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Proton Magnetic Resonance Spectroscopy in the Frontal and Temporal Lobes of Neuroleptic Naive Patients with Schizophrenia

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Studies with proton magnetic resonance spectroscopy (MRS) have reported abnormalities in N-acetyl-aspartate (NAA), amino acids (AA) and choline (Cho) to creatine (Cr) ratios associated with schizophrenia. We report data on the three ratios in a sample of 18 neuroleptic naive patients with first-episode schizophrenia (eight studied in the dorsolateral prefrontal and 10 in the midtemporal lobe) and 24 healthy controls (14 studied in prefrontal and 10 in midtemporal lobes). Frontal lobe proton spectra were acquired with the stimulated-echo acquisition mode (STEAM) pulse sequence (echo time 21 ms, repetition time 2 s). Temporal lobe proton spectra were acquired with the point-resolved spectroscopy (PRESS) pulse sequence (echo time 16–21 ms, repetition time 2 s). Upon comparison with normal controls, NAA/Cr ratios were reduced in patients both for the frontal and the temporal lobe. By contrast, Cho/Cr ratios were slightly elevated in frontal and reduced in temporal lobes; whereas, AA/Cr ratios were normal in frontal and markedly increased in the temporal lobe. The reduced NAA/Cr ratios suggest lower neuronal viability in patients and is consistent with findings of reduced brain volume in both frontal and temporal regions.
[Neuropsychopharmacology 20:131–140, 1999]

KEY WORDS: *Schizophrenia; Proton magnetic resonance spectroscopy*

Magnetic resonance imaging (MRI) and spectroscopy (MRS) provide noninvasive, risk-free methods with which to study the origins and the time course of progression of neuropsychiatric disorders. The development of spatial localization methods, which sample the relative levels of mobile metabolites from a volume of tissue defined from an MR image, has provided a basis for integrating the biochemical information obtained by MRS with the anatomical and pathological information obtained from MRI. In vivo MRS studies of schizophrenia have examined two primary nuclei, phosphorus (Calabrese et al. 1992; Deicken et al. 1995; Keshavan et al. 1991; Keshavan et al. 1993; Pettegrew et al. 1993, 1995, 1991; Shioiri et al. 1994; Stanley et al. 1995b; Stanley et al. 1994) and proton (Bertolino et al. 1996, Buckley et al. 1994; Choe et al. 1994; Fukuzako et al. 1995; Nasrallah et al. 1994; Radda and Taylor 1985; Stanley et al. 1996; Yurgelun-Todd et al. 1996; Yurgelun-Todd et al. 1993). Phosphorus MRS can detect alterations in the levels of compounds involved in the bioenergetics of cellular metabolism, such as inorganic phosphate, adenosine triphosphate (ATP), and phosphocreatine. Additional composite resonances from phosphorus monoesters (PME) and phosphorus diesters (PDE) can also be detected. Phosphorus MRS in schizophrenia research has revealed abnormalities with high-energy phosphates as well as alterations in membrane phospholipid metabolism (Pettegrew et al. 1995). Proton MRS can de-

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Received October 30, 1997; revised March 11, 1998; accepted April 15, 1998.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/99/$–see front matter
PII S0893-133X(98)00063-3

tect brain metabolites such as N-acetyl-aspartate (NAA), creatine (Cr), choline (Cho), myo-inositol (mI), macromolecule proteins, and amino acids (AA). NAA ranks as the second most prevalent amino acid in the brain. Because NAA is found exclusively in neurons (Birken and Oldendorf 1989), NAA/Cr levels may reflect neuronal viability and integrity. Creatine is a compound involved in the regulation of cellular energy metabolism. The creatine resonance observed by proton MRS, is a combination of creatine and phosphocreatine. Trimethyl ammonium residues primarily representing choline are detected with MRS. The choline resonance is a composite of a number of choline-containing compounds. These include phosphocholine, glycerophosphocholine, acetylcholine, and cytidine diphosphate choline, as well as choline itself. However, the most prominent form of choline in the brain, phosphatidylcholine, is, for the most part, not detected by MRS because of its restricted immobile form (Cohen et al. 1995). Choline levels are inherently linked to membrane biochemistry, and changes in choline levels may reflect pathological changes in these structures. Myo-inositol has been identified as a glia-specific marker (Brand et al. 1993). Most of the MRS literature has reported the resonances between 2.2 and 2.6 ppm as a composite of glutamate, glutamine, gamma-amino butyric acid (GABA), and aspartate. Behar reported the detection of broad resonances from macromolecules that underlie a significant portion of proton MRS window from 1.9 to 2.6 ppm (Behar et al. 1994). These resonances are broader than the resonances from simple amino acids, such as glutamate, glutamine, and GABA. For convenience, we use a generic term, amino acid (AA), to describe this composite of resonances in the region between 2.2 and 2.6 ppm of the proton spectrum. This region will have a component of proton methylene resonances from macromolecule proteins as well as such amino acids as glutamate, glutamine, aspartate, and GABA.

Although the definitive assignment of the resonances in the AA region of the in vivo proton MR spectrum remains debated, the ability of proton MRS to detect glutamate may be of particular importance for schizophrenia because of the glutaminergic hypothesis for this disorder (Coyle 1996; Olney and Farber 1995). Studies on the pathophysiology of schizophrenia have reported neuroanatomical, neurochemical, and neurophysiologic changes in frontotemporolimbic systems (Gur and Pearlson 1993; Kotrla and Weinberger 1995), and the possibility of neuronal dysfunction and increased excitation has also been suggested (Gur et al. 1995; Olney and Farber 1995).

Spectroscopy studies have reported abnormalities in several brain regions in schizophrenia, including the frontal lobe, temporal lobe, hippocampus–amygdala, and basal ganglia (Bertolino et al. 1996; Buckley et al. 1994; Calabrese et al. 1992; Choe et al. 1994; Deicken et al. 1995; Fukuzako et al. 1995; Keshavan et al. 1991; Keshavan et al. 1993; Nasrallah et al. 1994; Pettegrew et al. 1993; Pettegrew et al. 1995; Radda and Taylor 1985; Shioiri et al. 1994; Stanley et al. 1995b; Stanley et al. 1994; Stanley et al. 1996; Yurgelun-Todd et al. 1996; Yurgelun-Todd et al. 1993). These metabolic findings converge with reports of volume reduction and aberrant functional activity for glucose metabolism and cerebral blood flow in these brain regions (Gur et al. 1995; Gur and Pearlson 1993; Kotrla and Weinberger 1995). For example, lower NAA levels in temporolimbic brain regions in schizophrenia (Bertolino et al. 1996; Fukuzako et al. 1995; Renshaw et al. 1995; Yurgelun-Todd et al. 1996; Yurgelun-Todd et al. 1993) are consistent with reports of volume reduction in neuroanatomic MRI examinations (Barta et al. 1990; Breier et al. 1992; Lieberman et al. 1992; Shenton et al. 1992; Suddath et al. 1989) and with postmortem abnormalities. (Arnold et al. 1995; Bogerts et al. 1990; Brown et al. 1986; Jeste and Lohr 1985). Detection of amino acids, which would include glutamate, remains essential for assessing the presence of excitatory dysfunction.

Most proton MRS studies in schizophrenia have been conducted in patients who have been ill and treated for several years. The importance of examining neuroleptic naive first-episode patients has been recognized in neurobiologic investigations. MRS provides a unique biochemical measure that may be altered in the presence of neuroleptic medications. Thus, the assessment of the neuroleptic naive should be of great interest. However, this strategy has been applied in a limited way to MRS research (Buckley et al. 1994; Choe et al. 1994; Pettegrew et al. 1991; Stanley et al. 1995b; Stanley et al. 1996). This may reflect the difficulty in accruing this patient population. The goal of the present study was to determine, in neuroleptic naive first-episode patients, alterations of the metabolites detectable by proton MRS in frontal and temporal lobe regions implicated in schizophrenia.

METHODS

Subjects

Eighteen neuroleptic naive first-episode patients and 24 healthy controls participated. They were included in two samples evaluated consecutively. The first study of the frontal lobe (FRO) included eight patients (six men, two women) and 14 controls (nine men, five women). The second study of the temporal lobe (TEM) included 10 patients (six men, four women) and 10 controls (six men, four women). The studies were sequential, FRO first and TEM second, and participants were consecutive admissions to the Mental Health Clinical Research Center (MHCRC) who met study requirements. This between-subjects design was necessitated by the length

of the procedure permitting evaluation of the integrated neuroanatomic and metabolic measures during the same imaging session. The decision was based on our experience with first-episode patients who can generally tolerate such studies without medication and with support throughout the procedure. The age (mean ± SD) of the subject groups in the frontal region was 26.4 ± 6.6 years for patients and 27.7 ± 6.8 for controls and in the temporal region was 27.0 ± 5.0 and 34.2 ± 6.2. Because the controls with temporal lobe measures turned out to be significantly older than the controls with frontal lobe measures, t = 2.40, df = 22, $p = .025$, analyses were repeated, entering age as a covariate. This did not affect the results reported.

The patients were first-episode and neuroleptic naive individuals assessed and followed by the Mental Health Clinical Research Center (MHCRC). For all, it was the first psychiatric presentation. They were referred from the acute schizophrenia in-patient service at the Hospital of the University of Pennsylvania ($n = 16$) and two were studied as outpatients. Patients had a DSM-IV diagnosis of schizophrenia ($n = 10$) or schizophreniform disorder ($n = 8$) established by comprehensive medical, neurological, and psychiatric evaluations (SCID-P) (Spitzer et al. 1994a), as detailed earlier (Gur et al. 1991). Age of onset was defined as the presentation of psychotic symptoms in the context of functional decline. This was determined by history obtained from patient, family, medical, and school records. MRS studies were conducted upon admission before administration of neuroleptics. The MHCRC has extensive experience in assisting patients through neuroimaging studies. They were followed longitudinally, and all patients with schizophreniform disorder at study entry (five men, three women) who met criteria for schizophrenia at follow-up are included. The healthy controls, recruited by newspaper advertisement, were free of medical, neurological, and psychiatric disorders (Spitzer et al. 1994b). Thus, subjects had no history of a disorder or event that might potentially affect brain function, except for schizophrenia in the patients. Informed consent was obtained before participation in the study. Sample characteristics are presented in Table 1.

Table 1. Clinical Characteristics of Patients

	Frontal Lobe		Temporal Lobe	
	Mean	**SD**	**Mean**	**SD**
Age	26.4	6.6	27.0	5.0
Education	13.0	1.8	13.5	2.6
Age at onset	21.4	4.6	23.4	4.4
In/outpatient	7/1		9/1	
Schizophreniform	2		6	
Schizophrenia	6		4	
BPRS (total)	46.2	6.3	44.4	14.8
SANS[a]	1.7	.9	2.2	1.0
SAPS[a]	2.4	.4	2.3	1.0

[a] Represents the average of the global ratings across subscales.

MRS Procedures

Magnetic resonance studies were performed on a 1.5 T Signa MR Scanner equipped with a spectroscopy software package (GE Medical Systems, Milwaukee, WI, USA). The standard head coil was employed for the routine anatomical imaging sequence (sagittal T1- and axial T2-weighted) and image-guided single-voxel spectroscopic acquisition. The dorsolateral prefrontal region was studied using a stimulated-echo acquisition mode (STEAM) localization technique. The single volume of interest (VOI) was of the dimensions 20 mm × 20 mm × 20 mm. The VOI was placed blindly to diagnosis by trained investigators using standard anatomic landmarks and procedures developed in our laboratory for regional MRI measurements. (Cowell et al. 1994; Turetsky et al. 1995) (see Figure 1a). The voxel was positioned just above the ventricles in predominantly white matter based upon the anatomic images. Water suppression was achieved by using three chemical shift-selective (CHESS) radio-frequency pulses followed by a dephasing gradient applied on each of the three axes. The sequence parameters included the following: spectral bandwidth of 2,500 Hz, TR 2,000 ms, TE 21 ms, mixing time 10.6 ms, 2,048 complex points 8-step phase cycling, and 256 acquisitions. The midtemporal region was studied using a point-resolved spectroscopy sequence (PRESS). The single volume of interest (VOI) was of the dimensions 15 mm × 15 mm × 20 mm, and placed following the same procedures as the frontal region using anatomic landmarks for the midtemporal region (see Figure 1b). The voxel was positioned along the superior temporal gyrus based upon the anatomic images. Water suppression was achieved by using three (CHESS) radio-frequency pulses followed by a dephasing gradient applied on each of the three axes. The sequence parameters included the following: spectral bandwidth of 2,500 Hz, TR 2,000 ms, TE 16-21 ms, 2,048 complex points 8-step phase cycling, and 256 acquisitions. Gradient shimming on the VOI and optimization of the water suppression were performed before the start of the acquisition. The left or the right hemisphere were measured in a counterbalanced order. More recently our efficiency improved to where, in some subjects (five patients, five controls), we were able to measure both hemispheres without compromising the quality of the study. Although it may lessen a lateralized effect, in these cases the average of the two hemispheres was used. The spectral acquisition time was 8 to 10 min per voxel, and the total examination time, including MRI and MRS studies, approximated 1 hour.

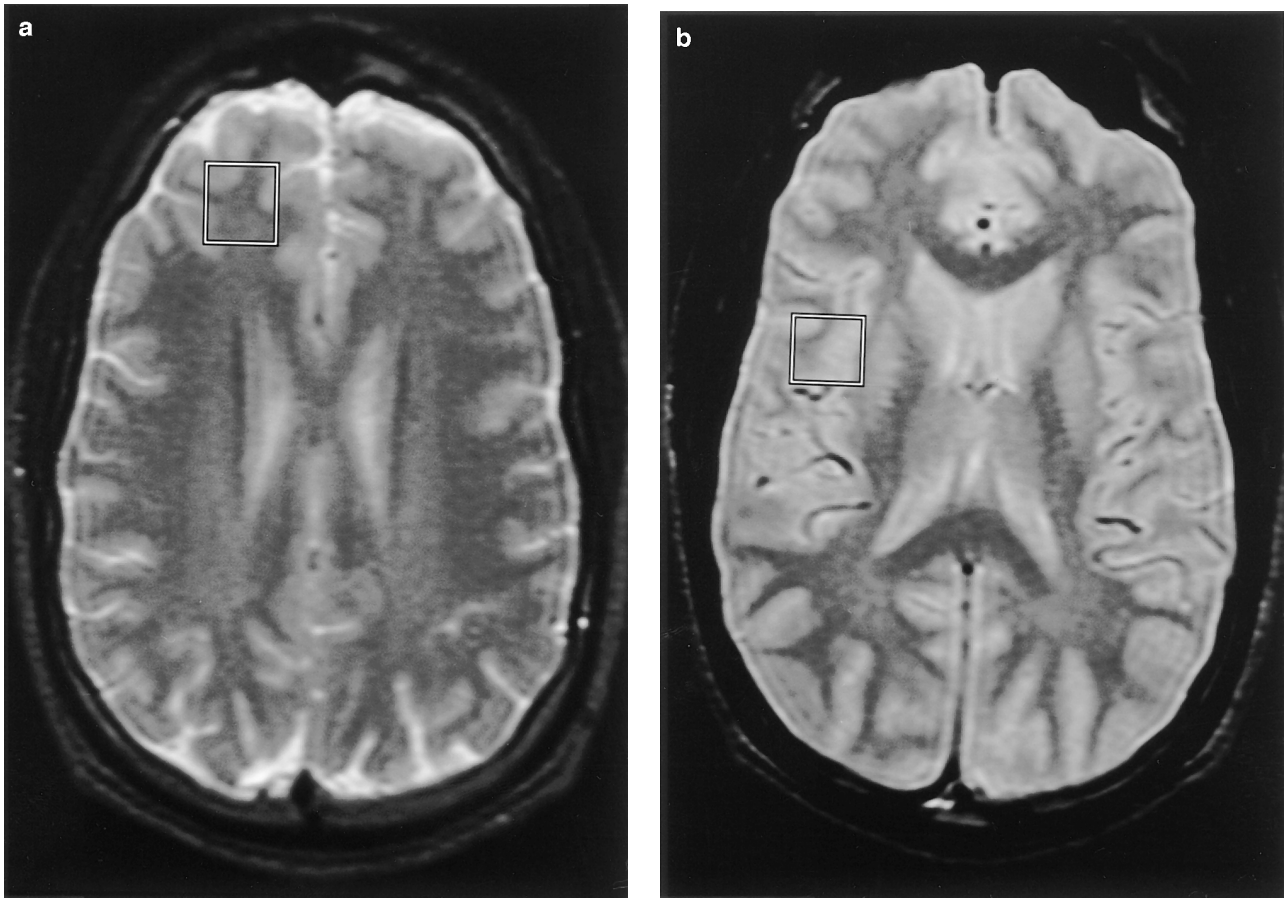

Figure 1. **(a)** Illustration of the placement for voxel of interest (VOI) in the dorsolateral prefrontal region; **(b)** illustration of the placement for voxel of interest (VOI) in the midtemporal region.

The data used in this report was accrued over the course of several years. Original data acquisition was performed using STEAM for localization in the frontal lobe. At that time, STEAM was more robust than PRESS. STEAM provides greater voxel delineation definition than PRESS. In the region of the frontal lobe, the lipids originating from the scalp and the susceptibility artifacts from the sinuses can interfere with metabolite detection. Although PRESS can be used in the frontal lobe, artifacts may contaminate the spectra. As MR technology progressed, the PRESS localization method employed digitally crafted pulses. The improvement of the PRESS sequence at 1.5 T makes it very attractive to use on the temporal lobe at a site above the ear. Software upgrades changed the limit on the lowest available echo time for PRESS resulting in our reported range of 16 to 21 ms. The differences in echo time have a minimal effect on the spectra at echo times below 50 ms. (Ernst and Hennig 1991). Studies varying the echo time from 16 to 21 ms were performed in our laboratory on phantom solutions of brain metabolites as well as normal volunteers confirming no significant effect. Multiple scans at each echo time were obtained in the phantom solutions. The major metabolite ratios (NAA/Cr, Cho/Cr, and mI/Cr) show a sample variance less than 0.005. The areas obtained from the amino acid region demonstrate a sample variance of less than 0.00003.

These two localization methods provide similar information and have equivalent power to detect changes. However, the results from the localization methods cannot be directly compared. The patient data are compared with data from healthy controls in a particular region.

A future aim of this protocol is to compare proton MRS data obtained at 1.5 T with that at 4 T. The pulse power requirement of spectroscopy localization techniques at high field is larger than that at 1.5 T. Current limitations with coil designs and other hardware at 4 T make it more technically feasible to perform STEAM for these comparison studies.

The spectral processing was performed with ProNMR (Softpulse Software, Guelph, Ontario, Canada) using zero filling to 4 K datapoints, 1 Hz line broadening applied in the time domain, Fourier transformation, and zero-order phase and baseline correction. Areas under the peaks, including the AA region, were esti-

mated using a Marquardt fitting routine to Lorentzian lineshapes in the frequency domain. From this method, metabolite ratios were calculated. Subtraction of the fitted spectrum with the raw spectrum shows only residuals that are the same as the amplitude of the baseline noise.

The biochemical information obtained using single-voxel proton MRS for specific regions provided a variety of metabolic measures that distinguished cell loss from differences in neurotransmitter activity. Typical ^{1}H single-voxel spectra obtained from the frontal lobe and the temporal lobe in study subjects, controls and patients, are shown in Figures 2 to 5. The voxel dimensions for these studies were typically 4.5 cm^3 or 8 cm^3. Several peaks can be readily identified from the spectra. The peak assignments were made based upon the published literature, and the chemical shifts were determined using NAA as a chemical shift standard. The following metabolites were identified: N-acetyl aspartate (NAA, 2.0 ppm, 2.6 ppm), creatine and phosphocreatine (Cr, 3.0 ppm, 3.9 ppm), choline-containing compounds (Cho, 3.2 ppm) and myo-inositol (mI, 3.5 ppm). The region between 2.1 and 2.6 ppm contains peaks from macromolecule proteins along with glutamate, glutamine, gamma-amino butyric acid (GABA), and aspartate residues. These peaks could not be resolved because of the overlap of resonances. Other peaks from glutamate and glutamine are present in the region between 3.6 and 3.8 ppm. Residual lipid signals as well as macromolecule proteins were identified in the region between 0.5 and 1.5 ppm.

Data Analysis

The ratios for each region served as dependent measures in a single multivariate analysis of variance (MANOVA), with two grouping factors: Diagnosis (patients, controls) by Region group (FRO, TEM), and one repeated-measures factor: Index (NAA/Cr, Cho/Cr, AA/Cr). Significant interactions were decomposed with univariate analyses of variance (ANOVAs) and further with *t* statistics using 2-tailed tests (Michels and Rosner 1996; Rothman 1990).

RESULTS

Water-suppressed proton spectroscopy was employed in the initial metabolic assessment of neuroleptic naive patients. We examined the frontal and temporal regions implicated in schizophrenia to determine NAA/Cr, Cho/Cr, and AA/Cr indices. Our finding of a 3-way interaction of diagnosis by region by index suggests regionally specific abnormalities in schizophrenia. In the frontal region, we observed reduced NAA, slightly increased Cho, and normal AA ratios. In the temporal region, all indices were abnormal, with reduction of both NAA and Cho, while AA was markedly elevated. The amino acid region consisted of composite resonances between 2.2 and 2.6 ppm.

The overall MANOVA showed significant main effects of Diagnosis, Hotelling–Lawley Trace = 0.98, F = 11.78, df = 3,36, $p < .0001$, Region, Hotelling–Lawley

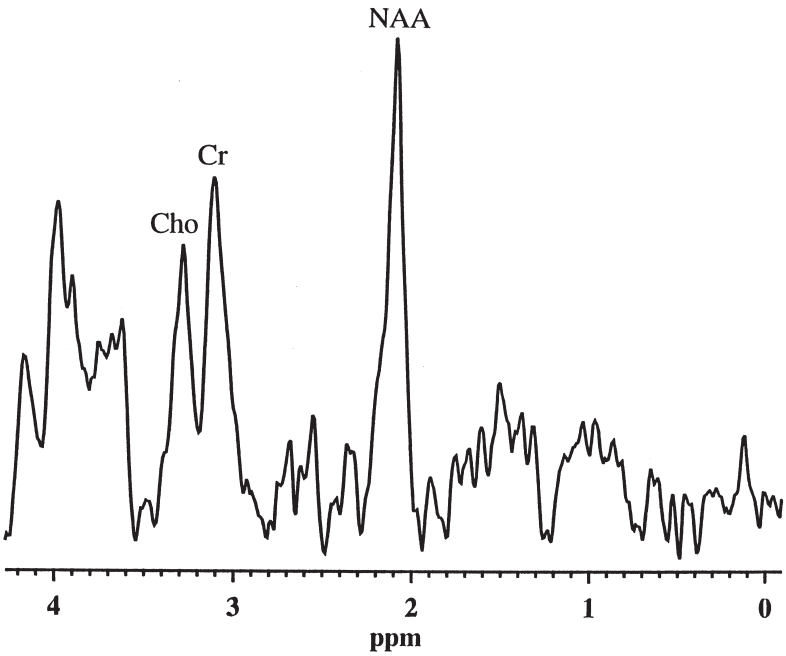

Figure 2. Proton spectra of left dorsolateral prefrontal region of a neuroleptic naive patient acquired with the STEAM pulse sequence.

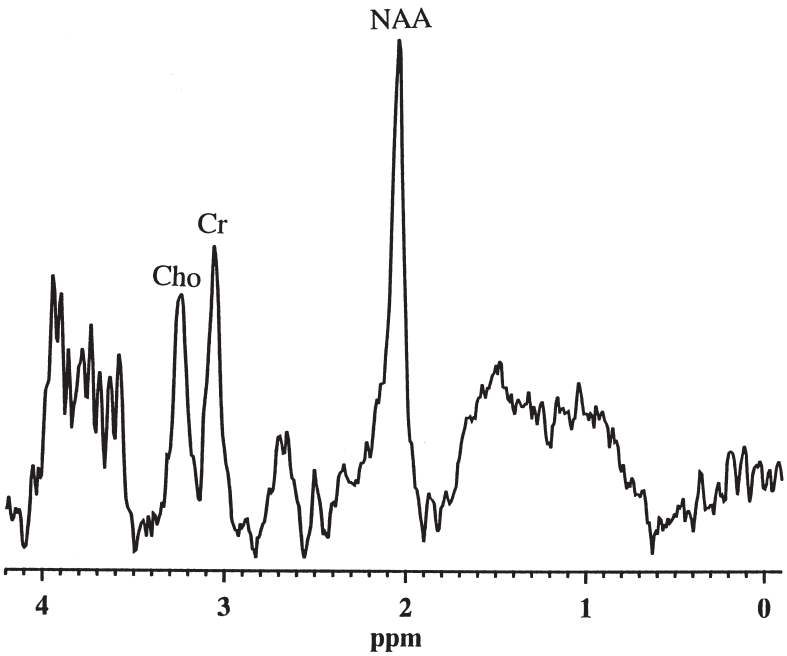

Figure 3. Proton spectra of left dorsolateral prefrontal region of a healthy control acquired with the STEAM pulse sequence.

Trace = 0.48, F = 5.80, df = 3,36, p = .0024, and Index, Hotelling–Lawley Trace = 2.63 F = 48.66, df = 2,37, p = .0001. There was a Diagnosis x Region interaction, Hotelling–Lawley Trace = 0.83, F = 9.96, df = 3,36, p = .0001, Diagnosis x Index interaction, Hotelling–Lawley Trace = 0.82, F = 15.24, df = 2,37, p = .0001, and an Index x Region interaction, Hotelling–Lawley Trace = 0.39, F = 7.15, df = 2,37, p = .0024. The three-way interaction of Diagnosis x Region x Index was also highly significant, Hotelling–Lawley Trace = 0.76, F = 14.04, df = 2,37, $p < .0001$.

Followup ANOVAs for the FRO group showed significant main effects of Diagnosis, F = 16.69, df = 1,20, p = .0006, and Index, F = 82.36, df = 2,40, p = .0001, and a Diagnosis x Index interaction, F = 23.56, df = 2,40, p = .0001. As can be seen in Figure 6a, this reflected lower NAA/Cr ratios in patients compared to controls, t = 7.01, df = 20, p = .0001, higher Cho/Cr ratios in patients, t = −2.39, df = 20, p = .0266, and equal values of AA/Cr.

The same analysis for the TEM group did not show a main effect of Diagnosis, $F < 1$, but a main effect for In-

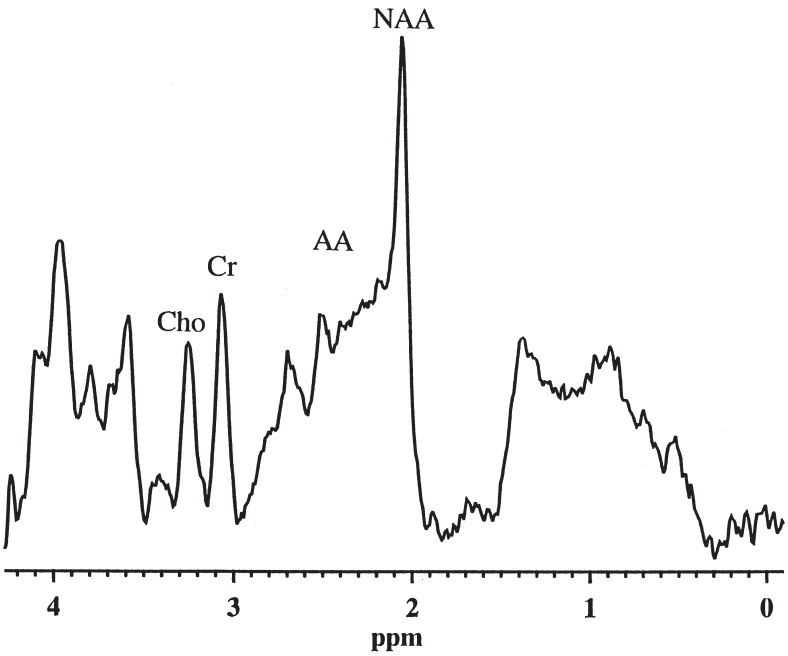

Figure 4. Proton spectra of right midtemporal region of a neuroleptic naive patient acquired with the PRESS pulse sequence.

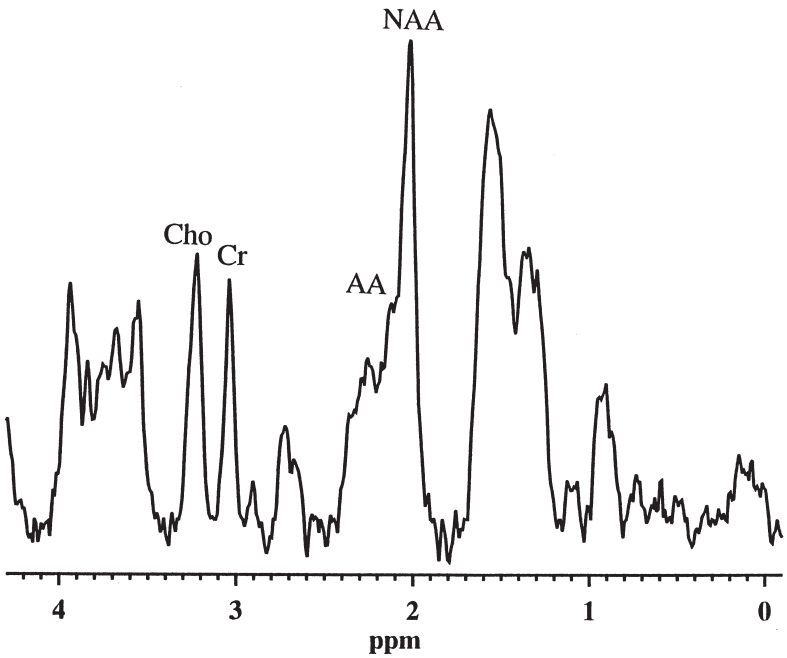

Figure 5. Proton spectra of right midtemporal region of a healthy control acquired with the PRESS pulse sequence.

dex, F = 3.91, df = 2,36, p = .0289 and a Diagnosis x Index interaction, F = 10.05, df = 2,36, p = .0003. As can be seen in Figure 6b, patients compared to controls had both lower NAA/Cr ratios, t = 2.54, df = 17, p = .0210, and lower Cho/Cr ratios, t = 3.15, df = 17, p = .0059, but higher AA/Cr ratios, t = 2.76, df = 11.3, p = .0181 [df are for unequal variances because the variance for patients was significantly higher, F′ = 7.76, df = 9,9, p = .005].

DISCUSSION

The NAA/Cr reduction in the frontal lobe replicates earlier reports, (Bertolino et al. 1996; Choe et al. 1994) and is consistent with the hypothesis of decreased neuronal viability. Reduced NAA/Cr suggests synaptic pruning or other neuronal or axonal loss (Feinberg 1982). The evaluation in the Cho/Cr ratio may be indicative of alterations in lipid metabolism in the frontal lobe. This also corroborates findings from structural MRI studies that reported reduced frontal lobe volume in schizophrenia (Andreasen et al. 1990), and some functional imaging studies reporting reduced cerebral blood flow and glucose metabolism (Gur and Pearlson 1993; Kotrla and Weinberger 1995). The results for the temporal lobe *suggest* neuronal loss in this region, but the mechanism for this loss may be different, because the level of choline is also reduced, whereas, the level of

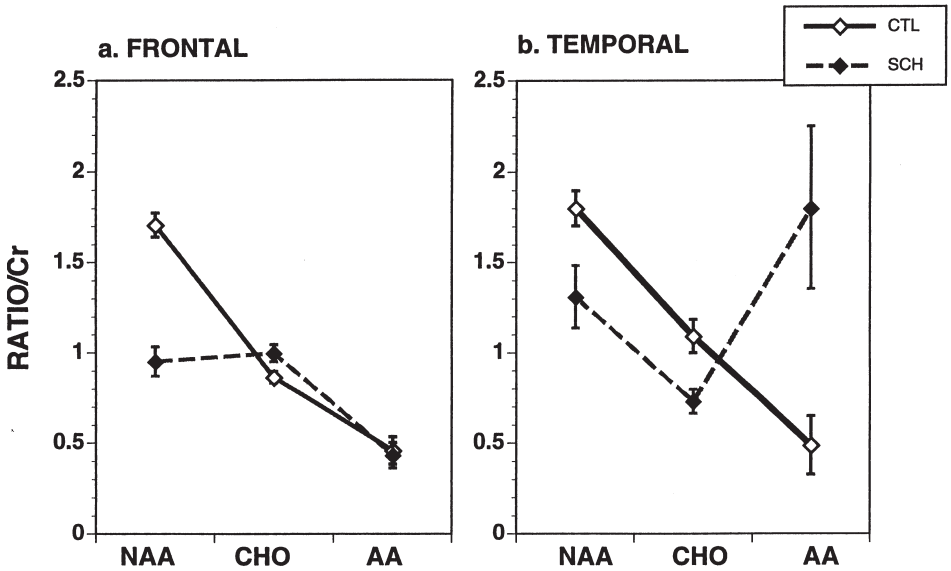

Figure 6. **(a)** Metabolite ratios (mean ± SEM) for NAA, Cho, and AA to Cr in the frontal lobes of patients with schizophrenia (filled diamonds) and healthy controls (open diamonds); **(b)** metabolite ratios (mean ± SEM) for NAA, Cho, and AA to Cr in the temporal lobes of patients with schizophrenia (filled diamonds) and healthy controls (open diamonds).

amino acids, the peaks that resonate between 2.2 and 2.6 ppm, increased. The effects in the temporal lobe region follow along with earlier findings for NAA and Cho (Fukuzako et al. 1995; Renshaw et al. 1995; Yurgelun-Todd et al. 1996; Yurgelun-Todd et al. 1993) and are consistent with the hypothesis of temporal lobe dysfunction in schizophrenia (Gur et al. 1994; Gur et al. 1995). The observation of increased AA, which includes resonances attributable to proteins and amino acids, can be examined within the context of schizophrenia. The elevations in this region of the spectrum could be attributed to an elevation of glutamate in the temporal lobe, perhaps associated with abnormally high levels of neuronal excitation. *The effect should be replicated on larger samples to merit speculation on its significance for understanding the pathophysiology of schizophrenia.* However, several investigators have hypothesized increased glutaminergic activity (Coyle 1996; Olney and Farber 1995; Stanley et al. 1995a) and neuronal "overactivation" (Gur et al. 1995). Alternatively, GABA, a major inhibitory neurotransmitter, has also been implicated in schizophrenia. Our results could suggest a process that results in the elevation of GABA. However, because glutamate is the most abundant free amino acid in the brain, and GABA is found much lower in concentration levels, our findings hold more relevance implicating a glutamatergic process. Relative abundance is not the only criteria for MR visibility. Factors such as mobility and sampling echo time will influence signal intensities and areas. The inability to resolve the large number of composite resonances along with MR visibility factors prohibits definite assignment of amino acid resonances. Future MRS studies will need to employ techniques (spectral editing) or MRS at higher field strengths (i.e., 4 T) to examine these metabolites separately. *The significant finding of this report is to note the elevation of composite resonances.*

Other studies have corrected for the degree of overlap between NAA and the broad amino acid resonances in the MRS spectral window from 1.9 to 2.6 ppm (Stanley et al. 1996). After applying a correction, the study reported no significant differences in the NAA level in the left dorsolateral prefrontal cortex. Accounting for the increased AA/Cr in our report along with decreased NAA/Cr would have the opposite result, compared to that of the prior report (Stanley et al. 1996). As demonstrated in our spectra (Figures 2–5), the region between 0.5 and 1.5 ppm shows either a single broad resonance or multiple resonances in both patients and healthy controls. This region has been attributed to lipids as well as to macromolecule proteins. The regions selected for spectroscopy (dorsolateral prefrontal and midtemporal) are subject to lipid signal as well as susceptibility artifacts that arise from the scalp and sinus cavities. These signals routinely appear between 0.5 and 1.5 ppm. However, the region between 2.2 and 2.6 ppm in patient and healthy control temporal lobe spectra (Figures 4, 5) demonstrates the elevation of amino acids typically observed in the patients without signal contamination from lipids and artifacts.

The presence of the abnormalities we have observed in first-episode patients, studied before any neuroleptic exposure, negates the possibility that they are a result of medication. However, the timing of these processes cannot be determined. The disease onset, defined by presence of psychotic symptoms in the context of functional decline, antecedes first psychiatric presentation by 4 to 5 years. Thus, even when patients are accrued at their first episode, the disease process has taken its course. On the other hand, the metabolic abnormalities are evident in schizophrenia patients where duration of illness was less than 6 months. Keshavan et al. 1991) described a patient who exhibited PME and PDE levels in the P-31 MRS spectra (similar to those reported above for schizophrenia) well before the development of psychotic symptoms. The possibility of synaptic pruning (Feinberg 1982; Huttenlocher 1979) in schizophrenia has been suggested in postmortem data where cytoskeletal abnormalities were noted in brains of patients who had schizophrenia (Arnold et al. 1991). This abnormal pruning could result in neuronal loss, as well as an upregulation of the postsynaptic dopaminergic receptors. The net result of these processes would decrease the NAA/Cr levels observed by proton MRS.

This study has several limitations, thus its results should be considered as encouraging, but preliminary. Most importantly, the sample size in each group is small and precludes correlation with clinical data. Future studies can use faster acquisition protocols and obtain data on multiple regions in the same subject, and this will enhance the power of contrast between frontal and temporal effects that, in the present study, were made in a between-subjects design. Such studies can also obtain simultaneous bilateral measures for testing the hypothesis of lateralized dysfunction in schizophrenia (Gur et al. 1995). The intersubject positioning of the voxel in the frontal and temporal lobes may be another variable. While attempting to minimize susceptibility factors (sinus, ear, skull cavity), voxel position between subjects may vary. Different locations and different inclusion of gray and white matter can contribute to different metabolite levels increasing the variability of the results. This is particularly important with the amino acid resonances. Also, the comparison with previous studies mentioned may be of limited utility, because many were performed in the mesial temporal lobe at a level caudal than the present study. Although this study had a 7 year age difference between some normal and schizophrenia subjects in the temporal region, a recent study found no significant difference in the baseline choline levels of normal subjects (Cohen et al. 1995). Furthermore, when corrected for age, the metabolite indices maintained their significant difference. Finally,

the present study is cross-sectional and does not permit correlations between changes in metabolites and clinical response. These limitations notwithstanding, the results suggest that early cellular dysfunction may be associated with the neuroanatomic and functional abnormalities observed already in first-episode schizophrenia.

ACKNOWLEDGMENTS

This research was supported by the National Institute of Health grants MH-49390, MH-43880, MH-01336, MH-42191, RR-0040, and RR-02305.

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