(i) title page

The full title of the paper:

Longitudinal study examining abnormal white matter integrity using a tract-specific analysis in individuals with a high risk for psychosis

A short running title:

Longitudinal WM abnormalities in ARMS

The authors:

Junichi Saito, MD,[1] Masaaki Hori, MD, PhD,[2] Takahiro Nemoto, MD, PhD,[1] Naoyuki Katagiri, MD, PhD,[1] Keigo Shimoji, MD, PhD,[3] Shinya Ito, PhD,[4,5] Naohisa Tsujino, MD, PhD,[1] Taiju Yamaguchi, MD, PhD,[1] Nobuyuki Shiraga, MD, PhD,[6] Shigeki Aoki, MD, PhD,[2] Masafumi Mizuno, MD, PhD[1]

[1] Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan

[2] Department of Radiology, Juntendo University School of Medicine, Tokyo, Japan

[3] Department of Diagnostic Radiology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

[4] Department of Social Medicine, Toho University School of Medicine, Tokyo, Japan

[5] Department of Public Health, Fukushima Medical University School of Medicine, Fukushima,

Japan

[6] Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan

Corresponding author

Takahiro Nemoto

Department of Neuropsychiatry, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, 143-8541, Tokyo, Japan

E-mail address: takahiro.nemoto@med.toho-u.ac.jp

Tel: +81-3-3762-4151

Fax: +81-3-5471-5774

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(ii) abstract and key words

Abstract

Aim: Although volume reductions in the grey matter have been previously observed in individuals with an at-risk mental state (ARMS) for psychosis, the features of white matter integrity and their correlation with psychiatric symptoms remain unclear.

Methods: Forty-six ARMS subjects were examined using magnetic resonance imaging (MRI) to acquire diffusion tensor imaging (DTI) images; the subjects were also evaluated using the Scale of Prodromal Symptoms at baseline and at 52 weeks. Sixteen healthy controls also underwent MRI scanning. The DTI results were longitudinally analyzed using a tract-specific analysis to measure the fractional anisotropy (FA) values of the entire, genu, trunk, and splenium of the corpus callosum (CC).

Results: During the 52-week study period, 7 patients developed psychosis (ARMS-P) and 39 did not (ARMS-NP). In the entire CC and the genu, trunk, and splenium of the CC, the FA values of the ARMS subjects were each significantly smaller than the respective values of the healthy controls at baseline. In the genu and trunk, the baseline FA values in the ARMS-NP group were, paradoxically, smaller than those of the ARMS-P group at baseline. Regarding the association between the FA values and psychiatric symptoms, a reduction in the FA value in the genu was significantly correlated with a deterioration of negative symptoms among the ARMS subjects.

Conclusion: Abnormal white matter integrity in the CC may predict the long-term outcome of patients with prodromal psychosis, since negative symptoms are associated with poor functioning.

Keywords: at-risk mental state, corpus callosum, diffusion tensor imaging, psychosis, schizophrenia

(iii) text

1. Introduction

Postmortem studies of patients with schizophrenia have revealed reductions in the dendric branch, spine and synapse density, and these reductions are thought to be involved in the pathophysiology of the disorder.[1] Morphological studies using magnetic resonance imaging (MRI) have shown that patients with schizophrenia exhibit reductions in overall brain volume (-0.07% in annualized volume change), whole brain gray matter (GM) (-0.59%), frontal GM, frontal white matter (WM) (-0.32%), parietal WM (-0.32%) and temporal WM (-0.39%) and an increase in lateral ventricular volume (+0.36%), compared with healthy controls (HCs).[2] MRI studies of WM have led to the disconnection hypothesis[3] and have revealed that the corpus callosum (CC) of patients with schizophrenia is significantly smaller than that of HCs.[4,5] Even in patients with first-episode schizophrenia, the size of the CC was significantly smaller than that of HCs.[4-6] The CC is well known as a decisively important area of fibers connecting bilateral hemispheres. In a review, Jea et al.[7] reported that a callosotomy causes disconnection syndrome, including supplementary motor area syndrome, alien hand syndrome, memory deficits and poor emotional description (alexithymia).[7] Kubota et al.[8] suggested that schizophrenia was associated with alexithymia and reduced WM integrity in the CC.[8] Friston[9] reviewed the disconnection hypothesis of schizophrenia and proposed an abnormal functional connectivity between the prefrontal and temporal regions.[9] Crow[10] suggested

that the symptoms of schizophrenia arise from the consequences of variations in inter-hemispheric connection.[10] van der Knaap and van der Ham reviewed[11] the dysfunction of inter-hemispheric connections, mainly in the frontal and temporal region, and their correlation with behavioral abnormalities in patients with schizophrenia.[11]

Diffusion tensor imaging (DTI) reflects the direction and magnitude of water diffusion on MRI signals,[12,13] and the fractional anisotropy (FA) value, which is a scalar quantity from 0 to 1, is the most commonly used index of DTI. DTI provides useful information for determining the orientation of fiber tracts. Lim et al.[14] showed that widespread FA value reductions in WM integrity occur before volume reductions in WM in patients with schizophrenia.[14] Although there are indications that the FA value might be inaccurate in cases with complex tracts and should be interpreted with caution,[15] FA values are still commonly used in DTI studies. In the present study, we used the FA value as an index of WM integrity.

Because of global demands for early interventions for schizophrenia, the presence of an at-risk mental state (ARMS) for psychosis has attracted much attention in recent years. Pantelis et al.[16] reported GM volume reductions in the right inferior frontal gyrus and other areas in ARMS subjects. DTI studies examining WM have also been performed for ARMS subjects. As a result, the FA values in the superior longitudinal fasciculus (SLF);[17] the right superior and the left middle frontal lobe area;[18] the right and the left superior frontal lobe area;[19] and the splenium and body of the CC, the

left inferior longitudinal fasciculus (ILF), the SLF and inferior fronto-occipital fasciculus (IFOF), the right external capsule, the retrolenticular internal capsule, and the posterior corona radiate[20] were found to be smaller in ARMS subjects than in HCs. However, von Hohenberg et al.[21] reported nonsignificant reductions in FA values in ARMS subjects when examined using tract-based spatial statistics (TBSS). In a DTI study comparing ARMS subjects who did not develop psychosis (ARMS-NP) and ARMS subjects who developed psychosis (ARMS-P), Bloemen et al.[19] showed that the FA values in the right uncinate fasciculus (UNC), SLF and IFOF and in the left SLF, ILF and IFOF were smaller in the ARMS-P patients than in the ARMS-NP patients at baseline. On the other hand, the FA values in the left posterior thalamic radiation, ILF and IFOF were larger in the ARMS-P patients than in the ARMS-NP patients at baseline. However, Karlsgodt et al.[17] and Carletti et al.[20] reported negative differences in the FA values in both ARMS-NP and ARMS-P patients at baseline. Domen et al.[22] followed the siblings of patients with schizophrenia for 3 years and showed that the whole brain mean FA values of the siblings were smaller than those of HCs at all the time points.

Regarding the association between WM integrity and psychiatric symptoms, Skelly et al.[23] showed that positive symptoms scores on the Positive and Negative Symptom Scales (PANSS) were negatively correlated with FA values in the left UNC, the right sagittal stratum, and the left SLF, while negative symptoms scores were positively correlated with a small area near the right insula in

patients with schizophrenia. Cheung et al.[24] showed that the PANSS positive symptoms scores were positively correlated with FA values in the right frontal lobe, the left anterior cingulate gyrus, the left superior temporal gyrus, the right middle temporal gyrus, the right middle cingulate gyrus, and the left cuneus; the negative symptoms scores, however, were not correlated with any areas in patients with first-episode schizophrenia. Lee et al.[25] showed that the positive and negative symptoms scores in the Brief Psychiatric Rating Scale were positively correlated with FA values in the right IFOF in patients with first-episode schizophrenia. Asami et al.[26] reported that the FA value in the left cerebrum was associated with negative symptoms in schizophrenia. Thus, consistent results regarding the association between FA values and psychiatric symptoms have not yet been obtained. The CC is one area of WM in which a relatively large FA reduction has been reported in patients with schizophrenia.[27] Rigucci et al.[28] showed that the FA value of the CC was smaller in first-episode schizophrenia patients and even in ARMS-P patients than in HCs. Canu et al.[29] showed that the FA values of the body, tapetum and splenium were smaller in ARMS patients than in HCs. Furthermore, Carletti et al.[20] showed that the FA value of the CC was smaller in ARMS-P patients than in ARMS-NP patients in a longitudinal study, suggesting that the FA value could be a predictor of the development of psychosis.

In our previous study, we simultaneously investigated the FA values of the CC using TBSS as an index of WM integrity and sub-threshold positive symptoms using the Scale of Prodromal

Symptoms (SOPS) in ARMS subjects.[30] The results showed that the FA values for the CC were significantly smaller in ARMS subjects than in HCs and that the change in the FA values for the CC was correlated with the change in sub-threshold positive symptoms.[30] These results provided significant knowledge to the study of ARMS; however, which portion of the tracts passing through the CC affected the FA value and the relationship with the positive symptoms remained unclear. Therefore, further investigation of the specific tracts passing through the CC, especially those connecting the bilateral frontal lobes (which are thought to play important roles in psychiatric symptoms), and longitudinal evaluations of negative symptoms, disorganization symptoms, and general symptoms, in addition to positive symptoms, in ARMS subjects are needed.

Although TBSS is the standard approach for analyzing DTI data, it can cause a mis-assignment during the skeleton projection procedure, which is known to be FA-based, especially if tracts with high FA values exist in the neighborhood of the CC and the cingulate bundle.[31] To avoid a mis-assignment and to extract specific tracts, a regions of interest (ROI) analysis was necessary. The ROI analysis is thought to be more sensitive than TBSS for the detection of FA changes and is useful for detecting fine abnormalities in specific WM tracts.[32-35] We used a tract-specific analysis (TSA), which is a kind of ROI analysis, to measure the FA values in the present study.[36] Taoka et al.[37] showed that a TSA was superior to other ROI analyses in terms of its ability to detect differences in FA values clearly between tracts.[37] Because ARMS is a state in the development of schizophrenia,

the change in FA values are expected to be smaller than those for schizophrenia. Thus, we thought that a TSA would enable tiny changes in FA values to be identified, even in ARMS subjects.

Although we used the same subjects as those examined in our previous study, [30] the present study was aimed at clarifying the following ambiguous issues in ARMS patients: (1) to identify specific tracts passing through the genu, trunk and splenium of the CC and to calculate the FA values for each of these tracts using TSA, and (2) to examine the associations between the FA values of these tracts and negative, disorganization, and general symptoms, as well as positive symptoms, on a longitudinal basis.

METHODS

Participants

Individuals aged 40 years or younger at the time of their initial visit to the Mental Health Center at the Toho University Omori Medical Center, Tokyo, completed the Prevention Through Risk Identification, Management and Education (PRIME) Screen-Revised (PS-R) screening procedure for the detection of ARMS candidates.[38,39] After this screening, the Structured Interview for Prodromal Symptoms (SIPS) was administered to diagnose ARMS.[40] Forty-six ARMS subjects participated in the current study (Table 1). All the subjects were individually followed up for 52 weeks; all the subjects underwent MRI scans and completed the SIPS/SOPS at baseline and at 52 weeks.

Sixteen HCs were recruited at Toho University (Table 1). The ages of the HCs and ARMS subjects were not statistically different. The HCs underwent MRI scans only at baseline. The exclusion criteria included a history of neurological disorder, alcohol dependence, and substance abuse, as diagnosed according to the DSM-IV criteria.

To determine handedness, we used the Edinburgh handedness inventory[41] for both the HCs and ARMS subjects at baseline. The education levels of the HCs and ARMS subjects were determined based on the following standards: graduation from elementary school, junior high school, high school, junior college, technical school, and university were considered as 6, 9, 12, 14, 14 and 16 years of study, respectively, at baseline.

Forty-six participants were included in the patient group, but 1 patient dropped out of the study. Forty-six patients underwent MRI scans, and 41 completed the SIPS/SOPS at baseline. Forty-five patients underwent MRI scans and 28 completed the SIPS/SOPS at 52 weeks.

All the participants provided informed consent. This study was approved by the Ethics Committee of the Toho University School of Medicine.

(Insert Table 1 about here)

MRI acquisition

The participants underwent MRI scans (EXCELART Vantage, XGV 1.5 T; Toshiba Medical Systems, Tokyo, Japan) using a five-channel head coil at the time of the first consultation as a baseline scan; DTI images were acquired using a single-shot spin-echo echo-planar sequence in 30 axial sections. The whole brain diffusion-weighted images were recorded along 6 gradient directions using a b-value of 1000 s/mm^2 together with un-weighted (b = 0) images. For each image, we used the following parameters: field of view = 260 × 260 mm^2; matrix size, 128 × 128; number of slices, 30; voxel resolution, 1.02 × 1.02 × 5 mm^3; TE = 100 ms; TR = 7668 ms; average number of signals, 3. We rescanned the ARMS subjects using the same instrument at 52 weeks after the baseline scan.

Image analysis

The fiber tractography technique was initiated by Mori et al.,[42] and we used dTV.II.SR and VOLUME ONE v1.72 developed by Masutani et al.[43] for the analyses. The DTI datasets were transferred to an offline computer. First, the DICOM files for each DTI acquisition were converted into a single multivolume analysis format by MRIcro,[44] and then the data were converted into a vol format file using the software VOLUME ONE v1.72. Finally, the data were processed using dTV.II.SR. Fiber tracts were created by interpolating along the z-axis to obtain data (voxel size, 1.0 × 1.0 × 1.0 mm^3). The FA color maps were created using 7 sets of images (6 sets with b = 1000 s/mm^2, 1 set with b = 0 s/mm^2). The specific fibers in the FA color maps were identified based on a

previous study.[45] In the DTI color maps, the colors red, green, and blue were assigned to the left-right, anteroposterior, and craniocaudal directions, respectively. To minimize the inter-rater bias, the tract measurements were performed by one author (J. S.). Because we wanted to evaluate the global microstructural changes in this study, we analyzed the resulting FA color maps.

The seed regions of interest (ROIs), including areas in the entire, genu, trunk, and splenium of the CC, were placed manually. As a number of studies have shown associations between psychiatric symptoms and prefrontal dysfunction in patients with schizophrenia,[46] we were greatly interested in the CC sub-region connected with the prefrontal lobe. We considered that the genu, trunk and splenium of the CC connect to the frontal, parieto-temporal and occipital lobe, respectively, and divided the CC into 3 sub-regions: the most anterior area was defined as the genu (CC1 of Hofer and Frahm's schema[47]), the most posterior area was defined as the splenium (CC5), and the remaining middle area was defined as the trunk (CC2-CC4). The regions from CC1 to CC5 were defined as the entire CC. A scheme is shown in Fig. 1 (genu, trunk, and splenium from anterior to posterior, respectively). The FA value of each region was calculated by the mean of FA value in multiple pieces of voxels based on the tracts which passed the midsagittal plane of the CC sub-region. The threshold values for line-tracking termination were set at FA > 0.18 for the tractographic images. As an example, the set of tracts that passed through the genu, trunk and splenium of the CC are displayed in Fig. 2. Voxelization of the CC and its sub-regions (i.e., the entire CC and the genu, trunk and

splenium) were performed. The mean FA value in co-registered voxels was displayed by dTV.II.SR.

(Insert Figs. 1 and 2 about here)

Evaluation of psychiatric symptoms

The ARMS subjects completed the SIPS/SOPS evaluations. The SOPS consists of five items for Positive Symptoms (P-score), six items for Negative Symptoms (N-score), four items for Disorganization Symptoms (D-score), and four items for General Symptoms (G-score). There are seven anchor points, from 0 (Never or Absence) to 6 (Severe or Extreme), for each of the items. The diagnostic criteria for a prodromal status were as follows: P-scores of 0 to 2 on the SOPS were considered to indicate a non-prodromal status, P-scores of 3 to 5 were considered to indicate a prodromal status, and a P-score of 6 was considered to indicate a psychotic state.[40]

Statistical analysis of imaging data and psychiatric symptoms

The statistical analysis was performed using SPSS 22.0 software. In cross-sectional studies, the Mann-Whitney U test was used to examine the FA value and the SOPS score in the HCs versus the ARMS subjects at baseline or in the ARMS-NP subjects versus the ARMS-P subjects at baseline and

at 52 weeks. In addition, the Mann-Whitney U test was also used to examine gender differences in the FA values. To analyze the correlation between the FA values and the SOPS scores in the ARMS subjects, the Spearman rank order correlation was used. We examined the correlations between the FA values for the genu, trunk, and splenium of the CC at baseline and the SOPS scores at baseline and at 52 weeks. Then, we calculated the changes in the FA values in the genu, trunk, and splenium of the CC over 52 weeks (ΔFA in the genu, trunk, and splenium) as well as the changes in the SOPS scores (ΔP-, ΔN-, ΔD-, and ΔG-score) in the same manner. We also examined the correlations between the changes in the FA values and the changes in the SOPS scores.

RESULTS

Follow-up

Seven individuals developed full-blown psychosis (ARMS-P); the remaining 39 individuals had not developed psychosis (ARMS-NP) according to the SIPS/SOPS at 52 weeks after the baseline study. The ages of the subjects were not statistically different between the ARMS-NP and ARMS-P groups.

Vulnerability for psychosis

The baseline FA values for the entire, genu, trunk, and splenium of the CC in the ARMS subjects and the HCs are shown in Table 1. In all the regions, the FA values of the ARMS subjects were significantly smaller than those of the HCs.

Predictor of the development of full-blown psychosis

The FA values for the genu, trunk, and splenium of the CC in the ARMS-P and ARMS-NP groups at baseline and at 52 weeks are shown in Table 2. The FA values in the genu and trunk at baseline and in the trunk at 52 weeks were significantly smaller in the ARMS-NP group than in the ARMS-P group.

The SOPS scores at baseline and at 52 weeks in the ARMS-P and ARMS-NP groups are shown in Table 2. At baseline and at 52 weeks, the P-, N-, D-, and G-scores in the ARMS-P group were not significantly different from the corresponding scores in the ARMS-NP group. When the sub-scores were taken into consideration, however, the G4 score (Impaired Tolerance to Normal Stress) in the ARMS-NP (4.18 ± 1.19) was significantly lower than that in the ARMS-P (5.57 ± 0.53) at baseline. The other sub-scores were not significantly different between the two groups at baseline or at 52 weeks.

(Insert Table 2 about here)

Association between FA values and psychopathology

Among the ARMS subjects, no correlations were observed between the FA values in the genu, trunk, and splenium at baseline and the P-, N-, D-, and G-scores at baseline or at 52 weeks. Regarding the longitudinal analyses, the correlations between the changes in FA values in the CC and the changes in psychiatric symptoms (P-, N-, D-, and G-scores) are described in Table 3. The reduction in the FA value in the genu over 52 weeks was correlated with a deterioration of negative symptoms (ΔN-score; r = -0.539, $P = 0.004$) (Fig. 3) in the ARMS subjects.

(Insert Fig. 3 about here)

(Insert Table 3 about here)

DISCUSSION

Factors related to vulnerability

WM abnormalities are thought to be involved in the pathogenesis of schizophrenia and other psychotic disorders because they affect neural connections in the brain.[48-51] Patel et al.[52] reported that the FA values in the splenium of the CC in patients with schizophrenia were smaller than those in HCs in a DTI study; however, the FA values in the genu were not different. Although reductions in

the FA values for the genu and trunk of the CC have not been previously reported, Ellison-Wright et al.[53] recently demonstrated that the FA values in the genu, trunk, and splenium were smaller in patients with schizophrenia than in HCs in a DTI study.

A previous study using MRI in ARMS subjects showed significant WM volumetric differences between ARMS subjects and HCs at baseline.[54] Carletti et al.[20] showed that the FA values in the trunk and splenium of the CC in ARMS subjects and first-episode psychosis patients were linearly smaller than those of HCs at baseline in a DTI study. In our previous study using TBSS, the FA values were significant smaller in the CC of ARMS subjects than in HCs,[30] and in the present study using TSA, the same finding was obtained in the CC. Moreover, we revealed reductions in the FA values in specific tracts in the entire CC as well as the genu, trunk and splenium of the CC in ARMS subjects in the present study. These results suggest that the reductions in the FA values in these areas had already begun during the stage of ARMS. The FA values of the CC (for the entire CC and the genu, trunk, and splenium) seem to reflect a vulnerability to psychosis. To our knowledge, the reduction of the FA value in the genu that was observed in the ARMS subjects is a novel finding. Park et al.[55] revealed that the genu of the CC connects the left prefrontal cortex with the right prefrontal cortex in HCs in a DTI study. The prefrontal cortex is known to be deeply involved in processing speed and working memory.[56] During the performance of the n-back task, hypoactivation of the dorsolateral prefrontal cortex has been observed in patients with schizophrenia.[57] Thus, a

decline in cognitive function seems to have already appeared as a reduction in FA values at the stage of ARMS; however, further research is required.

Regarding factors related to the level of anisotropy, Beaulieu[58] reviewed DTI studies of WM and mentioned that anisotropy depended on the water diffusion phenomenon and that the tissues of the nervous system were highly anisotropic. A reduction in anisotropy may be caused by a decrease in myelination, while a higher anisotropy may be caused by an increase in neuronal density. Williams et al.[59] showed that a significant decrease in astrocyte density in the midline of the CC was observed in patients with schizophrenia, compared with HCs. Thus, the FA values observed in the present study may represent changes in the nerve tissues.

Predictor of the development of full-blown psychosis

Another study examining ARMS subjects showed that the gray matter volumes in the right medial temporal, lateral temporal, and inferior frontal cortex and the bilateral cingulate cortex at baseline were smaller in ARMS-P subjects than in ARMS-NP subjects.[16] Hence, the abnormalities in WM integrity were expected to be more prominent in the ARMS-P subjects than in the ARMS-NP subjects. Although we initially hypothesized that the baseline FA values of the ARMS-P group would be significantly smaller than those of the ARMS-NP group, paradoxical results were obtained for the genu and trunk. Our sample of ARMS-P subjects (n = 7) was rather small, and caution is needed

when interpreting the results of the statistical analysis; however, these paradoxical findings may have been caused by the different durations of illness (DUIs) at baseline. In other words, the morphological brain changes and the speed of such changes might have varied at the time of the subjects' first visit. Unfortunately, we did not evaluate the DUI in the present study. Carletti et al.[20] showed that the FA values in the CC at baseline were not different between an ARMS-NP and an ARMS-P group. In their study, they also reported that the FA value in the trunk of the CC tended to increase in the ARMS-NP group over the course of time; however, the value decreased in the ARMS-P group.[20] They suggested that the transition to psychosis in ARMS subjects is associated with longitudinal changes in WM integrity.[20]

Regarding the SOPS sub-scores, a higher G4 (Impaired Tolerance to Normal Stress) score indicates a poorer tolerance to stress. In the present study, the ARMS-P group was less tolerant of stress than the ARMS-NP group at baseline. Devylder et al.[60] also demonstrated that stress tolerance was impaired to a greater degree in ARMS patients than in HCs.[60] A decrease in stress tolerance might be involved in the transition to full-blown psychosis.

FA values and psychopathology

Some previous MRI studies have examined the prediction of onset and the psychopathology of schizophrenia using imaging data obtained during a longitudinal follow-up of ARMS subjects and

patients with schizophrenia. Although van Haren et al.[61] followed patients with schizophrenia for 2 years and attempted to predict their outcome based on GM volume at baseline, they did not find any associations. We also attempted to examine the association between FA values for the CC at baseline with the SOPS scores at 52 weeks; however, no significant correlations were detected. Therefore, we focused on the changes in the FA values in the CC over 52 weeks (ΔFA in the genu, trunk, and splenium) and the changes in the SOPS scores over 52 weeks (ΔP-, ΔN-, ΔD-, and ΔG-score). A significant negative correlation was observed between the ΔFA in the genu and the ΔN-score ($r = -0.539$, $P = 0.004$) in the ARMS subjects. Our previous study showed a correlation between the change in FA values and the change in sub-threshold positive symptoms.[30] In the present study, we investigated the FA values of specific tracts in the CC (the genu, trunk and splenium) and newly showed a negative correlation between the change in the FA value in the genu of the CC and the change in negative symptoms. These results suggest that the progressive disruption of WM as measured using TSA, which enables tiny changes in the FA values to be detected, is associated with a deterioration in negative symptoms. To our knowledge, the association between longitudinal changes in FA values and changes in negative symptoms in ARMS subjects is a novel finding, despite the relatively small sample size of the present study and the limited ROI set in the CC. A previous study showed a negative correlation between the FA value in the anterior part of the CC and negative symptoms measured using the Scale for the Assessment of Negative Symptoms in patients

with schizophrenia.[62] Lang et al.[63] suggested that although the outcome of schizophrenia is heterogeneous, negative symptoms predict a poor outcome.[63]

The results of the present study suggest that negative symptoms reflect the integrity of the genu of the CC and/or functions of the frontal lobe.

Limitations

The present study had some limitations. We used an MRI with 6 gradient directions during the DTI acquisitions. Because the MRI device that we used was intended for clinical applications, and not for research purposes, the presently analyzed data was unfortunately not collected using the latest MRI technology. Therefore, great care is needed in interpreting the present results; nevertheless, our longitudinal results are likely to provide useful information for future studies. Another MRI-related limitation was the voxel size. We used an anisotropic voxel size of 1.02 × 1.02 × 5 mm^3 based on the MRI performance in the present study. The acquisition of iso-voxel images would be desirable so as to avoid preferential averaging of the fiber orientations.[64] However, other DTI studies using an anisotropic voxel size have achieved highly valid results;[65,66] thus, our anisotropic voxel data obtained in the present study is thought to be valid.

In addition, the sample size of the ARMS-P group was relatively small because the rate of individuals who developed psychosis over the 52-week follow-up period was only 15.2% (7

ARMS-P subjects and 39 ARMS-NP subjects). However, this rate is consistent with previous studies.[67]

The FA and the mean, radial and axial diffusivity (MD, RD, and AD) values should be measured in DTI-based tractography. We adopted the FA value in the present study because the FA value is commonly used as an index of microstructural integrity and is highly sensitive to microstructural changes.[68] However, a technical limitation regarding the measurement of FA values should be mentioned: an exact single diffusion tensor cannot be obtained in situations where variously oriented nerve fibers are included in a single voxel.[69]

Although we used FA in the present study, several advanced diffusion imaging methods are presently in use, including diffusion kurtosis imaging (DKI) and free water imaging (FWI).[69] However, we were unable to use these techniques because of technical limitations; further study using these technique is needed in the future.

Conclusion

Smaller FA values for the CC seem to indicate a vulnerability to psychosis. The progressive disruption of WM in the genu of the CC may predict the long-term outcome, since negative symptoms are generally associated with poor functioning. In addition, stress tolerability may affect the transition to full-blown psychosis.

(iv) acknowledgments

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(v) disclosure statement

Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

(Vi) Author Contributions

Contributors

JS, NK and MM designed the study and wrote the protocol. TN, NT and TY were involved at the conceptualization level of the project. JS and NK collected the data. JS, NK, KS and MH analyzed the data. SA and NS contributed to support analysis the data. SI contributed to the statistical analysis. JS and TN interpreted the data. JS wrote the first draft of this manuscript. TN and MM contributed to the writing, editing and revision of the manuscript. All authors contributed to and have approved the final manuscript.

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(viii) figure legends

Figure Legends

Fig. 1. Sub-regions in the corpus callosum. Purple: genu; blue: trunk; gray: splenium.

Fig. 2. Set of tracts passing through the genu, trunk and splenium of the corpus callosum (Purple: genu; blue: trunk; gray: splenium).

Fig. 3. Scatter plot of the ΔFA in the genu and ΔN-score in ARMS subjects (n = 26). The reduction of FA in the genu at 52 weeks was correlated with the ΔN-score ($r = -0.539$, $p = 0.004$). FA, fractional anisotropy; N, negative symptoms.

(x) tables

Table 1. ARMS subjects vs. healthy controls at baseline

	ARMS subjects (n=46)	Healthy controls (n=16)	Z/ χ^2	P
Male/ Female	13/33	8/8	2.51	0.11
Age (years)	22.93 ± 6.46	23.19 ± 2.86	-0.77	0.44
Handedness (Right/ Left)	43/ 3	16/ 0	1.10	0.30
Education (years)	11.59 ± 2.75	12.75 ± 1.61	-1.37	0.17
FA value at baseline				
Entire CC	0.45 ± 0.01	0.46 ± 0.01	-3.09	0.00
Genu	0.47 ± 0.02	0.48 ± 0.02	-2.30	0.02
Trunk	0.41 ± 0.02	0.43 ± 0.02	-3.36	0.00
Splenium	0.47 ± 0.02	0.48 ± 0.02	-2.19	0.03

† Values are mean ± standard deviation or n.

‡ The Chi-square analysis was used to examine sex and handedness, and the Mann-Whitney U test was used to examine age, education, and FA value between the two groups.

ARMS, at-risk mental state; FA, fractional anisotropy; CC, corpus callosum.

Table 2. FA values and SOPS scores at baseline and at 52 weeks

	ARMS-P	ARMS-NP	Z	P
FA value at baseline	(n=7)	(n=39)		
Genu	0.48 ± 0.01	0.47 ± 0.02	-2.56	0.01
Trunk	0.44 ± 0.03	0.42 ± 0.02	-2.45	0.01
Splenium	0.48 ± 0.02	0.47 ± 0.02	-1.01	0.31
FA value at 52 weeks	(n=5)	(n=39)		
Genu	0.47 ± 0.01	0.47 ± 0.02	-1.15	0.25
Trunk	0.43 ± 0.02	0.41 ± 0.02	-2.71	0.01
Splenium	0.48 ± 0.02	0.47 ± 0.01	-1.85	0.06
SOPS scores at baseline	(n=7)	(n=34)		
P score	19.14 ± 4.67	17.94 ± 4.32	-0.42	0.67
N score	18.86 ± 8.11	19.32 ± 4.40	-0.02	0.99
D score	8.57 ± 3.69	8.38 ± 3.66	0.00	1.00
G score	15.43 ± 2.94	12.91 ± 3.29	-1.67	0.10
SOPS scores at 52 weeks	(n=6)	(n=22)		
P score	15.83 ± 4.36	13.68 ± 5.52	-0.82	0.41
N score	14.33 ± 4.50	15.55 ± 5.95	-0.65	0.52
D score	5.33 ± 4.27	5.23 ± 3.79	-0.06	0.96
G score	9.50 ± 4.59	8.86 ± 4.45	-0.28	0.78

† Analysis was carried out only for subjects without missing data.

‡ Values are mean ± standard deviation.

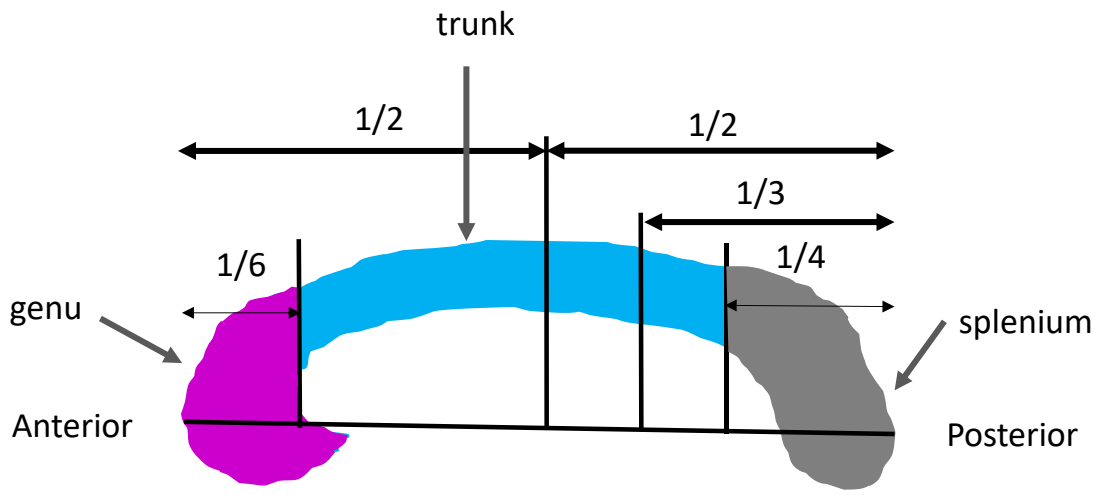
ARMS, at-risk mental state; ARMS-NP, ARMS subjects who did not develop psychosis in 52 weeks; ARMS-P, ARMS subjects who developed psychosis in 52 weeks; FA, fractional anisotropy; CC, corpus callosum; SOPS, the Scale of Prodromal Symptoms; P, Positive Symptoms; N, Negative Symptoms; D, Disorganization Symptoms; G, General Symptoms.

Table 3. Correlations between FA values in the corpus callosum and SOPS scores

	FA values at baseline					
	Genu		Trunk		Splenium	
ARMS	R	P	R	P	R	P
At baseline (n = 41)						
P score	-0.531	0.041	-0.215	0.635	-0.245	0.821
N score	-0.174	0.971	-0.177	0.596	-0.213	0.830
D score	-0.129	0.683	-0.344	0.273	-0.252	0.723
G score	-0.109	0.807	-0.074	0.605	0.099	0.568
At 52 week (n = 28)						
P score	-0.255	0.309	-0.085	0.715	0.176	0.191
N score	-0.212	0.430	-0.045	0.866	0.245	0.111
D score	-0.136	0.604	-0.388	0.049	0.120	0.376
G score	-0.137	0.627	-0.083	0.697	0.245	0.120
	ΔFA values					
	Δgenu		Δtrunk		Δsplenium	
ARMS	R	P	R	P	R	P
Δpsychiatric symptoms (n = 26)						
ΔP score	-0.357	0.068	-0.094	0.642	-0.161	0.423
ΔN score	-0.539	0.004	-0.199	0.320	-0.041	0.841
ΔD score	-0.202	0.312	0.269	0.175	-0.211	0.290
ΔG score	-0.217	0.278	0.071	0.726	-0.018	0.928

† Analysis was carried out only for subjects without missing data.

ARMS, at-risk mental state; FA, fractional anisotropy; CC, corpus callosum; ΔP, Positive Symptoms score change over 52 weeks; ΔN, Negative Symptoms score changes over 52 weeks; ΔD, Disorganization Symptoms score change over 52 weeks; ΔG, General Symptoms score change over 52 weeks.



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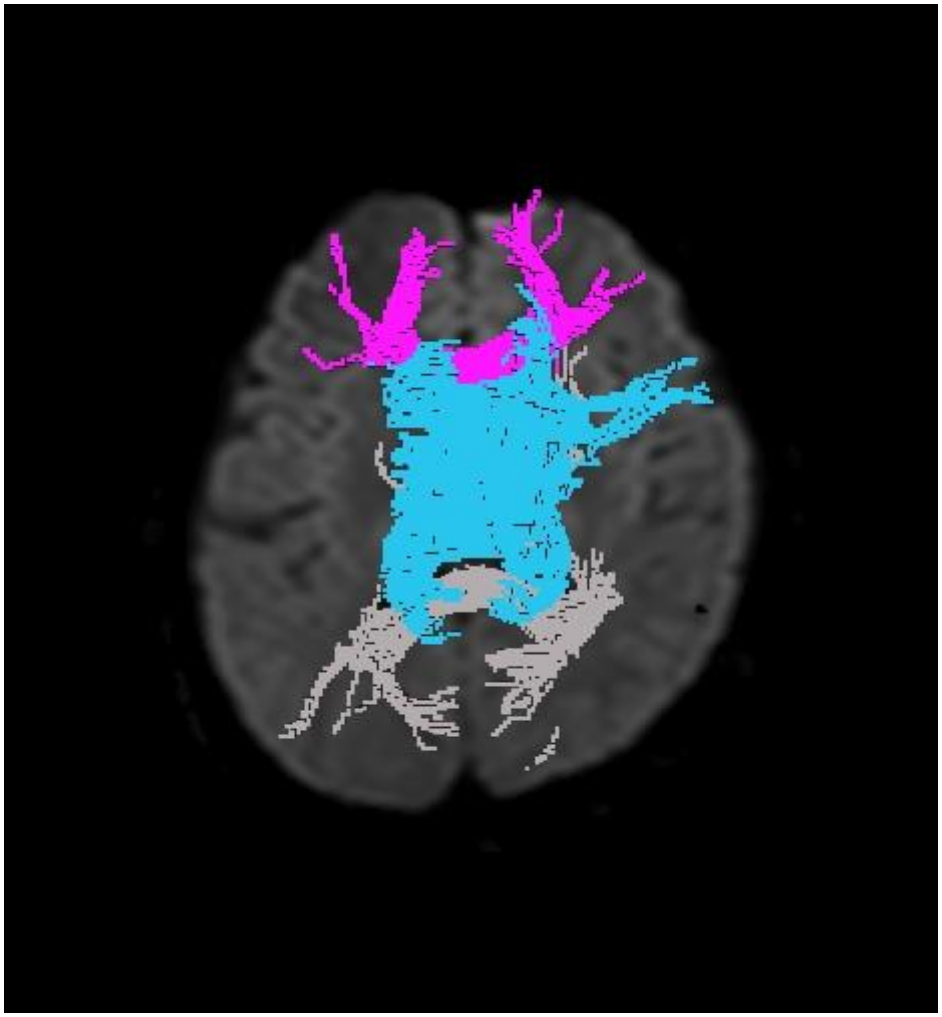

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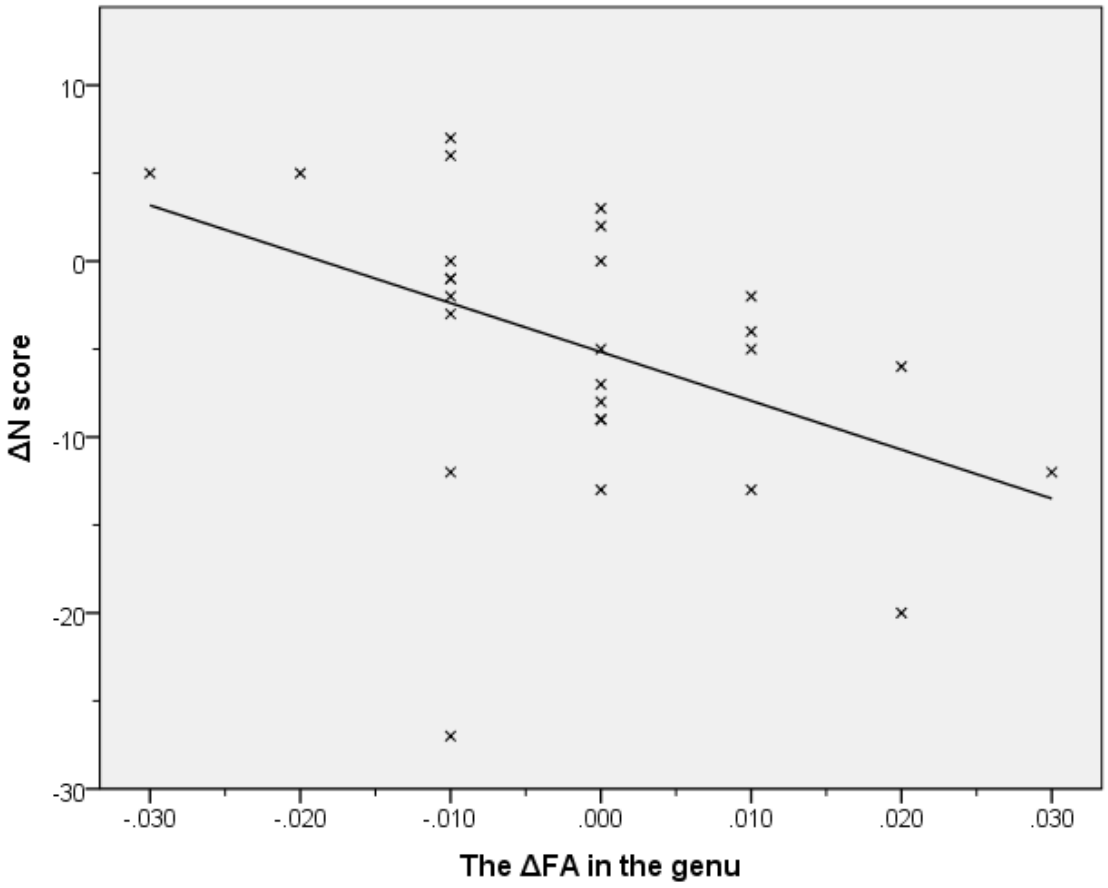

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