Proton Magnetic Resonance Spectroscopy (1H MRS) in Schizophrenia: Investigation of the Right and Left Hippocampus, Thalamus, and Prefrontal Cortex

by Pascal Delamillieure, Jean-Marc Constans, Jesús Fernandez, Pépine Braço, Karim Benali, Patrick Courthéoux, Florence Thibaut, Michel Petit, and Sonia Dollfus

Abstract

Single voxel proton magnetic resonance spectroscopy (1H MRS) was used to study the metabolites N-acetyl-aspartate (NAA), choline (CHO), and myo-inositol (ml) in order to test a neuroregenerative hypothesis in schizophrenia (decrease of NAA, increase of CHO, and increase of ml) and a cerebral asymmetry of these metabolites. 1H MRS was performed in 17 schizophrenia patients and 14 healthy subjects in three cerebral areas highly involved in the pathophysiology of schizophrenia (the prefrontal cortex, the thalamus, and the hippocampus). The ratio amplitudes between metabolites and creatine plus phosphocreatine (Cr) were determined. No difference in the metabolites existed between patients and healthy subjects. However, relationships were noted between NAA/Cr and age in the thalami of the schizophrenia patients (r = -0.37; p = 0.14) and healthy subjects (r = -0.52; p = 0.05). A significant correlation was observed between NAA/Cr and age of onset of illness in the hippocampi of schizophrenia patients (r = -0.59; p < 0.05). Moreover, NAA/Cr was lower in the right than in the left prefrontal cortex in both schizophrenia patients and healthy subjects. There was no relationship between the metabolites and duration of illness or dose of antipsychotics. These findings might suggest a neuroregenerative process in the hippocampi of schizophrenia patients with late onset of illness, and the NAA/Cr ratio could be a marker of aging in the thalamus.

Keywords: Schizophrenia, magnetic resonance spectroscopy, brain chemistry, thalamus, hippocampus, prefrontal cortex.


In the past decade, neuroanatomical studies documented cerebral impairments in schizophrenia such as lateral ventricular enlargement (Andreasen et al. 1982; Nasrallah et al. 1986), reduction of volume of temporal lobes (Bogerts et al. 1985; Breier et al. 1992; Marsh et al. 1994; Fukuzako et al. 1996), and decrease in thalamus size (Andreasen et al. 1994). Davis et al. (1998) recently described a bilateral increase in the size of the ventricle over a 4-year interval in a Kraepelinian subgroup. DeLisi et al. (1997b) also demonstrated significant progressive cortical atrophy in a subset of schizophrenia patients using magnetic resonance imaging (MRI). Other abnormalities provide evidence of a neuroregenerative process like the gliosis observed in the periventricular structure of the diencephalon, the periaqueductal region of the mesencephalon, and the basal forebrain (Stevens 1982; Casanova 1991). These studies have provided evidence of alterations of cerebral structures, but the nature of the neurobiological process that could be at the origin of schizophrenia symptoms is still unknown. A neuroregenerative process could be investigated with 1H MRS, which is commonly used to measure NAA, ml, CHO, and Cr. NAA is an intraneuronal metabolite that reflects the number or the viability of the neurons or axons; it is absent in glial cells (Birken and Oldendorf 1989, Urenjak et al. 1993). Up to now, most 1H MRS studies have focused on NAA in schizophrenia and have led to inconsistent results. Several studies (Maier 1995; Yurgelun-Todd et al. 1996), although not all (Buckley et al. 1994; Heimberg et al. 1998; Bartha et al. 1999), have reported a decrease of NAA/Cr in the temporal lobes of chronic treated schizophrenia patients. This reduction of NAA/Cr was present in first episode patients (Renshaw et al. 1995). In the dorso-lateral prefrontal cortex, the NAA was reduced in chronic treated schizophrenia patients in some studies (Bertolino et al. 1996), while other authors did not observe any...
change of NAA/Cr in frontal lobes of chronic treated schizophrenia patients (Buckley et al. 1994; Fukuzako et al. 1995; Williamson et al. 1998). In vitro ml has been shown to be present in only glial, not neuronal, cells (Brand et al. 1993). Glial proliferation, observed in multiple sclerosis, brain tumors, and reactive gliosis (Tedeschi et al. 1995). Fukuzako et al. (1995) found an increase of CHO/Cr in the left temporal lobe of chronic schizophrenia patients compared to healthy subjects, whereas Maier (1995) found a decrease of CHO in the left hippocampus of the treated schizophrenia subjects.

In order to test the neurodegenerative hypothesis in schizophrenia, in this study we examined whether a decrease of NAA and an increase of ml and CHO occur in schizophrenia patients compared to healthy subjects.

In addition, the purpose of the present investigation was to study metabolic lateralization effects in the different volumes of interest. In fact, a defect of asymmetry was investigated because disturbances in asymmetry are particularly striking in schizophrenia and may provide a neurologic substrate for the pathophysiology of the illness (Petty 1999). Frontal asymmetry reversal and reduction were described in chronic schizophrenia patients (Luchins et al. 1979). Hemispherical differences in metabolic concentration with higher Phosphocreatine (PCr)/β-ATP were observed in the left temporal lobe compared to the right temporal lobe of chronic schizophrenia patients (Calabrese et al. 1992). The aim of the study was also to investigate cerebral asymmetry or reverse asymmetry in schizophrenia patients compared to healthy subjects.

These abnormalities were studied in the prefrontal cortex, the thalamus, and the hippocampus, which are particularly involved in schizophrenia (Weinberger 1987; Andreasen et al. 1994; Silbersweig et al. 1995).

Methods

Subjects. Seventeen right-handed schizophrenia patients (14 males and 3 females, 5 inpatients and 12 outpatients) who met DSM-IV (American Psychiatric Association 1994) criteria were recruited. The diagnoses were established by two senior psychiatrists using all the information available from clinical observations, medical records, and key informants. All patients were examined using the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). The mean age of the schizophrenia group was 31.25 years (standard deviation [SD] = 6.09), with a mean age of onset of illness (age at first episode) of 22.82 years (SD = 5.41) and a length of illness (time between the onset of illness and the MRS examination) of 8.42 years (SD = 5.45). All the treated patients were in a stabilized phase, defined by no change in antipsychotic doses for 2 months. All medicated patients were treated with antipsychotics (antipsychotic daily doses were converted into chlorpromazine equivalents [Davis 1976]), and five also received adjunctive anticholinergic drugs; five patients were drug-naive.

The patients were classified as residual (n = 9), paranoid (n = 4), disorganized (n = 1), and undifferentiated (n = 3).

The handedness was defined by the Edinburgh inventory (Oldfield 1971). Patients had no history of head injury, past or present neurological or organic disorders, alcoholism, or drug abuse that was evaluated by urine tests. Table 1 shows the characteristics of the patients.

Fourteen healthy subjects (11 males and 3 females) were recruited by advertisement. The mean age was 30.14 years (SD = 6.39). They were matched with patients for age, educational level (elementary, secondary, university and up), sex, and handedness (all were right-handed). None of the controls had any psychiatric disorders evaluated by a psychiatrist with the Diagnostic Interview Schedule (Robins et al. 1981), organic illness, alcoholism, or drug abuse. Seven healthy subjects (50%) had not completed high school. After complete description of the study to the subjects, written informed consent was obtained.

\[ \text{Table 1. Characteristics of the patients} \]

<table>
<thead>
<tr>
<th>Educational level (n = 17)</th>
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<tbody>
<tr>
<td>Elementary (n, %)</td>
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<td>Secondary (n, %)</td>
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<td>University (n, %)</td>
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<th>Antipsychotics (n = 12)</th>
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<tr>
<td>Amisulpride (n, %)</td>
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<tr>
<td>Flupentixol (n, %)</td>
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<tr>
<td>Haloperidol (n, %)</td>
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<td>Loxapine (n, %)</td>
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<td>Penfluridol (n, %)</td>
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<td>Pimozide (n, %)</td>
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<td>Pipotiazine (n, %)</td>
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<th>PANSS (n = 17), mean ± SD</th>
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<tr>
<td>Positive scale</td>
</tr>
<tr>
<td>Negative scale</td>
</tr>
<tr>
<td>General psychopathology scale</td>
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</table>

Note.—PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
MRS Examination. MRI and spectroscopy were performed on a General Electric (GE) Signa 1.5 Tesla MR Imaging system (GE Medical Systems, Milwaukee, WI) using a standard quadrature head coil. $T_2$ weighted fast-spin echo images were used to obtain sagittal and axial views of the brain. The average voxel size studied was 9 cm$^3$ in the left and the right medial prefrontal cortex, thalamus, and hippocampus. The volumes of interest were prescribed from the axial slices and an image of the volumes of interest was obtained to confirm accurate localization (figure 1). Water unsuppressed and water suppressed with chemical shift selective (CHESS) and stimulated echo acquisition mode (STEAM)-localized spectra (Repetition Time [TR] = 1,500 msec, Echo Time [TE] = 30 msec, mixing time = 13.7 msec, 128 averages) were acquired in 4 minutes, 12 seconds (Frahm et al. 1989a, 1989b). There were 2,048 data points collected during an acquisition with a spectral width of 2,500 Hz. The spectral processing was performed on a SUN Sparc Station 10, with SA/GE software provided by GE (Spectroscopic Application for GE). Before processing the spectra, the value of the line width (Lw) of Cr was computed by fitting the peak in the frequency domain by Fourier transformation and without using any other function (no apodization, for example). The spectra were processed using zero-filling to 8K data-points, (1-Lw) Hz line broadening in the time domain and zero-order phase, and a simple baseline correction (direct current [DC] offset) in the frequency domain after Fourier.

Figure 1. VOIs localized on series of T1 axial $^1$H MRS images

Note.—$^1$H MRS = proton magnetic resonance spectroscopy; VOIs = volumes of interest.

$^1$VOIs (3 x 1.5 x 2, 5–10 ml) were placed respectively in the right and left prefrontal cortex (A, D), thalamus (B, E), and hippocampus (C, F).
transformation. The (1-Lw) Hz line broadening was used to normalize the Lw of all peaks. An Lw of 1 for Cr was therefore obtained. Before the fitting procedure, the spectra were downscaled by the value of the amplitude of Cr. In this way a normalization of the amplitude and Lw of creatine to 1 was obtained. Peak amplitudes were determined using a Levenberg-Marquardt fit to a Gaussian line shape. MRS metabolite concentration was expressed as the ratio of peak amplitudes (NAA/Cr, CHO/Cr, and ml/Cr) (figure 2). The total time of acquisition was 1 to 2 hours; it was not always possible to acquire spectra successfully from all regions of interest. Spectra were rejected for different reasons: first, if the resolution between the CHO and creatine peaks was not at least 50 percent of the distance from peak maximum to apparent baseline; and second, if the spectral resolution or the signal-to-noise ratio was not acceptable for a good analysis (ratio amplitude peak/maximum noise > 4).

Figure 2. Proton spectra of healthy subject’s left thalamus, acquired with the STEAM pulse sequence at TE = 30 ms

Note.—CHO = choline; Cr = creatine plus phosphocreatine; ml = myo-inositol; NAA = N-acetyl-aspartate; STEAM = stimulated echo acquisition mode; TE = echo time.
Statistical Analysis. Statistical analyses were carried out on Statview 5.7 software. The ratios for each region served as dependent measures in a multivariate analysis of variance (MANOVA), with two grouping factors (patients, controls) by region group (prefrontal cortex, hippocampus, and thalamus) and on repeated measures (NAA/Cr, CHO/Cr, and ml/Cr). Interactions were decomposed with univariate analysis of variance (ANOVA). All these tests were considered significant when p values were less than 0.05. Correlations between metabolite ratios and age, age of onset of illness, length of illness, and dose of antipsychotics were performed with Pearson’s test.

Results

The overall MANOVA did not show significant main effects of diagnosis. Followup ANOVA showed significant main effects of lateralization in the prefrontal cortex.

Thalamus. Table 2 shows the means of the metabolite ratios in the right and left thalamus in schizophrenia and healthy subjects. No difference was found between the left and the right and between schizophrenia patients and healthy subjects. Figure 3 shows the relationships between NAA/Cr and age in healthy (r = -0.52; p = 0.05) and schizophrenia (r = -0.37; p = 0.14) subjects. No correlation was noted between metabolite ratios and age of onset of illness, length of illness, and dose of antipsychotics.

Prefrontal cortex. Fourteen schizophrenia patients (12 males and 2 females) were analyzed using MRS. For three subjects, the spectra in this region were not analyzed because they did not meet the criteria for a good analysis (very bad signal-to-noise ratio). Table 3 shows the means of the metabolite ratios in the right and left prefrontal cortex in schizophrenia and healthy subjects. The NAA/Cr was significantly lower in the right than in the left prefrontal cortex in both schizophrenia patients and healthy subjects, but no difference was noted between patients and controls.

Hippocampus. Fourteen schizophrenia patients (12 males and 2 females) were analyzed with MRS. As with the prefrontal cortex, the spectra were not analyzed for three subjects because they did not meet the criteria for a good analysis (very bad signal-to-noise ratio). Table 4 shows the means of the metabolite ratios in the right and left hippocampus in schizophrenia and healthy subjects. No difference was found between the right and left hemispheres in healthy and schizophrenia subjects. No difference was noted between patients and controls.

Figure 4 shows a significant correlation between hippocampic NAA/Cr and age of onset of illness in schizophrenia patients (r = -0.59; p < 0.05). No relationship was noted between metabolite ratios and in particular NAA and age (r = -0.24), length of illness (r = 0.30), and dose of antipsychotics (r = 0.28).

Discussion

The major findings of this study were a significant correlation between NAA/Cr and age of onset of illness in the hippocampi of schizophrenia patients, a lower NAA/Cr in the right than in the left prefrontal cortex in both schizophrenia patients and healthy subjects, and a negative relationship between NAA/Cr and age in the thalami of healthy subjects. In contrast, we did not find any difference of NAA/Cr, ml/Cr, and CHO/Cr between schizophrenia patients and healthy subjects. There were no correlations between age of onset of illness and metabolite ratios in the prefrontal cortex and thalamus or between the length of illness and metabolite ratios in the prefrontal cortex, thalamus, and hippocampus.

Table 2. Means ± standard deviations of metabolite peak amplitude ratios in left and right thalamus in schizophrenia patients and healthy subjects

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Thalamus</th>
<th>Controls</th>
<th>Schizophrenia subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>1.36 ± 0.15</td>
<td>1.36 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>1.41 ± 0.14</td>
<td>1.36 ± 0.22</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>Left</td>
<td>0.89 ± 0.08</td>
<td>0.88 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.94 ± 0.10</td>
<td>0.88 ± 0.15</td>
</tr>
<tr>
<td>CHO/Cr</td>
<td>Left</td>
<td>0.57 ± 0.08</td>
<td>0.53 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.59 ± 0.06</td>
<td>0.55 ± 0.09</td>
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Figure 3. Negative correlation between age and NAA/Cr in the thalamus of controls \((r = -0.52; p = 0.05)\) and schizophrenia patients \((r = -0.37; p = 0.14)\).

Note.—Cr = creatine plus phosphocreatine; NAA = N-acetyl-aspartate.

Decreased NAA levels have been observed by \(^1\)H MRS in some cerebral pathologies involving cell damage and loss (Arnold et al. 1992). The absence of change of NAA/Cr in schizophrenia patients compared to healthy subjects confirms some previous results. Fukuzako et al. (1995) and Buckley et al. (1994) did not find a decrease of NAA/Cr in the frontal lobes in chronic schizophrenia patients. Williamson et al. (1998) did not find a decrease of NAA in the medial prefrontal cortex in chronic schizophrenia patients. Bertolino et al. (1996) did not observe any difference of metabolite ratios between chronic patients and controls in thalami, but ml/Cr was not tested. However, a decrease of either NAA/Cr or NAA was observed by other authors in the frontal areas (Bertolino et al. 1996, 1998; Deicken et al. 1997; Cecil et al. 1999) or temporal areas (Maier 1995; Bertolino et al. 1996, 1998; Fukuzako et al. 1996; Yurgelun-Todd et al. 1996; Cecil et al. 1999) of chronic schizophrenia patients. There was a trend toward a higher NAA/Cr in the temporal lobe in schizophrenia patients compared to controls. This trend could be due to the patients with early onset of illness (figure 4), suggesting an active process or neuronal dysfunction in this subtype of patients. Our result concerning the CHO/Cr is consistent with several earlier reports.

Table 3. Means ± standard deviations of metabolite peak amplitude ratios in left and right prefrontal cortex in schizophrenia patients and healthy subjects

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Prefrontal cortex</th>
<th>Controls</th>
<th>Schizophrenia subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>Left</td>
<td>1.40 ± 0.25</td>
<td>1.41 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>1.33 ± 0.17</td>
<td>1.25 ± 0.23</td>
</tr>
<tr>
<td>CHO/Cr</td>
<td>Left</td>
<td>0.90 ± 0.15</td>
<td>0.99 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.94 ± 0.08</td>
<td>0.92 ± 0.17</td>
</tr>
<tr>
<td>ml/Cr</td>
<td>Left</td>
<td>0.65 ± 0.14</td>
<td>0.65 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.66 ± 0.11</td>
<td>0.60 ± 0.16</td>
</tr>
</tbody>
</table>

1 Significant difference between right and left \((F = 4.27, df = 1, 24, p = 0.05)\).

Table 4. Means ± standard deviations of metabolite peak amplitude ratios in left and right hippocampus in schizophrenia patients and healthy subjects

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Hippocampus</th>
<th>Controls</th>
<th>Schizophrenia subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>Left</td>
<td>1.14 ± 0.16</td>
<td>1.26 ± 0.29</td>
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<tr>
<td></td>
<td>Right</td>
<td>1.16 ± 0.13</td>
<td>1.25 ± 0.16</td>
</tr>
<tr>
<td>CHO/Cr</td>
<td>Left</td>
<td>0.95 ± 0.09</td>
<td>0.90 ± 0.12</td>
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<tr>
<td></td>
<td>Right</td>
<td>0.94 ± 0.10</td>
<td>0.90 ± 0.13</td>
</tr>
<tr>
<td>ml/Cr</td>
<td>Left</td>
<td>0.79 ± 0.11</td>
<td>0.69 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.74 ± 0.08</td>
<td>0.69 ± 0.14</td>
</tr>
</tbody>
</table>
Figure 4. Negative correlation between age of onset of illness and hippocampic NAA/Cr of schizophrenia patients ($r = -0.59; p < 0.05$).

Note.—Cr = creatine plus phosphocreatine; NAA = N-acetyl-aspartate.

(Fukuzako et al. 1996; Williamson et al. 1998) but is different from those of Cecil et al. (1999), who reported an increase of the CHO/Cr ratio in the frontal lobe of chronic schizophrenia patients compared to healthy subjects. There was also no difference in temporal CHO/Cr in patients compared to controls. This is consistent with some previous studies (Yurgelun-Todd et al. 1996). CHO is known to increase in neurodegenerative process as demyelinating lesions (DeStephano et al. 1995).

In our study, prefrontal, thalamic, and hippocampic ml/Cr were similar in patients and control subjects. The discrepancies between our findings and those of other researchers could be due to the differences of size and localization of the volume of interest (VOI) or the clinical characteristics of the patients. Indeed, in our study, only the medial and not the dorsolateral prefrontal cortex was studied, and the VOI was wider than in other studies. Another explanation is the heterogeneity of schizophrenia. These points can be considered as limitations of the study and could contribute to these differences.

As ml has been identified as a glial cell marker (Urenjak et al. 1993), the absence of increase of ml is an argument against a glial reaction. Therefore, our results did not support the hypothesis of a neurodegenerative process in schizophrenia because no decrease of NAA/Cr and no increase of ml/Cr and CHO/Cr were found in the three areas (hippocampus, thalamus, and prefrontal cortex). However, a significant correlation between NAA/Cr and age of onset of illness in the hippocampi of schizophrenia patients was found ($r = -0.59; p < 0.05$) (figure 4). This result was close to Fukuzako et al. (1995), who observed this correlation in the temporal lobes of chronic schizophrenia patients. Thus, assuming that NAA is a neuronal or axonal number or viability marker, a decrease of NAA/Cr with age of onset might suggest a neurodegenerative process in hippocampi but only in a subtype of schizophrenia characterized, as some authors have already suggested (DeLisi 1992; Murray et al. 1992), by a late onset of illness. This result was not due to the age of the subjects, because no correlation between age and metabolite ratios and in particular NAA in the hippocampus was found in the patients ($r = -0.24$) or the healthy subjects ($r = -0.19$). These results, which could reflect a neuronal loss or dysfunction without gliosis, might suggest a neurodegenerative process by apoptosis (there was no correlation between ml and CHO/Cr and age of onset of illness) in a subtype of schizophrenia with late onset of illness. Contrarily to Ende et al. (2000), who found a decrease of NAA with the duration of illness in the anterior cingulate region of chronic schizophrenia patients, no correlation between length of illness and metabolite ratios was found in the three areas.

The ratio NAA/Cr was significantly lower in the right than in the left prefrontal cortex in healthy subjects and patients, suggesting an asymmetry in the prefrontal cortex in both schizophrenia and healthy subjects. Measurements on computed tomography scans and postmortem brains have long suggested that the right frontal region in normal brains extends further forward and is wider than the left (LeMay 1976; Weinberger et al. 1982; Kertesz et al. 1990). Golden et al. (1981) found that there was a trend for a greater density in the left hemisphere than in the right hemisphere in both schizophrenia patients and control subjects. In the same way, Gur et al. (1980) found with a xenon-133 inhalation method a greater density of cells in the left than in the right hemisphere in schizophrenia patients (there were no controls). Thus, this asymmetry of NAA/Cr ratios could suggest a lower neuronal density in the right than in the left prefrontal cortex compatible with a wider right than left prefrontal cortex. However, an asymmetry reversal or reduction was not observed in schizophrenia patients, contrary to the observations of Bilder et al. (1994) and DeLisi et al. (1997a). These discrepancies could be due to the fact that these studies were structural imaging and not metabolic studies.

There was no asymmetry in the temporal lobe. Structural MRI studies have reported lateralized changes in the temporal lobes, such as a reduction of the left temporal lobe (DeLisi et al. 1990; Rossi et al. 1990). Indeed, these studies were focused on the planum temporale, while the VOI in our study was centered on the hippocampus. The planum temporale is well known to be asymmetric in healthy subjects, and a large study of literature has reported a reduction or a reverse asymmetry of this structure in schizophrenia patients (Rossi et al. 1990).
In consequence, the absence of asymmetry in metabolite ratios in our study was probably due to a difference of localization of the VOI.

A negative relationship between NAA/Cr and age in healthy subjects and a correlation (although not significant) in schizophrenia patients (figure 3) were found in the thalamus. This suggests that NAA might be a marker of aging in particular in the thalamus and that the older subjects were, the lower ratios of NAA/Cr were. This result is also consistent with Charles et al. (1994), who found that NAA was lower in older subjects in the voxel representing cortical and subcortical gray matter.

There was no relationship between metabolite ratios and dose of antipsychotics, contrary to the results of Shioiri et al. (1996), who found a significant positive correlation between the chlorpromazine equivalent antipsychotic dosage and the level of NAA. However, their result was found in striata, areas particularly involved in extrapyramidal symptoms secondary to antipsychotics.

Several technical limitations of the present study have to be considered. First, the voxels contained various proportions of gray matter and white matter. Determining these proportions could be informative because some studies in schizophrenia have reported a decrease in NAA in white but not in gray matter (Lim et al. 1998). It was also not possible to estimate the extent to which the prefrontal, hippocampal, and thalamic voxels contained tissue that was not within these structures. Therefore, the asymmetry that we found in the prefrontal cortex has to be confirmed in future studies with segmentation. The second limitation is the large size of the VOI. Third, absolute metabolic quantification, although preferable, was not feasible in our protocol. We used metabolite ratios because of the best reliability obtaining with this method compared to the method of absolute concentration. The fourth limitation involves the power of statistical analyses: for a significant difference of about 0.1 or 0.3 in metabolite ratio, the noncentrality parameter is 0.5 or 1.5, that is to say an estimating calculated power of 40 percent or 80 percent, respectively; the small size of our sample of patients and the great value of standard deviations may have dismissed true differences between patients and controls because of type II error in the statistical analyses. The fifth limitation is the possibility of effects of antipsychotic agents on NAA, although there was no difference between drug-naive and treated patients.

In conclusion, the present study might provide support for a neurodegenerative process, but only in some schizophrenia patients with a late onset of illness. However, this hypothesis needs to be confirmed in future studies with segmentation and a larger number of subjects.

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