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Structural brain network differences in bipolar disorder using with similarity-based approach

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Original Article

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Abstract

Objective: Previous studies have shown differences in the regional brain structure and function between patients with bipolar disorder (BD) and healthy subjects, but little is known about the structural connectivity between BD patients and healthy subjects. In this study, we evaluated the disease-related changes in regional structural connectivity derived from gray matter magnetic resonance imaging (MRI) scans. Methods: The subjects were 73 patients with BD and 80 healthy volunteers who underwent 3-Tesla MRI. Network metrics, such as the small world properties, were computed. We also performed rendering of the network metric images such as the degree, betweenness centrality, and clustering coefficient, on individual brain image. Then, we estimated the differences between them, and evaluate the relationships between the clinical symptoms and the network metrics in the patients with BD. Results: BD patients showed a lower clustering coefficient in the right parietal region and left occipital region, compared with healthy subjects. A weak negative correlation between Young mania rating scale and clustering coefficient was found in left anterior cingulate cortex. Conclusions: We found differences in gray matter structural connectivity between BD patients and healthy subjects by a similarity-based approach. These points may provide objective biological information as an adjunct to the clinical diagnosis of BD.

Significant outcome

- BD patients showed the lower clustering coefficient in some regions.
- Young mania rating scale was correlated with clustering coefficient.
- These regional network changes preceded gray matter volume changes.

Limitations

- We could not detect any change of small-worldness in BD patients.
- The spatial resolution of the images derived from the similarity-based approach was relatively low.
- We did not control for psychotropic drugs in the neuroimaging analyses.

Introduction

Bipolar disorder (BD) is one of the top 10 most debilitating of all illnesses (Hirschfeld & Vornik, 2005) and affects an estimated 1–3% of the population (Narrow *et al.*, 2002; Angst *et al.*, 2003; Merikangas *et al.*, 2007). Structural brain magnetic resonance imaging (MRI) meta-analysis in patients with BD has revealed structural changes in the cortical and subcortical prefrontal-limbic regions, involving the orbitofrontal cortex, ventral anterior cingulate cortex, insula, amygdala, and hippocampus (Strakowski *et al.*, 2005; Ellison-Wright & Bullmore, 2010; Hallahan *et al.*, 2011; Houenou *et al.*, 2011; Ganzola & Duchesne, 2017). Other MRI studies on BD have revealed increased cortical thickness in the temporoparietal region (Rimol *et al.*, 2010), while studies using diffusion tensor imaging have revealed white matter abnormalities in the anterior and posterior cingulate cortex, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and cerebellum (Versace *et al.*, 2010; Ambrosi *et al.*, 2013; Nortje *et al.*, 2013; Jenkins *et al.*, 2016).

Graph theoretical analyses of neuroimaging data have increased our understanding of the topological organisation of structural and functional brain networks (Bullmore & Sporns, 2009; Hosseini *et al.*, 2012). Graph theory has been used to describe brain morphology, with networks based on covariation of gray matter volume, white matter microstructure, or thickness between each area across people. Regarding the neural network in BD, previous studies have detected a reduced clustering coefficient and global efficiency (Leow *et al.*, 2013; Collin *et al.*, 2016; O'Donoghue *et al.*, 2017; Wang *et al.*, 2017). On the other hand, another study showed that the whole brain analysis revealed no significant difference between the BD patients and healthy subjects (Forde *et al.*, 2015).

In spite of the above advances in graph theory, it remains unclear which measures are the most appropriate to define nodes and edges in graph theory focussing on cortical morphology. Automated anatomical labelling (AAL) has been widely used to define the nodes (Tzourio-Mazoyer *et al.*, 2002), but the requirements of AAL might obscure subtle structural differences that are of particular interest in clinical populations. A previous study developed a new method for the construction of networks from individual cortices based on intracortical similarities in the gray matter (Tijms *et al.*, 2012). They showed that the network metrics calculated by the similarity-based method were similar to other studies measured by graph theoretical analyses, and high reproducibility of the measures. Their results demonstrate that intracortical similarities can be used to provide a robust statistical description of individual gray matter morphology, and some studies using this method revealed disease-related brain network changes in Alzheimer's disease (Tijms *et al.*, 2013) and multiple sclerosis (Rinkus *et al.*, 2019).

In this study, we examined differences in the structural brain network between BD and healthy subjects using a new, similarity-based approach.

Aims of the study

The aim of this study was to examine differences in structural brain network indices between participants with BD and healthy subjects using a new similarity-based approach. We hypothesised that parts of the network thought to play a role in controlling the emotion would show a connectivity change in patients with BD.

Methods

Participants

The subjects were 73 patients with depressed-BD and 80 healthy subjects. A consensus diagnosis by psychiatrist (MO, SH, or TT) was made according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edn. (DSM-5) criteria (American Psychiatric Association, 2013), on the basis of unstructured interviews; the Japanese version of the Mini-International Neuropsychiatric Interview (MINI [Sheehan *et al.*, 1998]), based on structured interviews; and the information from medical records. All patients were rated with the Hamilton Depression Rating scale (HAM-D) for their depressive symptoms (Hamilton, 1960) and with the Young mania rating scale (Young *et al.*, 1978). Daily doses of antidepressants were converted to imipramine equivalents, and daily doses of antipsychotics, including depot antipsychotics, were converted to chlorpromazine equivalents using published guidelines (American Psychiatric Association, 1997; Inada & Inagaki, 2015).

Controls were recruited from the community through local magazine advertisements and an announcement on our website. These participants were interviewed for enrolment by a research psychiatrist using the Japanese version of MINI. Participants were excluded if they had a prior medical history of central nervous system disease or severe head injury, or if they met the criteria for substance abuse or dependence. Those individuals who demonstrated a history of psychiatric illness or contact with psychiatric services were excluded from the control group.

After the studchary was explained to each participant, his or her written informed consent was obtained for participation in the study. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry, Japan, and complied with the Helsinki Declaration of 1975, as revised in 2008.

MRI data acquisition and processing

The MR studies were performed on a 3-T MR system (Philips Medical Systems, Best, the Netherlands). High spatial resolution, 3-dimensional (3D) T1-weighted images were used for the morphometric study. 3D T1-weighted images were acquired in the sagittal plane (repetition time [TR]/echo time [TE], 7.18/3.46; flip angle, 10°; effective section thickness, 0.6 mm; slab thickness, 180 mm; matrix, 384 × 384; field of view [FOV], 261 × 261 mm; number of signals acquired, 1), yielding 300 contiguous slices through the brain.

Postprocessing of the MRI data

We calculated the small world properties, such as gamma (the ratio of the network's cluster coefficient and that of its randomised version), lambda (the ratio of the average minimum path length of the network and that of its randomised version), and sigma (the small world coefficient, defined as the division of gamma and lambda) (Humphries *et al.*, 2006) by the similarity-based method (Tijms *et al.*, 2012). We also performed rendering of the network metric images, including the degree, the number of links connected to a node, betweenness centrality, the importance of the node in the network, the clustering coefficient, and the measure of network segregation using the same method (Tijms *et al.*, 2012). First, each individual 3D-T1 image was segmented using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/). Next, the segmented gray matter image was resliced to 2 × 2 × 2 mm. The network metric images were then calculated from the segmented gray matter image at native space. Briefly, nodes in these networks represent brain areas (regions of 3 × 3 × 3 voxels), and connections are based on similarity in the spatial structure of gray matter density values as quantified with a Pearson's correlation. Networks were binarised using subject-specific thresholds as determined with a random permutation method that ensured a similar chance to include at most 5% spurious correlations in the network (Noble, 2009; Kate *et al.*, 2018).

To evaluate network metric images voxel-basically, network images were normalised with the diffeomorphic anatomical registration using the exponentiated lie (DARTEL) registration method (Ashburner, 2007). First, each individual 3D-T1 image was coregistered and resliced to its native segmented 3D-T1 image as mentioned above. Next, the coregistered 3D-T1 image was normalised with DARTEL. Finally, the transformation matrix was applied to the network metric images. Then, each image was smoothed by using a 10 mm full-width at half-maximum Gaussian kernel.

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With respect to the regional gray matter volume differences between groups, we normalized the individual 3D-T1 image by VBM8. Each image was smoothed by using a 12 mm full-width at half-maximum Gaussian kernel.

Statistical analysis

The differences in age and education years between the BD patient group and healthy subjects were evaluated using a two sample *t*-test, the differences in gender were evaluated using a chi-squared test, and the differences in sigma, lambda, and gamma were evaluated using analysis of covariance (ANCOVA) controlling for age and gender. We estimated the association between the scores of HAM-D and the Young mania rating scale and the network metrics, such as sigma, lambda, and gamma, by partial correlation analyses controlling for age and gender. Statistical analyses were performed using SPSS Statistics for Windows 23.0 software (SPSS Japan, Tokyo).

Statistical analyses for degree, betweenness centrality, and clustering coefficient images and regional gray matter volume were performed using SPM8 software. Differences in network metrics between two groups were assessed using the two sample *t*-test controlling for age and gender. As for the clinical symptoms, we also evaluated the relationships between the scores of HAM-D and Young mania rating scale and MRI indices using the multiple regression model controlling for age and gender in the patients with BD. Only differences and correlations that met the following criteria were deemed significant. In these cases, a seed level of $p < 0.01$ (false discovery rate [FDR] corrected) and a cluster level of $p < 0.01$ (uncorrected) were adopted.

Results

The demographic and clinical characteristics of the participants are shown in Table 1. There was no significant difference in age, gender or education year between the groups. We detected no significant differences in small world properties between the two diagnostic groups. We analysed the correlations between the scores of HAM-D and the Young mania rating scale and the small world properties, but these did not reach statistical significance.

There were significant reductions of clustering coefficient in the left occipital region, and right parietal gyrus of BD patients (Fig. 1), compared with healthy subjects. There were no significant differences of regional betweenness centrality and gray matter volumes between them. We evaluated the relationships between the scores of HAM-D and Young mania rating scale and MRI indices in the patients with BD. However, there were no significant correlations between the MRI indices and clinical symptoms. Only a weak negative correlation between the Young mania rating scale and the clustering coefficient were detected at a low level (a seed level of $p < 0.001$ [uncorrected] and a cluster level of $p < 0.05$ [uncorrected]) in the anterior cingulate cortex (Fig. 2).

Table 1. Demographic and clinical characteristics of the subjects

Variable	Patients with bipolar disorder $n = 73$ Mean ± SD	Healthy subjects $n = 80$ Mean ± SD	*p*-value
Males : Females	35 : 38	36 : 44	0.75
Age, years	40.0 ± 10.3	40.5 ± 11.6	0.81
Education, years	14.9 ± 2.3	15.0 ± 2.6	0.76
Onset, years	27.6 ± 10.5	–	–
Antidepressant medication, mg/day*	62.3 ± 117.0	–	–
Antipsychotic medication, mg/day#	119.5 ± 324.9	–	–
Dose of lithium, mg/day	201.4 ± 319.9	–	–
HAM-D	11.8 ± 7.6	–	–
Young mania rating scale	1.7 ± 3.0	–	–
Gamma	1.40 ± 0.03	1.40 ± 0.03	0.44
Lambda	1.03 ± 0.00	1.03 ± 0.00	0.88
Sigma	1.36 ± 0.03	1.36 ± 0.03	0.41

HAM-D, Hamilton's depression rating scale.
*Imipramine equivalent.
#Chlorpromazine equivalent.

Discussion

BD patients showed a lower clustering coefficient in the right parietal region and left occipital region, compared with healthy subjects. We also found the negative correlation between the Young mania rating scale and clustering coefficient in the patients with BD. To our knowledge, this is the first study to evaluate the differences between BD patients and healthy subjects by a similarity-based approach using structural 3D-T1 images.

Previous diffusion tensor imaging studies found that BD patients showed fractional anisotropy (FA) reduction in the superior longitudinal fasciculus and fronto-occipital fasciculus, respectively (Versace *et al.*, 2010; Ambrosi *et al.*, 2013; Nortje *et al.*, 2013). The superior longitudinal fasciculus regulated the focussing of attention in different parts of space (Makris *et al.*, 2005), and the fronto-occipital fasciculus has been implicated in peripheral vision and processing of visuospatial information (Schmahmann, 2004). Therefore, any of these regions might also influence the visuo-spatial neuropsychologic dysfunction in BD (Sweeney *et al.*, 2000; Ferrier *et al.*, 2004).

By whole brain analyses, the global efficiency, which is the inverse of the average shortest path, and clustering coefficient were shown to be impaired in BD (Leow *et al.*, 2013; Collin *et al.*, 2016; O'Donoghue *et al.*, 2017; Wang *et al.*, 2017). However, one study showed a higher path length and clustering coefficient in BD patients than healthy subjects (Roberts *et al.*, 2016), and another showed that there was no significant difference in the whole brain network between BD patients and healthy subjects (Forde *et al.*, 2015). Disturbances in large-scale structural networks in BD appear subtle and are more likely to be confined to specific regions. The subtle changes in the whole brain network observed in BD may reflect alterations to the disrupted connectivity of some specific circuits (Perry *et al.*, 2019).

We detected that BD patients showed a negative correlation between the Young mania rating scale and clustering coefficient in the anterior cingulate cortex. Positron emission tomography (PET) study found a significant correlation between the activation in the anterior cingulate and the score of the Young mania rating scale (Rubinsztein *et al.*, 2001). Further, single photon emission computed tomography (SPECT) and resting state functional MRI studies detected that manic patients showed increased activity in the anterior cingulate (Goodwin *et al.*, 1997;

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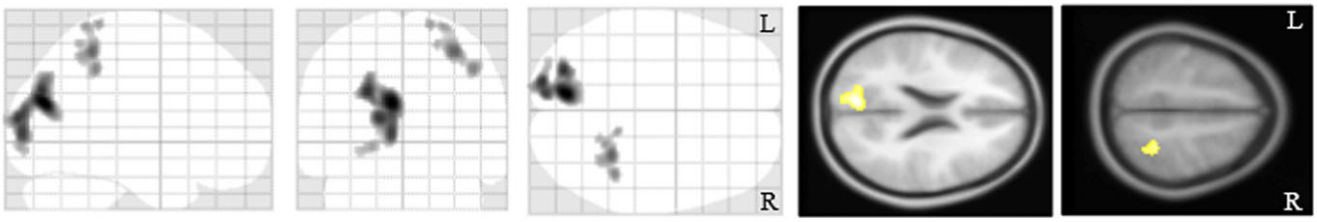

Fig. 1. Regional changes of network indices in patients with bipolar disorder. The patients with bipolar disorder showed significant reduction of clustering coefficient, compared with healthy subjects. R is right, and L is left. The background images were 'avg152T1' images, which are regarded as anatomically standard images in the SPM8.

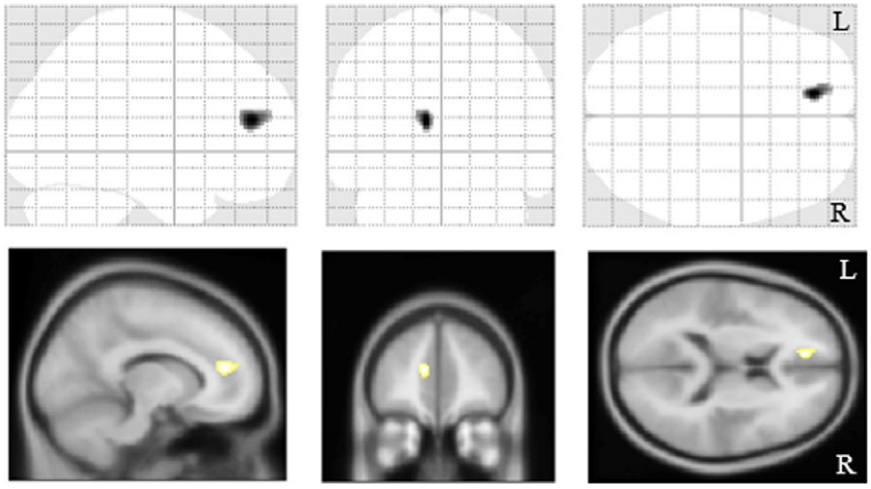

Fig. 2. Relationship between the network indices and Young mania rating scale in patients with bipolar disorder. There was significant negative correlation between Young mania rating scale and clustering coefficient of left anterior cingulate cortex in the patients with bipolar disorder. R is right, and L is left. The background images were 'avg152T1' images, which are regarded as anatomically standard images in the SPM8.

Blumberg *et al.*, 2000). It is known that anterior cingulate regulates the emotion and executive functions (Gasquoine, 2013). The activation of brain areas involving anterior cingulate in manic patients might result in the decrease of clustering coefficient in anterior cingulate.

There were limitations in this study. First, our imaging resolution of network metrics was relatively low. For that reason, this protocol was thought to be unsuitable to estimate the small regional disease-related changes. However, we did identify small changes such as the clustering coefficient in ACC, and our results might suggest that this protocol would be suitable for the whole brain analysis.

In conclusion, there were significant changes of network metrics in BD patients compared with the healthy volunteers, and these network changes preceded affective disorder-related regional gray matter volume changes. This point may provide objective biological information as an adjunct to the clinical diagnosis of BD.

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Author contributions. MO, NS and HM designed the experimental protocol. MO, TN, SH and TT carried out the experiments. MO analysed the data and wrote the first draft of this paper. NS, HM, and HK reviewed the manuscript. All authors contributed to and approved the final version.

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Conflict of interest. All authors declare that they have no conflicts of interest.

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