Quantitative Proton MR Spectroscopy Findings in the Corpus Callosum of Patients with Schizophrenia Suggest Callosal Disconnection

BACKGROUND AND PURPOSE: The callosal disconnectivity theory was previously proposed to explain the pathophysiology of schizophrenia. The goal of this study was to investigate the metabolic integrity of the corpus callosum in patients with schizophrenia by proton MR spectroscopy.

MATERIALS AND METHODS: Twelve first-episode and 16 chronic patients meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia and 28 age- and sex-matched control subjects were enrolled in the study. We measured the absolute concentrations of neurometabolites and T2 relaxation times of tissue water (T2_B) in the genu of the corpus callosum by using the internal water-reference method. The severity of symptoms in patients was rated by means of psychopathology scales. Differences in neurometabolite concentrations and T2_B values between the patients and control subjects were assessed. We also investigated the correlation of metabolite concentrations with the severity of symptoms.

RESULTS: N-acetylaspartate (NAA) concentrations were significantly lower in the first-episode as well as in chronic patients, compared with respective control subjects (P < .001). NAA concentrations in the first-episode and chronic patient groups were negatively correlated with both the Brief Psychiatry Rating Scale and the Scale for Assessment of Negative Symptoms scores (P < .001). There was a significant negative correlation between the NAA concentrations and the Scale for Assessment of Positive Symptoms scores in all patients (P = .028). T2_B values were significantly higher in the patients, compared with the control subjects (P < .001).

CONCLUSION: Decreased NAA concentration in the corpus callosum correlates with psychopathology in schizophrenia. This finding, together with prolonged T2_B values of the corpus callosum, supports the previously proposed callosal disconnection theory concerning the pathophysiology of schizophrenia.

The idea that schizophrenia might be a disorder of functional disconnection between the various regions of brain was first proposed by Wernicke in 1906. More recently, the disconnectivity theory has re-emerged in schizophrenia research. Today, there is increasing evidence pointing to the possibility of an abnormal cortical connectivity in the pathophysiology of schizophrenia. Diffusion tensor imaging (DTI) studies have demonstrated the compromised cerebral white matter tracts in patients with schizophrenia. Altered magnetization transfer (MT) ratios in frontotemporal white matter tracts and the genu of the corpus callosum, which might indicate either an axonal or a myelin-related pathology in schizophrenia, were found in patients with schizophrenia in MT imaging studies. Supporting the results of these structural imaging studies, the genetic studies revealed the altered expression of myelin-related genes, suggesting a disruption in oligodendrocyte function in schizophrenia.

Crow further specified the disconnectivity theory and proposed that schizophrenia might be a disorder of transcallosal misconnection. The corpus callosum is the major interhemispheric white matter tract, which plays very important roles in cognitive processes such as language, memory, and sensory-motor integration. Interhemispheric transmission of information, which allows the functional lateralization of cerebral hemispheres, decreases in schizophrenia. Functional and structural asymmetry in cerebral hemispheres in patients with schizophrenia suggests the possibility of altered interhemispheric connectivity. There are several morphometric studies revealing controversial results on the size and shape differences of the corpus callosum in schizophrenia. In a meta-analysis, Woodruff et al reported a small but significant decrease in the midsagittal area of the corpus callosum. Studies investigating shape differences in the corpus callosum showed that patients with schizophrenia had a more curved corpus callosum. In addition, the corpus callosum was one of the common locations showing a reduced diffusion anisotropy and MT ratio in previous DTI and MT imaging studies investigating white matter integrity in patients with schizophrenia. Moreover, the structural MR imaging studies conducted in patients with schizophrenia revealed altered signal-intensity changes and decreased attenuation in the corpus callosum.

Proton MR spectroscopy (1H-MR spectroscopy) is a non-invasive method to investigate neurochemical changes in various pathologic and physiologic conditions. 1H-MR spectroscopy can demonstrate subtle neuroaxonal dysfunction, even in normal-appearing cerebral tissue on conventional MR imaging and DTI. The goal of this study was to investigate the metabolic integrity of the corpus callosum in patients with schizophrenia and to test the “callosal disconnection theory” by using 1H-MR spectroscopy. We hypothesized that microstructural abnormalities in the corpus callosum of patients with schizophrenia might cause axonal dysfunction and lead...
to changes in neurometabolite concentrations, which could be detected by quantitative $^1$H-MR spectroscopy. We sought to measure the absolute concentrations of major neurometabolites and $T_2$ relaxation times of tissue water ($T_2B$) in the corpus callosum of patients with schizophrenia. Additionally, we investigated the relationship of neurometabolite concentrations with $T_2B$ values and the severity of symptoms. We studied the first-episode and relapsing chronic patients in acute phases of illness.

Methods

Subjects

We studied 28 inpatients (19 men and 9 women) with a diagnosis of schizophrenia after Structured Clinical Interviews for DSM-IV Axis I Disorders (SCID) data. Twelve of the patients (8 men and 4 women) were in the first episode of illness, and the remaining 16 (11 men and 5 women) were chronic patients presenting in the acute phase of illness (Table 1). A patient was accepted in his/her first psychotic episode when a previous diagnosis of possible psychosis, antipsychotic treatment, or inpatient care was ruled out. The mean $\pm$ SD duration of untreated psychosis (DUP) was 11.20 $\pm$ 10.20 months in the patients in the first episode. Chronic illness was defined as an interval of illness that had lasted at least 3 years following the diagnosis of schizophrenia. Diagnosis of schizophrenia in first-episode patients was confirmed through a re-interview by using the SCID data on the sixth month following their discharge.

Although 10 of the first-episode patients were drug-naive at admission, only 2 were drug-naive at the time the $^1$H-MR spectroscopy examinations were performed. Although 8 of the first-episode patients were receiving risperidone (mean dose, 3.9 mg/day), 2 of them were receiving olanzapine (mean dose, 12.5 mg/day). The mean interval between the admissions and $^1$H-MR spectroscopy examinations was 7.8 days in first-episode patients. On the other hand, all of the chronic patients were taking antipsychotic drugs, both at admission and at the time the $^1$H-MR spectroscopy examinations were performed. Four patients were taking risperidone (mean dose, 5.5 mg/ day), 3 patients were taking quetiapine (600 mg/day), 2 patients were taking olanzapine (12.5 mg/day), and 5 patients were taking different types of antipsychotics (mean haloperidol-equivalent dose was 12.5 mg/day).

Twenty-eight age- and sex-matched volunteer subjects (14 controls for each patient group) were enrolled in the study as a control group. Each patient group (first episode and chronic) had equal education levels with its respective control group ($P > .05$). The control subjects underwent medical, neurologic, and psychiatric (by using the Structured Clinical Interview for DSM-III-R-Non-Patient Edition by experienced interviewers) evaluation. Patients having any organic disorder, causing psychosis or cognitive impairment, were excluded from the study. Exclusion criteria for the patients and control subjects also included any contraindication for MR imaging, alcohol, or drug abuse; and any history of neurodegenerative disease, seizure, central nervous system infection, cerebrovascular disease, diabetes mellitus, and head trauma causing loss of consciousness that lasted more than 30 minutes or that required hospitalization. All the patients and control subjects were right-handed (Edinburgh Handedness Inventory).

Written informed consent was obtained from 25 patients whose clinical states were stable enough to have a level of factual understanding of research consent forms and from all of the control subjects. Informed consent was taken from legal representatives of 3 patients whose clinical states were insufficient. The study was approved by the local Human Subject Committee.

Clinical Assessment

The psychopathologic state of patients was evaluated through the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Scale for the Assessment of Negative Symptoms (SANS). All measures were collected by 2 trained raters. Inter-rater reliabilities for BPRS, SANS, and SAPS scores were acceptable ($r = 0.78$, $r = 0.76$, and $r = 0.83$, respectively). Clinical assessments, MR imaging, and $^1$H-MR spectroscopy examinations were performed within the same week.

Cranial MR Imaging

All patients underwent conventional cranial MR imaging and $^1$H-MR spectroscopy examinations on a 1.5T superconducting whole-body MR imaging scanner and spectroscopic system (Symphony Maestro; Siemens, Erlangen, Germany) by using a standard quadrature head coil. Cranial MR images were acquired to position the MR spectroscopy volume of interest (voxel) and to identify any cerebral pathology defined in the exclusion criteria. MR images included the following: 1) axial fast spin-echo (SE) $T_2$-weighted images ($TR = 5790$ ms, $TE = 103$ ms, $NEX = 2$, echo-train length = 16, matrix = $368 \times 512$, $5790$ ms, $TE = 103$ ms, $NEX = 2$, echo-train length = 16, matrix = $368 \times 512$,

![Table 1: Clinical and demographic characteristics of the patients and control subjects*](image-url)

|                      | FE Patients ($n = 12$) | Controls ($n = 14$) | Chronic Patients ($n = 16$) | Controls ($n = 14$) | All Patients ($n = 28$) | All Controls ($n = 28$) |
|----------------------|------------------------|---------------------|-----------------------------|---------------------|-------------------------|------------------------|
| Age (y)              | 25.50 $\pm$ 7.56       | 25.16 $\pm$ 5.35    | 29.31 $\pm$ 11.41           | 28.93 $\pm$ 10.24   | 27.65 $\pm$ 9.46        | 27.32 $\pm$ 8.58       |
| Male/Female          | 8/4                    | 9/5                 | 11/5                        | 9/5                 | 19/9                    | 18/10                  |
| Education (y)        | 10.33 $\pm$ 4.47       | 10.33 $\pm$ 3.89    | 11.00 $\pm$ 3.65            | 11.00 $\pm$ 3.40    | 10.71 $\pm$ 3.96        | 10.71 $\pm$ 3.56       |
| Age at onset (y)     | 24.83 $\pm$ 5.30       | –                   | 22.37 $\pm$ 8.72            | –                   | 23.35 $\pm$ 7.13        | –                      |
| No. of hospitalizations | –                    | –                   | 4.30 $\pm$ 3.90              | –                   | –                       | –                      |
| DUP (months)         | 11.20 $\pm$ 10.20      | –                   | –                           | –                   | –                       | –                      |
| Duration of illness (months) | –               | –                   | 83.25 $\pm$ 68.65           | –                   | –                       | –                      |
| Psychopathology scores |                        |                     |                             |                     |                         |                        |
| BPRS                 | 58.75 $\pm$ 8.60       | 67.56 $\pm$ 11.18   | 63.92 $\pm$ 10.96           | –                   | –                       | –                      |
| SANS                 | 40.00 $\pm$ 17.62      | 50.37 $\pm$ 26.93   | 45.92 $\pm$ 23.60           | –                   | –                       | –                      |
| SAPS                 | 36.58 $\pm$ 17.11      | 43.87 $\pm$ 15.89   | 40.75 $\pm$ 16.52           | –                   | –                       | –                      |

Note: -- FE indicates first-episode; – data not available; DUP, duration of untreated psychosis; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

* Data are given as mean $\pm$ SDs except where indicated.
section thickness = 5 mm, intersection distance = 1.2 mm); 2) coro-
nal SE T1-weighted images (TR = 530 ms, TE = 30 ms, NEX = 2, 
matrix = 196 × 256, section thickness = 3 mm, intersection dis-
tance = 1 mm); and 3) sagittal fast SE T2-weighted images (TR = 
5790 ms, TE = 103 ms, NEX = 4, echo-train length = 16, matrix = 
196 × 256, section thickness = 3 mm, intersection distance = 1 mm).

1H-MR Spectroscopy: Data Acquisition and Signal-
Intensity Processing
Single-voxel 1H-MR spectroscopy examinations of the patients and 
control subjects were conducted in the same session with conven-
tional cranial MR imaging. On sagittal images, the corpus callosum 
was divided into subregions as described by Witelson33 and Highley 
et al34 (Fig 1A). Voxels were placed into the superior and posterior 
genu of the corpus callosum by excluding CSF around the corpus 
callosum (Fig 1B). The localization of both water-suppressed and 
unsuppressed proton spectra were acquired by applying a stimulated 
echo acquisition mode (STEAM, TR = 3.5 seconds) sequence. Water 
suppression was performed with 3 chemical shift selective saturation 
pulses at the water resonance. The number of acquisitions for water-
suppressed and unsuppressed spectra was 246 and 16, respectively. T2 
values of metabolites and tissue water had to be calculated to correct 
signal-intensity decays caused by T2 (transverse) relaxations. There-
fore, we obtained proton spectra with TE values of 30, 38, 48, 65, 84,
135, and 300 ms with water suppression. TE values for water-sup-
pressed spectra were 30, 48, 84, 135, 300, 470, and 800 ms. Because T1 
(longitudinal) relaxation does not affect the metabolite concentra-
tions measured with TR values above 3 seconds at 1.5T, a TR value of 3.5 
seconds, without T1 correction, was used. Spectral postprocessing 
included zero filling to 2048 points, an exponential filter correspond-
ing to 1 Hz of line broadening, Fourier transformation, zero order 
phase, and automatic baseline corrections by polynomial interpola-
tion. Spectra with a full width at half maximum smaller than 0.1 ppm 
were included in the statistical analysis.

Quantification of MR spectroscopy measurements and calcu-
lization of metabolite concentrations were performed by using the inter-
metal-water reference method.35,36 Major metabolite peaks were assigned 
to N-acetylaspartate (NAA) between 2.01 and 2.03 ppm, creatine (Cr) 
between 3.01 and 3.03 ppm, and choline (Cho) between 3.21 ppm and 
3.23 ppm. Calculation of T2 values and T2-corrected signal-intensity 
peak areas for water-suppressed and unsuppressed spectra is an opti-
mization problem that involves minimizing the squared error be-
tween the actual values of the measurement and the estimated func-
tion values evaluated at measurement points (MatLab; MathWorks, 
Natick, Mass). A monoexponential curve was fit to the metabolite 
peak area values. A double-exponential curve-fitting was performed 
for unsuppressed water spectra. CSF contamination was measured by 
using the difference in T2 decay between the brain tissue and CSF. The 
attenuation of brain tissue is accepted as ρ = 1.04 kg/L, and metabolite 
concentrations were calculated in millimoles per kilogram brain.36

Study-specific phantom tests for calibration measurements and 
for testing the reproducibility of 1H-MR spectroscopy measurements 
were performed every week. In the phantom studies, we used a spheric 
phantom containing 0.1 mol/L sodium acetate and 0.1 mol/L/L 
lactate. We measured acetate concentration with the internal water-
reference method by using the same TR and TE values. The variation 
in the measured acetate concentration in phantom studies was below 
7%.

Statistical Analysis
Statistical analyses of the results were performed by using SPSS 11.0 
for Microsoft Windows (SPSS, Chicago, Ill). The differences in metab-
olate concentrations and T2B values between each patient and con-
control group were investigated by analysis of variance. Correlation of 
metabolite concentrations with psychopathology scale scores was ex-
amined by using regression analysis. The relationship between metab-
olate concentrations and the duration of illness in chronic patients was 
assessed. Correlation between neurometabolite concentrations and 
DUP in first-episode patients was also tested. We also investigated the 
difference in metabolite concentrations between male and female pa-
patients by using the t test. The Bonferroni correction was applied for 
multiple comparisons. In the analyses, a P value of less than .05 was 
considered to indicate a statistically significant difference.

Results
All the spectra obtained from the patients and control subjects 
were deemed to be of good quality (Fig 2A–D). Moreover, the metabolite concentrations measured in the control subjects 
were consistent with the metabolite concentrations reported in 
previous studies.35,36 Clinical findings and demographic characteristics of the patients and their control subjects are 
presented in Table 1. There was no significant difference in the 
SANS and SAPS scores between the first-episode and chronic 
patients (P > .05). An uncorrected comparison test revealed 
significantly higher BPRS scores in chronic patients than in 
first-episode patients. However, the significance was lost after 
correction for multiple comparisons (P = .08).

Mean NAA concentration in all patients (first-episode and 
chronic patients together) was 8.91 ± 0.84 mmol/kg brain, 
compared with a value of 10.40 ± 0.44 mmol/kg brain in con-
control subjects (Table 2). The difference in NAA concentrations
On the other hand, the NAA concentrations of patients in the first-episode patient group (\( r = 0.34 \), \( P = .18 \)) in this group. In addition, there was no significant association between the NAA concentrations and DUP values in the first-episode patients (\( r = 0.23 \), \( P = .47 \)). The NAA concentrations of the chronic patients did not correlate with the duration of illness (\( r = 0.03 \), \( P = .89 \)).

Cr and Cho concentrations between first-episode and chronic patient groups and their respective control groups showed no significant difference (\( P > .05 \)) (Table 2). There was no relationship between both Cr and Cho concentrations and psychopathology scale scores (\( P > .05 \)). The Cr and Cho (Cr: \( r = 0.66 \), \( P = .31 \); Cho: \( r = 0.25 \), \( P = .42 \)) concentrations did not correlate with the duration of illness in the chronic patients. There was no association between the Cr and Cho (Cr: \( r = 0.30 \), \( P = .33 \); Cho: \( r = 0.25 \), \( P = .42 \)) concentrations and DUP in the first-episode patients. No sex predilection was noted for the metabolite concentrations (\( P > .05 \)).

The mean T2_B value of all patients was 77.23 \( \pm \) 11.97 ms, compared with a mean value of 59.25 \( \pm \) 7.35 ms in the control subjects (\( P < .001 \)). The T2_B values in both first-episode (\( P < .001 \)) and chronic patient (\( P < .001 \)) groups also differed significantly from those of the respective control subjects. There was no significant difference in T2_B values of first-episode and chronic patients (\( P = .51 \)). Likewise, no association between the T2_B values and duration of illness was present in the chronic patients (\( r = 0.16 \), \( P = .55 \)). The T2_B values did not correlate with the DUP in the first-episode patients (\( r = 0.28 \), \( P = .37 \)). The T2_B values did not correlate with the psychopathology scale scores in any of the patient groups (\( P > .05 \)).

### Discussion

Reciprocal and proper interaction of different cortical regions is required for information processing in the brain. Functional integration of spatially remote cognitive events is achieved by corticocortical connections. A disruption of corticocortical connections may lead to cognitive impairments. The connectivity theory involving the pathophysiology of schizophrenia is based on the hypothesis that an abnormality in cerebral cortical interconnections could cause or contribute to cognitive disturbances and symptoms of schizophrenia.2-4 Hoffman and McGlashan37 defined a neural network computer simulation model of reduced corticocortical connectivity in schizophrenia. Their simulation model could explain some of the positive psychotic symptoms of schizophrenia such as auditory hallucinations. The results of previous DTI and MR spectroscopy studies pointed to the presence of an axonal and/or a myelin-related pathology in schizophrenia.5-10,38 DTI measures diffusibility of water molecules in brain parenchyma. Dense packing of axonal fibers and myelination of axons decrease the diffusion rate of water molecules perpendicular to white matter tracts and leads to anisotropy. Thus, anisotropy reflects the structural integrity of axonal fibers and myelination. Pathologies causing demyelination or axonal loss may result in decreased anisotropy. The corpus callosum was found to be one of the common locations with reduced anisotropy in patients with schizophrenia.5-8 Because some of the structural studies selectively indicated abnormalities in the genu of the corpus callosum, we investigated the superior and posterior parts of the genu.5,17,25,26 Axonal fibers crossing the

![Fig 2. A-D. The proton MR spectra (STEAM, TR = 3.5 seconds) obtained from a first-episode patient with different TE values (TE = 30, 65, 135, and 300 ms, respectively) show the major neurometabolite peaks (NAA at 2.02 ppm, Cr at 3.02 ppm, and Cho at 3.22 ppm).](image-url)
crease in NAA concentration.42 On the contrary, increased neuronal mitochondria.39 NAA is believed to be exclusively coenzyme A aspartate by D-aspartate activity in 1H-MR spectroscopy studies.40 Pathologies that cause decreased callosal NAA concentration plays a role in the pathophysiology of schizophrenia.

Schizophrenia is accepted as a genetically mediated neurodevelopmental disease.47 The neurodevelopmental theory of schizophrenia states that genetically mediated pathogenetic factors, long before the onset of formal psychotic symptoms, lead to abnormal changes in the normal course of neurodevelopment, resulting in subtle abnormalities in neurons and neural circuits. The early presentation of cognitive dysfunctions before the onset of psychotic symptoms supports the neurodevelopment theory. The difference in NAA concentrations between first-episode and chronic patients was not significant in our study. This finding shows that the pathology causing a decrease in callosal NAA concentration plays a role in the pathophysiology of schizophrenia.

Pure myelin-related pathologies may cause a decrease in NAA concentration at 1H-MR spectroscopy.41 Decreased callosal NAA concentration observed in our patients may result from a myelin-related pathology or oligodendrocyte dysfunction. Histologic studies suggesting the presence of a myelin-related pathology or oligodendrocyte dysfunction in schizophrenia are present in the English literature.48-51

Table 2: The metabolite concentrations and T2B values of the patients and control subjects*

| Subjects            | N-acetylaspartate (mmol/kg brain) | Creatine (mmol/kg brain) | Choline (mmol/kg brain) | T2B Values (ms) |
|---------------------|-----------------------------------|--------------------------|------------------------|-----------------|
| First-episode group |                                   |                          |                        |                 |
| Patients (n = 12)   | 8.97 ± 0.82                       | 3.63 ± 0.23              | 1.21 ± 0.08            | 76.17 ± 12.26   |
| Controls (n = 14)   | 10.41 ± 0.45                      | 3.56 ± 0.27              | 1.18 ± 0.07            | 57.93 ± 6.85    |
| Significance        | P < .001                          | P = .54                  | P = .39                |                 |
| Chronic group       |                                   |                          |                        |                 |
| Patients (n = 16)   | 8.86 ± 0.89                       | 3.68 ± 0.35              | 1.22 ± 0.09            | 78.03 ± 12.09   |
| Controls (n = 14)   | 10.40 ± 0.44                      | 3.72 ± 0.25              | 1.26 ± 0.10            | 60.57 ± 7.85    |
| Significance        | P < .001                          | P = .66                  | P = .99                |                 |
| Combined group      |                                   |                          |                        |                 |
| Patients (n = 28)   | 8.91 ± 0.84                       | 3.65 ± 0.30              | 1.24 ± 0.11            | 77.23 ± 11.97   |
| Controls (n = 28)   | 10.40 ± 0.44                      | 3.64 ± 0.27              | 1.22 ± 0.10            | 59.25 ± 7.35    |
| Significance        | P < .001                          | P = .84                  | P = .45                |                 |

*Data are given as mean ± SD.
A decrease in attenuation of oligodendrocytes in the frontal cortex of patients with schizophrenia was found in another postmortem study. A link between schizophrenia and the reduced expression of 2′,3′-cyclic nucleotide 3′-phosphodiesterase gene, a marker of myelin forming cells, has been demonstrated in a recent study. Oligodendrocytes and myelin increase neuronal conduction velocity by their insulating properties and provide extrinsic support for axons. Myelin-related pathologies impair neuroaxonal conduction in white matter tracts and consequently cause corticocortical disconnections. Metachromatic leukodystrophy, for instance, is a dysmyelinating metabolic white matter disease, which demonstrates the pathophysiologic linkage between corticocortical disconnection and psychotic symptoms. Patients with adult-onset metachromatic leukodystrophy frequently present psychotic symptoms. Similarly, a myelin-related pathology causing reduced corticocortical connectivity may lead to the symptoms of schizophrenia.

Pure water has a T2 relaxation time of around 3 seconds. Owing to an interaction of water molecules with nonequivalent molecules in brain parenchyma, the T2 relaxation time of brain can be much shorter. In brain parenchyma, the T2 relaxation time of water molecules in brain parenchyma, the T2 relaxation time of water molecules trapped between myelin bilayers (myelin water) constitutes a smaller fraction of tissue-water fraction in brain and has a T2 relaxation time of approximately 80–100 ms. Water molecules trapped between myelin bilayers (myelin water) constitute a smaller fraction of tissue-water and have a shorter T2 relaxation time (approximately 20 ms) than intra- and extracellular water and CSF. Because water trapped between myelin bilayers is proportional to the myelin content of the tissue, T2b can provide indirect measurement of the myelin content of this tissue. Demyelinating diseases decrease the myelin water fraction and prolong the T2b value. In our study, the T2b values in patients were significantly prolonged compared with those of control subjects. A myelin-related pathology or decrease in axonal attenuation may be the cause of prolonged T2b in our patients. Theoretically, any factor or pathology that is able to alter the intrinsic magnetic field within tissue may change T2 relaxation times. Prolonged T2 relaxation time in the genu of the corpus callosum was reported in a recent MR imaging study of patients with schizophrenia. T2 relaxation times in the frontal white matter of patients with schizophrenia was also prolonged. In these studies, the authors proposed that decrease in the myelin water fraction might be the cause of prolonged T2 relaxation times. In our study, the accompaniment of a prolonged T2b value with reduced NAA concentration suggests the presence of an axonal or myelin-related pathology in the corpus callosum in patients with schizophrenia. A prolonged T2b value was associated neither with the duration of illness nor with the severity of psychopathology in our study. This finding is consistent with the possibility that the pathology altering the T2b value has a neurodevelopmental basis.

Phosphorylcholine and glycerophosphorylcholine, which are the precursors of cell membrane synthesis and the breakdown products of myelin and cell membrane, contribute to Cho peak at proton MR spectra. The lack of difference in Cho concentration between the patients and control subjects showed that there was no active demyelination ongoing in the corpus callosum of the patients with schizophrenia.

All of our patients were in the acute phase of illness. Therefore, all the patients except 2 were under antipsychotic treatment during the 1H-MR spectroscopy examinations. Due to ethical considerations, we could not increase the number of drug-naïve patients to compare metabolite concentrations of antipsychotic-naïve patients and the patients under antipsychotic treatment. Hence, we could not exclude the potential effect of antipsychotic drugs on neurometabolite concentrations. This may be accepted as a limitation of our study. However, lack of a difference in NAA concentrations between the first-episode and chronic patients demonstrated that chronic antipsychotic treatment did not lower the NAA concentration in the corpus callosum of the patients. There are controversial results in the previous literature involving the effect of antipsychotic drugs on NAA concentration. In one of the longitudinal 1H-MR spectroscopy studies, Bertolino et al.
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