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 (T2b) 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 T2b 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). T2b 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 T2b 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 MRI 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 noninvasive 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 disconnectivity 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

Received December 21, 2006; accepted after revision April 17, 2007.
From the Departments of Neuroradiology (K.A.) and Psychiatry (A.U., S.C.), MR Research Unit, Istanbul Medical School, Istanbul University, Capa, Istanbul, Turkey.
Please address correspondence to Kubilay Aydin, MD, Adnan saygun caddesi, M.Salihrustu bey sokak, Ulus Konaklari No:8/12, Ulus, Istanbul, Turkey; e-mail: dr.aydinik@superonline.com
DOI 10.3174/ajnr.A0691

Copyright 2007 by American Society of Neuroradiology.
The chronic patients were taking antipsychotic drugs, both at admis-
sion, only 2 were drug-naive at the time the ${ }^{1} \mathrm{H}$-MR spectroscopy
examinations were performed. Although 8 of the first-episode pa-
tients were receiving 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 3 patients were taking different types of antipsychotics (mean haloperidol-equivalent dose was 12.5 mg/day).

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

Note: –, 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 ± SDs except where indicated.

To changes in neurometabolite concentrations, which could be
detected by quantitative ${ }^{1} \mathrm{H}$-MR spectroscopy. We sought to
measure the absolute concentrations of major neurometabo-
lites and T2 relaxation times of tissue water (T2w) in the corpus
callosum of patients with schizophrenia. Additionally, we in-
vestigated the relationship of neurometabolite concentrations
with T2w 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. 12 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, antipsy-
chotic treatment, or inpatient care was ruled out. The mean ± SD
duration of untreated psychosis (DUP) was 11.20 ± 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 diagno-
sis of schizophrenia. Diagnosis of schizophrenia in first-episode pa-
tients 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 ad-
mission, only 2 were drug-naive at the time the ${ }^{1} \mathrm{H}$-MR spectroscopy
examinations were performed. Although 8 of the first-episode pa-
tients were receiving risperidone (mean dose, 3.9 mg/day), 2 of them
were receiving olanzapine (mean dose, 12.5 mg/day). The mean in-
terval between the admissions and ${ }^{1} \mathrm{H}$-MR spectroscopy examina-
tions was 7.8 days in first-episode patients. On the other hand, all of
the chronic patients were taking antipsychotic drugs, both at admis-
sion and at the time the ${ }^{1} \mathrm{H}$-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 3 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 con-
trols for each patient group) were enrolled in the study as a control
group. Each patient group (first episode and chronic) had equal edu-
cation 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 con-
trol 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. In-
fomed 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 Neg-
ative 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 ${ }^{1} \mathrm{H}$-MR spectroscopy examinations
were performed within the same week.

#### Cranial MR Imaging

All patients underwent conventional cranial MR imaging and
${ }^{1} \mathrm{H}$-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 spectro-
scopy volume of interest (voxel) and to identify any cerebral pathology
defined in the exclusion criteria. MR images included the following:

1. Fast spin-echo (SE) T2-weighted images (**TR** = 5790 ms, **TE** =
103 ms, **NEX** = 2, **echo-train length** = 16, **matrix** = 368 × 512,
section thickness = 5 mm, intersection distance = 1.2 mm); 2) coronal SE T1-weighted images (TR = 530 ms, TE = 30 ms, NEX = 2, matrix = 196 × 256, section thickness = 3 mm, intersection distance = 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 conventional cranial MR imaging. On sagittal images, the corpus callosum was divided into subregions as described by Witelson33 and Highley et al.34 (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. Therefore, we obtained proton spectra with TE values of 30, 38, 48, 65, 84, 135, and 300 ms with water suppression. TE values for water-unsuppressed spectra were 30, 48, 84, 135, 300, 470, and 800 ms. Because T1 (longitudinal) relaxation does not affect the metabolite concentrations measured with TR values above 3 seconds at 1.5T, a TR value of 3.5 seconds was considered to indicate a statistically significant difference.

Quantification of MR spectroscopy measurements and calculation of metabolite concentrations were performed by using the internal-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 optimization problem that involves minimizing the squared error between the actual values of the measurement and the estimated function 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/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 metabolite concentrations and T2B values between each patient and control group were investigated by analysis of variance. Correlation of metabolite concentrations with psychopathology scale scores was examined by using regression analysis. The relationship between metabolite 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 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 control subjects (Table 2). The difference in NAA concentrations
between the patients and control subjects was statistically significant ($P < .001$) (Fig 3). NAA concentration of all patients was negatively correlated with the BPRS ($r = -0.59, P = .001$) and SANS scores ($r = -0.68, P < .001$) (Fig 4A, -B). The association of NAA concentrations with SANS scores was also statistically significant ($r = -0.41, P = .028$; Fig 4C).

In the first-episode patient group, the mean NAA concentration of patients was $8.97 \pm 0.82$ mmol/kg brain, compared with a mean value of $10.41 \pm 0.45$ mmol/kg brain in the respective control group (Table 2). The difference in NAA concentrations between the first-episode patient group and the respective control group was statistically significant ($P < .001$). In the chronic patient group, the mean NAA concentration of the patients was $8.86 \pm 0.89$ mmol/kg brain, compared with a mean value of $10.40 \pm 0.44$ mmol/kg brain in the respective control group ($P < .001$). The difference between the NAA concentrations of the first-episode and chronic patient groups was not statistically significant ($P = .66$). In the first-episode patient group, the NAA concentrations of the patients were negatively correlated with the SANS ($r = -0.81, P = .001$) and BPRS ($r = -0.67, P = .025$) scores. However, there was no correlation between the NAA concentrations and SAPS scores in the first-episode patient group ($r = -0.27, P = .39$). On the other hand, the NAA concentrations of patients in the chronic patient group were significantly associated with BPRS ($r = -0.60, P = .014$) and SANS ($r = -0.76, P = .001$) scores.

Conversely, there was no relationship between the NAA concentrations and SAPS scores ($r = -0.34, P = .18$) 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 concentrations did not correlate with the duration of illness in the chronic patients. There was no association between the Cr and Cho concentrations and DUP in the first-episode patients. No sex predilection was noted for the metabolite concentrations ($P > .05$).

The mean $T_{2B}$ 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 $T_{2B}$ 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 $T_{2B}$ values of first-episode and chronic patients ($P = .5$). Likewise, no association between the $T_{2B}$ values and duration of illness was present in the chronic patients ($r = 0.16, P = .55$). The $T_{2B}$ values did not correlate with the DUP in the first-episode patients ($r = 0.28, P = .37$). The $T_{2B}$ 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.\(^4\) Hoffman and McGlashan\(^3\) 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.\(^5\) DTI measures diffusibility of water molecules in brain parenchyma. Dense packing of axonal fibers and myelination of axons decreases 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.\(^5\) 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.\(^5\) Axonal fibers crossing the
Neuronal activity in both physiologic and pathologic conditions may cause an increase in NAA concentration. Thus, neuroaxonal activity–dependent changes in NAA concentration demonstrate a close relationship between neuroaxonal functional status and NAA. Decreased NAA concentration in the corpus callosum in our patients may be due to decreased axonal attenuation, axonal dysfunction, or both. Histologic studies conducted to investigate the corpus callosum of patients with schizophrenia revealed controversial results. Although most of them showed no difference between patients and control subjects, Highley et al reported a significant sex-specific decrease in both the cross-sectional area and axonal fiber attenuation of the corpus callosum favoring female schizophrenics. No sex predilection was noted for the metabolite concentrations in our study. The correlation between decreased NAA concentration and severity of psychotic symptoms suggests that the pathology causing a decrease in callosal NAA concentration plays a role in the pathophysiology of schizophrenia.

Schizophrenia is accepted as a genetically mediated neurodevelopmental disease. 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 neurodevelopmental theory. The difference in NAA concentrations between first-episode and chronic patients was not significant in our study. This finding shows that the pathology leading to decreased NAA concentration in the corpus callosum is present at the beginning of illness. Furthermore, the lack of a relationship between NAA concentrations and the duration of illness suggests that neuroaxonal pathology leading to the decreased NAA concentration is not a progressive process during the clinical course of schizophrenia.

Pure myelin-related pathologies may cause a decrease in NAA concentration at 1H-MR spectroscopy. 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. In an electron
A decrease in attenuation of oligodendrocytes in the frontal cortex of patients with schizophrenia was found in another postmortem study.16 The gene expression analyses revealed differential expression of myelination-related genes, suggesting a disruption in oligodendrocyte function in schizophrenia.11,12,51 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.52 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.52 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 nonaqueous molecules in brain parenchyma, the T2 relaxation time of brain T2n is much shorter. In brain parenchyma, myelin-water, intracellular/extracellular water, and CSF contribute to T2n.33 Intra- and extracellular water constitutes the major 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, T2n can provide indirect measurement of the myelin content of this tissue. Demyelinating diseases decrease the myelin water fraction and prolong the T2n value. In our study, the T2n 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 T2n 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.29 T2 relaxation times in the frontal white matter of patients with schizophrenia was also prolonged.53 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 T2n 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 T2n 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 T2n 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.40 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-naive patients to compare metabolite concentrations of antipsychotic-naive 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 al55 reported an elevation of NAA/Cr ratio in response to antipsychotic...
medication. However, this finding could not be confirmed in the other studies. In addition, recently reported animal studies have shown that antipsychotic medication does not alter neuro-metabolite concentrations measured by 1H-MR spectroscopy.56

In conclusion, the prolonged T2 relaxation time of tissue water in the corpus callosum and the correlation of decreased NAA concentration with the severity of psychosis are the outstanding findings of this study. Finally, our results support the previously proposed callosal disconnection theory in schizophrenia.

References
1. Wernicke C. Grundriss der Psychiatrisch. Leipzig, Germany: Thieme; 1906
3. Friston KJ. The disconnection hypothesis. Schizophr Res 1998;30:115–23
14. Crow TJ, Ball J, Bloom SR, et al. The outstanding findings of this study. Finally, our results support the previously proposed callosal disconnection theory in schizophrenia. Am J Psychiatry 2005;162:1219–25