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Microstructural changes of the nucleus accumbens due to increase of estradiol level during menstrual cycle contribute to recurrent manic episodes—A single case study

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ABSTRACT

We examined a rapid-cycling bipolar disorder patient who demonstrated manic episode regularly at around day 7 of the menstrual cycle. We hypothesize that gonadal hormones may induce a state-dependent change in cerebral microstructure and function. Following this hypothesis, the serum levels of estradiol and progesterone were analyzed and diffusion tensor imaging data were examined between the manic and euthymic states of the patient. Estradiol levels increased in the late follicular phase at manic state when compared to the luteal or early follicular phase at euthymic state. DTI results showed that the patient had increased fractional anisotropy values at manic state in the bilateral nucleus accumbens (NAc) and its connected areas, which is a major projection field of the mesolimbic dopamine (DA) system, perhaps reflecting microstructural changes due to neuronal activation related to manic episodes. According to these results, we consider that the mesolimbic DA system of this patient has hypersensitivity to estradiol, and elevation of the estradiol level increases the activity of the dopaminergic system, which in turn may contribute to recurrent manic episodes. Our findings provide a clue for understanding how fluctuations in gonadal hormone may amplify or ameliorate the symptomatology of psychiatric disorders related to the menstrual cycle.

1. Introduction

Affective fluctuations during the menstrual cycle have been studied (Akdeniz and Karadağ, 2006). A few previous case presentations of patients, including a report of a woman with bipolar disorder (BPD), showed experienced specific mood episodes in certain periods of the menstrual cycle, such as the premenstrual period (Kukopulos et al., 1985; D'Mello et al., 1993) and luteal phase (Becker et al., 2004). However, the mechanisms underlying the illness phases related to the menstrual cycle have not been investigated. In the present study we report a rapid-cycling bipolar disorder patient who regularly demonstrated manic episode starting in the follicular phase and continuing for about 2 weeks.

In our case of recurrent manic episodes related to the phases of the menstrual cycle, we hypothesize that fluctuations of gonadal hormones may induce a state-dependent change in cerebral microstructure and function that result in a recurrence of the manic symptoms. According to this hypothesis, the serum levels of estradiol and progesterone were analyzed at manic and euthymic states of the patient. In order to elucidate the regional microstructural changes related to manic symptoms, we performed exploratory voxel-based analysis and compared DTI images between the patient and healthy subjects. We expected that the patient would show manic state-dependent brain microstructural changes in the regions related to manic symptoms, which were affected by the fluctuations of gonadal hormones related to the phases of the menstrual cycle.

2. Materials and methods

2.1. Patient and healthy control subjects

The patient was a 32-year-old right-handed woman. She had no history of alcohol or illicit drug abuse. Since age 21, she had recurrent manic episodes every

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month and numerous admissions to psychiatric units. At the age of 31, she was admitted to our psychiatric hospital. Since she was admitted to our psychiatric hospital, we observed her mood episodes for more than one year. During this period, in all of her menstrual cycles (MCs), the patient demonstrated manic episodes regularly beginning at around day 7 in the follicular phase. Her manic episodes continued for about two weeks, around ovulation, with euthymic state intervals. She had a natural 28-day menstrual cycle and did not take oral contraceptives at all during her recurrent manic/mood episodes. We diagnosed her as rapid-cycling bipolar disorder based on the structured clinical interview for DSM-IV axis I disorder (SCID) (First et al., 1997). We tried several mood-stabilizing medications, electroconvulsive therapy (ECT) treatments, but her manic episodes continued to recur.

To examine the mechanisms underlying the illness phases related to the menstrual cycle, the serum levels of estradiol and progesterone were analyzed twice: first at the euthymic state before the manic state (day 23 of MC), and second at the manic state (day 12 of MC). To replicate the relation of the gonadal hormones and the manic state, we performed a second analysis of gonadal hormones during another menstrual cycle [first at euthymic state (day 2 of MC), and second at manic state (day 12 of MC)].

For the purpose of investigating brain microstructural changes in manic episode compared to before and after manic episode, DTI was performed three times: first at the euthymic state before the manic state (day 23 of MC), second at the manic state (day 12 of MC), and third at the euthymic state following the previous manic state (day 2 of MC). We could not do further imaging analysis for replicating the results because of refusal by the patient. During the analyses of serum gonadal hormones and MRI scans, the patient was in a drug-free condition, taking no mood stabilizers or antipsychotic drugs.

Thirty-four healthy control subjects (11 female/23 male, age: 28.3 ± 6.4 years) were recruited from the local area by poster advertisement. Exclusion criteria for healthy subjects were a history or present diagnosis of any DSM-IV axis I diagnosis or any neurological illness. The patient and controls were subjected to a series of standardized, quantitative measurements of manic and depressive symptoms [Young Mania Rating Scale (YMRS) (Young et al., 1978), Montgomery Asberg Depression Rating Scale (MADRAS) score (Montgomery and Asberg, 1979), and Hamilton Rating Scale for Depression (HAMD-17) (Hamilton, 1960)] on the day of the MRI scan.

After complete description of the study, written informed consent was obtained from the patient and the healthy controls. The study was approved by the medical ethics committee of the National Cerebral and Cardiovascular Center in Japan.

2.2. Hormone assay

Blood was withdrawn via the median antebrachial vein. Sera were separated by centrifugation at 3200 rpm for 7 min and sent to Ikagaku CO., LTD (Kyoto, Japan), where the serum concentrations of estradiol and progesterone were measured by direct chemiluminescence, using Siemens ADVIA® Centaur™ Immunoassay System. For normal ranges of estradiol and progesterone for the menstrual phase, we used the laboratory data provided by Ikagaku CO., LTD determined from multiple subjects.

2.3. Data acquisition of MRI

All MRI examinations were performed by 3-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an 8-channel phased-array brain coil. Diffusion-weighted MR images were obtained with a locally modified single-shot echo-planar imaging (EPI) sequence by parallel acquisition at a reduction (ASSET) factor of 2, in the axial plane. Imaging parameters were as follows: TR=17 s; TE=72 ms; b=0, 1000 s/mm^2; acquisition matrix, 128×128; field of view (FOV), 256 mm; section thickness, 2.0 mm; no intersection gap; 74 sections. The reconstruction matrix was the same as the acquisition matrix, and 2 mm × 2 mm × 2 mm isotropic voxel data were obtained. Motion probing gradient (MPG) was applied in 55 directions, the number of images was 4144, and the acquisition time was 15 min and 52 s.

To reduce blurring and signal loss arising from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring the DTI scans. To correct for motion and distortion from eddy current and B0 inhomogeneity, FMRIB software (FMRIB Center, Department of Clinical Neurology, University of Oxford, Oxford, England; http://www.fmrib.ox.ac.uk/fsl/) was utilized. B0 field mapping data were also acquired with the echo time shift (of 2.237 ms) method based on two gradient echo sequences.

High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence (TR=12.8 ms, TE=2.6 ms, flip angle=8°, FOV, 256 mm; 188 sections in the sagittal plane; acquisition matrix, 256×256; acquired resolution, $1 \times 1 \times 1$ mm^3). T2-weighted images were obtained using a fast-spin echo (TR=4800 ms; TE=101 ms; echo train length (ETL)=8; FOV=256 mm; 74 slices in the transverse plane; acquisition matrix, 160×160, acquired resolution, $1 \times 1 \times 2$ mm^3).

2.4. Imaging processing

FA images and three eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$) were generated from each individual using FMRIB software. First, brain tissue was extracted using the Brain Extraction Tool in FSL software. Diffusion-weighted images for each of the 55 directions were eddy-corrected, subsequent to which FA values were calculated at each voxel using the FSL FMRIB Diffusion Toolbox.

Image preprocessing and statistical analysis were carried out using SPM8 (Wellcome Department of Imaging Neuroscience, London, England). Each subject's echo planar image was spatially normalized to the Montreal Neurological Institute echo planar image template using parameters determined from the normalization of the image with a b value of 0 s/mm^2 and the echo planar image template in SPM8.

Normalized gray and white matter images were generated from each individual T1-weighted image using the VBM8 toolbox with SPM8 software (Ashburner and Friston, 2000).

Normalized images were spatially smoothed using an isotropic Gaussian filter (6-mm full-width at half-maximum).

2.5. Voxel-based analysis

Exploratory voxel-based analysis was performed using SPM8 software. FA and gray/white matter images were compared between the patient and healthy subjects with Jack-knife analysis. Statistical inferences were made with a voxel-level threshold of $p < 0.05$, after family-wise error correction for multiple comparisons, with a minimum cluster size of 50 voxels.

Spherical VOIs (3-mm radius) were determined from regions where the patient showed significantly higher or lower FA values than controls. The center of the spherical VOIs was determined from the MNI coordinate with peak t-value. The regional FA value was calculated by averaging values for all voxels within the spherical VOIs placed on the regions of FA images of controls and patient at euthymic and manic states. The same VOIs were applied to $\lambda 1$, $\lambda 2$ and $\lambda 3$ images. $\lambda 1$–$\lambda 3$ Values were extracted, and mean diffusivity (MD) [$(\lambda 1+\lambda 2+\lambda 3)/3$], axial ($\lambda 1$) and radial diffusivity ($[\lambda 2+\lambda 3]/2$) were compared (Alexander et al., 2007).

To examine the effect of age on white matter integrity in our study, we examined the relationship between the regional FA values in the VOIs and age by Pearson's correlation analysis. To assess the effect of gender on white matter integrity in our study, we compared the regional FA values between male and female controls by t-test.

3. Results

3.1. Demographic and clinical data

Table 1 summarizes the demographic and clinical characteristics of the patient and controls. Manic and depressive symptoms were assessed on the day of the MRI session at euthymic and manic states. The patient showed manic symptoms at only manic states, and no manic or depressive symptoms at euthymic states. None of the control subjects showed manic or depressive symptoms at the examination.

3.2. Estradiol and progesterone levels in the patient's blood

As shown in Table 2, because of the normal menstrual cycle phase, estradiol levels increased in the late follicular phase at manic state when compared to the luteal or early follicular phase

Table 1
Demographic characteristics of the analysis of the patient and controls.

Characteristic	Patient	Controls (n=34)
Age, y	33	28.3 ± 6.4
Female, No (%)	–	11 (32%)
Young Mania Rating Scale	0 At euthymic state 42 at manic state	0 For all controls
MADRAS score	0 At both states	1.0 ± 1.7
HAM-D score	0 At both states	1.1 ± 1.6

MADRAS, Montgomery Asberg Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale.