Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle

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Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved September 15, 2005 (received for review April 5, 2005)

The orbitofrontal cortex (OFC) has been implicated in the representation of emotional stimuli, assignment of emotional valence/salience to stimuli, stimulus-reinforcement association learning, motivation, and socio-emotional control. Using functional magnetic resonance imaging in female subjects without premenstrual mood symptoms, we found that OFC activity to emotional linguistic stimuli varies depending on the menstrual cycle phase. Specifically, anterior-medial OFC activity for negative vs. neutral stimuli was increased premenstrually and decreased postmenstrually. The inverse pattern was seen in the lateral OFC. These findings suggest that specific subregional OFC activity to emotional stimuli is modulated across the menstrual cycle. The data also demonstrate that menstrual cycle phase is an important consideration in further studies attempting to elucidate the neural substrates of affective representation.

functional MRI | brain | mood | emotion | women

Despite a vast literature describing sex hormone influences on the central nervous system and a growing emotional neuroscience literature, there are few data concerning the effects of menstrual cycle phase on the neurobiology of emotional processing in humans. This neuroimaging study specifically probes emotion and limbic activity across the menstrual cycle in women carefully characterized as having no premenstrual mood symptoms. Our results implicate the orbitofrontal cortex (OFC) as a key limbic region in which activity in response to emotional stimuli and behavioral demands is influenced by menstrual cycle phase.

Damage to the OFC has long been associated with socio-emotional dyscontrol (1–4). Patients with OFC lesions are prone to disadvantageous decision-making, perhaps because of an inability to evoke appropriate somatic-feeling states that would inform advantageous response selection. The OFC has been implicated in inhibitory control and emotional regulation, and has been hypothesized to have a specific role in emotion-influenced decision making (5–7).

There is abundant evidence for OFC involvement in motivational operations (8). Rapid stimulus-reinforcement association learning is implemented in the OFC (8), and the OFC is important for the alteration of stimulus–reward associations (9). The OFC appears to respond to the pleasantness of some stimuli (10, 11) as well as to the unpleasantness of other stimuli (8, 12–15).

Regarding emotional processing, a metaanalysis of functional neuroimaging studies on OFC function supports a medio-lateral gradient for representation of positive and negative stimuli, respectively, and an anterio-posterior gradient for complex (higher-order/polymodal) and simple (lower-order/unimodal) stimuli, respectively (16). However, some studies have found medial OFC activity to negative stimuli or lateral OFC activity to positive stimuli (17–19). Key issues in understanding these discrepancies include sensory modalities of presented stimuli, stimulus characteristics that may confound valence differences, and individual subject differences, such as menstrual cycle phase in female subjects. Another issue confounding OFC findings is the susceptibility of this region to artifacts resulting from magnetic field inhomogeneities in regions near bone-tissue or air-bone interfaces. Our laboratory has developed a modified *z*-shimming algorithm to reduce susceptibility artifact at the base of the brain, thus improving the ability to study neural activity in the OFC (20) (see *Methods*).

We applied blood oxygen level-dependent (BOLD) functional MRI (fMRI) and Statistical Parametric Mapping to study neural response to emotional words in the context of a Go/No-go inhibitory control task in women carefully characterized as having no premenstrual mood symptoms (PMS). Alterations in this response were examined across the menstrual cycle, in the premenstrual (late luteal) phase and the postmenstrual (late follicular) phase (counterbalanced for order). These cycle time points of scanning were selected because we are interested in studying affective processing across the natural menstrual cycle, particularly as it relates to menstrual cycle-dependent mood disorders, most notably premenstrual dysphoric disorder (PMDD). Therefore, we have selected the two time points in the menstrual cycle when women with PMDD are most symptomatic (late-luteal, days −1 to −5) and least symptomatic (late-follicular, days 8–12). Here, we have specifically studied women with no PMS in their own right and as a baseline against which women with severe PMS, meeting DSM-IV criteria for PMDD, can be studied. This fMRI study of the menstrual cycle employs neuropsychological probes specifically designed to investigate emotional processing and behavioral control to characterize limbic circuit function across the menstrual cycle.

Our results demonstrate differential medial and lateral OFC response to emotional stimuli, which is enhanced in the medial OFC in the context of inhibition, across the menstrual cycle in women with no subjective complaints of mood alterations across the menstrual cycle. Given the role of the OFC in modulating primary regions for emotional behavior, including the amygdala and hypothalamus (21–24), the results support a model of increased top-down modulation of limbic activity during the premenstrual phase. This increased activity may be primary or compensatory. These results, showing differential OFC activity across the menstrual cycle in normal healthy women, also indicate that menstrual cycle phase needs to be carefully considered when examining the neural substrates of emotion, and may shed light on the conflicting results among neuroimaging studies in this area.

Methods

Subjects. Participants consisted of 12 normal women (mean age, 28; range, 22–35). Subjects gave informed consent before study participation (part of a Weill Medical College Institutional Review Board-approved protocol). Subjects were right-handed, native English speakers. No subjects had any history of illicit substance abuse or dependence. No subjects were using oral contraceptives or

Conflict of interest statement: No conflicts declared.

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: OFC, orbitofrontal cortex; BOLD, blood oxygen level-dependent; fMRI, functional MRI; PMDD, premenstrual dysphoric disorder; DSRP, Daily Record of Severity of Problems.

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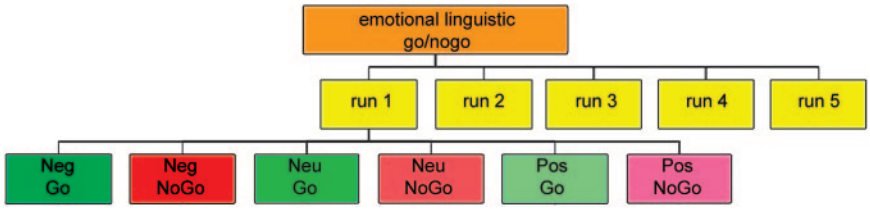

Fig. 1. Schematic figure of the neuropsychological paradigm architecture.

psychoactive medication. Subjects were recruited as asymptomatic normal controls for an ongoing study of PMDD. A structured psychiatric diagnostic interview (SCID) was used to ensure that subjects did not have any Axis I psychiatric diagnoses. Subjects completed a PMMD symptom severity self-rating, the Daily Record of Severity of Problems (DRSP) (developed by Jean Endicott and Wilma Harrison), for 2 months. The DRSP contains 24 symptoms that are scored daily on a 1- to 6-point Likert Scale. DRSP symptom items include irritability, tension, depression, loss of control, sleep-disturbance, fatigue, food cravings, physical symptoms, and social withdrawal. Symptom scores were averaged over days 6–10 after onset of menses (postmenstrual phase) and over days 1–5 before onset of menses (premenstrual phase). For inclusion in the study, subjects were required to have no items scored over 2.5 in the postmenstrual phase, no mood items scored over 2.5 in the premenstrual phase, and no physical symptoms scored over 4 in the premenstrual phase. Handedness was assessed with the Edinburgh Handedness Scale, and vocabulary level was estimated with the Word Recognition Aptitude Test.

Subjects were scanned at two points in the menstrual cycle, once in the follicular (8–12 days after the onset of menses) and once in the luteal (1–5 days before the onset of menses) phase. All subjects completed an ovulation kit before the premenstrual scan to time premenstrual scanning to the luteinizing hormone surge. The scans were performed in counterbalanced order, such that six subjects completed the follicular scan first and six subjects completed the luteal scan first, to avoid a time/order effect.

Stimuli. Stimuli consisted of 80 negative, 80 neutral, and 80 positive words, balanced across categories for frequency, length, and part of speech (nouns and adjectives/verbs). Examples are as follows: negative: *rape, assault, death, cancer*; neutral: *bookcase*, *clarinet*, *rotate*; positive/rewarding: *safe*, *gentle*, *delighted*.

Subjects were scanned during performance of an emotional linguistic go/no-go task developed to investigate neurocircuitry underlying the interaction between emotion and motor inhibition. Our laboratory has previously demonstrated increased amygdala response to threatening words, and has been using the specificity of linguistic stimuli to study limbic function (25). Behavioral response was operationalized according to orthographically based cues, such that subjects were instructed to perform a right index finger button-press immediately after silently reading a word appearing in normal font (go trial) and to inhibit this response after reading a word in italicized font (no-go trial). The task was presented in block design comprised of 30 total blocks (six blocks per run, five total runs). The six blocks per run represent the six main conditions (neutral go, neutral no-go, negative go, negative no-go, positive go, positive no-go), presentation of which was balanced to control for order and time effects. Each block was comprised of 16 different words (trials) of the same valence; therefore, there were 80 trials per condition, 480 total trials per complete study session. Go blocks contained 16 go trials (100% go trials), whereas no-go blocks contained 10 go trials (62.5% go trials) and six no-go trials (37.5% no-go trials) to establish a prepotent motor response, but have ample no-go trials. In total, five blocks of each condition were presented (see Fig. 1).

Each of the 240 words (80 positive, 80 negative, 80 neutral) was presented twice, once within a go block and once within a no-go block. Each word appeared for 1 s, followed by an interstimulus interval of 1.25 s, for a total of 36 s per block. Each block was followed by 20 s of rest, with each run preceded and followed by two additional 32-s rest periods. During rest periods, subjects were instructed to look at a dash at the center of the screen, with their minds either blank or floating freely. Stimulus presentation and response collection was performed within the Integrated Functional Imaging System SA/E-Prime environment (IFIS-SA, MRI Devices, Waukesha WI; Psychology Software Tools, Pittsburgh).

After the emotional word go/no-go paradigm, subjects were removed from the scanner and given a memory test using a list of words consisting of the 240 stimuli seen during scanning (targets) randomly interspersed with 120 other words (distracters to control for false alarms), divided equally into negative, neutral, and positive categories, and balanced for the same qualities as the targets. They were instructed to read each word, and to circle those that they believed they had seen in the scanner. After completion of that task, subjects were also asked to rate the valence and intensity of each word on scales of -3 to $+3$. Subjects were told of the memory and ratings tasks before scanning.

Image Acquisition. Image data were acquired with a research dedicated GE Signa 3 Tesla MRI scanner (maximum gradient strength 40 mT/m, max gradient slew rate, 150 T/m per s) (General Electric, Waukesha, WI). T1-weighted whole-brain anatomical images were acquired by using a spoiled gradient recalled acquisition sequence with a resolution of $0.9375 \times 0.9375 \times 1.5$ mm^3. After shimming to maximize homogeneity, a series of 3T fMRI scans was collected by using gradient echo echo-planar imaging (repetition time = 1,200 ms; echo time = 30 ms; flip angle = 70°; FoV = 240 mm; 15 slices; 5 mm thickness with 1 mm interslice space; matrix = 64×64), with a modified z-shimming algorithm developed in our laboratory to reduce susceptibility artifact at the base of the brain (20).

Image Processing and Data Analysis. Before data analysis, SPM99 software (Wellcome Department of Imaging Neuroscience) was used to realign the functional echo-planar images to correct for slight head movement between scans and for differential spin excitation history, coregister the functional images to anatomical images for individual subjects, perform a stereotactic normalization to the standardized coordinate space of Talairach and Tournoux (Montreal Neurological Institute, MNI average 152 T1 brain) to spatially normalize for individual differences in brain morphology, and spatially smooth the normalized functional images with an isotropic Gaussian kernel (full width half maximum, 7.5 mm) to increase the signal to noise ratio. All coordinates presented are in MNI space.

To build the statistical model, a whole-brain voxel-by-voxel multiple linear regression model was used at the single subject level; this was comprised of the principal regressor, which consisted of the stimulus onset times convolved with a prototypical hemodynamic response function, and the covariates of no interest, which consisted of the first order temporal derivatives of the principal regressor,

global signal, realignment parameters, and scanning periods (26–28). Global signals were removed through proportional scaling. Effects at every brain voxel were estimated by a least squares algorithm, and the contrast image for each condition was generated, and these were then combined in a series of linear contrasts to assess specific regional group effects (29).

For group analyses, we used a random-effects model that accounts for intersubject variability and allows population-based inferences to be drawn (30). The conditions of interest were the six items of word type by go/no-go factors: positive go, neutral go, negative go, positive no-go, neutral no-go, and negative no-go. Two repeated measures of these six conditions from the luteal and follicular phases were analyzed within the context of a general linear model. The linear contrast of the cycle phase $\times$ word type interactions of interest generated statistical parametric maps (SPMs) of the t statistic (SPM$\{t\}$), which was transformed to a unit normal distribution (SPM$\{Z\}$).

The statistical significance of the group-level comparison was assessed based on gaussian random field theory as implemented in SPM99. An initial t map threshold of $P = 0.001$ (uncorrected) was used. Because we had a region-specific hypothesis for limbic areas, a region-of-interest analysis was performed. For *a priori* regions of interest, anatomical masks (as defined by automated anatomical labeling; ref. 31) were used for small volume correction in SPM99. For unspecified regions, whole-brain correction was used. Activations were considered significant if the corresponding voxelwise P value was <0.05 corrected. Figs. 1–3 and the cluster sizes in Tables 1 and 2 are presented for $P < 0.01$ to show the spatial extent of activations.

Supporting Information. For further details, see *Supporting Text* and Figs. 4 and 5, which are published as supporting information on the PNAS web site.

Results

Word Valence, Inhibitory Tone, and Symptom Ratings. Twelve subjects were scanned in the premenstrual and postmenstrual phases of the menstrual cycle while performing an emotional linguistic go/no-go task developed to investigate the neurocircuitry underlying emotion and the interaction between emotion and motor inhibition (see *Methods* and Fig. 1). Subject response times suggest successful induction of inhibitory tone as reflected by significantly slower responses in no-go vs. go blocks ($P < 0.001$). After scanning, subjects rated the three types of words as significantly different in valence (negative vs. neutral: $P < 0.001$, negative vs. positive: $P < 0.001$, positive vs. neutral: $P < 0.001$). There was no significant difference in the pre- and postmenstrual week DRSP mood ratings.

Functional Imaging Data. Neuroimaging data were analyzed to determine significant cycle dependent effects (see *Methods*). As the main aim of the study was to evaluate cycle-dependent changes in brain activity the comparisons of interest are always in the setting of premenstrual (luteal) phase of the menstrual cycle vs. postmenstrual (follicular) phase of the menstrual cycle contrasts. Here, the [(Luteal vs. Follicular) (Negative Go vs. Neutral Go)] contrast represents the change in response to negative words, controlled for neutral words, from the luteal phase of the menstrual cycle to the follicular phase of the menstrual cycle. Increased medial OFC BOLD response was seen to negative vs. neutral words in the luteal vs. follicular phases of the menstrual cycle (Fig. 2 and Table 1). The opposite pattern was seen in the lateral OFC, where decreased BOLD response was seen to negative vs. neutral words in the luteal vs. follicular phases of the menstrual cycle (Fig. 2 and Table 1). Of note, the difference in the lateral OFC appears to be primarily driven by the negative word condition (Fig. 2*c*), whereas the difference in the medial OFC appears to be driven by a combination of the negative and neutral word conditions (Fig. 2*b*). Subjects also showed a decrease in activity in the luteal vs. follicular phases of the menstrual cycle in the left insula and middle cingulate (Table 1). The OFC response to positive words paralleled the OFC response to neutral words (Figs. 2 *b* and *c*) and no significant difference was seen in the OFC in the [(Luteal vs. Follicular) (Positive Go vs. Neutral Go)] contrast. The positive vs. neutral word contrast resembled the negative vs. neutral word contrast across the menstrual cycle in the middle cingulate, where a decrease was seen ($x = -6, y = 21, z = 15, Z = -3.87$). The only other significant finding for this contrast was an increase in the right dorsolateral prefrontal cortex ($x = 57, y = 18, z = 27, Z = 3.59$).

In contrast, the [(Luteal vs. Follicular) (Negative No Go vs. Neutral No Go)] comparison represents the change in response to negative words, controlled for neutral words, in the context of an inhibitory task from the luteal phase of the menstrual cycle to the follicular phase of the menstrual cycle. Increased medial OFC BOLD response was seen to negative no-go vs. neutral no-go words in the luteal vs. follicular phases of the menstrual cycle (Fig. 3 and Table 2). This difference parallels that seen in the same area for the negative go vs. neutral go contrast (Fig. 3*b*), although it covers a wider area (Fig. 3*a*). The OFC response to positive no-go words paralleled the OFC reponse to neutral no-go words (Fig. 3*b*), and no significant difference was seen in the [(Luteal vs. Follicular) (Positive No Go vs. Neutral No Go)] contrast.

The neuroimaging findings indicate that in the premenstrual vs. postmenstrual phases, lateral OFC, posterior cingulate, and left insula activity are decreased (Fig. 2 *a* and *c*) in response to negative vs. neutral stimuli, but not in the context of an inhibitory task (Fig. 3*a*). In contrast, medial OFC activity in the premenstrual vs. postmenstrual phases is increased for the negative vs. neutral words (Fig. 2 *a* and *b*), and this increase is enhanced in the context of an inhibitory task (Fig. 3). Overall, the OFC response to positive words paralleled the OFC response to neutral words (Figs. 2 *b* and *c* and 3*b*).

Discussion

Our findings indicate that OFC representations of emotionally valenced linguistic stimuli change across the menstrual cycle and with additional task demands. These findings suggest that OFC responses to negative vs. neutral or positive linguistic stimuli are greater in the premenstrual phase of the menstrual cycle in medial regions and greater in the postmenstrual phase of the menstrual cycle in lateral regions. Furthermore, these results expand findings of valence dissociations in OFC subregions for emotional stimuli to a group of psychologically well characterized female subjects studied across the menstrual cycle in the context of an explicit word driven paradigm. We have also explored the effect of inhibition/impulse control on this menstrual cycle-dependent activity.

These findings can be seen in the context of current models of OFC function. Anatomically, the OFC has been divided into two broad subregions based on neuroanatomical connectivity. The connectivity of the orbital networks is primarily within lateral or medial OFC areas, respectively, with weak connections between lateral and medial OFC areas (32). The lateral granular part is connected to medial and dorsal parts of the basal nucleus of the amygdala, sensory areas, premotor areas, and the posterior cingulate (32–35). The sensory input to the lateral OFC originates from all of the sensory modalities (8, 36): gustatory, olfactory, somatosensory, auditory, and visual (34, 37), and has therefore been conceptualized as receiving the outputs of all of the "what" processing systems (8). The medial agranular/dysgranular part is closely connected to the hippocampal formation, the anterior cingulate, and ventrolateral parts of the basal nucleus of the amygdala. The medial OFC also has stronger reciprocal connections with the hypothalamus than the lateral OFC (22). In addition to its connections to the hypothalamus, the medial OFC may influence arousal and behavior through its connections with the cholinergic system (38), the ventral tegmental area, the basal ganglia (39, 40), and the amygdala (23, 24). Amygdalar and

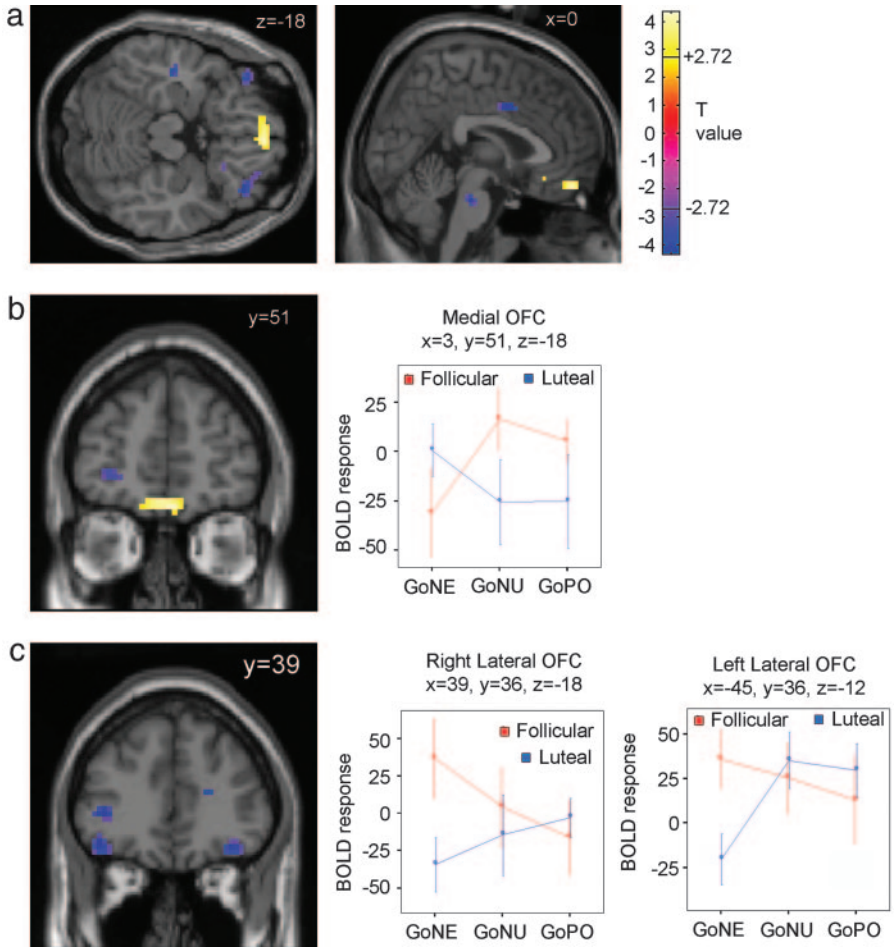

Fig. 2. OFC activity in response to emotional stimuli across the menstrual cycle. (*a*) Axial ($z = -18$) and sagital ($x = 0$) sections showing increased medial OFC and decreased lateral OFC activity for the negative go vs. neutral go condition in the premenstrual (luteal) vs. postmenstrual (follicular) phases of the menstrual cycle. Color coding in the scale represents study specific *t* values (right = right). (*b*) A coronal section at $y = 51$ showing increased medial OFC activity for the negative go vs. neutral go condition in the premenstrual vs. postmenstrual phases of the menstrual cycle. The graph shows BOLD response (arbitrary units) at the medial OFC point showing maximum activity in the premenstrual vs. postmenstrual phases of the cycle to negative go vs. neutral go words (3, 51, −18). Activity is shown for negative go (GoNE), neutral go (GoNU), and positive go (GoPO) words relative to a resting baseline in the premenstrual and postmenstrual phases. (*c*) A coronal section at $y = 39$ showing decreased right and left lateral OFC activity for the negative go vs. neutral go condition in the premenstrual vs. postmenstrual phases of the menstrual cycle. The graph shows BOLD response (arbitrary units) at the right lateral (39, 36, −18) and left lateral (−45, 36, −12) OFC points showing minimum activity in the premenstrual vs. postmenstrual phases of the cycle to negative go vs. neutral go words. Activity is shown for negative go (GoNE), neutral go (GoNU), and positive go (GoPO) words relative to a resting baseline in the premenstrual and postmenstrual phases.

pathologic limbic activity in depression have been hypothesized to be modulated by ventral prefrontal regions, including the OFC (21).

On the basis of the described anatomical connectivity, a distinction has been proposed between a medial prefrontal network providing a viscero-motor link, and a lateral orbital network providing multimodal sensory processing (32, 37). Within the framework of this model, our results would suggest that medial OFC activity concerned with emotion-related viscero-motor control is enhanced premenstrually (increased in the luteal as compared to follicular phases) and further enhanced premenstrually in the context of an inhibitory task, whereas lateral OFC activity concerned with sensory/evaluative functions is suppressed premenstrually. An interpretation of this increased viscero-motor control in response to negative stimuli premenstrually is that the limbic system may be more excitable premenstrually, and hence a greater degree of top-down modulation of limbic activity is required when exposed to negative stimuli at this phase in the menstrual cycle.

Visceral arousal and bodily reactions induce feeling states that affect subjective emotional experience (41). A central role for insular cortex in mediating subjective feeling states (42) and transient skin conductance responses (43) (a widely used objective measure of conscious and unconscious emotional processing and attention; ref. 41) has been suggested by functional neuroimaging. The OFC has reciprocal connections with the cingulate and insular

Table 1. Regions showing differential BOLD activity in the luteal versus follicular phases of the cycle for the Negative Go vs. Neutral Go contrast (uncorrected $P < 0.001$)

Region	Coordinate, *x, y, z*	*Z* score	Corrected *P*	Cluster, mm³
Increases				
Medial OFC	(3, 51, −18)	3.27	0.044	1,242
Decreases				
Left lateral OFC	(−45, 36, −12)	−3.84	0.021	1,161
Right lateral OFC	(39, 36, −18)	−3.62	0.038	972
Middle cingulate	(0, 3, 39)	−4.02	0.014	1,944
Left insula*	(−45, −3, 3)	−3.59	0.047	1,458

*Submaxima of cluster with peak coordinate (−45, −6, 3).

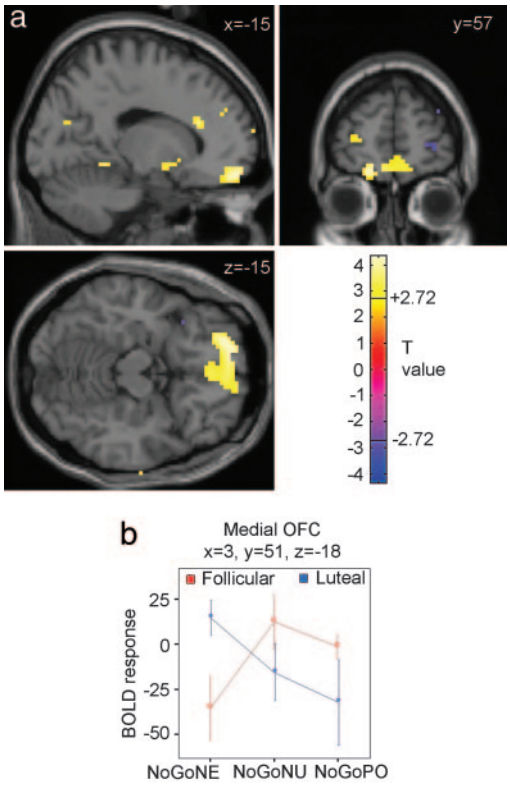

Fig. 3. OFC activity in response to emotional stimuli in the context of behavioral inhibition across the menstrual cycle. (*a*) Axial ($z = -15$), coronal ($y = 57$), and sagital ($x = -15$) sections showing increased medial OFC activity for the negative no-go vs. neutral no-go condition in the premenstrual (luteal) vs. postmenstrual (follicular) phases of the menstrual cycle. Color coding in the scale represents study specific *t* values (right = right). (*b*) The graph shows BOLD response (arbitrary units) at the medial OFC point showing maximum activity in the premenstrual vs. postmenstrual phases of the cycle to negative-go vs. neutral-go words (3, 51, −18). Activity is shown for negative no-go (NoGoNE), neutral no-go (NoGoNU), and positive no-go (NoGoPO) words relative to a resting baseline in the premenstrual and postmenstrual phases.

cortices (34, 38). Our findings of premenstrual decreases in the insula and cingulate in response to negative stimuli support the notion of increased top-down modulation of limbic and viscero-motor activity in our subjects (who experience no subjective premenstrual mood complaints).

In addition to the distinction between a medial prefrontal network involved in viscero-motor processing and a lateral orbital network involved in multimodal sensory processing, medial and lateral OFC functional dissociations have also been described for representations of valence. Functional dissociation between medial and lateral orbitofrontal cortex for positive and negative emotional valence has been shown for olfactory stimuli (15). This finding has supported a model whereby the medial orbitofrontal cortex codes for pleasantness and the lateral orbitofrontal cortex codes for unpleasantness (16). However, running counter to this model, some studies have found increased medial OFC activity to negative stimuli or increased lateral OFC activity to positive stimuli (17–19). These conflicting results indicate that, for valance encoding in the OFC, the distinction between medial and lateral might be not as simple as the encoding of positive as opposed to negative stimuli and might depend on stimulus modality and complex aspects of stimulus processing. These discrepancies may also be explained by methodological considerations (e.g., signal-to-noise issues in acquiring BOLD measurements and other individual subject differences). As shown here, female subject heterogeneity with respect to menstrual cycle phase of scanning may also affect studies probing the neural substrates of emotional valence.

Table 2. Regions showing differential BOLD activity in the luteal versus follicular phases of the cycle for the Negative No Go vs. Neutral No Go contrast (uncorrected $P < 0.001$)

Increases	Coordinate, *x, y, z*	Z score	Corrected *P*	Cluster, mm³
Medial OFC	(−15, 57, −15)	3.67	0.044	14,283
Medial OFC	(−6, 42, −18)	3.25	0.043	Submaxima of (−15, 57, −15)

Studies examining OFC representations of valenced stimuli parallel a functionally overlapping regional dissociation within the OFC found in the literature on reward and punishment. Functional dissociation between anterior-medial and posterior-lateral orbitofrontal cortex during negative and positive emotional processing respectively has been shown in numerous neuroimaging studies (11–13, 15, 17–19). A recent metaanalysis of neuroimaging studies has led to the proposal of two distinct trends of OFC neural activity (16). One is a posterior–anterior distinction with more complex or abstract reinforcers (monetary loss or aesthetic pleasure) represented more anteriorly in the OFC than simpler reinforcers (taste or pain). The second is a medial–lateral distinction where medial OFC regions monitor reward value and lateral OFC regions evaluate the punishment value of stimuli (5, 16). Our results in the postmenstrual phase are consistent with this model, with medial OFC activity greater for neutral/positive stimuli and lateral OFC activity greater for negative stimuli. In contrast, in the premenstrual phase, the lateral OFC activity evaluating punishment-like negative stimuli is suppressed and the medial OFC activity evaluating reward-like positive stimuli is suppressed, and is further suppressed in the context of an inhibitory task. Thus, our results indicate that menstrual cycle phase and behavioral/cognitive task demands can influence the size and subregional localization of valence-dependent activity in the OFC.

There are a number of possible mechanisms for these region specific brain responses to menstrual cycle phase. Gonadal hormones have been shown to influence the CNS in a large number of varied ways (44). All members within the family of ligand-gated ion channels have been shown to be modulated by steroids (45), including the GABA-gated chloride channel (46) and a number of glutamate receptors (45). Estrogen effects on the CNS include actions on gene expression, rapid actions on neuronal excitability, effects on second messenger systems (including cAMP, mitogen-activated protein kinase, calcium homeostasis), and neuroprotective effects (44). Estrogen receptors have been found in brain areas including the hypothalamus, cerebellum, hippocampus, cerebral cortex, and olfactory bulbs. Cholinergic, serotonergic, noradrenergic, and dopaminergic neurotransmitter systems all respond to sex hormones (44). Estrogen replacement has been shown to increase spine density in the prefrontal cortex of female rhesus monkeys, providing a morphological basis for estrogen enhancement of prefrontal cortical function (47). Thus, estrogen and progesterone affect neuronal circuitry and represent the most probable causes of functional neural changes across the menstrual cycle.

It is important to note that we are not studying the effect of specific hormone levels on the brain in this study. Those points in the menstrual cycle that correspond with sustained affective changes in many women do not correspond with homogenous hormone states, and it is the relationship between brain function and changes in affective processing across the natural menstrual cycle that interests us here. Behavioral effects of hormones don't directly map onto blood levels in the physiologic range (i.e., hormone levels have not been found to correlate with PMDD symptoms; refs. 48–50). Many behavioral effects of estrogen and progesterone are delayed from the peak of circulating hormone

levels in animal studies, and, in humans, relatively sustained mood states persist across time periods where hormone levels are changing.

One limitation in any such study is the reliance on human subjects to record their menstrual cycle status and self-reported symptoms. The advantage of the DRSP is that it is recorded on a daily basis, thus minimizing retroactive symptom recording.

There have been few neuroimaging studies exploring differences across the menstrual cycle (51–53). One fMRI study of the menstrual cycle used a semantic decision language task contrasted with a letter-matching perceptual task (53). Another had all subjects perform a word-stem completion task, a mental rotation task, and a simple motor task (52). In both of these studies, menstrual cycle phase had strong effects on the size of brain activations related to the cognitive tasks but had little effect on the brain activity related to the perceptual or motor tasks. In summary, the two previous studies exploring fMRI of the menstrual cycle demonstrate task and region specific cycle phase changes in neural activity. In contrast, our examination of responses to emotional stimuli demonstrated cycle phase reversal in a pattern of region-specific brain response. Also of interest is a structural MRI study that demonstrated higher OFC relative to amygdala volume in women compared to men, which may relate OFC structure and function to behavioral evidence for sex differences in emotional processing (54).

Our data highlight clear differences in OFC response to differential emotional word stimuli across the menstrual cycle. Our subject group was chosen for their lack of premenstrual mood symptoms; therefore, their pattern of OFC activation across the menstrual cycle may serve as a baseline against which differential stimulus-specific activations can be seen in women with premenstrual symptoms. Within the framework of the models discussed above, these data can be interpreted as premenstrual enhancement of top-down modulation of limbic activity and enhancement of viscero-motor control, with accompanying suppression of sensory evaluative function in women with no premenstrual mood symptoms. These findings also indicate that future investigations of OFC function should strive to take menstrual cycle phase into account. Such findings can contribute to the development of models of OFC function that integrate the effects of stimulus modality, stimulus complexity, contextual differences, gender, hormone effects, and other individual differences. These features are an important consideration in understanding the effect of the menstrual cycle on the neural substrates of emotion, and have pathophysiological and therapeutic implications for menstrual cycle-sensitive psychiatric conditions.

We thank Luke Chang, Jude Allen, Josefino Borja, Michael Silverman, James Root, Tracy Butler, and Wolfgang Engelein for their help on this project; and Jane Epstein, Mary Jeanne Kreek, and Charles Gilbert for valuable advice during the conceptualization of this project. This work was supported by the DeWitt Wallace Fund of the New York Community Trust, the David Clayson Memorial Fund, and National Institutes of Health Medical Scientist Training Program Grant GM07739 (to X.P.).

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