the FDG PET

method, which integrates activity over a longer period (primarily the first 15 min after the radiotracer injection).

The participants in our study performed a simple auditory CPT to standardize their thoughts during the scans. It is possible that the task could affect glucose metabolism differently in PMDD than in control subjects. The CPT activates a complex network of brain structures, including the cingulate gyrus and other cortical regions (46). Previous studies of healthy subjects during performance of similar auditory vigilance tasks have indicated lower glucose metabolism in the mid-cingulate cortex during task performance, as compared to a resting state (47,48). There is no reason, however, to believe that the group difference in cerebellar activity related to menstrual phase was an artifact of the task.

The correlation of the increase in cerebellar activity from the follicular to late luteal phase, with parallel worsening of mood ($p = 0.018$), implicates cerebellar dysfunction as contributing to the symptomology of PMDD. The cerebellum does not show an abnormality in many imaging studies of subjects with affective or anxiety disorders (49,50,51). However, various investigations have implicated the cerebellar vermis in affective processing (17-23,52) and PMDD is a unique menstrual cycle –linked syndrome, not a subset of depressive disorder.

This study is limited by small sample size but one of its strengths is the inclusion of subjects with prospectively characterized PMDD who were well screened to exclude co-morbid psychiatric disorders. The follicular and late luteal phase timing of the scans was also carefully controlled. Further studies addressing cerebellar circuitry and investigating GABA_A receptor biology in the cerebellum could deepen our knowledge of the pathogenesis of PMDD and might lead to new treatments for this debilitating disorder.

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References

1. Backstrom T, Andersson A, Andree L, Birzniece V, Bixo M, et al. Pathogenesis in menstrual cycle-linked CNS disorders. *Ann N Y Acad Sci* 2003;1007:42–53. [PubMed: 14993039]
2. Wittchen HU, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med* 2002;32:119–132. [PubMed: 11883723]
3. Halbreich U, Borenstein J, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology* 2003 3:1–23.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th. Washington DC: American Psychiatric Press; 1994.
5. Rubinow DR, Hoban MC, Grover GN, Galloway DS, Roy-Byrne PP, Anderson R, Merriam GR. Changes in plasma hormones across the menstrual cycle in patients with menstrually related mood disorder and in control subjects. *Am J Obstet Gynecol* 1988;158:5–11. [PubMed: 2962499]
6. Rubinow DR, Schmidt PJ. Gonadal steroid regulation of mood: The lessons of premenstrual syndrome. *Frontiers in Neuroendocrinology* 2006;27:210–216. [PubMed: 16650465]

7. Rubinow DR, Schmidt PJ. The Neuroendocrinology of menstrual cycle mood disorders. *Ann NY Acad Sci* 1995;771:648–659. [PubMed: 8597438]
8. Epperson CN, Haga K, Mason GF, Sellers E, Gueorguieva R, Zhang W, et al. Cortical γ -aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder. *Arch Gen Psychiatry* 2002;59:851–858. [PubMed: 12215085]
9. Smith MJ, Adams LF, Schmidt PJ, Rubinow DR, Wasserman EM. Abnormal luteal phase excitability of the motor cortex in women with premenstrual syndrome. *Biol Psychiatry* 2003;54:757–762. [PubMed: 14512217]
10. Jovanovic H, Cerin A, Karlsson P, Lundberg J, Halldin C, Nordstrom AL. A PET study of 5-HT_{1A} receptors at different phases of the menstrual cycle in women with premenstrual dysphoria. *J Nucl Med* 2006;148:185–193.
11. Protopopescu X, Tuescher O, Pan H, Epstein J, Root J, Chang L, et al. Toward a functional neuroanatomy of premenstrual dysphoric disorder. *J Affect Disord* 2008;108(1):87–94. [PubMed: 18031826]
12. Oldfield, RC. *Neuropsychologia*. Vol. 9. 1971. The assessment and analysis of handedness: the Edinburgh inventory; p. 97–113.
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 20:22–33. [PubMed: 9881538]
14. Endicott J, Nee J, Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. *Arch Womens Ment Health* 2006;9:41–9. [PubMed: 16172836]
15. Beck AT, Ward CH, Meldelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71. [PubMed: 13688369]
16. London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, Shinn AK, Miotto K, Learn J, Dong Y, Matochik JA, Kurian V, Newton T, Woods R, Rawson R, Ling W. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry* 2004;61(1):73–84. [PubMed: 14706946]
17. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* 1998;121(Part 4):561–579. [PubMed: 9577385]
18. Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. *Brain* 2006;129(2):290–292. [PubMed: 16434422]
19. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum – insights from the clinic. *The Cerebellum* 2007;6:254–267. [PubMed: 17786822]
20. Kimbrell TA, Ketter TA, George MS, Little JT, Benson BE, Willis MW, et al. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biol Psychiatry* 2002;51:237–252. [PubMed: 11839367]
21. Bench CH, Friston KJ, Brown RG, Scott LC, Frackowiak RSJ, Dolan RJ. The anatomy of melancholia – focal abnormalities of cerebral blood flow in major depression. *Psychol Med* 1992;22:607–615. [PubMed: 1410086]
22. Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Willis MW, et al. Effects of mood state and illness course on cerebral glucose metabolism in bipolar disorders. *Biol Psychiatry* 2001;49:97–109. [PubMed: 11164756]
23. Strick PL, Dum RP, Fiez JA. Cerebellum and non-motor function. *Annual Rev Neurosci* 2009;32:413–434. [PubMed: 19555291]
24. Brickley SG, Cull-Candy SG, Farrant M. Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABA_A receptors. *J Physiol* 1996;497(Pt 3):753–9. [PubMed: 9003560]
25. Caruncho HJ, Puia G, Mohler H, Costa E. The density and distribution of six GABA_A receptor subunits in primary cultures of rat cerebellar granule cells. *Neuroscience* 1995;67(3):583–93. [PubMed: 7675188]
26. Rapkin AJ, Morgan M, Goldman L, Braunn DW, Simone D, Mahesh VB. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol* 1997;90:709–714. [PubMed: 9351749]

27. Poromaa IS, Smith S, Gulinello M. GABA receptors, progesterone and premenstrual dysphoric disorder. *Arch Womens Ment Health* 2003;6(1):23–41. [PubMed: 12715262]
28. Mihalek RM, Banerjee PK, Korpi ER, Quinlan JJ, Firestone LL, Mi ZP, et al. Attenuated sensitivity to neuroactive steroids in gamma-aminobutyrate type A receptor delta subunit knockout mice. *Proc Natl Acad Sci USA* 1999;96(22):12905–10. [PubMed: 10536021]
29. Sundström I, Andersson A, Nyberg S, Ashbrook D, Purdy RH, Bäckström T. Patients with premenstrual syndrome have a different sensitivity to a neuroactive steroid during the menstrual cycle compared to control subjects. *Neuroendocrinology* 1998;67(2):126–38. [PubMed: 9508043]
30. Sundström I, Andersson A, Nyberg S, et al. Patients with premenstrual syndrome have a different sensitivity to a neuroactive steroid during the menstrual cycle compared to control subjects. *Neuroendocrinology* 1998;67(2):126–138. [PubMed: 9508043]
31. Smith SS. Premenstrual steroids. *Cell Mol Life Sci* 2001;58:1263–1275. [PubMed: 11577983]
32. Majewska MD, Harrison NL, Schwartz RD, Baker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. *Science* 1986;232(4753):1004–1007. [PubMed: 2422758]
33. Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3 α -hydroxy-5 α [β]-pregnane-20-one: Endogenous metabolites of progesterone that are active at the GABA_A receptor function. *Brain Res* 1991;561:157–161. [PubMed: 1686744]
34. Majewska MD. Neurosteroids: Endogenous bimodal modulators of the GABA-A receptor. Mechanism of action and physiological significance. *Prog Neurobiol* 1992;38(4):379–395. [PubMed: 1349441]
35. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuroendocrinol* 2000;21(1):1–56. [PubMed: 10662535]
36. Majewska MD, Dermirgören S, London ED. Binding of pregnenolone sulfate to rat brain membranes suggests multiple sites of steroid action at the GABAA receptor. *Eur J Pharmacology* 1990;189:307–315.
37. Mostallino MC, Mura ML, Maciocco E, Murru L, Sanna E, Biggio G. Changes in expression of the delta subunit of the GABA (A) receptor and in receptor function induced by progesterone exposure and withdrawal. *J Neurochem* 2006;99(1):321–32. [PubMed: 16879715]
38. Smith SS, Gong QH, Li X, Moran MH, Bitran D, Frye CA, Hsu FC. Withdrawal from 3 α -OH-5 α -Pregnan-20-One using a pseudopregnancy model alters the kinetics of hippocampal GABA_A-gated current and increases the GABA_A receptor α 4 subunit in association with increased anxiety. *J Neurosci* 1998;18(14):5275–5284. [PubMed: 9651210]
39. Smith SS, Gong QH, Hsu FC, Markowitz RS, French-Mullen JM, Li X. GABA_A receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. *Nature* 1998;392(6679):926–930. [PubMed: 9582073]
40. Stell BM, Brickley SG, Yang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by δ subunit-containing GABA_A receptors. *Proc Natl Acad Sci* 2003;100(24):14439–14444. [PubMed: 14623958]
41. Maguire JL, Stell BM, Rafizadeh M, Mody I. Ovarian cycle-linked changes in GABA(A) receptors mediating tonic inhibition alter seizure susceptibility and anxiety. *Nat Neurosci* 2005;8(6):797–804. [PubMed: 15895085]
42. Maguire J, Mody I. Neurosteroid synthesis-mediated regulation of GABA(A) receptors: relevance to the ovarian cycle and stress. *J Neurosci* 2007;27(9):2155–62. [PubMed: 17329412]
43. Biggio F, Gorini G, Caria S, Murru L, Mostallino MC, Sanna E, Follesa P. Plastic neuronal changes in GABA(A) receptor gene expression induced by progesterone metabolites: in vitro molecular and functional studies. *Pharmacol Biochem Behav* 2006;84(4):545–54. [PubMed: 16914187]
44. Gulinello M, Gong QH, Li X, Smith SS. Short-term exposure to a neuroactive steroid increases alpha4 GABA(A) receptor subunit levels in association with increased anxiety in the female rat. *Brain Res* 2001;910(1-2):55–66. [PubMed: 11489254]
45. Laurie DJ, Seeburg PH, Wisden W. The distribution of 13 GABAA receptor subunit mRNAs in the rat brain. II. Olfactory bulb and cerebellum. *J Neurosci* 1992;12(3):1063–76. [PubMed: 1312132]

46. Riccio CA, Reynolds CR, Lowe P, Moore JJ. The continuous performance test: a window on the neural substrates for attention? *Arch Clin Neuropsychol* 2002;17(3):235–72. [PubMed: 14589726]
47. Cohen RM, Semple WE, Gross M, Nordahl TE, DeLisi LE, Holcomb HH, King AC, Morihisa JM, Pickar D. Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sci* 1987;40(20):2031–9. [PubMed: 3494899]
48. Cohen RM, Semple WE, Gross M, King AC, Nordahl TE. Metabolic brain pattern of sustained auditory discrimination. *Exp Brain Res* 1992;92(1):165–72. [PubMed: 1486951]
49. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 2003;54:515–528. [PubMed: 12946880]
50. Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev* 2009;33(5):699–771. [PubMed: 19428491]
51. Bremner JD. Brain imaging in anxiety disorders. *Expert Rev Neurother* 2004;4(2):275–84. [PubMed: 15853569]
52. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. *Neuroimage* 2009;44:489–501. [PubMed: 18835452]

Figure 1.

Effect of premenstrual dysphoric disorder (PMDD), menstrual phase and mood on cerebellar activity. The gray-scale images (neurological orientation) depict slices through a T1 structural MR image in standard space (Montreal Neurological Institute), where positive values of the x, y, and z coordinates approximately represent mm to the right, anterior and superior relative to the origin (the sagittal midpoint of the anterior commissure). The sagittal slices (left column) are 8 mm to the right, the coronal slices (middle column) are 60 mm posterior and the axial slices (right column) are 24 mm inferior, relative to the origin. The color bars indicate t-values exceeding 2.82 ($p < 0.005$) in clusters containing > 100 contiguous voxels. Right side of image represents right side of brain. Top row: clusters where Group (PMDD, Control) interacted with Menstrual Phase (Follicular, Late Luteal). Middle row: clusters where activity was greater during the late luteal than the follicular phase in PMDD patients. Bottom row: clusters where activity was greater to the extent that mood score was worse across the two menstrual phases in PMDD patients.

Table 1
Follicular and late luteal phase plasma concentrations of estradiol (pg/ml) and progesterone (ng/ml)

Estradiol follicular	PMDD	89.95 ± 54.95
	Control	95.33 ± 92.86
Estradiol late luteal	PMDD	86.76 ± 51.58
	Control	115.21 ± 115.91
Progesterone follicular	PMDD	0.83 ± 0.67
	Control	1.02 ± 0.42
Progesterone late luteal	PMDD	5.50 ± 5.27
	Control	6.76 ± 7.53

Values shown are means ± s.d.

Table 2
Severity of Problems (DRSP) and composite mood score in women with premenstrual dysphoric disorder (PMDD) and control subjects

DRSP Symptom	Phase of Menstrual Cycle	
	Follicular (days 8-12)	Late luteal (last 5 premenstrual days)
Decreased interest in activities		
PMDD	1.30 ± .38	3.60 ± 1.30
Control	1.03 ± .12	1.00 ± .00
Bloated		
PMDD	1.09 ± .20	4.36 ± .83
Control	1.02 ± .06	1.37 ± .72
Depressed		
PMDD	1.20 ± .32	3.05 ± 1.28
Control	1.00 ± .00	1.12 ± .28
Anxious		
PMDD	1.42 ± .98	3.59 ± 1.16
Control	1.17 ± .41	1.27 ± .45
Mood swings		
PMDD	1.25 ± .72	3.53 ± 1.31
Control	1.07 ± .18	1.22 ± .33
Irritability		
PMDD	1.36 ± .62	4.15 ± .84
Control	1.03 ± .08	1.12 ± .30
Increased appetite		
PMDD	1.26 ± .36	3.88 ± 1.49
Control	1.00 ± .00	1.23 ± .43
Fatigue		
PMDD	1.30 ± .53	4.14 ± 1.22
Control	1.13 ± .21	1.07 ± .18
Headaches		
PMDD	1.12 ± .20	1.80 ± .95
Control	1.15 ± .32	1.10 ± .23
Breast pain		
PMDD	1.03 ± .12	3.50 ± 1.17
Control	1.00 ± .00	1.49 ± .85
Impaired concentration		
PMDD	1.16 ± .20	3.40 ± 1.53

Phase of Menstrual Cycle		
DRSP Symptom	Follicular (days 8-12)	Late luteal (last 5 premenstrual days)
Insomnia	Control	1.03 ± .12
	PMDD	1.16 ± .30
	Control	1.06 ± .17
Composite mood score	PMDD	5.73 ± 2.69
	Control	4.08 ± 0.29
		16.02 ± 4.18
		4.74 ± 1.12

Values shown are means ± s.d. of self-report scores averaged for each subject over the periods shown, except for the composite mood score, which are means ± s.d. on the respective day of PET scanning.

Table 3
Effect of premenstrual dysphoric disorder (PMDD), menstrual phase and mood on cerebellar brain activity

VOXEL of PEAK EFFECT	CLUSTER			
	x	y	z	p k
Menstrual phase × Group Interaction ^a				
24	-60	-40	0.010	972
Effects of menstrual phase in the PMDD group ^b				
8	-46	-24	0.003	1213
Covariation of mood change with activity change (PMDD only) ^c				
8	-48	-26	0.018	849

Whole-brain statistical parametric t-maps were thresholded at $p < .005$ ($t > 2.82$) with clusters containing > 100 contiguous voxels. The only clusters that were significant for spatial extent (size) after volume correction were in the cerebellum.

^aThis interaction represents either increase from F to LL in PMDD subjects, decrease in control subjects, or both. The opposite interaction (decrease from F to LL in PMDD subjects, increase in control subjects) generated no significant clusters.

^bThis contrast represents an increase from F to LL in PMDD subjects. The other possible effects (decrease from F to LL in PMDD subjects, increase or decrease between menstrual phases in control subjects) generated no significant clusters.

^cThis contrast represents areas where activity was higher to the extent that mood was worse. The opposite relationship (activity was higher to the extent mood was better) generated no significant clusters. x, y and z represent approximately mm to the right, anterior, and superior, respectively, of the midpoint of the anterior commissure, p= volume-corrected spatial-extent probability, k = number of voxels, F=follicular, LL=late luteal.