Abnormal Asymmetry of White Matter Integrity in Schizophrenia Revealed by Voxelwise Diffusion Tensor Imaging

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Abstract: A number of magnetic resonance imaging (MRI) studies have revealed morphological cortical asymmetry in the normal human brain, and reduction or inversion of such hemispheric asymmetry has been reported in schizophrenia. On the other hand, diffusion tensor imaging (DTI) studies have reported inconsistent findings concerning abnormal asymmetry of white matter integrity in schizophrenia. Our aim was to confirm whether there is reduced or inverted asymmetry of white matter integrity in the whole brain in schizophrenia. For this study, 26 right-handed schizophrenia patients, and 32 matched healthy control subjects were investigated. Voxelwise analysis of DTI data was performed using the tract-based spatial statistics. The fractional anisotropy (FA) images were normalized and projected onto the symmetrical white matter skeleton, and the laterality index (LI) of FA, determined by $2 \times (\text{left} - \text{right}) / (\text{left} + \text{right})$, was calculated. The results reveal that schizophrenia patients and healthy controls showed similar patterns of overall FA asymmetries. In the group comparison, patients showed significant reduction of LI in the external capsule (EC), and posterior limb of the internal capsule (PLIC). The EC cluster revealed increased rightward asymmetry, and the PLIC cluster showed reduced leftward asymmetry. Rightward-shift of FA in the EC cluster correlated with negative symptom severity. Considering that the EC cluster includes the uncinate and inferior occipitofrontal fasciculi, which have connections to the orbitofrontal cortex, abnormal asymmetry of white matter integrity in schizophrenia may play a crucial role in the pathogenesis of schizophrenia, through the altered connectivity to the orbitofrontal cortex. *Hum Brain Mapp* 33:1741–1749, 2012. © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

A number of postmortem and imaging studies have revealed morphological asymmetry in the human brain, such as the right frontal and left occipital extensions (“petalia” or “torque”) [Barrick et al., 2005; Chiu and Damasio, 1980; LeMay, 1977], and left greater than right asymmetry of the Heschl’s gyrus and planum temporale [Dorsaint-Pierre et al., 2006; Geschwind and Levitsky, 1968]. These anatomical asymmetries are considered as the neural underpinnings of functional lateralization, such as language lateralization to the left hemisphere. Abnormality of such cerebral asymmetry has long been hypothesized in schizophrenia [Crow, 2000], and reduced or inverted cerebral asymmetries of gray matter in schizophrenia have been revealed in recent magnetic resonance imaging (MRI) studies [Bilder et al., 1994; Hirayasu et al., 2000; Kawasaki et al., 2008; Oertel et al., 2010], although with some inconsistencies [Deep-Soboslay et al., 2010; Takao et al., 2010].

Diffusion tensor imaging (DTI) is a non-invasive MRI technique that provides information about white matter tracts and their organization based on water diffusion, and is sensitive to subtle white matter microstructural abnormalities. Fractional anisotropy (FA) is the most commonly used DTI index and a high FA value indicates high white matter tract integrity. DTI studies of healthy human brains, which utilize the tractography, or region of interest (ROI) methods, revealed leftward asymmetry of FA in such areas as the arcuate fasciculus (AF), subinsular part of the uncinate fasciculus (UF), inferior occipitofrontal fasciculus (IOFF) [Rodrigo et al., 2007], and the posterior limb of the internal capsule (PLIC) [Westerhausen et al., 2007]. Rightward asymmetry of FA was found in the optic radiation and anterior part of the AF [Thiebaut de Schotten et al., 2010], and in the extrainsular part of the UF [Rodrigo et al., 2007]. While some studies of schizophrenia patients reported reduced leftward asymmetry in the superior occipitofrontal fasciculus (SOFF) [Kunimatsu et al., 2008], anterior cingulum bundle (CB) [Wang et al., 2004], and the UF [Kubicki et al., 2002], others did not find such abnormal asymmetry in schizophrenia in CB [Kubicki et al., 2003], UF and anterior thalamic radiation [McIntosh et al., 2008], AF, UF, and inferior longitudinal fasciculus (ILF) [Phillips et al., 2009], or AF, CB, ILF, IOFF, and UF [Voineskos et al., 2010].

Voxel-based morphometry (VBM) [Ashburner and Friston, 2000] is an automated method for structural MRI data, and suitable for exploring cerebral asymmetry in the whole brain. So far, only two studies have applied VBM to DTI data of schizophrenia [Park et al., 2004; Takao et al., 2010], and a report by Takao et al. [2010] is the only study which directly compared FA asymmetry between patients

and healthy controls. However, it did not find abnormal FA asymmetry in schizophrenia. A recently developed voxelwise analysis technique, called tract-based spatial statistics (TBSS) [Smith et al., 2006], maps each subject’s DTI data onto a common white matter tract center (“skeleton”), and is robust for registration confounds, which can be problematic in the application of VBM to DTI data. Thus, TBSS is considered to be more suitable than VBM for whole brain exploration of FA asymmetry.

In this study, our goal was to confirm whether there is regionally reduced, or inverted asymmetry of white matter integrity in schizophrenia, using a novel and robust voxelwise analysis method of TBSS. Because abnormal brain asymmetry is considered to play a crucial role in the pathophysiology of schizophrenia, we also examined if such abnormal asymmetry is correlated with the psychopathology.

MATERIALS AND METHODS

Participants

Twenty-six right-handed schizophrenia patients were studied. Their diagnosis was based on the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Twenty patients were diagnosed as paranoid type, two patients as disorganized type, two patients as catatonic type, one patient as residual type, and one patient with schizoaffective disorder. None of the patients were comorbid with other psychiatric disorders. All patients were receiving antipsychotic medication. The positive and negative syndrome scale (PANSS) [Kay et al., 1987] was used to assess the severity of clinical symptoms. Since PANSS has been revealed to have five symptom dimensions [Lancon et al., 1998, 2000; Lindenmayer et al., 1994a,b, 1995; Wolthaus et al., 2000], we used the five-factor model. We employed the model of Lancon et al. [1998], which consists of 24 items from the original 30 items of PANSS, and has subscales of negative factor (7 items), positive factor (5 items), activation factor (5 items), depressive factor (4 items), and cognitive factor (3 items). Thirty-two right-handed healthy controls were recruited, and matched with the patient group in age, gender, and predicted IQ level. The predicted IQ was measured by the Japanese Version of the National Adult Reading Test short form (JART-25) [Matsuoka and Kim, 2007; Matsuoka et al., 2006], which is considered to reflect the premorbid IQ of patients with schizophrenia. The controls had no history of psychiatric illness, as determined by the non-patient edition of the SCID, and there was no history of psychotic disorders among their first-degree relatives. Exclusion

criteria for all individuals included a history of head trauma, neurological illness, serious medical or surgical illness, and substance abuse. After receiving a complete description of the study, all participants gave written informed consent. The study design was approved by the Committee on Medical Ethics of Kyoto University, and conforms to the provisions of the Declaration of Helsinki.

MRI Acquisition

DTI data were acquired using single-shot spin-echo echo-planar sequences, on a 3.0-T MRI unit (Trio; Siemens, Erlangen, Germany) with a 40-mT m⁻¹ gradient and a receiver-only eight-channel phased-array head coil. The scanning parameters were as follows: TE = 96 ms, TR = 10,500 ms, 96 × 96 matrix, FOV = 192 × 192 mm², 70 continuous axial slices of 2.0 mm thickness, 81 non-collinear axis motion probing gradient, $b = 1,500 \text{ s mm}^{-2}$. The $b = 0$ images were scanned preceding every nine diffusion weighted images, thus consisting of 90 volumes in total.

DTI Data Processing and Laterality Index Calculation

All DTI data processing and statistical analyses were performed using the programs in FSL version 4.1.4 (<http://www.fmrib.ox.ac.uk/fsl>). Source data were corrected for eddy currents and head motion by registering all data to the first $b = 0$ image, with affine transformation. The fractional anisotropy (FA) maps were calculated using the FDT program. For voxelwise statistical analysis, TBSS version 1.2 was used. First, usual TBSS steps were performed: all FA data were normalized into a common space using the nonlinear registration tool FNIRT [Andersson, 2007a,b]; normalized FA images were averaged to create a mean FA image, which was then thinned to create an original skeleton taking only the centers of white matter tracts. This original skeleton was thresholded at FA of 0.2. Then a symmetrical version of the skeleton was created by the *tbss_sym* script. First, the original (asymmetrical) skeleton was thickened by one voxel; the mean FA image was flipped left-right and averaged to create a symmetrical mean FA image, and thinned to create the initial symmetrical skeleton. This initial symmetrical skeleton was masked by the dilated original skeleton. Finally, the masked skeleton was flipped left-right, and the overlapping part between the non-flipped and flipped skeleton was taken as the final “symmetrical skeleton,” which keeps correspondence to the original skeleton. Then *tbss_sym* allocated voxel values of each subject’s normalized FA data onto the final symmetrical skeleton, by searching the local maxima along the perpendicular direction from the skeleton. Each subject’s skeletonized FA image was flipped, and the laterality index (LI) image was calculated for each subject by following formula:

$$2 \times (\text{original} - \text{flipped}) / (\text{original} + \text{flipped})$$

The *fslmaths* and *fslswapdim* scripts did this processing, and then statistical analysis was performed on this skeletonized LI data. In the LI image, each voxel value represents $2 \times (L - R) / (L + R)$, where L denotes the left hemisphere FA, and R the right hemisphere FA. Positive values on the left side of the image indicate that the left hemisphere had higher FA than the right hemisphere counterpart ($L > R$), and negative values indicate that the right is higher than the left ($L < R$).

Voxelwise Statistical Analysis

Voxelwise permutation-based nonparametric inference [Nichols and Holmes, 2002] was performed, using the FSL Randomize version 2.5. As the right and left sides of the LI image are mirror images of each other, we used only the left side for statistical analysis to reduce the number of multiple comparisons. We employed the analysis of covariance design in general linear model framework, with age and gender as nuisance covariates. We first confirmed the overall patterns of FA asymmetry of the controls and patients by [1 0 0 0] (i.e., $L > R$) and [-1 0 0 0] ($L < R$) contrasts for the controls, and [0 1 0 0] and [0 -1 0 0] for the patients. The group comparison of LI was performed, testing both controls-patients ([1 -1 0 0] for the design matrix, testing reduced leftward asymmetry or increased rightward asymmetry for patients than controls) and patients-controls ([-1 1 0 0], increased leftward or reduced rightward asymmetry for patients) contrasts. All the testing was performed with 10,000 permutations. The statistical threshold was set at $P < 0.05$, correcting for multiple comparisons by the threshold-free cluster enhancement (TFCE) [Smith and Nichols, 2009]. TFCE does not need an arbitrary cluster-forming threshold, while preserving the sensitivity benefits of clusterwise correction. Anatomical correspondence was identified with reference to the Johns Hopkins University DTI-based White Matter Atlas (<http://cmrm.med.jhmi.edu>) [Mori et al., 2005].

Correlational Analysis

The mean LI of each significant cluster was calculated for every subject using *fslstats* script, and correlation with PANSS subscales (negative, positive, activation, depressive, and cognitive factors) were explored for patients using the SPSS version 12.0 (SPSS, Chicago). As the initial exploration of the data showed significant, or trend level violation of the assumption of normal distribution in most of the five subscales, Spearman’s rank correlation coefficient was used. Because of the relatively small sample size and exploratory nature of this correlational analysis, correction for multiple comparisons was not applied, and an uncorrected P -value of 0.05 was regarded as the statistical threshold of significance.

TABLE I. Demographic, psychological, and clinical characteristics of the participants

	Schizophrenia (<i>n</i> = 26)		Control (<i>n</i> = 32)		Statistics
	Mean	S.D.	Mean	S.D.	
Age (years)	34.5	8.9	39.0	11.0	N.S. ^a
Gender (male/female)	16/10		16/16		N.S. ^b
JART25 predicted full scale IQ	104.5	10.3	108.2	8.9	N.S. ^a
Age of onset (years)	23.2	5.4	—	—	—
Duration of illness (years)	11.3	8.0	—	—	—
Medication (mg day ⁻¹ , HPD equivalent) ^c	10.2	6.6	—	—	—
Atypical only/typical only/both ^d	18/1/7		—	—	—
PANSS negative factor	15.2	4.23			
Positive factor	11.4	3.6			
Activation factor	7.4	1.5			
Depressive factor	8.3	2.6			
Cognitive factor	5.7	1.2			

^aTwo-tailed *t* tests, $\alpha = 0.05$.^bTwo-tailed χ^2 test, $\alpha = 0.05$.^cHaloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia [Inagaki and Inada, 2008, 2010; Lehman et al., 2004].^dAtypical only = patients who were taking atypical antipsychotics. Typical only = patients taking typical antipsychotics. Both = patients taking both typical and atypical antipsychotics.

We further investigated the correlation between mean LI and duration of illness, to examine if the progressive pathological process is underlying such abnormal asymmetry in schizophrenia. Pearson's correlation coefficient was used, and the statistical threshold was set at $P < 0.05$.

Medication Effect

To examine the possible confounding effect of medication on white matter asymmetry in schizophrenia, we performed a correlational analysis between LI and medication using TBSS. A multiple regression analysis was performed with haloperidol equivalent dose as the explanatory variable, and age and gender as nuisance covariates, and both positive and negative correlations were tested. The tests were performed with 10,000 permutations. The statistical threshold was set at $P < 0.05$, correcting for multiple comparison by TFCE.

RESULTS

Demographic and Clinical Data

The demographic and clinical data are shown in Table I. Many patients were in the chronic stage with mild symptom severity. A majority of the patients were taking atypical antipsychotics.

Imaging Data

In the within-group analyses, there were a number of clusters that showed significant leftward and rightward asymmetry, and schizophrenia patients and healthy con-

trols showed similar overall asymmetry patterns (see Fig. 1). Clusters of significant leftward asymmetry included the CB, anterior part of the corpus callosum (CC), the corticospinal tract (CST) at the level of the cerebral peduncle and PLIC, and clusters of significant rightward asymmetry included frontal and parietal white matter that contained anterior and posterior corona radiata, anterior limb of the internal capsule (ALIC), and temporal white matter beneath the Heschl's gyrus. The superior longitudinal fasciculus (SLF) showed rightward asymmetry in the patient group, but not in the healthy controls.

In the group comparison, schizophrenia patients showed two clusters of significant LI reductions compared with controls: one cluster was located at the anteroinferior part of the external capsule (EC), which included the UF and IOFF, and the other cluster was located at the PLIC (Fig. 2 and Table II). The EC cluster was located in the area that showed rightward asymmetry in schizophrenia, but not in the controls, indicating increased rightward asymmetry in schizophrenia. On the other hand, the PLIC cluster was located in the region where leftward asymmetry was found in the healthy controls, but not in the patients, indicating reduced leftward asymmetry in patients (see Fig. 3). There was no significant cluster of LI increase in the schizophrenia patients compared with healthy controls.

In the correlational analysis, mean LI of the EC cluster showed significant negative correlation with the negative factor of PANSS ($\rho = -0.524$, $P = 0.006$) (see Fig. 4). This correlation was still significant when the statistical threshold was set at $P < 0.01$ (Bonferroni correction for five subscales). The other four subscales did not show significant correlation with the EC cluster. Mean LI of the PLIC cluster did not show significant correlation with any of the

Figure 1.

Regions of significant leftward and rightward asymmetry in healthy controls and schizophrenia patients ($P < 0.05$ corrected with threshold-free cluster enhancement) are shown overlaid on the mean FA image and on the left side of the symmetrical skeleton mask (yellow). Red indicates leftward asymmetry, and blue indicates rightward asymmetry. Abbreviations: hc = healthy controls, sc = schizophrenia patients.

five subscales. Duration of illness did not show a significant correlation with the mean LI of the EC or PLIC clusters. In the analysis of medication effect, no significant correlation between LI and medication was found.

DISCUSSION

The aim of this study was to confirm abnormal asymmetry of white matter integrity in schizophrenia patients. There are three main findings: first, both schizophrenia patients and healthy controls showed approximately a similar pattern of leftward and rightward asymmetry of white matter integrity. Second, this is the first study to demonstrate abnormal white matter asymmetry in schizophrenia using TBSS. Third, the abnormal white matter asymmetry was associated with the negative symptoms of schizophrenia.

The overall patterns of asymmetry revealed in our within-group analyses, were largely consistent with the results of previous VBM-style DTI studies [Park et al., 2004; Takao et al., 2010]. The former study reported leftward asymmetry of FA in such areas as the anterior part of the CC, CB, optic radiation, and the superior cerebellar peduncle, and rightward asymmetry in the ALIC, UF, SLF, and in the anterior and superior prefrontal white matter in healthy controls. These asymmetries were less evident in patients. The latter study showed leftward asymmetry in the AF, the CB, the anterior part of the CC, and in the corticospinal tract, including the internal capsule, and rightward asymmetry in the frontal and parietal white matter and bottom of the EC as the common asymmetry pattern between schizophrenia and controls.

Our group comparison revealed a rightward-shift of asymmetry of white matter integrity in schizophrenia in two clusters. Among them, increased rightward

Figure 2.

Regions of significant laterality index (LI) reduction in the external capsule (**A**) and posterior limb of the internal capsule (**B**) in schizophrenia patients compared with healthy controls ($P < 0.05$, corrected by threshold-free cluster enhancement) are shown (green), overlaid on the mean FA image and the left side

of the symmetrical skeleton mask (yellow). To aid visualization, significant regions are thickened using `tbss_fill` script implemented in FSL. Note that the sagittal slice of Figure 2B also shows the external capsule cluster (the anterior one).

asymmetry was found in the anteroinferior part of the EC, which contained the UF and the IOFF. Previous studies showed inconsistent results of UF asymmetry in schizophrenia. An ROI study [Kubicki et al., 2002] showed rightward-shift of FA asymmetry in the UF of male schizophrenia patients compared with controls, consistent with our results. However, this rightward shift in schizophrenia patients was a reduction of leftward asymmetry shown in the healthy controls. On the other hand, a post-mortem study [Highley et al., 2002] showed rightward asymmetry of the cross-sectional area and axonal fiber count in UF, for both schizophrenia patients and healthy controls. A tractography study [Voineskos et al., 2010] reported that there were no group differences of LI in the UF. All of these studies used different modalities. One possible cause of this inconsistency may be that different parts of the UF have different asymmetry patterns, as revealed in an earlier study [Rodrigo et al., 2007]. TBSS is suitable to detect such asymmetries considering its voxelwise nature, and robustness to the misregistration confounds.

The correlational analysis revealed that increased rightward asymmetry in the EC cluster was associated with an

increased score of PANSS negative factor. One earlier study [Bilder et al., 1994] reported such an association in schizophrenia between abnormal brain torque and negative symptom. Of note, in our study, both of the two fibers

Figure 3.

Comparison of the results of within-group analyses and group comparison. (**A**) The external capsule cluster (green, right column) was located in the area that showed rightward asymmetry in schizophrenia (blue, middle column), but not in controls (left column). (**B**) The posterior limb of the internal capsule cluster (green, right column) was located in the region where leftward asymmetry was found in healthy controls (red, left column), but not in patients (middle column).

TABLE II. Regions of significant reduction of laterality index in schizophrenia patients ($N = 26$) relative to healthy controls ($N = 32$)

Anatomical region	t	MNI coordinate			Cluster size
		X	Y	Z	
EC	4.20	-21	24	-10	89
PLIC	4.36	-25	-16	11	9

Abbreviations: EC = external capsule, PLIC = posterior limb of internal capsule.

Figure 4.

Scatter plot of the correlation between mean laterality index (LI) of the external capsule cluster and the negative factor of PANSS in patients ($\rho = -0.524$, $P = 0.006$).

included in the EC cluster have a connection to the orbito-frontal cortex (OFC); the UF connects the OFC and the medial prefrontal cortex with the anterior part of the temporal lobe including the amygdala [Ebeling and von Cramon, 1992], and the IOFF connects the OFC to the posterior temporal cortices [Mandonnet et al., 2007]. The OFC plays a crucial role in emotion and reward processing [Kringelbach and Rolls, 2004], and abnormal white matter asymmetry at the UF and/or IOFF shown in our study may cause abnormal input to the OFC. This may lead to dysfunction of the OFC in associating emotion with behavior, accurately decoding the emotional context which guides behavior, and evaluating the consequence of actions in terms of positive or negative outcomes [Levy and Dubois, 2006]. As a consequence, it results in the “emotional-affective apathy” [Levy and Dubois, 2006], which includes emotional blunting, loss of interest to daily-life activities, decreased reward sensitivity, and decreased involvement in affective aspects of life; i.e., the negative symptoms in schizophrenia.

The other cluster showing rightward-shift in schizophrenia was found in the PLIC, where reduction of normal leftward asymmetry was found. Previous MRI studies described abnormalities in this white matter region in schizophrenia, showing a reduced volume of the left PLIC [Yoshihara et al., 2008], and a reduced FA in both the left and right PLIC [Mitelman et al., 2007] in schizophrenia. Within the PLIC, thalamocortical projection fibers are intermingled with the CST fibers. Thus, one possible interpretation is that the abnormal asymmetry found in our study is a representation of abnormal connectivity of the thalamocortical circuit in schizophrenia.

The duration of illness did not show an association with abnormal asymmetry in either EC or PLIC clusters. This suggests that such abnormal asymmetry in schizophrenia is not a progressive process. Medication also showed no

association with white matter asymmetry in patients. Thus, our results are considered to be independent of medication effects. Consistent with our findings, one earlier study [Kawasaki et al., 2008] investigated the correlation between the asymmetry index of gray matter and the duration of illness and medication, and did not find any significant correlation. To confirm these negative findings, however, further studies are required.

Gender difference in the brain structure is a matter of great interest. Although our sample size is too small, especially with the number of female patients, to investigate the effect of gender on asymmetry, we performed supplementary analyses dividing the subjects into four subgroups; male controls, female controls, male patients, and female patients. We examined the asymmetry patterns within each subgroup, and tested for the effect of gender and the gender-by-diagnosis interaction. The statistical method is described in detail in the Supporting Information material. The overall patterns of asymmetry of four subgroups were largely similar to the pattern revealed in the within-group analyses for patients and controls, though female patients showed slightly less significant clusters (Supporting Information Fig. S1). There was no main effect of gender, or gender-by-diagnosis interaction. Further study with increased number of subjects is necessary to strengthen this issue.

Our study has several limitations. First, it is difficult to tell exactly which fiber tract in the EC or PLIC cluster contributed to the abnormal white matter asymmetry in schizophrenia, as multiple fiber tracts are contained in both regions. Therefore, caution needs to be taken for interpretation of these results. Second, our patients had relatively high IQs and mild symptom severity, and may not be representative of the general population of schizophrenia patients. Third, and this may be associated with the high IQ in our patient population, the majority of our patients presented with paranoid schizophrenia, and their intellectual and cognitive abilities are comparatively preserved. This may have affected the current results. For these issues, and to ascertain our findings, a study with a more widely distributed sample population would be necessary.

CONCLUSION

Our study revealed abnormal asymmetry of white matter integrity in schizophrenia, using voxelwise analysis. The abnormal white matter asymmetry at the EC cluster was associated with negative symptoms. Altered input to the OFC through the UF and/or IOFF may cause dysfunctional processing of emotion and reward, leading to emotional apathy, one core symptom of negative syndrome.

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