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Journal of Affective Disorders xx (2007) xxx – xxx
JOURNAL OF AFFECTIVE DISORDERS
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Research report

Toward a functional neuroanatomy of premenstrual dysphoric disorder

Xenia Protopopescu [a,b,*], Oliver Tuescher [a,c], Hong Pan [a], Jane Epstein [a], James Root [a], Luke Chang [a], Margaret Altemus [d], Margaret Polanecsky [e], Bruce McEwen [b], Emily Stern [a], David Silbersweig [a]

[a] *Functional Neuroimaging Laboratory, Department of Psychiatry, Weill Medical College of Cornell University, United States*
[b] *The Rockefeller University Laboratory of Neuroendocrinology, United States*
[c] *Department of Neurology, Albert-Ludwigs-University, Freiburg, Germany*
[d] *Department of Psychiatry, Weill Medical College of Cornell University, United States*
[e] *Iris Cantor Women's Health Center, Department of Obstetrics and Gynecology, Weill Medical College of Cornell University, United States*

Received 17 April 2007; received in revised form 7 September 2007; accepted 26 September 2007

Abstract

Background: Premenstrual dysphoric disorder (PMDD) is a prevalent disorder in the spectrum of affective illness, and is associated with significant morbidity. The neurobiology of this underdiagnosed and undertreated illness is poorly understood. A functional magnetic resonance imaging (fMRI) probe of fronto-limbic function was used to advance understanding of PMDD pathophysiology.
Methods: We applied BOLD fMRI and Statistical Parametric Mapping to study neural response to emotional words in the context of an emotional Go/NoGo inhibitory control task. We examined alterations in this response across the menstrual cycle, in the premenstrual (late luteal) phase and the postmenstrual (late follicular) phase.
Results: In the premenstrual (*vs.* postmenstrual) phase, PMDD subjects, compared with asymptomatic subjects, showed an increased amygdala response to negative *vs.* neutral stimuli, and a decreased ventral striatum response to positive *vs.* neutral stimuli. PMDD subjects failed to show the asymptomatic subjects' patterns of increased medial and decreased lateral orbitofrontal cortex (OFC) response to negative *vs.* neutral stimuli in the premenstrual *vs.* postmenstrual phase. This decreased premenstrual medial OFC response to negative stimuli in PMDD subjects was further enhanced in the context of behavioral inhibition.
Limitations: Further studies with larger numbers of subjects are needed.
Conclusions: The results support a neurobiological model of enhanced negative emotional processing, diminished positive emotional processing, and diminished top-down control of limbic activity in PMDD during the premenstrual phase. These findings provide a basis for a neurocircuitry model of PMDD, and have implications for studies of mood/emotional regulation across the human menstrual cycle in health and disease.

Keywords: Menstrual cycle; Premenstrual dysphoric disorder (PMDD); Functional magnetic resonance imaging (fMRI); Hormones; Amygdala; Orbitofrontal cortex (OFC)

* Corresponding author. Functional Neuroimaging Laboratory, Department of Psychiatry, Box 140, Rm 1302, Weill Medical College of Cornell University, 1300 York Ave., New York, NY 10021, United States. Tel.: +1 212 988 7383; fax: +1 212 746 5722.
E-mail addresses: xoprotop@med.cornell.edu, xeniap@gmail.com (X. Protopopescu).

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doi:10.1016/j.jad.2007.09.015

1. Introduction

Premenstrual dysphoric disorder (PMDD) is characterized by emotional symptoms (depression, anxiety, affective lability, irritability, anhedonia, a sense of being overwhelmed or out of control) which recur premenstrually, and result in marked functional impairment. This disorder, which occurs in 2–10% of reproductive-age women, represents a severe variant of the premenstrual syndrome (PMS) reported to occur in 20–40% of the same population (2000; Freeman, 2003).

While it is known that ovarian hormones have effects on the brain, and have been linked to the development of affective symptoms, it is notable that individuals who suffer from PMDD show no consistent difference in sex steroid concentrations from normal controls (Backstrom et al., 2003). Rather, they appear to display an increased neurobehavioral response to these hormones (Backstrom et al., 2003). Studies on PMDD have shown abnormal hypothalamic–pituitary regulation across the menstrual cycle (Roca et al., 2003) and abnormal luteal phase cortical excitability (Smith et al., 2003). To date, the only functional neuroimaging study of PMDD used single photon emission computed tomography to examine regional CBF (rCBF) in 7 women with severe PMS and 7 control subjects (Buchpiguel et al., 2000). Decreases in rCBF in the temporal lobes (which correlated with changes in Hamilton–Depression scores) were found on the premenstrual scan in PMS patients (Buchpiguel et al., 2000).

We have previously reported that women with no premenstrual affective symptoms, who underwent fMRI scanning while engaged in an emotional/linguistic Go/NoGo task designed to probe emotional and inhibitory processes and their interaction, displayed increased medial orbitofrontal cortex (mOFC) activity in response to negative *vs.* neutral words in the pre- *vs.* postmenstrual phase, enhanced in the context of an inhibitory task, consistent with a model of increased top-down modulation of negative emotional processing in the premenstrual phase (Protopopescu et al., 2005). Our study examines brain function at those times of the menstrual cycle when women who suffer from PMDD report being most and least symptomatic, another recent fMRI study investigating menstrual cycle-dependent brain activity focused on menstrual cycle times of greatest expected hormonal divergence and found higher blood oxygen level-dependent (BOLD) responses in a number of limbic regions associated with negative emotional processing in the early follicular *vs.* midcycle phase (Goldstein et al., 2005).

Given the phenomenology of PMDD (Landen and Eriksson, 2003), it is reasonable to posit that PMDD patients (*vs.* asymptomatic controls) in the pre- *vs.* postmenstrual phase would display enhanced processing of negative emotion, diminished inhibitory control (particularly in the context of negative emotion), and diminished processing of positive emotion. This might be reflected by, respectively, increased amygdala activity to negative words, decreased mOFC activity to negative words, particularly in the context of an inhibitory task, and decreased ventral striatum response to positive words. The current study was designed to assess such a neurocircuitry model of PMDD.

2. Methods and materials

2.1. Subjects

Subjects were excluded for menstrual cycles outside the range of 24–35 days, symptom ratings inconsistent with either PMDD or asymptomatic status, and failure to perform the task. All subjects gave informed consent prior to participation in the IRB-approved protocol.

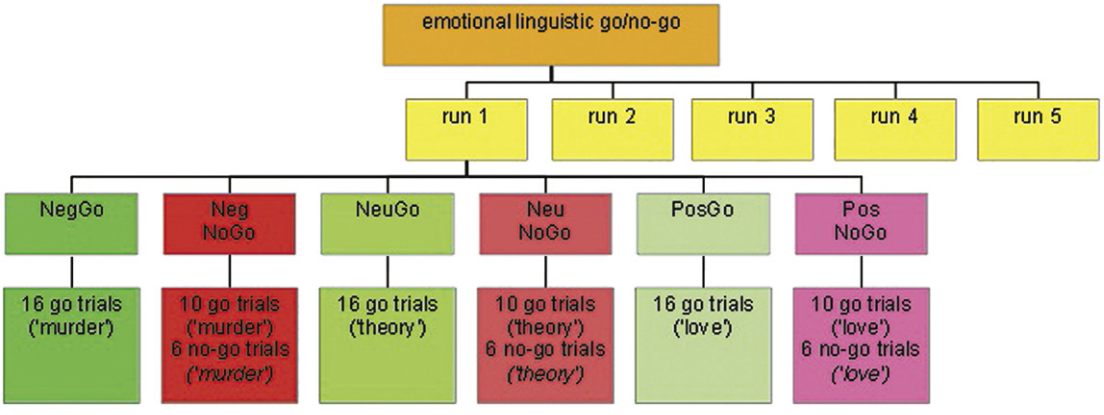

Fig. 1. Schematic figure of the neuropsychological paradigm architecture.

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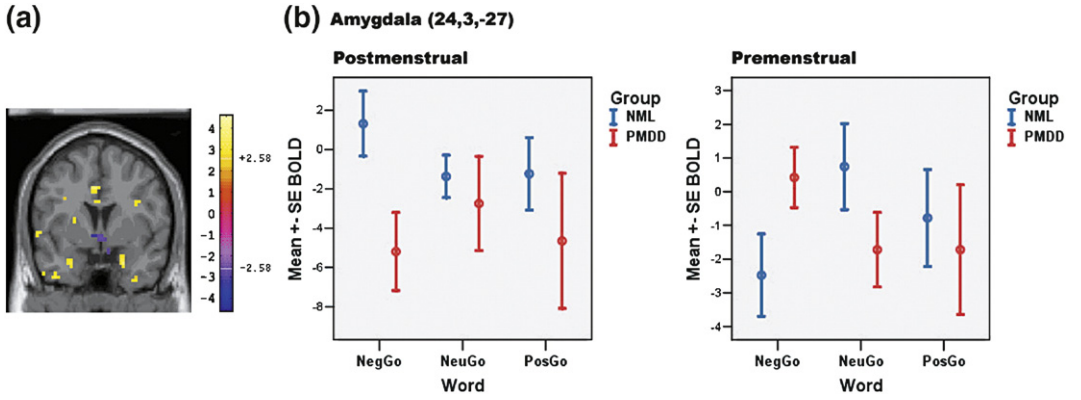

Fig. 2. A coronal section at $y=3$ showing increased amygdala activity for the NegGo *vs.* NeuGo condition, in pre- *vs.* postmenstrual phases of the menstrual cycle, in PMDD *vs.* asymptomatic subjects. Color-coding in the scale represents study-specific t values. (right=right) The bar plot shows BOLD response (arbitrary units) at the amygdala point showing maximum activity in PMDD *vs.* asymptomatic subjects, in pre- *vs.* postmenstrual phases, to NegGo *vs.* NeuGo words (24, 3, −27). Activity is shown for NegativeGo (NegGo), NeutralGo (NeuGo), and PositiveGo (PosGo) words, relative to a resting baseline, in PMDD and asymptomatic subjects in pre- and postmenstrual phases.

Valid fMRI data sets were available for 8 PMDD (mean age=27.4, range=22–33) and 12 asymptomatic (mean age=28, range=22–35) subjects, while behavioral results were available for 9 PMDD subjects (mean age=28, range=22–33) and 11 asymptomatic subjects (mean age=28.6, range=22–35), who met study criteria. Normal subject fMRI data was previously published (Protopopescu et al., 2005).

All subjects were right-handed, native English speakers. None were taking oral contraceptives or psychoactive medication or had any current Axis I psychiatric disorder other than PMDD, as assessed by the SCID-IV and the Daily Record of Severity of Problems (DRSP) for at least 2 months (Endicott et al., 2006; Harrison et al., 1985). Past Axis I diagnoses were present in one PMDD subject who had a history of depressive episodes, bulimia and alcohol abuse. DRSP symptom scores were averaged over 5 days in the postmenstrual phase (days 6–10) and the premenstrual phase (days −5 to −1). For inclusion in the study, all subjects were required to have no items scored over 2.5 in the postmenstrual phase. Asymptomatic subjects had no mood items scored over 2.5 and no physical symptoms scored over 4 in the premenstrual phase. PMDD subjects were required to have at least 3 mood symptoms with an average rating >3 during the premenstrual phase, and to have a premenstrual phase score at least double that of the postmenstrual phase.

2.2. Paradigm and stimuli

Subjects were scanned once in the postmenstrual (8–12 days after onset of menses) and once in the premenstrual (1–5 days before onset of menses) phase, the two time-points in the menstrual cycle when women with PMDD are, respectively, least and most symptomatic. The fMRI-paradigm and stimuli (an emotional linguistic Go/NoGo task) have been previously described in detail (Fig. 1) (Protopopescu et al., 2005).

2.3. Image acquisition

Image data were acquired with a GE Signa 3 Tesla MRI scanner as previously described in detail (Protopopescu et al., 2005).

2.4. Image processing and data analysis

Modified SPM software was used for standard data preprocessing, a multiple linear regression model was

Table 1
Regions showing differential BOLD activity in PMDD *vs.* asymptomatic subjects, in premenstrual *vs.* postmenstrual phases of the menstrual cycle, for the NegativeGo *vs.* NeutralGo contrast (cluster size at voxel-wise $p<0.005$)

	MNI coordinate (x, y, z)	Peak Z-score	$P_{corrected}$	Cluster size (mm^3)
Increases				
Right amygdala	(24, 3, −27)	3.09	0.018	162
Left lateral OFC	(−21, 51, −3)	3.33	0.042	81
	(−45, 36, −12)*	*3.00*		*756*
Right lateral OFC	(30, 42, −12)	3.24	0.05	540
Decreases				
Medial OFC	(−6, 48, −15)	−3.56	0.018	432

* Secondary maximum within cluster (−21, 51, −3).

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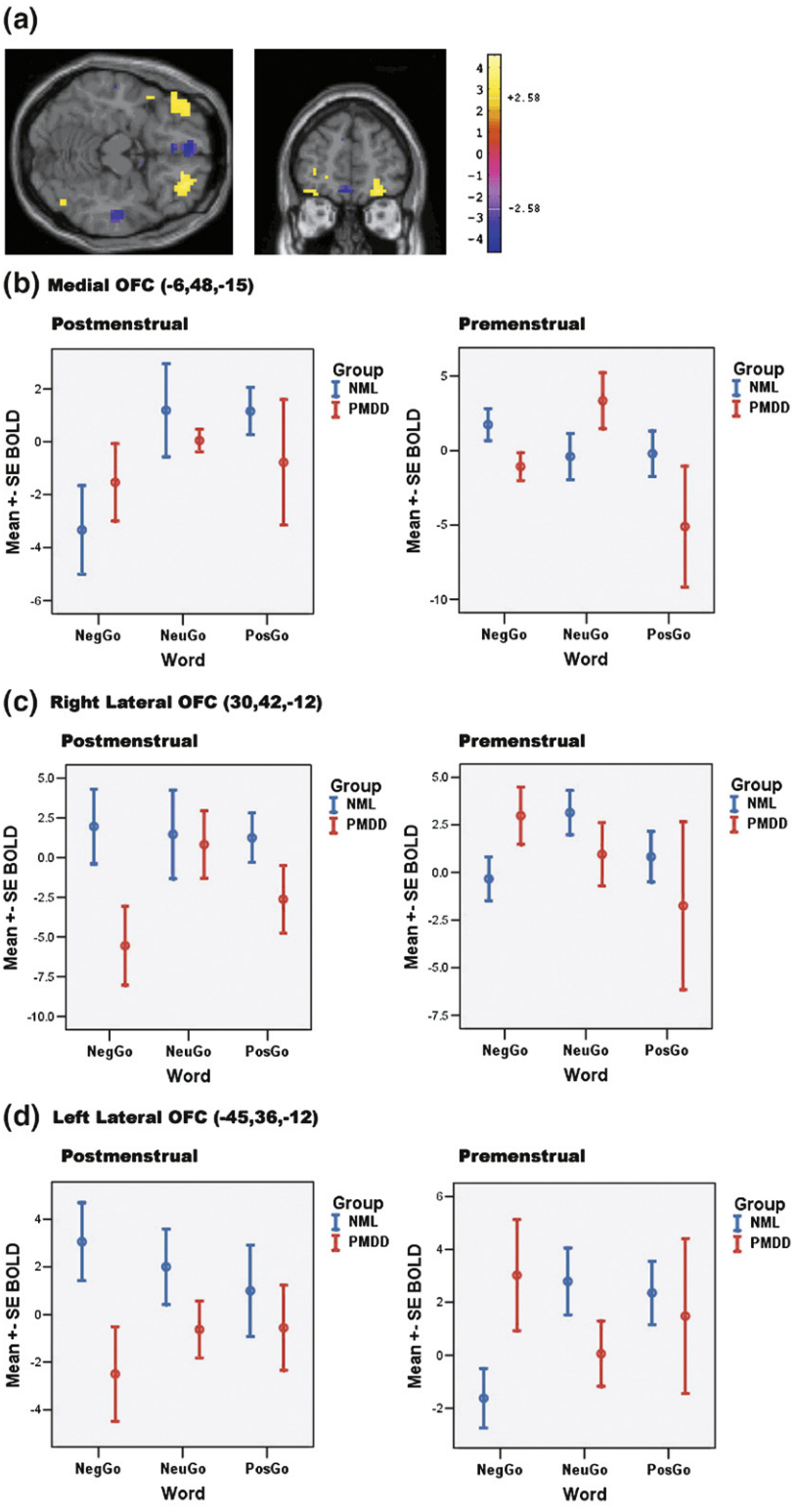
employed at the single subject level, and a random-effects model was used for group analysis as previously described in detail (Protopopescu et al., 2005).

The conditions of interest were the six Word Type by Go/NoGo factors: positive Go, neutral Go, negative Go, positive NoGo, neutral NoGo, and negative NoGo. Two



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repeated measures of these six conditions from the premenstrual and postmenstrual phases were analyzed within the context of a General Linear Model. Age and scan order (premenstrual or postmenstrual first) were entered as covariates of no interest in an ANOVA setting. The linear contrast of the Cycle Phase × Word Type interactions of interest generated statistical parametric maps (SPMs) of the t statistic (SPM$\{t\}$), which were transformed to a unit normal distribution (SPM $\{Z\}$).

The statistical significance of the group-level comparison/interaction was assessed based on Gaussian Random Field Theory as implemented in SPM. For *a priori* regions of interest, the predicted peaks are considered statistically significant if their initial voxel-wise uncorrected p-value <0.005 and family-wise-error corrected p-value <0.05 within anatomical masks (as defined by Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002) using small volume correction (SVC) function in SPM). For the amygdala, a slightly larger mask than the overly conservative AAL mask was used (Glascher et al., 2004). A NAcc mask was also used (Epstein et al., 2006). For unspecified regions, the comparisons at a regional peak are considered significant if initial uncorrected $p<0.001$ and corrected $p<0.05$ over the entire brain. The t-map renderings in the figures are thresholded at a voxel-wise $p_{\text{uncorr}}<0.01$ for purposes of presentation.

2.5. Behavioral data processing and analysis

Word ratings, word recognition, and Go/NoGo task performance (accuracy and reaction times) were analyzed. The DRSP symptom reports for the two scan days, as well as the pre- and postmenstrual phase average scores across two menstrual cycles were assessed. Verbal recognition memory performance and Go/NoGo task accuracy were evaluated by the bias-free discrimination index d' (estimated by the z-score of the false alarm rate minus the z-score of the hit rate) based on Signal Detection Theory. The recorded behavioral measures (verbal memory, Go/NoGo task performance accuracy, and Go/NoGo task reaction times) were examined in three-way repeated measures ANOVA with the factors of word valence, cycle phase, and subject group. Significant effects ($p<0.05$) were further assessed by exact statistics such as the Wilcoxon signed ranks test in view of the relatively small numbers of subjects. p-values reported are for 2-tailed tests. All tests were executed in SPSS (SPSS Inc, Chicago, IL.).

3. Results

3.1. Word valence and symptom ratings

Subjects rated the three words types as significantly different in valence ($p<0.001$). There was no significant difference in the pre- and postmenstrual week DRSP mood ratings in the asymptomatic subjects, while PMDD subjects showed significant differences between the pre- and postmenstrual "trait" (for all symptoms) and "state" (for all symptoms except for headache and muscle pain) DRSP ($p<0.05$).

3.2. Go/NoGo behavioral task results

Response times for all subjects suggested successful induction of inhibitory tone as reflected by significantly slower responses in NoGo *vs.* Go blocks ($p<.001$). Asymptomatic subjects demonstrated significantly faster reaction times to neutral (*vs.* negative or positive) words ($p=0.033$). PMDD subjects failed to demonstrate this faster reaction time to neutral words. Go/NoGo task performance accuracy was decreased in the pre- *vs.* postmenstrual phase in PMDD subjects ($p=0.011$). Go/NoGo performance accuracy for neutral words alone was decreased in the pre- *vs.* postmenstrual phase ($p=0.043$) in asymptomatic subjects.

3.3. Functional imaging data

Neuroimaging data were analyzed to determine significant cycle-dependent effects in the main pre-determined hypothesis-driven contrasts, representing negative emotion (Neg Go *vs.* Neu Go words), positive emotion (Pos Go *vs.* Neu Go words), and negative

Fig. 3. Axial ($z=-15$) and coronal ($y=48$) sections showing decreased medial OFC and increased lateral OFC activity, in PMDD *vs.* asymptomatic subjects, for the NegGo *vs.* NeuGo condition, in pre- *vs.* postmenstrual phases. Color-coding in the scale represents study-specific t values. (right=right) The first bar plots show BOLD response (arbitrary units) at the medial OFC point showing minimum activity in PMDD patients, *vs.* asymptomatic subjects, in pre- *vs.* postmenstrual phases, to NegGo *vs.* NeuGo words (−6, 48, −15). The following bar plots show BOLD response (arbitrary units) at the right lateral (30, 42, −12) and left lateral (−45, 36, −12) OFC points showing minimum activity in PMDD patients, *vs.* asymptomatic subjects, in pre- *vs.* postmenstrual phases, to NegGo *vs.* NeuGo words. Activity is shown for NegGo, NeuGo, and PosGo words, relative to a resting baseline, in PMDD and asymptomatic subjects in the pre- and postmenstrual phases. Note: There are two left lateral OFC minima (the other at −21, 51, −3); the one selected here is the one closer to the lateral OFC point found in contrasts for the asymptomatic subjects across the menstrual cycle, for ease of comparison.

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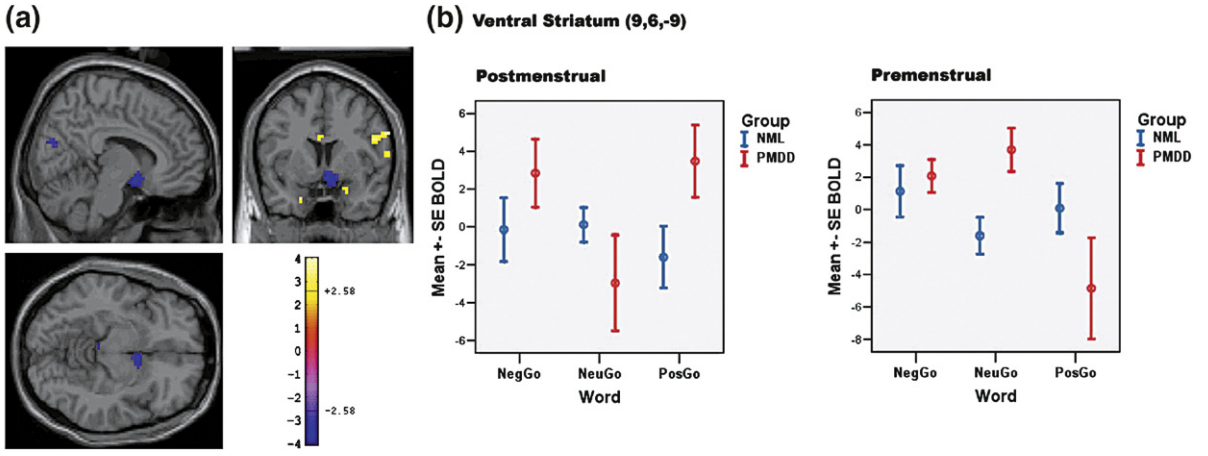

Fig. 4. Axial ($z=-9$), coronal ($y=6$), and sagital ($x=9$) sections showing decreased right ventral striatum activity, for the PosGo *vs.* NeuGo condition, in pre- *vs.* postmenstrual phases, in PMDD *vs.* asymptomatic subjects. Color-coding in the scale represents study-specific t values. (right=right) The bar plot shows BOLD response (arbitrary units) at the right nucleus accumbens point showing maximum activity, in PMDD *vs.* asymptomatic subjects in pre- *vs.* postmenstrual phases, to NegGo *vs.* NeuGo words (9, 6, −9). Activity is shown for NegGo, NeuGo, and PosGo words, relative to a resting baseline, in PMDD and asymptomatic subjects in pre- and postmenstrual phases.

emotion in the context of behavioral inhibition (Neg NoGo *vs.* Neu NoGo words) (see Methods). The contrasts of interest were always in the setting of pre- *vs.* postmenstrual phases of the menstrual cycle. Thus, the [(Pre *vs.* Postmenstrual) (NegGo *vs.* NeuGo)] interaction term represents the change in response to negative words, controlled for neutral words, from the premenstrual to the postmenstrual phase of the menstrual cycle.

PMDD *vs.* asymptomatic subjects showed positive effect of the [(Pre *vs.* Postmenstrual)(NegGo *vs.* NeuGo)] interaction in the right amygdala (Fig. 2, Table 1) and the lateral OFC (Fig. 3, Table 1), while negative effect was observed in mOFC in the same interaction term (Fig. 3, Table 1).

On the contrary, no significant effect was seen in the OFC in the [(Pre *vs.* Postmenstrual)(PosGo *vs.* NeuGo)] interaction. PMDD *vs.* asymptomatic subjects also showed negative effect in right ventral striatum (nucleus accumbens) in the [(Pre *vs.* Postmenstrual)(PosGo *vs.* NeuGo)] interaction ($x=9$, $y=6$, $z=-9$, $Z=-2.76$, $p=0.045$) (Fig. 4).

In the [(Pre *vs.* Postmenstrual)(NegNoGo *vs.* NeuNoGo)] interaction, PMDD subjects fail to show the

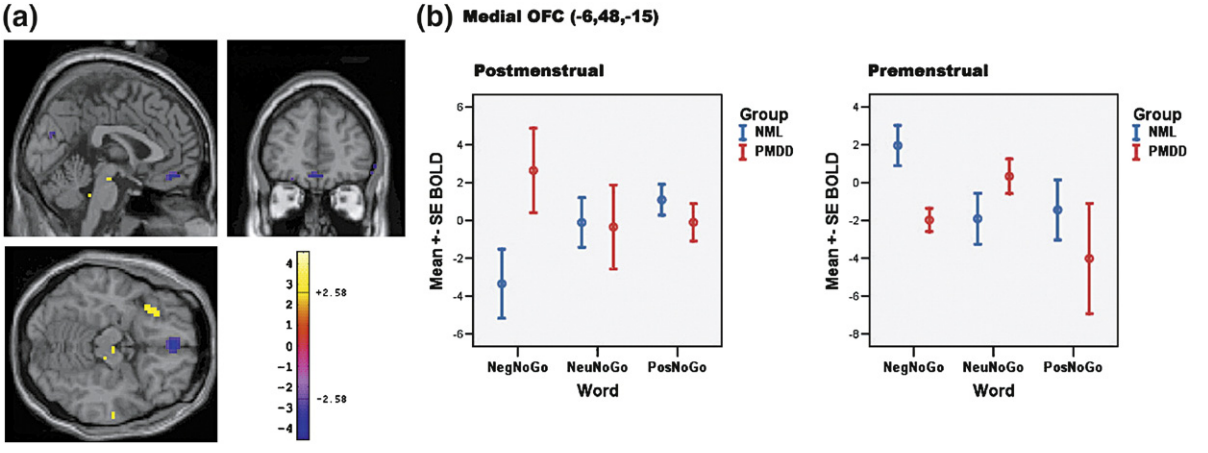

Fig. 5. Axial ($z=-15$), coronal ($y=45$), and sagital ($x=0$) sections showing decreased medial OFC activity for the NegNoGo *vs.* NeuNoGo condition, in pre- *vs.* postmenstrual phases, in PMDD *vs.* asymptomatic subjects. Color-coding in the scale represents study-specific t values. (right=right) The bar plot shows BOLD response (arbitrary units) at the medial OFC point showing maximum activity, in pre- *vs.* postmenstrual phases, to NegGo *vs.* NeuGo words in PMDD *vs.* asymptomatic subjects (−6, 48, −15). Activity is shown for NegNoGo, NeuNoGo, and PosNoGo words, relative to a resting baseline, in the premenstrual and postmenstrual phases.

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premenstrual enhancement of mOFC seen in asymptomatic subjects, and actually show the opposite pattern (Fig. 5).

4. Discussion

This study provides evidence for menstrual cycle-dependent abnormalities in cortico–striato–limbic circuits in subjects with PMDD relative to asymptomatic subjects. These findings place PMDD in the context of neurocircuitry models of a number of anxiety and affective disorders (Mayberg, 2003; Phillips et al., 2003) that emphasize an overactive amygdala with inadequate top-down governance by the prefrontal cortex.

The finding of increased amygdala activity to negative stimuli suggests a substrate for enhanced premenstrual negative emotional responsivity in PMDD (Phelps and LeDoux, 2005), and is consistent with reports of abnormally elevated amygdala CBF, BOLD response, and glucose metabolism in subtypes of depression spectrum diseases (Drevets, 2003). This increased activity may represent a bias or a valence-specific reactivity of amygdalar response and/or a dysfunction of ventral medial prefrontal cortical regions involved in emotional regulation/inhibition of amygdalar activation (Quirk et al., 2000).

The medial OFC is believed to modulate amygdalar output based on changing contingencies, through its projections from, and to (respectively), the lateral and central amygdalar nuclei (Kringelbach and Rolls, 2004). PMDD subjects (*vs.* asymptomatic subjects) demonstrated diminished premenstrual mOFC response to negative stimuli, as well as a failure to increase the activation of this region in the context of inhibitory demand. The failure of PMDD subjects to activate mOFC under these conditions may correspond with a failure of behavioral inhibition in the context of negative emotion. Indeed, PMDD subjects had significantly decreased accuracy of Go/NoGo task performance in the premenstrual (*vs.* postmenstrual) phase, consistent with subjective reports of premenstrual impulse control difficulties (Landen and Eriksson, 2003). As an operational probe of behavioral inhibition and frontal lobe dysfunction, the cycle-dependent impairment on this task demonstrated by PMDD subjects supports the hypothesis of difficulties with behavioral inhibition in the premenstrual phase. The OFC is involved in socio-emotional regulation and inhibitory control, and has been hypothesized to have a specific role in emotion-influenced decision-making (Damasio et al., 1990; Dolan, 1999; Kringelbach and Rolls, 2004). Therefore, a premenstrual decrease in activity in this region in response to an inhibitory task paired with negative stimuli may be a contributing substrate to socio-emotional dyscontrol in the context of negative emotion in PMDD.

On the basis of anatomical connectivity from animal studies, a distinction has been proposed between a medial prefrontal network providing a viscero-motor link, and a lateral orbital network providing multimodal sensory processing (Ongur and Price, 2000). Within the framework of this model, our results would suggest that, during the premenstrual phase, in PMDD *vs.* asymptomatic subjects, mOFC activity concerned with emotion-related viscero-motor control is diminished — more so in the context of an inhibitory task, while lateral OFC activity concerned with sensory/evaluative processing of negative stimuli is enhanced.

The ventral striatum, particularly the nucleus accumbens (NAcc), appears to be involved in processing a broad range of positive stimuli, and to respond to the emotional salience of a variety of stimuli, independent of their valence (Heimer, 2003; Phan et al., 2002). In the current study, asymptomatic subjects demonstrated a relatively constant right NAcc response to positive (*vs.* neutral) stimuli across the menstrual cycle, whereas PMDD subjects displayed a premenstrual decrease and postmenstrual increase in NAcc response to positive words. This finding suggests a contributing substrate to diminished premenstrual processing of positive emotion in PMDD. It is also consistent with prior work in our lab and the work of others demonstrating a failure of ventral striatal activation to positive stimuli in patients with depression *vs.* normal controls (Epstein et al., 2006; Tremblay et al., 2005).

A limitation of the current study is the modest size of the PMDD group. Future studies with increased numbers of patients will be important to further develop and characterize this neurocircuitry model of PMDD.

In sum, our findings of a premenstrual decrease in mOFC activity (enhanced with behavioral inhibition demands) in association with an increase in amygdala activity to negative words, suggests premenstrual limbic hyperresponsivity to negative stimuli combined with failure of top-down emotional behavioral control in patients with PMDD. Our additional finding in these subjects of a premenstrual relative decrease in ventral striatum activity to positive words, in the context of the current literature on this region and our own work on depression, suggests a deficiency in motivation/salience/reward circuitry processing, not just excesses in negative emotional processing. The findings of this first fMRI study of PMDD lay the groundwork for a functional neuroanatomic model of the disorder. Further characterization of the neurocircuitry of PMDD may allow for the development and evaluation of more

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specifically targeted treatments for this prevalent disorder, and shed light on the neural pathways through which ovarian hormones exert their effects on brain and behavior.

Role of funding source
None.

Conflict of interest
None reported.

Acknowledgments

This work was supported by the DeWitt Wallace Fund of the New York Community Trust, the David Clayson Memorial Fund, and NIH MSTP grant GM07739 (to X.P.). We would like to thank Jude Allen, Josefino Borja, Michael Silverman, Tracy Butler and Wolfgang Engelien for their help on this project. We would also like to thank Mary Jeanne Kreek and Charles Gilbert for valuable advice during the conceptualization and implementation of this project.

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Please cite this article as: Protopopescu, X., et al., Toward a functional neuroanatomy of premenstrual dysphoric disorder, J. Affect. Disord. (2007), doi:10.1016/j.jad.2007.09.015