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Research Report

Association between affective temperaments and regional gray matter volume in healthy subjects

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ABSTRACT

Background: Affective temperaments such as cyclothymic and hyperthymic temperaments have been regarded as potential antecedents of bipolar disorder but the neural substrates underlying these temperaments have not been identified. The aim of this study is to determine whether these temperaments are associated with specific neural substrates in regional brain morphology in healthy subjects.

Methods: We conducted a cross-sectional neuroimaging study of 60 healthy subjects (30 males and 30 females) with affective temperaments. All participants underwent the Mini-International Neuropsychiatric Interview (MINI) to screen for the past and present psychiatric disorder. The scores of cyclothymic and hyperthymic temperaments were measured by the Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire. We analyzed the association between voxel-based morphometry of the brain and these affective temperaments.

Results: Subjects classified as having high cyclothymic scores had a significantly larger gray matter volume of the left medial frontal gyrus (MFG) than low cyclothymic subjects. High hyperthymic males also had significantly larger gray matter volume of the left MFG than low hyperthymic males, but there was no difference in females. Subjects with both high cyclothymic and high hyperthymic temperaments demonstrated significantly larger gray matter volume of the left MFG than their counterparts. Region of interest analysis revealed that peaks of these clusters showed a significant positive correlation of the regional volume with temperament scores.

Limitations: The subjects were relatively young and the number was relatively small. Due to the nature of a cross-sectional research design, we could not determine the causal relationship between temperament and the volume changes.

Conclusions: These findings suggest that cyclothymic and hyperthymic temperaments in healthy subjects may have their morphological basis in the left MFG.

1. Introduction

Affective temperaments such as cyclothymic and hyperthymic temperaments have been regarded as potential antecedents of bipolar disorder and they have been called bipolar temperaments. Cyclothymic temperament shows a central dimension that includes rapid fluctuations in mood and emotional instability, while hyperthymic temperament displays extroversion, a high energy level, emotional intensity and little need for sleep (Rovai et al., 2013). The modern concept of affective temperaments also assumes a continuum between these temperaments and bipolar disorder and is supported by a small but growing literature (Akiskal et al., 2005; Akiskal and Pinto, 1999; Ghaemi et al., 2001; Harnic et al., 2013; Takeshima and Oka, 2013). A recent longitudinal study of 57 patients with initial cyclothymia or bipolar disorder not otherwise specified diagnoses, showed that 42.1% progressed to a bipolar II diagnosis and 10.5% progressed to a bipolar I diagnosis (Alloy et al., 2012). As for pharmacotherapy, 36 depressive patients with cyclothymic and/or hyperthymic temperaments were likely to be in remission on lithium but not on selective serotonergic inhibitors (Goto et al., 2011), suggesting that bipolar temperaments in depression may affect drug response (Terao, 2012).

The neural substrates of affective temperaments have not been extensively investigated. It has been, however, shown that

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cyclothymic scores in subjects with genetic risk of bipolar disorder were associated with the integrity of the bilateral internal capsules and the left temporal white matter (Sprooten et al., 2011). Recently, Serafini et al. (2011) reported that mood disordered patients with higher depressive, cyclothymic, irritable, anxious and lower hyperthymic temperament scores were likely to have greater white matter hyper-intensities than patients with higher hyperthymic temperament scores . Whereas Harada et al. (2013) reported a significant association between activation of the left inferior orbitofrontal cortex and hyperthymic temperament scores in healthy subjects in a functional magnetic resonance imaging (fMRI) investigation.

Recent meta-analyses of brain morphology in bipolar patients have shown reduction of regional gray matter volumes in the medial frontal gyrus including anterior cingulate cortex and bilateral fronto-insular cortex (Bora et al., 2010). In view of the putative association of affective temperaments with bipolar disorder, we have hypothesized that temperaments may be associated with the brain morphology. To the best of our knowledge, this potential association has not been investigated in healthy subjects without family history, and so the aim of the present study is to investigate whether cyclothymic and hyperthymic temperaments demonstrate associations with regional brain morphology in healthy subjects with neither history nor family history of psychiatric disorders.

2. Methods

2.1. Subjects

Sixty healthy Japanese subjects (30 males, 30 females) were recruited. The mean age of subjects was 26.7 (SD=5.63). All underwent screening for the past or present psychiatric disorder with the Mini-International Neuropsychiatric Interview (MINI). Based on the 17 items Hamilton Rating Scale for Depression (HAM-D) and Young Mania Rating Scale (YMRS), all were investigated regardless of whether they were in euthymic mood. The presence of psychiatric family history was also investigated by a question. All were right handed according to the Edinburgh handedness questionnaire. Magnetic Resonance Imaging (MRI) was not contraindicated in any subject. As gender effects in bipolar disorder have been reported (Jogia et al., 2012), the proportion of male and females was balanced and a factorial effect of gender was incorporated in the analyses. This study was approved by the ethical committee of Oita University Faculty of Medicine and a written informed consent was obtained from all subjects after explanation of this study.

2.2. Affective temperaments evaluation

The Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A) was used for bipolar temperament evaluation. TEMPS-A consists of 110 questions to measure 5 temperaments (depressive, cyclothymic, hyperthymic, irritable and anxious) and has been verified in 32 language versions and widely used in a number of epidemiological and clinical studies with psychiatric patients and healthy subjects. This scale has been developed by Akiskal and is widely used and confirmed to be reliable and valid internationally and in Japan (Akiskal et al., 2005; Goto et al., 2011; Sprooten et al., 2011; Serafini et al., 2011; Araki et al., 2012; Kohno et al., 2012). In the present study, subjects were divided into groups of high and low cyclothymic temperament by a cut-off of 4 points, and into high and low hyperthymic groups by a cut-off of 6 points. The cut-offs were determined from the mean scores of a non-clinical population of 1391 Japanese (Matsumoto et al., 2005).

2.3. MRI acquisition

Using a 3T MRI scanner (MAGNETOM Verio, Siemens, Erlangen, Germany), T1-weighted structural images were acquired for each subject with a 3-D magnetization prepared rapid gradient echo (MPRAGE) sequence in the sagittal plane (TR 2040 ms, TE 2.53 ms, TI 900 ms, the flip angle 9°, FOV 192 mm, and voxel size $1 \times 1 \times 1$ mm). We used a 32-channel coil for receiving RF. Total time for scanning was 4 min 28 s for each subject.

2.4. Image analysis

We used SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) which worked on Matlab 2012a for image analysis. We used VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm/download/) for pre-processing with the optimized voxel-based morphometry (VBM) (Good et al., 2001). Individual gray matter maps were normalized initially with a non-linear algorithm to the standard space of MNI152 brain. Then gray matter maps were averaged across subjects to generate a study-specific template, to which subjects' gray matter maps were spatially re-normalized non-linearly. Normalized gray matter maps were modulated by Jacobian determinants, and smoothed with an 8 mm FWHM Gaussian filter.

First, smoothed gray matter volumes (GMVs) were analyzed for the effects of temperament groups (high cyclothymic temperament group versus low cyclothymic temperament or high hyperthymic temperament group versus low hyperthymic temperament group) in a voxel-wise manner using General Linear Model (GLM). We investigated the main effects for temperament groups and gender, as well as for interaction of temperament groups and gender using GLM. We adapted age and total GMVs as covariates of no interest. Significance level was set to $p < 0.05$ with cluster-level multiple correction (Family-Wise Error; FWE corrected) and voxels with $p < 0.001$ (uncorrected) were identified within the significant cluster. Anatomical structures were defined with the Talairach Daemon Labels of WFU PickAtlas Tool (Maldjian et al., 2003).

Secondly, we performed a regions of interest (ROI) analysis to investigate regression between relative regional GMVs and cyclothymic or hyperthymic temperament score. The ROI was set at 10 mm diameter sphere, center of peak coordinate of the clusters, and the mean value within this ROI was obtained from each non-smoothed GMV image. Regional GMVs were calculated using get_totals.m custom Matlab code (http://www.cs.ucl.ac.uk/staff/G.Ridgway/vbm/get_totals.m) with ROI mask images, and relative regional GMVs were calculated by dividing by total GMVs and further multiplied by 100. The regression significance between relative regional GMVs and cyclothymic or hyperthymic temperament scores was analyzed using GLM. We then analyzed again for the effect of gender using ANCOVA.

We also evaluated the effect of both bipolar temperaments (subjects belonging to both high cyclothymic group and high hyperthymic group versus the others). Finally, ROI analyses were conducted as above to evaluate regression of relative regional GMVs across temperament scores. Statistics in ROI analysis were performed by IBM SPSS Statistics Version 21.

3. Results

3.1. Demographic data

All subjects had neither past nor present psychiatric illness. Moreover, they had no family psychiatric history. The mean score (SD) of HAM-D was 1.44 (1.88) and that of YMRS was 0.91 (0.87) and all subjects were determined to be in euthymic mood. The mean scores (SD) of cyclothymic and hyperthymic temperaments