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Research Report

Identification of the neural correlates of cyclothymic temperament using a working memory task in fMRI

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ABSTRACT

Background: Recently, we reported a significantly negative association of cyclothymic temperament scores with activations of the left lingual gyrus during esthetic judgments of paintings, suggesting that cyclothymic temperament may be associated with the left lingual gyrus. In view of potential associations of cyclothymic temperament, bipolar disorder and dementia, this study examined the relationship of temperament to lingual gyrus activity using a working memory task as a new context.
Methods: *N*-back tasks (0-, 1-, 2- and 3-back tasks) were performed on 34 healthy subjects using functional MRI. Multiple regression analyses were applied to measure the association between cyclothymic temperament scores and each of 4 beta images corresponding to 0-, 1-, 2- and 3-back tasks with gender, age and the other temperament scores (depressive, hyperthymic, irritable and anxious) as covariates.
Results: The whole brain analysis corrected for multiple comparisons revealed a significant activation of the left lingual gyrus associated with cyclothymic temperament scores in a new context—working memory for both 2- and 3-back tasks.
Limitations: The number of subjects was relatively small. The subjects were almost medical staff or students and the results should be interpreted with caution.
Conclusions: The present findings reconfirm that cyclothymic temperament may be associated with the left lingual gyrus.

1. Introduction

It is generally accepted that cyclothymic temperament is one of prodromal states of bipolar disorder. Moreover, bipolar patients may be more likely to suffer from memory impairment that further develops into dementia. For example, Burdick et al. (2010) showed that 33 patients with bipolar disorder demonstrated clinically significant deficits on verbal learning and memory as measured by the California Verbal Learning Test. Furthermore, Kessing et al. (1999) showed that bipolar patients had a greater risk of suffering from dementia than patients with schizophrenia or neurosis during 21 years of follow-up. These findings suggest potential associations of cyclothymic temperament, bipolar disorder and dementia. As such, it is possible that a working memory task can help to identify the neural correlates of cyclothymic temperament.

Recently, using fMRI, we found a significantly negative association between cyclothymic temperament as measured by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A) (Akiskal et al., 2005a) and percent signal changes of the left lingual gyrus during esthetic judgments of paintings, suggesting that cyclothymic temperament may be associated with the left lingual gyrus (Mizokami et al., 2014b). The reason why we used the esthetic judgment task of paintings is that creativity has been associated with bipolar disorder (Rybakowski, 2011; Santosa et al., 2007; Strong et al., 2007) and an association has been shown between creativity and cyclothymic temperament (Vellante et al., 2011). Previously, Akiskal et al. (2005b) reported

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that artists had four times the cyclothymic temperament of a comparison group (43% vs. 10%), suggesting that artistic creativity may be associated with cyclothymic temperament. In view of the association between creativity and cyclothymic temperament and that between creativity and esthetic performance, we used an esthetic judgment task of paintings in relation to cyclothymic temperament.

In our fMRI previous study (Mizokami et al., 2014b) a region of interest (ROI) approach was used to examine the left lingual gyrus and bilateral cuneus in relation to temperament. This method was used because these regions were shown to be activated in the comparison of esthetic appreciation of paintings vs. photographic analogs, suggesting that they might represent the specific neural correlates of esthetic appreciation for paintings (Mizokami et al., 2014a). In the present study, we attempted a whole brain analysis and, instead of using the esthetic judgment task, we used a working memory task as a new context.

2. Methods

2.1. Subjects

Thirty four healthy subjects (26 men and 8 women, 26.9 ± 6.15 of mean $\pm$ SD with range 20–41 years) performed *n*-back working memory task, although 1 subject showed missing data and was excluded. Therefore, 33 subjects' data (25 men and 8 women, 26.4 ± 5.70 years with range 20–39) were analyzed. All subjects were right-handed and had normal or corrected to normal vision. Mental state was assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.), Hamilton Depression Rating Scale (HAM-D), and Young Mania Rating Scale (YMRS). All participants gave written informed consent according to procedures approved by the ethical committee at Oita University Faculty of Medicine.

2.2. Cyclothymic temperament identification

The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) was developed by Akiskal et al. (2005a). This scale consists of 110 questions to measure five temperaments (depressive, hyperthymic, cyclothymic, irritable and anxious) and has been verified in 32 language versions and is widely used in a number of epidemiological and clinical studies with psychiatric patients and healthy subjects. In Japan, the scale has been validated and widely used to identify affective temperaments (Matsumoto et al., 2005).

2.3. Working memory task design

During functional magnetic resonance imaging (fMRI) scanning, subjects completed a letter variant of the *n*-back task by Harvey et al. (2005). Task design was performed according to Mannie et al. (2010). Working memory load consisted of three levels of complexity: 1-, 2- and 3-back tasks. Subjects were required to indicate whether the letter presented on the screen (the target stimulus) matched with the previously presented letter (the cue stimulus). We used only the following letters: b, B, d, D, p, P, t, T, v, V. Subjects were then instructed to respond by pressing a key 1 or 2 if the target was identical or different from the cue. Subjects also performed a sensorimotor control task (0-back) during which they were required to respond to a pre-specified letter (x, X). All blocks consisted of a sequence of 10 letters. Letters were presented for 0.5 s with a fixed inter-stimulus interval of 1.5 s. Just before each task block, an instruction screen (0-, 1-, 2- and 3-back) was presented for 2 s. A 4 s of blank screen separated the instruction from the onset of the first letter. Task blocks were separated by 7 s of fixation cross. Four blocks of each condition were presented in a fixed pseudorandom order (0-, 1-, 2-, 3-, 1-, 3-, 2-, 0-, 2-, 1-, 0-, 3-, 1-, 0-, 3-, 2-back). All conditions were matched for the number of targets and upper/lower case letters presented. Stimuli were presented on a laptop using Presentation (version 14.1) and projected onto a translucent screen at the end of magnet's gurney. Subjects viewed the screen through a mirror attached to the head coil. Subjects' responses were identified via a MRI compatible keypad.

2.4. Analysis of performance data

Performance data such as mean accuracy and reaction time during each *n*-back tasks were compared using repeated measures of analysis of variance (ANOVA) and Turkey–Kramer's method as post-hoc test. Moreover, we investigated the association between cyclothymic temperament scores and accuracy and reaction time in each *n*-back task. For statistical analysis, Pearson's correlation was used.

2.5. fMRI image acquisition

fMRI images were collected using a Siemens magnetom verio 3 T MRI system. A time course series of 176 volumes was acquired with T2-weighted single shot gradient echo planner imaging (EPI) sequence. Each volume consisted of 36 slices, with each slice having thickness of 3 mm and a gap of 0.75 mm that covered almost the whole brain. Images were acquired in the axial plane (TR=3000 ms; TE=30 ms; FOV=210 mm; voxel size=$3 \times 3 \times 3\ mm^3$). The total acquisition time was 8 min 48 s, including periods for signal equilibration. T1-weighted structural images were acquired with 3-D magnetization prepared rapid gradient echo (MPRAGE) in the sagittal plane (TR=2040 ms; TE=2.53 ms; TI=900 ms; the flip angle was 9°; FOV=192 mm; voxel size=$1 \times 1 \times 1\ mm^3$).

2.6. fMRI image analysis

All fMRI analyses were performed in SPM8 (Statistical Parametric Mapping software, University College of London, London, UK; available at: http://www.fil.ion.ucl.ac.uk/spm/) on Matlab R2012a. Preprocessing (movement correction, normalization to the MNI EPI template, smoothing with an isotropic 8 mm FWHM kernel, and resampling to 2 mm cubic voxels) was initially performed. Each individual data set was carefully screened for data quality via inspection for image artifacts and excessive head motion (>3 mm head motion or 2° head rotation).

In the first level analysis, we used the following parameters; inter-scan interval 3 s, Microtime Resolution 36 slices, and Microtime Onset 18 slices. These values followed setting of MR acquisition. Each condition was modeled with a boxcar function and convoluted with a canonical hemodynamic response function. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 128 s. Serial autocorrelation was also corrected using AR model. We created 4 beta images in each subject: 0-, 1-, 2- and 3-back tasks.

The second level analysis was performed using multiple regression models. We obtained the association between cyclothymic scores and each of 4 beta images created in the first level with the inclusion of gender, age and the other temperament scores (depressive, hyperthymic, irritable and anxious) as covariates. Statistical thresholds were set at $p < 0.05$ at cluster level corrected for multiple comparisons with a standard peak level cutoff of $p < 0.001$.