Journal of Affective Disorders 140 (2012) 260–267

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Gray matter abnormalities in patients with premenstrual dysphoric disorder: An optimized voxel-based morphometry

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ARTICLE INFO

Article history:
Received 8 November 2011
Received in revised form 6 February 2012
Accepted 6 February 2012
Available online 29 February 2012

Keywords:
Premenstrual dysphoric disorder
Voxel based morphometry
Gray matter abnormality
Hippocampus
Parahippocampus

ABSTRACT

Background: Although brain neurochemistry is thought to play a role in the development of premenstrual dysphoric disorder (PMDD), neuroimaging studies of PMDD are sparse. We examined the extent to which gray matter (GM) abnormalities were present in women with PMDD compared to healthy controls.
Methods: 3.0 T magnetic resonance imaging scans of 15 women with PMDD and 15 healthy controls were compared using optimized voxel-based morphometry (VBM) analysis. A regression analysis was used to assess the relationship between GM density and PMDD-symptom severity.
Results: Our results showed significantly increased GM density in the hippocampal cortex and significantly decreased GM density in the parahippocampal cortex among women with PMDD compared to healthy controls. However, these GM abnormalities were not significantly associated with the severity of PMDD.
Limitation: Our inferences of the relationships between structural alterations and PMDD are drawn from a small sample, which may have increased the likelihood of type I error.
Conclusions: GM abnormalities in limbic and paralimbic cortices were found to be associated with the pathophysiology of PMDD. Etiology of PMDD is likely related to emotional processing and self-regulation. Our findings provide a basis of neurobiological model for PMDD.

1. Introduction

Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome (PMS) (Freeman, 2003). Women with PMDD present a mixture of mood, behavioral, and somatic symptoms that begin in the late luteal phase of the menstrual cycle and end shortly after menstruation begins (Meaden et al., 2005; Pearlstein et al., 2005). Such symptoms can be of sufficient severity to result in negative consequences in the home, social, and work lives of women (Pearlstein et al., 2000; Yang et al., 2008; Yonkers et al., 1997). The total length of time that women experience symptoms (seven days per month on average throughout their reproductive years) and the illness burden of PMDD are similar to those of dysthymic disorder and other common psychiatric conditions (Halbreich et al., 2003). Further, women with PMDD are more likely to have future major depressive disorder (MDD) and postpartum depression (Bloch et al., 2000; Hartlage et al., 2001).

Although premenstrual symptoms have long been recognized, only recently has the diagnostic criteria for PMDD been specified. Previously called premenstrual tension or PMS with a lack of diagnostic clarity, the Diagnostic and Statistical Manual of Mental Disorders (DSM) III—R has adopted the term "late luteal phase dysphoric disorder." It was subsequently renamed "PMDD" in the DSM-IV, and the disorder is characterized by specific positive symptoms (Cunningham et al., 2009).

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doi:10.1016/j.jad.2012.02.010

The pathophysiology of PMDD is not fully understood. Most previous studies have investigated ovarian hormones and neurotransmitters in the peripheral blood of women with PMDD. Estrogen, perhaps through its influence on the serotonin system, is linked to positive mood and wellbeing, whereas the decline of progesterone at the late luteal phase is linked to central nervous system changes in the γ-aminobutryic acid (GABA) and progesterone metabolites that interact with the GABA-A receptor complex (Backstrom et al., 2003; Birzniece et al., 2006; Smith et al., 2006; Sundstrom Poromaa et al., 2003). Rather than differences due to the absolute level of ovarian steroids, sensitivity of brain neurochemistry to alterations in the ovarian steroids may be related to PMDD pathophysiology (Kaura et al., 2007; Schmidt et al., 1994; Sundstrom et al., 1997; Thys-Jacobs et al., 2008).

The central nervous system is believed to play an important role in the development of PMDD; however, few neuroimaging studies have examined the neurological abnormalities of PMDD. Two previous positron emission tomography (PET) studies have reported preliminary evidence of an association between premenstrual symptomatology and brain serotonergic transmission (Eriksson et al., 2006; Jovanovic et al., 2006). In addition, a study using magnetic resonance spectroscopy found different cortical GABA level of follicular phase between women with PMDD and healthy controls (Epperson et al., 2002). Recently, a functional magnetic resonance imaging (fMRI) study found that women with PMDD showed a luteal phase-dependent negative bias in nonverbal processing of affective content (Protopopescu et al., 2008).

At present, there is no published study on structural MRI for PMDD patients. Using structural MRI in psychiatric disorders has become more useful and prevalent as newer techniques have developed. The use of voxel-based morphometry (VBM) has allowed the investigation of between-group differences in regional gray matter (GM) volumes in an automated fashion, without a need to define anatomical borders a priori and without intra- and inter-rater variability, as in methods based on regions of interest (Ashburner and Friston, 2000; Wright et al., 1995). In the VBM methodology, structural MRI scans are spatially normalized to an anatomical template, and segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) compartments (Ashburner and Friston, 2000). Subsequently, between-group GM comparisons are performed at each brain voxel, and statistical parametric maps are produced in stereotactic space showing the locations where significant group differences occur. Optimized versions of the VBM methodology allow the creation of study-specific templates that average MRI scans have acquired using the same equipment and imaging parameters (Good et al., 2002; Lochhead et al., 2004).

Therefore, we used optimized VBM, an established method of testing volumetric differences in the brain that is user-independent, fully automated, and allows for unbiased exploration of GM density changes across the whole brain (Ashburner and Friston, 2000). We aimed to examine the extent to which GM abnormalities were present in PMDD patients compared to healthy controls. In this study, we hypothesized that women with PMDD would have smaller GM density in the prefrontal and limbic/paralimbic areas that are known to be involved in regulating mood and emotional experiences.

2. Methods and materials

2.1. Subjects

Thirty premenopausal, non-pregnant women were recruited from advertisements posted at the Korea University Guro Hospital. All subjects were screened using psychiatric clinical interviews based on the DSM-IV-TR and a survey of premenstrual symptoms. Diagnoses of PMDD were confirmed through prospective daily symptom ratings for at least one menstrual cycle. PMDD was operationally diagnosed when women had a greater than 30% increase in symptom severity during the luteal phases of their cycles compared with the follicular phase (National Institute of Mental Health, 1983). Fifteen subjects with PMDD completed MRI scanning during their luteal phases. Fifteen healthy controls, matched for age and handedness, also completed MRI scanning during their luteal phases. Exclusion criteria were personal or family history of neurological disorders, any psychiatric disorder, and substance abuse or dependence. Women who had used psychotrophic or hormonal drugs for the past two months were also excluded.

All subjects were fully informed of the study protocol and provided written informed consent for participation. This study was approved by the Institutional Review Board of the Korea University Guro Hospital.

2.2. Measurements

Premenopausal Symptom Screening Tool (PSST; Steiner et al., 2003): The PSST includes a list of premenstrual symptoms as well as a measure of impairment in accordance with DSM-IV criteria for PMDD. It is a 4-point rating scale (no/mild/moderate/severe) and assesses the degree of severity and impact of premenstrual symptoms.

Daily Rating Form (DRF; Futterman and Rapkin, 2006; National Institute of Mental Health, 1983): This is a daily symptom scale assessing premenopausal symptoms. Subjects rate the severity of their symptoms on a 5-point Likert scale for one menstrual cycle. A within-cycle worsening in symptom scores of at least 30% from the follicular to luteal phase is required to meet diagnostic criteria for PMDD. The within-cycle percent change is calculated as follows: $\%\Delta = (\text{luteal score} - \text{follicular score}/\text{luteal score}) \times 100$.

2.3. Image acquisition

Three-dimensional structural MRI scans were acquired from a 3.0 T Siemens Trio whole-body imaging system (Siemens Medical Systems, Iselin, NJ, USA), using a T1-weighted magnetisation-prepared rapid gradient-echo (MP-RAGE) (1900 ms repetition time, 2.6 ms echo time, 220 mm field of view, 256×256 matrix size, 176 coronal slices without gap, $1 \times 1 \times 1$ mm^3 voxels, 16° flip angle, number of excitations = 1).

2.4. Voxel-based morphometry

An optimized VBM was performed to inspect GM change using SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London) implemented in MATLAB 7.0 (MathWorks, Natick, MA, USA) and