Analyses of the Disruption of White Matter Integrity in Schizophrenia Using Diffusion Tensor Fiber Tracking with Automatic Construction of Region of Interest

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Abstract The goal of this study was to find feasible indices for quantitative evaluation of sagittal stratum abnormalities in schizophrenic patients, by automatically establishing the region of interest during fiber tracking of a target bundle. We analyzed the sagittal stratum, including the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, using a fiber tracking and tractography technique with magnetic resonance diffusion tensor imaging. Diffusion tensor images were acquired from patients with schizophrenia and healthy subjects (controls), group-matched for age, sex, and handedness. We calculated thirteen indices representing the features of the tracked fibers. These were derived from the cross-sectional area of the tracked fibers in the starting area, fractional anisotropy, mean diffusivity, and curvature of the tracked streamline. These indices were compared between patients and control groups, and between the right and left hemispheres. We found significant differences in two indices between the patient and control groups; four indices indicating significant hemisphere effects in the patient group, and three indices showing significant differences between hemispheres in the control group. These results suggest that it may be possible to perform quantitative evaluation of sagittal stratum abnormalities in schizophrenia using these indices.

Keywords: diffusion tensor imaging, fiber tracking, tractography, schizophrenia, sagittal stratum.


1. Introduction

Recently, noninvasive measuring and imaging methods are widely used in clinical diagnosis. In particular, magnetic resonance imaging (MRI) is suitable for measuring the intravital structures of the human brain. Magnetic resonance diffusion tensor imaging (MR-DTI) is a noninvasive MRI method [1] that can measure in vivo diffusion phenomenon of water molecules reflecting thermal Brownian motion, using motion-probing gradients at multiple axes in at least six spatial directions. The magnitude of diffusion can be approximated by a symmetric 3D ellipsoid, where the shape and orientation of the diffusion ellipsoid are derived as a tensor in each voxel [2]. The cerebral white matter in the human brain consists largely of axons extending from the neuronal cell bodies to form connections with neurons in other brain areas [3]. A fiber tract is a large collection of axons. In the cerebral white matter, diffusion of water molecules parallel to fiber tracts is unrestricted, i.e., the movement is fast. On the other hand, diffusion perpendicular to fiber tracts is restricted, i.e., the movement is slow. Therefore, it is possible to obtain structural information about the cerebral white matter by quantitatively and qualitatively measuring the magnitude and direction of water diffusion in the white matter [4].

In addition, an increasing number of engineering approaches have become available for analyzing the brains of patients suffering from psychiatric disorders. Schizophrenia is the most debilitating of all adult psychiatric illnesses. The disease manifests positive and negative symptoms, cognitive impairments, and mood disorders. Patients with schizophrenia have delusions, experience hallucinations, and exhibit confused speech and grossly disorganized or catatonic behaviors. These symptoms constitute obstacles to daily living. Consequently, many patients depend on others to meet their daily living needs. The lifetime prevalence of schizophrenia is approximately 1% of the universal population. It is known that early initiation of antipsychotic medications results in a better long-term outcome [5]. This is why early diagnosis of schizophrenia is desirable. Quantifying the pathology allows early diagnosis and appropriate treatment during episodes.

Research on the cerebral white matter of schizophrenic patients using MR-DTI was first reported in 1998 [6]. That paper reported that schizophrenic patients showed diminished anisotropy in the frontal white matter, including the internal capsule and the white matter of the temporal lobe. Later, a widespread reduction in anisotropy was suggested in studies with larger numbers of patients [7, 8]. It was reported that fractional anisotropy (FA) of the inferior longitudinal fasciculus was reduced...
and that the reduction in the right hemisphere correlated negatively with measures of thinking disorder and with reductions in volume and FA of the arcuate fasciculus in schizophrenic patients using fiber tractography [7]. FA is an index of the anisotropy strength in each voxel [2]. Its definition is given in the section below. A reduction in FA and an increase in mean diffusivity (MD) of the thalamo-frontal white matter have also been demonstrated by fiber tractography [9]. MD indicates the volume of diffusion, unrelated to the direction [10]. Negative correlations of FA values with positive symptom scores on PANSS (positive and negative syndrome scale) were also found in the left uncinate fasciculus, right sagittal stratum, and left superior longitudinal fasciculus [11].

We previously showed that the cross-sectional area of fiber tractography was reduced in the superior longitudinal fasciculus of the right hemisphere [12]. Rowland et al. [13] also showed that FA in the superior longitudinal fasciculus of the right hemisphere was reduced in a schizophrenic patient [13]. Because FA reductions and MD increases in the corpus callosum have been observed in patients and unaffected relatives compared with healthy controls [14], schizophrenia is believed to be an endophenotype, and better treatment may be achieved through early diagnosis.

The goal of this study was to detect structural abnormalities in a target bundle by automatically establishing the region of interest during fiber tracking. In this study, we targeted the sagittal stratum, including the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, because in this region, FA reduction and negative correlation of FA with symptoms have been reported [7, 11]. In addition, we determined feasible indices for quantitative evaluation of sagittal stratum abnormalities in schizophrenic patients.

2. Methods

2.1 Subjects

A total of 35 subjects were scanned: 14 schizophrenic patients [aged (mean ± standard deviation) 35.0 ± 10.0 years, 7 males and 7 females, 13 right-handed and 1 left-handed] at Kyorin University Hospital who met the DSM-IV-TR criteria for schizophrenia, and 21 healthy subjects [aged 31.7 ± 7.6 years, 12 males and 9 females, 21 right-handed] as controls. There were no significant differences in age, gender, and handedness between the schizophrenic patients and control subjects.

All the subjects gave written informed consent to participate in this study, after receiving a full explanation of the procedures. The exclusion criteria for all the subjects were a history of convulsive disease or head injury, and a history of alcohol or substance dependence. In addition, the following were excluded as subjects: those with diabetes and hypertension, those who had undergone electroconvulsive therapy, and those whose MRI brain scans already showed clear abnormalities. Prior to implementing this study, we obtained approval from the Ethics Committee of the Kyorin University School of Medicine.

2.2 Image acquisition

DTI data were obtained using a 1.5 T Intera Achieva Nova Dual (Philips Electronics) installed at the Medical Satellite Yaesu Clinic. The imaging conditions were a TR of 2900 ms, a TE of 60 ms, six excitations, a 240 mm field of view (FOV), a voxel size of 0.9375 × 0.9375 × 5.0 mm³, an image matrix of 256 × 256, a slice thickness of 5.0 mm, no gap, 25–30 slices, six non-collinear directions of motion probing gradient (MPG) ([0.33, 0.67, −0.67], [0.67, 0.33, 0.67], [−0.67, 0.67, 0.33], [0.71, 0.71, 0], [0, 0.71, 0.71], [−0.71, 0, 0.71]), and a b value of 1000 s/mm². We also obtained b0 image at a b value of 0 s/mm².

2.3 Image processing

For preprocessing, we used the image processing software MRI Studio, including DTI Studio (version 3.0.3), ROI Editor (version 1.5), and DiffeoMap (version 1.7.3), which was developed with the support from the Laboratory of Brain Anatomical MRI and the Center for Imaging Science at Johns Hopkins University (https://www.mristudio.org/).

DTI Studio calculates the diffusion tensor, the first eigenvector and eigenvalue of the diffusion tensor, the FA value, and the trace using DTI data. The trace is three times the MD value. FA and MD are defined as

\[
FA = \sqrt{\frac{3[(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2]}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}
\]

(1)

\[
MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = D,
\]

(2)

where \(\lambda_1, \lambda_2, \) and \(\lambda_3\) are eigenvalues of the diffusion tensor obtained from MR-DTI. Therefore, FA has a value that ranges from 0 to 1. FA is 0 in isotropic diffusion, whereas it approaches 1 as anisotropy becomes strong. ROI Editor is used to apply skull stripping [15] to the calculated datasets using the 3D b0 images. Skull stripping converts the signal intensity to zero in voxels of the non-cerebral parenchyma, such as the cranial bone.

Then, all the images were resampled at a voxel size of 1 × 1 × 1 mm³ according to the atlas sample image of DiffusionMap, which has a 181 × 217 × 181 matrix and a voxel size of 1 × 1 × 1 mm³. We used single subject image on the MNI (Montréal Neurological Institute) coordinate constructed by MRI Studio (JHU MNI SS) for the atlas sample image. The directions perpendicular to the sagittal, coronal, and axial planes represented the x-axis, y-axis, and z-axis, respectively. When the original image size was greater than the atlas sample image at both ends of the x-axis and y-axis of the image, any redundant background was cut. When the original image size was smaller than the atlas sample image at both ends of the z-axis of the image, extra background was added automatically.

The linear transformation matrix was constructed using DiffusionMap based on the b0 images of each subject and the atlas sample image. We applied the matrix to all the resampled images, and each subject’s images were transformed linearly according to the atlas sample image.
The image intensity histogram of each subject’s image was matched to that of each atlas sample image automatically.

We created a nonlinear transformation matrix with DiffeoMap based on the large deformation diffeomorphic metric mapping (LDDMM) [16] fitted to the atlas sample image, using both the FA image and the trace image. Then, all the subject images were normalized using the transformation matrix.

2.4 Region of interest
The present study targeted the sagittal stratum, including the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, both of which are representative association fibers. The inferior longitudinal fasciculus connects the temporal and occipital lobes, passing through the outside of the inferior and dorsal horn of the lateral ventricle. The inferior fronto-occipital fasciculus connects the frontal and occipital lobes, passing through the ventrolateral edge of the lenticular nucleus. Disruption of the integrity of these tracts might reflect hypoactivity on the cortices connected by these nerve bundles. These two nerve bundles become aligned around the splenium of the corpus callosum, whereas they expand near the cerebral cortex. Therefore, we chose the central part of the two bundles for more accurate tracking.

The regions to start and to end fiber tracking were selected using a parcellation map corresponding to a normalized brain. In this parcellation map, both the gray matter and the white matter were separated into parcels according to the anatomical disposition. The brain tissue was parcellated into 159 regions based on the original parcellation map (JHU MNI SS WMPI Type II) in MRI Studio [15, 17, 18]. We chose the starting and ending regions on two distinct coronal planes. The starting region was restricted to the sagittal stratum area of the parcellation map on the starting coronal plane. The coronal planes were determined on the basis of the corpus callosum in the sagittal plane of the median line.

To address the individual differences in positions of nerve bundles, we selected the starting and ending planes for fiber tracking according to the number of tracked streamlines in each subject. Planes were selected where the maximum number of streamlines was tracked when changing the regions anteroposterior by up to 5% of the diameter of the corpus callosum in the sagittal plane of the median line from the initial regions. This ratio was decided through a trial and error process, and is useful for excluding the influence of position.

The right and left initial regions in the same coronal plane were determined separately. To set the region of interest in the target nerve bundles, we first selected the sagittal plane that included the median line using the location of the parcellations, including the corpus callosum in the right and left hemispheres. Figure 1 shows this sagittal plane in a color map of the normalized brain with the parcellation map. This figure was created with ROI Editor. The color map assigns the x, y and z components of the first eigenvector of the diffusion tensor in each voxel according to the intensities of the R, G and B colors, respectively. In the midline sagittal plane, we defined the anterior border (Fig. 1; (a)) and posterior border (b) of the corpus callosum, along with the anterior border of the splenium of the corpus callosum (d). After that, we established the coronal plane (e) that included the center of the splenium of the corpus callosum, as the initial starting plane for fiber tracking. In addition, we established the plane (f) 40% ahead of the diameter of the corpus callosum (e) from the posterior edge of the corpus callosum (Fig. (b) as the initial ending plane. In Fig. 1, region (g) represents the initial tracking region. When the starting and ending planes moved around the initial planes, the distance from the starting plane to the ending plane (g) did not change.

Extracting the axial slice of the color map that includes the ROI of the targeted bundle (Fig. 2 axial), we can see the left and right sagittal strata (including the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus) as areas surrounded by the red and blue frames, respectively. The purple and brown areas respectively indicate the left and right inferior fronto-occipital fasciculus.
occipital fasciculi. In this plane, (e) shows the initial starting plane for fiber tracking, and (f) represents the initial ending plane. Separate starting regions were set in the sagittal stratum parcellation on the starting coronal plane (Fig. 2 coronal) for the left and right hemispheres, while the ending region was set as the whole ending plane. The red frame represents the left initial starting region, and the blue frame is that of the right hemisphere. Line (h) on the coronal plane is the position of the axial slice shown on the left. Selection of these tracking regions was performed automatically based on the parcellation map of the normalized brain. Automatic ROI selection has better performance reproducibility than manual ROI selection [12] because the arbitrariness is minimized and non-targeted bundle is hardly tracked.

2.5 Fiber tracking
Fiber tracking was performed using a method that continuously searches for the point of the next step, beginning from each starting point individually in the starting region. We originally developed the tracking program using MATLAB for Windows (Version 7.6.0.324). The starting points were dispersed evenly on the plane of the starting region at a rate of 4 points per mm$^2$; i.e., each starting point had a cross-sectional area of 0.25 mm$^2$.

The direction of the fiber tracking was the direction of the first eigenvector corresponding to the largest eigenvalue of the diffusion tensor at the step point [4]. The first eigenvector at the step point was determined by interpolation based on the volume data among the center points of the nearest eight voxels around the step point. The step width, $h$, which is the distance from each step point to the next step point, was constant. For the present fiber tracking, the step width, $h$, was set at 0.5 mm. This was half of the voxel size and suitable for fiber tracking. The step point proceeded to the next step point via the Runge-Kutta method of the fourth order [19]. Interpolation using the volume data was performed for every Runge-Kutta stepping scheme.

Fiber tracking was terminated when the terminal conditions were met even before tracking reached the ending region. The terminal conditions were chosen based on the FA value at the present step point and the flip angle between the two stepping directions of the continuous steps.

The FA value at the present step point was calculated by interpolation using the volume data for the center points of the nearest eight voxels around the step point. Fiber tracking was terminated at a point with FA less than 0.25 because FA decreases where the nerve fibers are not aligned and tracking is considered to diverge from the targeted nerve bundles. This threshold has been reported in previous studies [12, 13].

Tracking was also terminated when the flip angle was greater than 45° so as to exclude a large angular shift, because the targeted bundles had a relatively linear configuration. We determined this threshold for the first time, since the axons in the sagittal stratum are considered not to curve quickly. In the actual tracking, although almost all flip angles were much smaller than 45° in successful trackings, we adopted 45° for additional coverage of slightly large angles, which are encountered sometimes during fiber tracking.

To identify and erase erroneously tracked streamlines, we selected, separately for the right and left hemispheres, the extracted streamline with the shortest length, and used that length as the baseline streamline length. Any streamline with a length exceeding 110% of the baseline streamline length was judged to be an erroneous tracking result and was thus eliminated from the streamline group. We determined this threshold by trial and error, excluding streamlines that were assumed to diverge from the targeted bundle. In setting this threshold, we paid attention not to eliminate the streamlines on the targeted bundles.

2.6 Statistics
For statistical analysis, we adopted S and Cu as morphometric indices as well as ‘FA’ and ‘MD’ as microstructural measurements. The values of FA and MD reflect fiber density, axonal diameter, and myelination in the white matter. In contrast, S is given by the thickness of the fiber bundle and Cu is associated with the shape of a mass of axons. Since fiber tracking is performed along the direction of axons, Cu characterizes the conformation of the fiber tract. We determined not only the microstructural indices but also the morphometric indices to measure the form of the nerve bundle and the direction of axons derived from fiber tracking.

We determined S as the cross-sectional area of the neuronal tract in the starting region. S was defined as 0.25 mm$^2$ multiplied by the number of tracked fibers until the ending region. The value of 0.25 mm$^2$ indicates the area of one starting point. The unit of index S is mm$^2$.

At each step point, we calculated the FA value, MD value, and curvature using the coordinates of the present, last, and next points (Cu). The curvature at the present point, $i_m$, was obtained using the following equation.

$$\text{Cu}(i_m) = \frac{2(|p_{m+1} - p_m| \times |p_m - p_{m-1}|)}{|p_{m+1} - p_m|^2|p_m - p_{m-1}|^2|p_{m+1} - p_{m-1}|}$$

where $p_m$ is the position vector at the present point $i_m$, and $m-1$ and $m+1$ represent the last and next points, respectively. For fiber tracking, the total curvature must be small because the nerve bundles with relatively straight configuration are targeted in this study. Large curvature reflects varying directions of the first eigenvector during tracking. The direction of the first eigenvector characterizes the integrity of axons in the tracked fiber.

The values of FA, MD, and Cu were calculated for each tracking step. Tracking was performed along the axonal fibers. The values were averaged for all steps in a single fiber and for all fibers in the hemisphere to evaluate the overall feature of the targeted bundle. The suffix ‘MM’ in the abbreviation of indices represents these entirely averaged indices.

In order to assess the inhomogeneity among the
characters of tracked fibers, we calculated the standard deviation of each averaged value in a single fiber for all fibers in a hemisphere. This inhomogeneity depends on the dispersion of axonal structures in a bundle. We named this index with the suffix ‘MSD’.

The standard deviations of FA, MD, and Cu for a single fiber were used to evaluate the inhomogeneity of the micro and macro structures along axons in a single fiber. We averaged the standard deviation for all fibers in a hemisphere. This index ended with ‘SDM’.

In addition, we expressed the value of the standard deviation for all tracked fibers by ‘SDS’. This index characterizes the dispersion of inhomogeneity in a single fiber among all of the tracked fibers in a hemisphere. It describes the intricate structure of the integral axons.

We here summarize all thirteen indices represented by S, FAMM, FAMSD, FASDM, FASDS, MDMM, MDMSD, MDSDM, MDSDS, CuMM, CuMSD, CuSDM, and CuSDS. These indices have no units except for S. All the indices were calculated separately for the right and left hemispheres in individual subjects.

We performed a two-way repeated measures analysis of variance (ANOVA) to compare all the indices with group as the between-group factor and hemisphere as the within-subject factor. For the factors having significant effects (significance level of $P<0.05$) or tending to have significant effects ($P<0.1$) in the ANOVA, separate $t$-tests were carried out for comparisons between the patient and healthy control groups, and between the left and right hemispheres. Statistical analyses were performed using MATLAB.

3. Results

Tracked fibers and FA maps for a representative subject from each group are displayed in Fig. 3. The coronal plane in the whole image represents the initial starting plane of fiber tracking. The coloring of the tracked fibers follows that of the color map. In the axial view, the tracked fibers and the axial plane are observed from the superior side. We can see each tracked fiber in the close-up image. These images were constructed using MATLAB.

The means and standard deviations of all the indices are graphed. A single asterisk indicates that the signed pair had a significant difference, with significance level $P<0.05$ in a $t$-test. The double asterisk indicates that the significance level is $P<0.01$.

Fig. 4 Means and standard deviations of all indices are graphed. A single asterisk indicates that the signed pair had a significant difference, with significance level $P<0.05$ in a $t$-test. The double asterisk indicates that the significance level is $P<0.01$.

Fig. 3 Tracked fibers and FA map of a representative schizophrenic patient and a healthy control subject. The coronal plane in the whole image indicates the initial starting region, and fibers are tracked toward the anterior side from the starting region. The coloring of the tracked fibers follows that of the color map. In the axial view, the tracked fibers and the axial plane are observed from the superior side.
were calculated separately for the right and left hemispheres in the patient and healthy control groups. The means and standard deviations of the thirteen indices for all the subjects are graphed in Fig. 4. In this graph, the mean value is shown as a bar graph and the standard deviation as the error bar. The blue and green bars show the patient group and the healthy control group, respectively. The results in the left hemisphere are displayed on the left side in each graph, and those in the right hemisphere on the right side.

Table 1 shows the results of ANOVA analyses. ANOVA revealed a significant group effect for MDSD; hemisphere effect for FAMM, FASDM, MDMM, MDSD, CuMM, CuMSD, CuSDM, and CuSDSD; and group-by-hemisphere interaction for MDSD. The group effect for S and MDSDM, hemisphere effect for MDSD, and group-by-hemisphere interaction for FAMSD tended to be significant in the ANOVA. No other significant effects were observed. Therefore, we examined these eleven indices by t-tests.

The results of t-tests are shown in Table 2. The group effect comparison between patients and healthy control subjects is shown in the upper half of Table 2. The lower half presents the hemisphere effect between the left and right hemispheres, separately for the patient group and the healthy control group.

For the group effect, the MDSDM and MDSDSD values in the patient group were significantly larger than those in the healthy control group (P<0.05). Patients’ FAMSD value tended to be larger than that of healthy subjects (P<0.1). No other significant differences were observed for the group effect.

For the hemisphere effect, the values in the right hemisphere were significantly larger than the values in the left for MDSD, CuMSD, CuSDM, and CuSDSD in the patient group. In addition, the patient values for FAMSD, MDSDM, and CuMM in the right hemisphere tended to be larger than those in the left hemisphere (P<0.1). In the healthy control group, FAMM and CuSDM in the right hemisphere were significantly larger than those in the left hemisphere, and only MDMM had a left value that was significantly larger than the right value (P<0.05). A trend of larger values in the right hemisphere than in the left hemisphere was observed for FASDM, CuMSD, and CuSDSD (P<0.1). No other significant differences were observed for the hemisphere effect.

These results are displayed in Fig. 4. Single and double asterisks show the indices that had significant differences in the t-test between the patient group and the healthy control group or between the left hemisphere and the right hemisphere (*P<0.05, **P<0.01).

4. Discussion

The findings in the present study illustrate significant differences between the patient and healthy control groups and between the left and right hemispheres in the sagittal stratum, including the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, obtained from fiber tracking and tractography.

Because MDSDM and MDSDSD showed significant group differences in the right hemisphere, it is reasonable that these two indices are appropriate as indices for quantitative evaluation of abnormalities in schizophrenic patients. These two indices represent the mean and standard deviation of the mean diffusivity for all the tracked fibers in a hemisphere, and of the standard deviations in a single tracked fiber. The mean diffusivity indicates the diffusion volume, unrelated to the direction. It is believed that the dispersion of brain tissue density may increase for all the tracked fibers when the standard deviation of the mean diffusivity is at a high level. The
finding of large values of these two indices in the patient group shows that the patients had greater dispersion of brain tissue density than the healthy control subjects for each tracked fiber and for all the tracked fibers. This suggests that areas with dense and sparse fibers are intermixed in the patients’ right sagittal stratum. Furthermore, MDSDSD was higher in the right hemisphere than in the left hemisphere in the patient group, but was not significantly different in the healthy control group. This suggests that the MDSDSD value increases in the right hemisphere of the patient group.

The between-hemisphere analysis of FAMM showed significant differences in the healthy control group but not in the patient group. Thus, this index may indicate a difference between the patient and control groups. FAMM is the average value of the mean FA of single tracked fibers for all the tracked fibers. The FA value is an index of the anisotropy strength. The fibers align tightly in a fiber tract when FA is large. The right hemispheric FA was larger than the left hemispheric value in the healthy control group, showing that the right sagittal stratum is denser in fibers than the left one.

In our previous study, we reported a reduction in S in the superior longitudinal fasciculus of schizophrenic patients, and a larger S in the right than in the left hemisphere in healthy controls[12]. S is an index that is proportional to the number of fibers tracked until the ending region. In this study, even though S did not show significant differences for group effect and hemisphere effect in patients, suggesting connectivity abnormality, significant inter-hemispheric differences in FAMM was observed in the healthy group but not in the patient group. The value of FAMM represents the entire FA value in all tracked fibers. When S of a bundle is small, then small FA values may be obtained throughout the whole fiber tracking. Thus, we propose that abnormality in the patient group is indicated by the significant difference in FAMM between hemispheres, rather than by the reduction of S. Furthermore, we did not find a significant inter-group difference in S due to the large degree of dispersion among the subjects. However, the mean values of patients’ S were reduced in both hemispheres. Although the fasciculus analyzed in this study was different from that of the previous study, the results seem to reflect similar features.

For MDMM, the right value was smaller than the left one in the healthy group, in contrast to the results for FAMM. These observed facts were consistent. Because the mean diffusivity reflects the density of brain tissue, a high mean diffusivity may indicate rough tissue because water molecules can easily move in matters with rough tissue. Hence, these results suggest that the fiber tract in the right hemisphere is denser than that in the left one. On the other hand, the patient group did not have a hemisphere effect for MDMM. This suggests that the densities of the sagittal stratum tissues in both hemispheres are almost equal.

Skelly et al. [11] found FA reduction in the right
inferior fronto-occipital fasciculus, and a negative correlation between FA and PANSS positive symptom score in the sagittal stratum. In the present study, we observed no significant inter-group differences in indices associated with the FA value. However, we showed increased MDSDM and MDSDSD in the patient group. Both of these indices represent inhomogeneity of tissue density along the orientation of axons. Since the FA value is considered to decrease in the area where the integrity of axons is disrupted, tissue inhomogeneity increases in that area. Therefore, the increases in MDSDM and MDSDSD imply that our present observation is consistent with that in the previous study. In addition, the previous study showed only the mean values of FA, whereas we evaluated the degree of tissue homogeneity by calculating several indices associated with the standard deviations of the parameters measured.

Significant hemisphere effects for CuMSD and CuSDSD were observed in the patient group, but not in the healthy group. However, the indices tended to be different between the left and right hemispheres in the healthy control group. Hence, it is difficult to say that these indices show differences in hemisphere effect between patient and control groups, and could be used as indices to quantitatively evaluate the abnormalities of patients. In addition, CuSDM showed significant hemisphere differences in both groups. This index also cannot be used as an index for quantitative evaluation of the disease. Although this might be caused by the limited number of directions of MPG, the variability of the first eigenvector directions may not be affected by the disease because the indices derived from the curvature do not indicate differences between patients and healthy subjects.

In the present study, although we analyzed images with not so high resolution, we were able to obtain some evidence of likely abnormality in schizophrenic patients. This observation with our indices agrees with the results reported by previous research. A relatively long time is often required to obtain high resolution images. However, we had to perform short imaging to reduce the stress on the subjects and the effect of their head motion. The imaging resolution was sufficient to evaluate the abnormality in schizophrenia through measurements by fiber tracking in this study.

The manual ROI setting in our previous study [12] had a shortcoming of arbitrariness in determining the starting area in fiber tracking. We resolve this crucial problem by the proposed automatic ROI construction, avoiding the inherent error in the previous study. As a result, accuracy of ROI construction was improved in the proposed scheme.

5. Conclusion

In the present study, we showed that automatic ROI construction was appropriate for the detection of abnormality in schizophrenic patients. In addition, we analyzed the structural abnormalities in the white matter of the sagittal stratum, including the inferior longitudinal and inferior fronto-occipital fasciculi, in schizophrenic patients using automatic ROI construction and a fiber tracking technique on MR-DTI data. From the analyses, we found significant differences between the patient and control groups in the two indices: MDSDM and MDSDSD. Furthermore, four (FAMM, MDMM, MDSDM, and MDSDSD) and three indices (FAMM, MDMM, and MDSDSD) indicated significant hemisphere effects in the patient group and healthy control group, respectively. The index S, which we observed a significant effect in our previous study, did not show a significant difference between groups. Rather than S, FAMM indicated abnormality in the present study. Although our novel indices associated with Cu did not show definitive differences between groups in this study, they might be useful indices for evaluation in fiber tracking of more curved bundles. These results suggest the feasibility of using FAMM, MDMM, MDSDM, and MDSDSD as indices for quantitative evaluation of disruption in sagittal stratum integrity in schizophrenia. We hope that these indices are promising for the evaluation of the white matter abnormality for other bundles. Future studies would validate our expectation.

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References


Utako YAMAMOTO, et al: Disruption of White Matter Integrity in Schizophrenia

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