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

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This information is current as of April 16, 2024.

*AJNR Am J Neuroradiol* published online 26 September 2007

<http://www.ajnr.org/content/early/2007/10/03/ajnr.A0691.citation>

ORIGINAL  
RESEARCHK. Aydin  
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S. Cakir**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 (T<sub>2B</sub>) 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 T<sub>2B</sub> 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 ( $P = .028$ ). T<sub>2B</sub> 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 T<sub>2B</sub> 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.<sup>1</sup> More recently, the disconnectivity theory has re-emerged in schizophrenia research.<sup>2-4</sup> 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.<sup>5-8</sup> 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.<sup>9,10</sup> 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.<sup>11,12</sup>

Crow<sup>4</sup> 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.<sup>13</sup> Interhemispheric transmission

of information, which allows the functional lateralization of cerebral hemispheres, decreases in schizophrenia.<sup>14,15</sup> 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.<sup>16-20</sup> In a meta-analysis, Woodruff et al<sup>21</sup> 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.<sup>22-24</sup> 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.<sup>5,7-10</sup> Moreover, the structural MR imaging studies conducted in patients with schizophrenia revealed altered signal-intensity changes and decreased attenuation in the corpus callosum.<sup>25,26</sup>

Proton MR spectroscopy (<sup>1</sup>H-MR spectroscopy) is a non-invasive method to investigate neurochemical changes in various pathologic and physiologic conditions. <sup>1</sup>H-MR spectroscopy can demonstrate subtle neuroaxonal dysfunction, even in normal-appearing cerebral tissue on conventional MR imaging and DTI.<sup>27</sup> 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 <sup>1</sup>H-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.

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DOI 10.3174/ajnr.A0691

**Table 1: Clinical and demographic characteristics of the patients and control subjects\***

	FE Group		Chronic Group		Combined Group	
	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 ± 5.76	25.16 ± 5.35	29.31 ± 11.41	28.93 ± 10.24	27.65 ± 9.46	27.32 ± 8.58
Male/Female	8/4	9/5	11/5	9/5	19/9	18/10
Education (y)	10.33 ± 4.47	10.33 ± 3.89	11.00 ± 3.65	11.00 ± 3.40	10.71 ± 3.96	10.71 ± 3.56
Age at onset (y)	24.83 ± 5.30		22.37 ± 8.72		23.35 ± 7.13	
No. of hospitalizations	–		4.30 ± 3.90		–	
DUP (months)	11.20 ± 10.20		–		–	
Duration of illness (months)	–		83.25 ± 68.65		–	
Psychopathology scores						
BPRS	58.75 ± 8.60		67.56 ± 11.18		63.92 ± 10.96	
SANS	40.00 ± 17.62		50.37 ± 26.93		45.92 ± 23.60	
SAPS	36.58 ± 17.11		43.87 ± 15.89		40.75 ± 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 ± SDs except where indicated.

to changes in neurometabolite concentrations, which could be detected by quantitative <sup>1</sup>H-MR spectroscopy. We sought to measure the absolute concentrations of major neurometabolites and T2 relaxation times of tissue water (T2<sub>B</sub>) in the corpus callosum of patients with schizophrenia. Additionally, we investigated the relationship of neurometabolite concentrations with T2<sub>B</sub> 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.<sup>28</sup> 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 ± 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 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 <sup>1</sup>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 <sup>1</sup>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 <sup>1</sup>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 con-

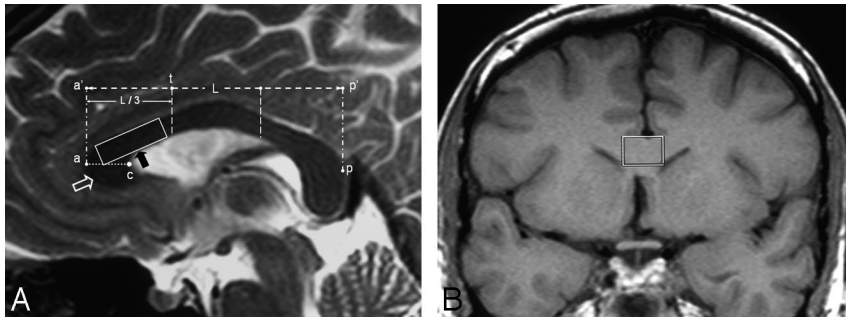
trols for each patient group) were enrolled in the study as a control group. Each patient group (first episode and chronic) had equal education levels with its respective control group ( $P > .05$ ). The control subjects underwent medical, neurologic, and psychiatric (by using the *Structured Clinical 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<sup>29</sup> 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).<sup>30-32</sup> 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 <sup>1</sup>H-MR spectroscopy examinations were performed within the same week.

### Cranial MR Imaging

All patients underwent conventional cranial MR imaging and <sup>1</sup>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) T2-weighted images (TR = 5790 ms, TE = 103 ms, NEX = 2, echo-train length = 16, matrix = 368 × 512,



**Fig 1.** A and B, MR images showing the MR spectroscopy voxel placement. A, Midline sagittal T2-weighted MR image (TR/TE/NEX, 6790/103 ms/4) of a first-episode patient shows the  $^1\text{H}$ -MR spectroscopic voxel placement. The maximal anteroposterior length (L) of the corpus callosum is identified (between points a' and p'). The line drawn perpendicular to the a'p' line at the anterior one-third point (point t) constitutes the posterior border of posterior genu region (separates the posterior genu from anterior midbody region). The horizontal line (line ac) drawn from the most anterior point of the corpus callosum (point a) to the "crook" of the genu (point c) separates the superior genu above and the inferior genu (open white arrow) below. The  $^1\text{H}$ -MR

spectroscopic voxel (black arrow) is placed into the superior and posterior genu of the corpus callosum. B, Coronal T1-weighted MR image (TR/TE/NEX, 530/30 ms/2) demonstrates the voxel placement into the genu of the corpus callosum.

section thickness = 5 mm, intersection distance = 1.2 mm); 2) coronal SE T1-weighted images (TR = 530 ms, TE = 30 ms, NEX = 2, matrix =  $196 \times 256$ , 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 =  $196 \times 256$ , section thickness = 3 mm, intersection distance = 1 mm).

### ***$^1\text{H}$ -MR Spectroscopy: Data Acquisition and Signal-Intensity Processing***

Single-voxel  $^1\text{H}$ -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 Witelson<sup>33</sup> and Highley et al<sup>34</sup> (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, without T1 correction, was used. Spectral postprocessing included zero filling to 2048 points, an exponential filter corresponding to 1 Hz of line broadening, Fourier transformation, zero order phase, and automatic baseline corrections by polynomial interpolation. 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 calculation of metabolite concentrations were performed by using the internal-water reference method.<sup>35</sup> 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  $\rho = 1.04 \text{ kg/L}$ , and metabolite concentrations were calculated in millimoles per kilogram brain.<sup>36</sup>

Study-specific phantom tests for calibration measurements and for testing the reproducibility of  $^1\text{H}$ -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%.

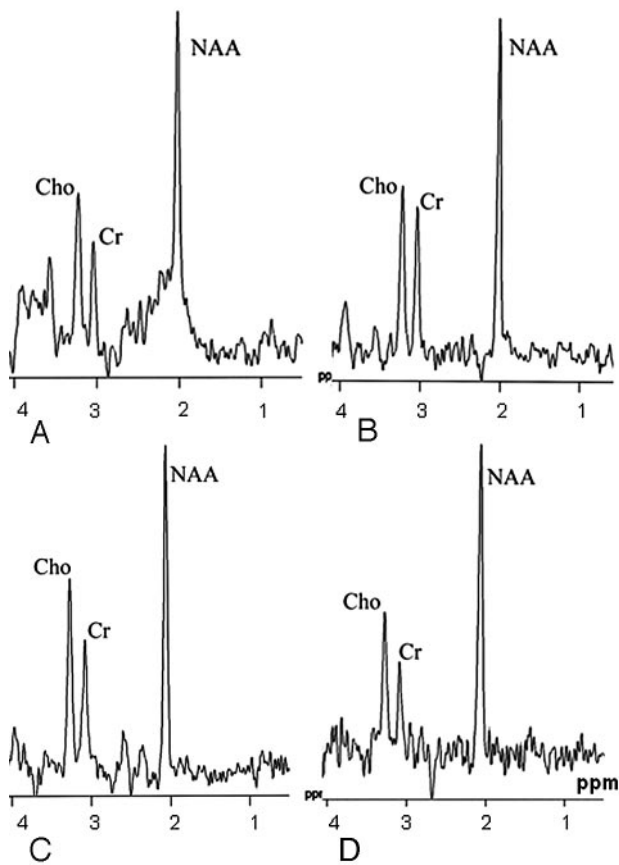
### ***Statistical Analysis***

Statistical analyses of the results were performed by using SPSS 11.0 for Microsoft Windows (SPSS, Chicago, Ill). The differences in metabolite concentrations and T2<sub>B</sub> 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.<sup>35,36</sup> 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  $8.91 \pm 0.84 \text{ mmol/kg brain}$ , compared with a value of  $10.40 \pm 0.44 \text{ mmol/kg brain}$  in control subjects (Table 2). The difference in NAA concentrations



**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).

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 SAPS 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 (Cr:  $r = 0.26, P = .31$ ; Cho:  $r = 0.26, P = .40$ ) 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  $T_{2B}$  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 ( $P > .05$ ).

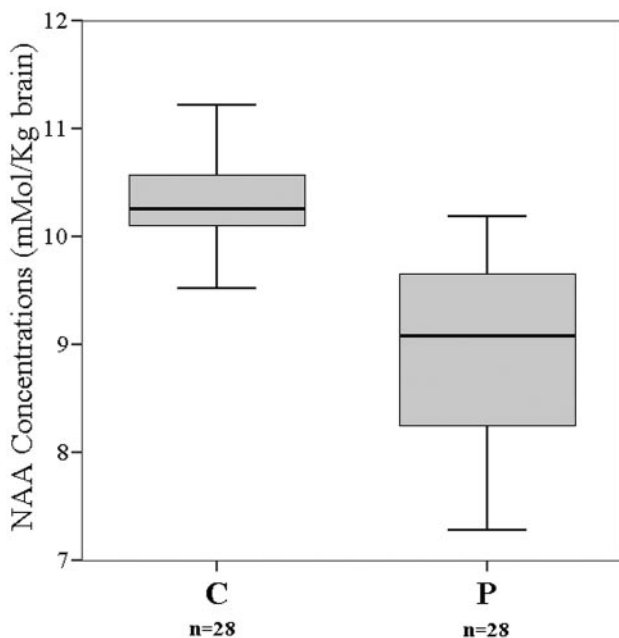
## Discussion

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 disconnectivity 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.<sup>2-4</sup> Hoffman and McGlashan<sup>37</sup> 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.<sup>5-10,38</sup> 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.<sup>5-8</sup> 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.<sup>5,17,25,26</sup> Axonal fibers crossing the

**Table 2: The metabolite concentrations and T<sub>2</sub><sub>B</sub> values of the patients and control subjects\***

Subjects	Metabolite Concentrations (mmol/kg brain)			T <sub>2</sub> <sub>B</sub> Values (ms)
	N-acetylaspartate	Creatine	Choline	
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	P < .001
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	P < .001
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	P < .001

\*Data are given as mean ± SD.



**Fig 3.** The box-plot graph demonstrates the distribution of NAA concentrations around the median values of all patients (P) and of the control subjects (C). The horizontal lines dividing the boxes represent the median values. The upper and lower edges of the boxes represent the upper and lower quartiles (medians of the upper and lower 50% of the values), respectively. The vertical lines (whiskers) are 1.5 times the inner quartile spread in length, which is measured from the median.

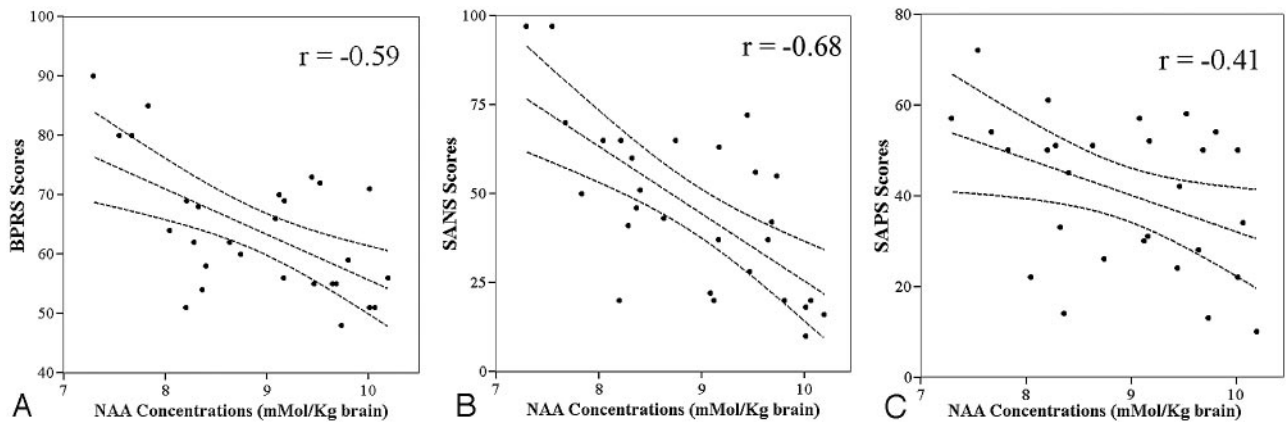
genu region of the corpus callosum connect frontal regions of cerebral hemispheres. Microstructural abnormality in the callosal fibers located in genu of the corpus callosum may lead to decreased interhemispheric connectivity and functional specialization in the frontal and temporal lobes, which have been suggested to occur in patients with schizophrenia.<sup>4</sup>

NAA is a free amino acid that is biosynthesized from acetyl coenzyme A aspartate by D-aspartate N-acetyltransferase in neuronal mitochondria.<sup>39</sup> NAA is believed to be exclusively found in neurons and neuronal processes (axons and dendrites). Moreover, it is used as a marker of neuroaxonal integrity in <sup>1</sup>H-MR spectroscopy studies.<sup>40</sup> Pathologies that cause neuronal loss or impairment of neuroaxonal functions decrease NAA concentration.<sup>41</sup> Likewise, neuroaxonal dysfunction, even without neuronal loss, may cause a reversible decrease in NAA concentration.<sup>42</sup> On the contrary, increased

neuronal activity in both physiologic and pathologic conditions may cause an increase in NAA concentration.<sup>43,44</sup> 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.<sup>45,46</sup> Although most of them showed no difference between patients and control subjects, Highley et al<sup>34</sup> 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.<sup>47</sup> 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 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 <sup>1</sup>H-MR spectroscopy.<sup>41</sup> 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.<sup>48-51</sup> In an electron



**Fig 4.** A–C, The scatter plots show the relationships between the NAA concentrations (mmol/kg brain) of all patients and the severity of symptoms. The lines between the 95% confidence curves represent linear regression lines. A, The negative correlation between the NAA concentrations and BPRS scores ( $r = -0.59$ ,  $P = .001$ ). B, The relationship between the NAA concentrations and severity of negative symptoms (SANS scores) ( $r = -0.68$ ,  $P < .001$ ). C, The association ( $r = -0.41$ ,  $P = .028$ ) of NAA concentrations with the severity of positive symptoms (SAPS scores).

microscopic study, ultrastructural changes, necrosis of oligodendrocytes, and damage of myelin lamellae were reported.<sup>49</sup> A decrease in attenuation of oligodendrocytes in the frontal cortex of patients with schizophrenia was found in another postmortem study.<sup>48</sup> The gene expression analyses revealed differential expression of myelination-related genes, suggesting a disruption in oligodendrocyte function in schizophrenia.<sup>11,12,51</sup> 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.<sup>51</sup> 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.<sup>52</sup> 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 T2<sub>B</sub> is much shorter. In brain parenchyma, myelin-water, intracellular/extracellular water, and CSF contribute to T2<sub>B</sub>.<sup>53</sup> 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, T2<sub>B</sub> can provide indirect measurement of the myelin content of this tissue. Demyelinating diseases decrease the myelin water fraction and prolong the T2<sub>B</sub> value. In our study, the T2<sub>B</sub> values in patients were significantly prolonged compared with those of control subjects. A myelin-related pathology or decrease in axonal at-

tenuation may be the cause of prolonged T2<sub>B</sub> 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.<sup>54</sup> T2 relaxation times in the frontal white matter of patients with schizophrenia was also prolonged.<sup>53</sup> 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 T2<sub>B</sub> 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 T2<sub>B</sub> 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 T2<sub>B</sub> 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.<sup>40</sup> 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 <sup>1</sup>H-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 <sup>1</sup>H-MR spectroscopy studies, Bertolino et al<sup>55</sup> 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 <sup>1</sup>H-MR spectroscopy.<sup>56</sup>

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 psychopathology are the outstanding findings of this study. Finally, our results support the previously proposed callosal disconnection theory in schizophrenia.

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