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N-acetyl-aspartate levels in the dorsolateral prefrontal cortex in the early years of schizophrenia are inversely related to disease duration

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Abstract

Magnetic resonance spectroscopy studies in schizophrenia have revealed consistently reduced *N*-acetyl aspartate (NAA) levels in chronic patients, but not in recent-onset patients. Studies on the relationship between this marker and disease duration have commonly been negative, although it is also true that they have been conducted in patients with long-standing disease. We compared NAA levels in the dorsolateral prefrontal cortex in 16 recent-onset patients (duration: 1.8 ± 0.6 years), 19 chronic patients (duration: 9.7 ± 6.1 years), and 20 healthy controls. We studied the NAA/creatine and choline/creatine ratios in the dorsolateral prefrontal cortex in both hemispheres, controlling for the effect of age. Chronic patients had significantly lower NAA/Cr ratios in the left hemisphere compared to recent-onset patients and healthy controls, with no difference in Cho/Cr ratio. There were no differences between controls and recent-onset patients. There was a significant inverse relationship between left-side NAA/Cr and disease duration, suggesting that prefrontal NAA levels may progressively decrease in schizophrenia. Taken within the context of the existing literature, these results indicate that this process may be limited to the early years following the onset of the disease. Therefore, reduced prefrontal levels of NAA may be limited to chronic schizophrenia patients.
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Keywords: *N*-acetyl aspartate; Schizophrenia; Prefrontal lobe; MRS; Neurodegeneration; Disease duration

1. Introduction

N-acetyl aspartate levels are ostensibly associated with the amount of viable neuronal tissue (Urenjak et al., 1993) and can therefore be considered a marker of neuronal density per volume of brain tissue. Compar-

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Table 1
Review of MRS studies on NAA levels in anterior brain regions, including the prefrontal cortex in chronic and first-episode patients

	N (males)	Age	Treatment-naïve (Yes/No)	Duration	Region	Method	Association with duration	Main findings
(1) Chronic patients								
Buckley et al. (1994)	27 (15)	30.8 (7.0)	N	7.8 (6.5)	Left frontal and temporal	Single voxel, Metabolite levels	No	↓ frontal NAA in male but not female patients
Deicken et al. (1997a, b)	24 (21)	35.7 (12.2)	N	16.5 (11.9)	Frontal	MRSI, ratios WM and GM	No	↓ frontal NAA/Cr, unrelated to medication dosage
Lim et al. (1998)	10 (10)	43.6 (5.9)	N	18.7	Frontal (GM and WM)	Voxels, ratios	Not reported	↓ volume of PF GM ↓ NAA signal in WM
Bertolino et al. (1998a)	12 (9)	35.0 (5.4)	Y(5)/N (7 untreated)	12.9 (5.2)	Multiple	MRSI, ratios	No	↓ NAA/Cr and ↓ NAA/Cho bilaterally in hippocampus and DLPF
Bertolino et al. (1998b)	14 (11)	16.4 (1.7)	N	Not reported	Multiple	MRSI, ratios	No	↓ NAA signal in hippocampus and DLPF
Callicott et al. (2000)	36 (30)	Not reported	N	Not reported	Multiple	MRSI	Not reported	Bilateral ↓ NAA/Cr, significantly associated with negative symptoms
Block et al. (2000)	25 (18)	35.6 (8.3)	N	11.5 (9.1)	Frontal, BG	Voxels, ratios	No	↓ left frontal NAA/Cho versus unaffected relatives
Delamillieure et al. (2000)	22	Not reported	N	Not reported	Medial frontal, ant. cingulate	Single voxel, ratios	No	↓ NAA/Cr only in deficit patients; no differences treated vs. untreated
Ende et al. (2000)	19 (9)	34.6 (9.1)	N	9.7 (5.7)	Anterior cingulate	MRSI, Metabolite levels	Yes, $r=-0.59$	↓ NAA signal in patients in anterior cingulate
Bustillo et al. (2001)	25 (13)	41	N	22–16	Caudate, left frontal	Voxels, CSF, corrected metabolite levels	Not reported	↓ left frontal NAA in haloperidol-treated; correlated with motor dexterity
Bertolino et al. (2001)	23 (18)	36.9 (8.1)	N	Not reported	Multiple	MRSI	No	↑ NAA signal with antipsychotics in DLPF cortex
Delamillieure et al. (2002)	17 (14)	31.2 (6.1)	N	8.4 (5.4)	Medial PF, thalamus, hippocampus	Voxel, ratios	No	No NAA differences between patients (mostly residual) and controls
Yamasue et al. (2002)	15 (10)	30.4 (7.0)	N	7.8 (4.9)	Anterior cingulate	Single voxel	No	↓ NAA/Cho (correlated with negative symptoms and gray matter volume) and ↑ Cho/Cr

Table 1 (*continued*)

	N (males)	Age	Treatment-naïve (Yes/No)	Duration	Region	Method	Association with duration	Main findings
(1) Chronic patients								
Ende et al. (2003)	13	33.7 (7.0)	N	10.9 (7.3)	Thalamus, BG, hippocampus	MRSI	No	↓ NAA signal in hippocampus and thalamus, but not putamen
(2) First-episode patients								
Stanley et al. (1996)	29 (25)	26 (7)	Y(11), N(18)	2–18	DLPF	Single voxel	Not reported	Differences in glutamine (recent-onset vs. chronic); No differences NAA (patients vs. controls)
Cecil et al. (1999)	18 (12)	27	Y	3.6–5.0	PF, medial temporal	Single voxel	Not reported	↓ NAA/Cr in PF; ↑ Cho/Cr in PF and ↓ Cho/Cr in medial temporal
Fannon et al. (2003)	33 (18)	25	Y(12)/ N(13)	0.7	DLPF, hippocampus, BG	Voxels	No	↓ hippocampal NAA/Cr ratio in naïve but not in treated patients; no ↓ NAA/Cr ratio in DLPF cortex
Bertolino et al. (2003)	24 (17)	23.7 (6.1)	N	0.4 (0.3)	DLPF, hippocampus	MRSI	No	↓ NAA/Cr but not ↓ NAA/Cho; related to working-memory performance (+) and to negative symptoms (−)

PF: prefrontal; GM: gray matter; WM: white matter; DLPF: dorsolateral prefrontal; MRSI: magnetic resonance spectroscopy imaging; CSF: cerebrospinal fluid; BG: basal ganglia. Age and duration are shown in years as mean (S.D.).

ative studies in controls and schizophrenics reveal that there are decreased levels of *N*-acetyl-aspartate (NAA) in chronic patients in the hippocampus (Deicken et al., 1998; Ende et al., 2003; Maier et al., 1995; Nasrallah et al., 1994) and the thalamus (Deicken et al., 2000; Ende et al., 2001; Omori et al., 2000), as well as in the medial temporal lobe (Deicken et al., 2000; Fukuzako et al., 1999) and prefrontal cortex (Bertolino et al., 1996, 1998b; Block et al., 2000). Other studies have reported a decrease in NAA signal intensity, limited to the prefrontal white matter in chronic patients (Lim et al., 1998). However, the results in recent-onset patients are more contradictory (Keshavan et al., 2000). In this type of patients, low NAA levels have not been detected in the dorsolateral and temporal–limbic regions (Bartha et al., 1999; Stanley et al., 1996), although such low levels have been detected in the prefrontal cortex in neuroleptic-naïve (Cecil et al., 1999) and schizophreniform psychosis patients by magnetic resonance spectroscopy imaging (MRSI) (Bertolino et al., 2003). However, in the latter study (Bertolino et al., 2003), all but two patients ($n=24$) had NAA/Cr ratios within the range of the normal controls. Another recent report described low NAA levels in the hippocampus but not in the prefrontal (PF) cortex in first-episode schizophrenic patients (Fannon et al., 2003).

A pattern of lower NAA levels limited to chronic patients (at least in the cortex) would be consistent with a degenerative process in schizophrenia after the onset of symptoms. Recent publications report evidence supporting the neurodegenerative hypothesis of

schizophrenia (Lieberman, 1999; Woods, 1998), as well as problems interpreting the neuroimaging data (DeLisi, 1999). The excessive loss of prefrontal gray matter seen in this disease, as observed in longitudinal studies (Gur et al., 1998; Rapoport et al., 1999), supports such a degenerative process. No similar longitudinal studies on NAA levels have been published to date. Nevertheless, if schizophrenia (at least in some clinical forms) includes a degenerative process, a negative relationship between these levels and disease duration would be expected.

However, a relationship between disease duration and NAA levels is not seen consistently. Different groups have found that the duration of schizophrenia and NAA levels were unrelated in the frontal (Bertolino et al., 1996; Buckley et al., 1994; Deicken et al., 1997a; Delamillieure et al., 2002), hippocampal (Bertolino et al., 1998a), and cingulate regions (Deicken et al., 1997b) (Table 1). Only one group found an inverse association between disease duration and NAA levels in the anterior cingulate cortex (Ende et al., 2000).

One factor that may contribute to the absence of such an association is that almost all of the studies evaluated patient samples with a long mean disease duration (Bertolino et al., 1998a; Buckley et al., 1994; Deicken et al., 1997b) (Table 1). If the highest rate of NAA decrease (related to the degenerative process) does occur at onset, it is possible that a relationship between this marker and disease duration might not be observed in patient samples with longer-standing disease. In this regard, there are data indicating that the highest prefrontal grey matter volume loss (perhaps associated with NAA values) occurs around illness onset (Gur et al., 1998; Pantelis et al., 2003). Furthermore, clinical and cognitive impairment appears to be more marked during the early years of the disease (Hoff et al., 1999), which would be compatible with a more marked degenerative process during those initial years. Gur et al. (1998) reported that the decrease in frontal volume was more pronounced in first-episode patients (mean duration: 2.8 years) than in previously treated patients (mean duration: 8.5 years). The results reported by Rapoport et al. (1999) in adolescent patients point in the same direction.

Thus, it seemed interesting to study the relationship between NAA and disease duration in the early years following the onset of symptoms, after enough time has elapsed for this potential effect to be observed. To accomplish this, we studied two cohorts, one of recent-onset schizophrenic patients and another of chronic patients. To our knowledge, there are no published studies comparing chronic and recent-onset patients. Both groups in our study had a shorter disease duration than those in most previous studies. Our hypothesis was that chronic patients would have lower NAA levels than recent-onset patients and that there would be an inverse relationship with disease duration throughout the early period (first decade) of the disease.

2. Patients and methods

2.1. Subjects

Thirty-five right-handed patients were enrolled in this study. All were diagnosed with schizophrenia (33 paranoid, 2 undifferentiated; DSM-IV criteria). In order to homogenize the clinical patient profile, residual schizophrenia was an exclusion criterion. Diagnosis was confirmed using a semi-structured clinical interview (SCID, patient version) and information provided by relatives and clinical staff. Mean disease duration was 6.06 years (S.D. $\pm$ 6.12). Two subgroups of patients were enrolled in the study. The first subgroup consisted of 16 recent-onset (RO) cases (10 males) with a disease duration shorter than 2 years. In patients with a disease duration of less than 6 months at enrollment, the diagnosis was confirmed after 6 months of follow-up. The second subgroup consisted of 19 chronic (CR) cases (13 males) (Table 2). Subjects were enrolled on admission to a short-term care unit during a psychotic crisis (6) or during outpatient follow-up (29).

We used the PANSS to evaluate clinical symptoms (Table 2). Chronic patients presented more negative symptoms (differences in positive and general symptom scores were not statistically significant), had a longer disease duration ($p < 0.001$), and were consistently older ($p < 0.001$) than the group of recent-onset patients. We evaluated parental socioeconomic level using the Hollingshead Index (Hollingshead and Frederick, 1953).

All patients had been on a stable medication regimen for at least 3 months prior to enrollment.

Table 2
Sociodemographic and clinical characteristics (PANSS subscales) of patients and controls

	Recent-onset ($N=16$)	Chronic ($N=19$)	Controls ($N=20$)
Age	23.2 (2.7)	33.7 (6.9)**	28.4 (7.8)
Duration (years)	1.6 (0.9)	9.8 (9.0)**	
Age at onset (years)	21.6 (5.1)	23.1 (5.5)	
Education (years)	12.1 (3.3)	12.9 (0.9)	13.1 (1.1)
Parental socioeconomic level	2.0 (1.1)	2.1 (0.9)	2.0 (0.9)
Height (cm)	167.5 (8.5)	170.6 (8.8)	171.8 (7.1)
Positive symptoms	15.8 (5.9)	19.6 (8.9)	
Negative symptoms	18.0 (9.1)	25.1 (9.3)*	
General symptoms	39.1 (10.9)	42.3 (11.1)	

Data expressed as mean (S.D.). Significant differences between patients groups are indicated with asterisks (*$p<0.05$; **$p<0.01$; Student's *t*-test).

RO subjects received risperidone (dosage: 5.8 ± 2.1 mg/day). Two subjects in this group received benzotropine (2 mg/day) and two received propranolol (20 mg/day). In the CR group, 8 patients were treated with clozapine (391 ± 227 mg/day) and 11 with olanzapine (14.1 ± 9.1 mg/day). Six patients (three from each group) also received benzodiazepines (four for insomnia and two as an anxiolytic agent).

After providing written information, we obtained the written informed consent of the patients and their relatives. The ethics committees of the participating centers endorsed the study.

The study also included a group of 20 healthy controls (11 males), with an educational level below college and no significant differences from patients with respect to parental education or socioeconomic level (Table 2). There were no significant differences in the ages of male (29.2 ± 9.6) and female (27.7 ± 4.7) controls. Exclusion criteria for patients and controls were: residual schizophrenia, neurological disease, MRI findings deemed clinically relevant from a neurological perspective by a radiologist blind to diagnosis, history of cranial trauma with loss of consciousness, substance abuse during the past 3 years (other than caffeine or nicotine), history of axis I psychiatric disorders or treatment (other than schizophrenia in patients), or current treatment with a known CNS depressant or stimulant (in controls).

2.2. Imaging methods

2.2.1. Spectral acquisition

Proton spectra were acquired using a Philips 1.5 T Gyroscan ACS scanner, with a localized single voxel point resolved spectroscopy (PRESS) sequence (Bottomley, 1987) (TE = 136 ms; TR = 1500 ms; 128 repetitions, voxel volume = 7.5 ± 2.5 cc). Sample volumes were placed in the right and left dorsolateral prefrontal cortex (Fig. 1). The water signal was suppressed using chemical shift selective suppression (CHESS).

2.2.2. Signal processing

Pre-processing included the following steps: noise filtering (-2 Hz exponential multiplication); elimination of the first three signal points to prevent artifacts in the spectrum baseline; and removal of the residual water signal by HSVD (Boogaart et al., 1994). Signal processing was performed by time domain analysis, quantifying the resonances of interest with an iterative non-linear method (AMARES) (Vanhamme et al., 1997).

N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho) metabolite resonance intensities were quantified. NAA and Cho values are expressed in relative units, as ratios to Cr. Left-side data were obtained in 28 out of 35 patients (13 RO; 21 males; age: 30.5 ± 8.8) and 16 controls (8 males; age: 28.6 ± 7.8) and right-side data in 31 patients (13 RO; 19 males; age: 30.3 ± 8.2) and 15 controls (9 males; age: 28.3 ± 7.7). The spectra of the remaining subjects could not be analyzed due to susceptibility or motion artifacts.

2.3. Statistics

The significance of differences in NAA/Cr and Cho/Cr among the groups was assessed by covariance analysis (ANCOVA), using group as the factor and age as the covariate. Age was included as a covariate, since it was different in patients and controls, and also to eliminate any potential changes in NAA/Cr and Cho/Cr associated with age variation. No significant interaction between age and group was observed for any of the variables, validating our design of ANCOVA. In addition to the overall group effect, post-hoc tests were made with the adjusted means to find differences between group pairs. All the comparisons were per-

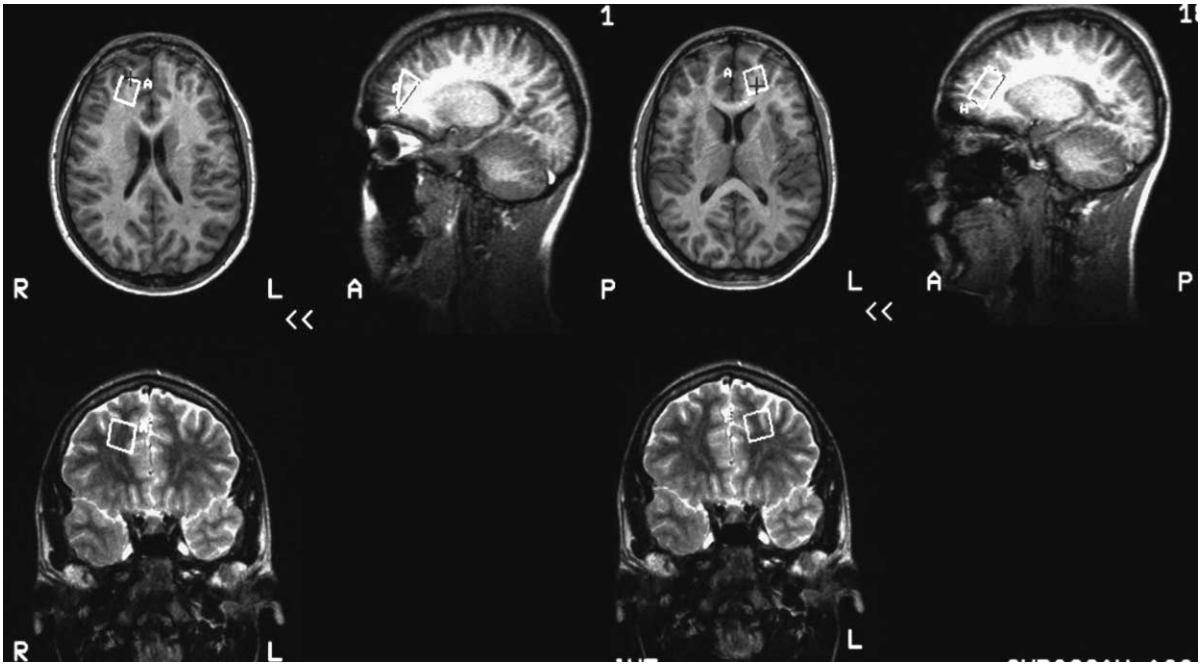

Fig. 1. Localization of MRS volume in right and left sides.

formed separately for both the left and right sides. The relationship between NAA/Cr and disease duration was assessed by regression analysis and also by partial correlation to eliminate the effect of age.

3. Results

There were no significant gender-related differences in NAA/Cr ratios in controls, either on the right

Table 3
Bilateral NAA/Cr and Cho/Cr ratios in patients and controls

	Left hemisphere		Right hemisphere	
	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
Recent-onset	2.12 (0.43)**	1.21 (0.63)	1.99 (0.50)	1.01 (0.30)
	$N=13$	$N=13$	$N=13$	$N=13$
Chronic	1.59 (0.29)	1.17 (0.46)	1.91 (0.50)	1.19 (0.49)
	$N=15$	$N=15$	$N=17$	$N=17$
Controls	1.91 (0.34)*	1.08 (0.30)	2.11 (0.53)	1.22 (0.38)
	$N=16$	$N=16$	$N=15$	$N=15$

Asterisks indicate statistically significant differences when compared with chronic patients in the ANCOVA post-hot tests (see Section 2).

*$p<0.05$.

**$p<0.01$.

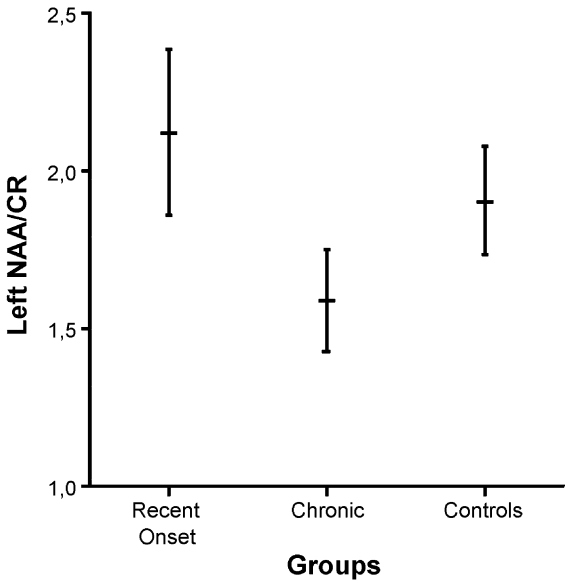

Fig. 2. Bar graph showing differences in the left NAA/Cr ratio among the three groups. Bars indicate 95% confidence intervals around the mean.

(males, 2.3 ± 0.6; females, 1.9 ± 0.5) or left side (males, 1.9 ± 0.5; females, 1.9 ± 0.3). Table 3 shows the pooled NAA/Cr and Cho/Cr ratios in males and females in the three groups.

In the left side of the brain, the ANCOVA showed an overall significant group effect ($F = 3.76$, $p < 0.03$), whereas post-hoc test indicated a significantly lower NAA/Cr ratio in chronic patients compared to controls (difference between adjusted means: -0.30, $p < 0.05$) and also compared to recent-onset patients (difference between adjusted means: -0.49, $p < 0.01$) (Fig. 2). There were no differences in left-side NAA/Cr ratios between the RO and control groups. No significant right-side differences were observed. There were also no significant differences among the groups in the Cho/Cr ratio in either side.

We compared the left-side NAA/Cr ratio in chronic patients treated with clozapine to those treated with olanzapine using Student's *t*-test. This was done to rule out the possibility that the decrease in this ratio seen in chronic cases could be attributed to the subgroup of patients resistant to classical neuroleptics. The mean NAA/Cr ratios in patients treated with clozapine (1.48 ± 0.23) were not significantly different from those treated with olanzapine (non-treatment-resistant according to the usual criteria) (1.66 ± 0.28).

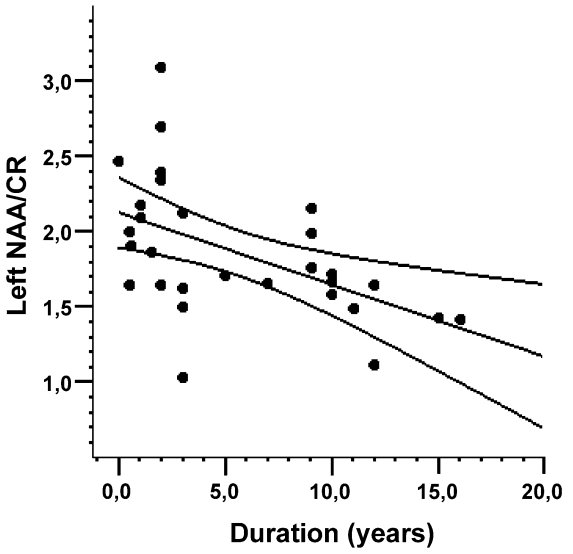

Fig. 3. Relationship between disease duration (in years) and left NAA/Cr ratio. The 95% confidence interval is shown.

The left-side NAA/Cr ratio showed a significant inverse correlation with disease duration in the entire group of RO and CR patients ($r = -0.48$; $p < 0.01$; Fig. 3). We found no significant correlation in the right side. When controlling for the effect of age, the partial correlation coefficient between NAA and disease duration was still significant on the left side ($r = -0.38$; $p < 0.05$). There was no significant correlation between disease duration and Cho/Cr ratios in either hemisphere.

4. Discussion

The most remarkable finding in this study was the correlation between disease duration and the left dorsolateral prefrontal (DLPF) NAA/Cr ratio in schizophrenic patients, together with a significant decrease in the NAA/Cr ratio in the CR subgroup versus controls.

Most studies have failed to find a relationship between NAA levels and disease duration (Table 1). A possible explanation for the discrepancy with our results resides in the difference in disease duration in the respective samples. The mean disease duration in our sample was lower than those reported in other similar studies. Our results, taken together with those of previous studies, suggest that the decrease in NAA may occur primarily in the early years of the disease (< 10 years, approx.). However, there is one report of no NAA decrease in adolescent patients (Bertolino et al., 1998b). Despite the fact that the Bertolino's study did not report disease duration, the mean patient age was only 16.4 years (S.D. ± 1.7), suggesting a too narrow disease duration range to uncover any possible association. On the other hand, a decrease in NAA ratios during the early years of the disease would be in keeping with the inverse association reported between negative symptoms and NAA ratios (Callicott et al., 2000; Yamasue et al., 2002), as negative symptoms seem to increase during that period (McGlashan, 1988).

Our results, i.e., significant differences in the NAA/Cr ratio only when comparing controls with chronic patients, are consistent with those reported by Stanley et al. (1996). On the other hand, Cecil et al. (1999) observed lower NAA concentrations in the DLPF cortex in neuroleptic-naïve patients, although

the patients in that study ($n = 8$) had a mean disease duration of 5 years, despite the lack of treatment, thereby qualifying their disease course as sub-chronic.

It could be argued that the decrease in the NAA/Cr ratio in patients with a longer disease duration could be solely an effect of age. Such an age effect was reported by Grachev et al. (2001) in a study comparing NAA levels in subjects ages 19 to 31 years versus subjects ages 40 to 52 years. The latter had slightly different NAA levels. A decrease in NAA levels has also been related to senile atrophy (Lundbom et al., 1999), likewise a process related to aging. Angelie et al. (2001) studied the changes in NAA levels in controls ages 20 to 70, finding a variation rate of 4.6% per decade. Along the same lines, Brooks et al. (2001) found a decrease of only 12% between ages 20 and 70 years. Finally, other authors report no age-dependent reduction in NAA, particularly in the frontal (Harada et al., 2001) and parietal (Saunders et al., 1999) lobes. Whatever the possible confounding effect of aging, our results were obtained after statistically controlling for the effect of age.

It still remains to be confirmed whether or not the reduction in NAA is similar in males and females. Most studies thus far have been of predominantly male samples. The study of Buckley et al. (1994) suggests that this decrease may be restricted to male patients. On the other hand, the results of the study of Ende et al. (2000) point in the opposite direction, as it found reduced NAA levels and an inverse relationship with disease duration in a predominantly female group of patients (10 out of 19). A conclusive assessment of this issue would require the use of more gender-balanced samples. Our group of controls included a higher proportion of females. However, it is unlikely that this imbalance altered our comparison of NAA levels versus patients, since no differences were found between controls and the group of RO patients, which had the same gender ratio as the CR group. Furthermore, an absence of gender differences in healthy controls has been reported in cortical areas (Angelie et al., 2001) and the DLPF cortex (Grachev et al., 2001), which coincides with our own data.

The lower NAA/Cr ratio in our CR group versus the RO group might simply reflect clinical differences. Although this possibility can only be ruled out through a longitudinal follow-up of recent-onset patients, there are various arguments against it. Firstly, a relationship with disease duration would not be expected. Secondly, the data in the literature consistently show that chronic patients have reduced NAA levels, regardless of clinical profile (Keshavan et al., 2000). Thirdly, there were no substantial differences in the symptom profiles in our groups. They were all living in the community and, although the chronic ones presented a higher negative symptom score, this was reasonably expected based on disease course.

We cannot rule out the possibility that the decrease in the NAA/Cr ratio in our chronic patients may be due to the persistence of active psychotic symptoms, a situation that might be different in less severe forms of schizophrenia. This possibility is suggested by the results of Delamillieure et al. (2002), who did not find a decreased NAA/Cr ratio in chronic patients in a study in which the majority of patients belonged to the residual subtype. However, since most studies in chronic schizophrenia patients consistently find a decrease in cortical NAA, and these levels correlated with disease duration in our group, we may speculate that NAA levels would be likely to decrease in future in most of our RO patients.

Other evidence also supports a decrease of NAA levels with disease duration. In a sample that partially overlaps the cases in this study, we have found a relationship between excess prefrontal cortical CSF volume and disease duration, corrected for the effect of age (Molina et al., 2002). Excess cortical CSF volume is considered a transversal marker of neurodegeneration (Woods, 1998). Disease duration and gender distribution were similar in both studies, thereby supporting the hypothesis that neurodegenerative phenomena may occur during this period of time in schizophrenia. Other indirect evidence in favor of this possibility is the increase in the amount of membrane breakdown products (PDE, phosphodiesterases) in the initial stages, but not in chronic schizophrenics (Stanley et al., 1995), and the higher mononuclear phagocyte/macrophage ratio in CSF in psychotic relapses that resolve with treatment (Nikkilä et al., 1999). These findings are suggestive of some form of neuronal tissue destruction during psychotic episodes, more frequent in the early years of the disease.

In chronic patients, there is also the possible confounding factor that treatment may somehow alter NAA levels. However, this seems unlikely, since

previous studies have shown that neither typical nor atypical antipsychotics reduce NAA levels. On the contrary, atypical antipsychotics may even increase them (Bertolino et al., 2001). A recent report points in the same direction, since only treatment-naïve patients had reduced NAA/Cr ratios versus controls (Fannon et al., 2003). Experimental studies have also failed to detect changes in NAA/Cr ratio in rats when different antipsychotics were administered (Lindquist et al., 2000). Thus, it is unlikely that the lower NAA/Cr ratio observed in chronic patients is attributable to a treatment effect.

In our sample, no significant differences in Cho/Cr ratio were detected. This result is in contradiction with previous reports of slightly increased levels of choline in male patients with relatively short disease duration (Buckley et al., 1994) as well as in untreated patients (Cecil et al., 1999). Therefore, further studies are warranted. The main limitation of our study was its cross-sectional sample. Some of the explanations suggested for our findings can be only confirmed using a pure longitudinal design, following patients from onset. Another limitation derives from the use of single voxel spectroscopy, which prevented us from assessing a larger number of brain areas. However, one of the advantages of this study was the composition of our patient sample, spanning a broad range of disease durations, from onset to 16 years of evolution, with most patients having a relatively short disease duration and a confirmed diagnosis even in those subjects with the shortest durations.

In conclusion, the data from this study support the hypothesis of a progressive decrease in the left dorsolateral NAA/Cr ratio in schizophrenia, which, in the context of previous findings, suggests that this process may occur during the years following onset of the disease. Reduced prefrontal NAA levels may therefore be a finding more limited to chronic patients.

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