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

Kiwamu Matsuoka a,c, Fumihiko Yasuno a,b,*, Makoto Inoue c, Akihide Yamamoto b, Takashi Kudo d, Soichiro Kitamura a, Koji Okada a, Kuniaki Kiuchi a, Jun Kosaka a, Hidehiro Iida b, Toshifumi Kishimoto a

a Department of Psychiatry, Nara Medical University, 840 Shijocho, Kashihara, Nara 634-8522, Japan
b Department of Investigative Radiology, National Cerebral and Cardiovascular Center, Suita, Japan
c Department of Psychiatry, National Hospital Organization Yamato Mental Medical Center, Yamatokoriyama, Japan
d Department of Psychiatry, Osaka University Health Care Center, Toyonaka, Japan

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A B S T R A C T
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.

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1. Introduction
Affective fluctuations during the menstrual cycle have been studied (Akdéniz 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
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 1 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 mood rating scales at each visit. The patient was assessed on the day of the MRI session at euthymic and manic states, and no manic or depressive symptoms at euthymic states. The patient showed manic symptoms at only manic states. The patient and controls were assessed on the day of the MRI session at euthymic and manic states.

2.4. Imaging processing

FA images and three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) 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 $\lambda_1, \lambda_2, \lambda_3$ images, $\lambda_1-\lambda_3$ Values were extracted, and mean diffusivity (MD) [$\lambda_0 = \lambda_1 + \lambda_2 + \lambda_3$], 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

<table>
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<tr>
<th>Characteristic</th>
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<th>Controls (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33 Mann</td>
<td>28.3 ± 6.4</td>
</tr>
<tr>
<td>Female, No (%)</td>
<td>–</td>
<td>11 (32%)</td>
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<tr>
<td>Young Mania Rating Scale</td>
<td>0 At euthymic state</td>
<td>0 For all controls</td>
</tr>
<tr>
<td>MADRAS score</td>
<td>0 At both states</td>
<td>1.0 ± 1.7</td>
</tr>
<tr>
<td>HAM-D score</td>
<td>0 At both states</td>
<td>1.1 ± 1.6</td>
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MADRAS, Montgomery Asberg Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale.

### Table 2

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