REVIEW

PROTON MAGNETIC RESONANCE SPECTROSCOPY OF THE FRONTAL LOBE IN SCHIZOPHRENICS: A CRITICAL REVIEW OF THE METHODOLOGY

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Schizophrenic patients undergoing proton magnetic resonance spectroscopy show alterations in N-acetyl aspartate levels in several brain regions, indicating neuronal dysfunction. The present review focuses on the main proton magnetic resonance spectroscopy studies in the frontal lobe of schizophrenics. A MEDLINE search, from 1991 to March 2004, was carried out using the key-words spectroscopy and schizophrenia and proton and frontal. In addition, articles cited in the reference list of the studies obtained through MEDLINE were included. As a result, 27 articles were selected. The results were inconsistent, 19 papers reporting changes in the N-acetyl aspartate levels, while 8 reported no change. Methodological analysis led to the conclusion that the discrepancy may be due the following factors: (i) number of participants; (ii) variation in the clinical and demographic characteristics of the groups; (iii) little standardization of the acquisition parameters of spectroscopy. Overall, studies that fulfill strict methodological criteria show N-acetyl aspartate decrease in the frontal lobe of male schizophrenics.

KEY WORDS: **Spectroscopy. Proton. Frontal. Schizophrenia. Review.**

Neuroimaging techniques were introduced in schizophrenia research by the pioneering work of Jakobi and Winkler[1], showing an enlargement of the lateral ventricles in chronic schizophrenics. During the last eighty years there was strong advance in this field, from the improvement of existing techniques to the introduction of new research capabilities. Among the latter stands magnetic resonance spectroscopy (MRS).

MRS is a non-invasive, non-radioactive procedure that allows quantification of several metabolites in specific regions of the human brain[2-5]. Bloch and Purcell originally described its basic principles in 1946, but it was only in 1980 that Ackerman and coworkers developed the *in vivo* technique[6-7]. Since 1991 MRS has been used to identify chemical changes in the brain of schizophrenic patients[8].

Phosphorus and hydrogen are the most used atoms in MRS. While phosphorus spectroscopy (P^{31} MRS) makes possible the research of cell energy metabolism and neurodevelopment, hydrogen spectroscopy (better known as proton spectroscopy, H^1 MRS), provides information about neurotransmitter levels and neuronal integrity, in addition to measures of energy metabolism[9-11].

Among the substances identifiable by H^1 MRS, N-acetyl aspartate (NAA) - an amino-acid found in neurons - has been the most investigated compound, because its concentrations were found altered in various neuro-psychiatric pathologies[12-14]. A decrease in NAA levels has been associated to neuronal death, energetic deficit in the cell body, and axonal injury or lesion[15-16].

Studies in schizophrenic patients using spectroscopy have demonstrated alterations in NAA levels in some brain regions, such as the mesial temporal lobe and, to a lesser extent, in the frontal lobe[17-20]. Such findings are con-

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sistent with theoretical assumptions about an abnormal development of neuronal pathways in these brain regions.

Stanley et al.[21] have suggested that many inconsistencies found in reported results with MRS are due to fast and complex methodological changes. Thus, critical methodological analysis may lead to a better understanding of these results.

OBJECTIVE

This review aims at discussing methodological aspects of reported findings on frontal lobe H^1 MRS of schizophrenic patients.

METHOD

Empirical articles in English were searched through MEDLINE, between 1991 and March 2004 and only human studies were included. The key words were *spectroscopy* and *schizophrenia* and *proton* and *frontal*. In addition, articles cited in the reference list of the studies obtained through MEDLINE were included. As a result, 27 articles were reviewed.

The studies were divided into two groups for the analysis of clinical, demographic and procedural variables: the group of studies showing some kind of NAA alteration was named G+ and the group not evidencing any alteration of NAA levels, even if showing alteration of other metabolites was called G-. The group means of variables such as age, sex, use of antipsychotics, and echo time were compared.

RESULTS

The data analyzed are summarized on Table 1 (G+) and Table 2 (G-). Twenty-six studies included healthy volunteers as controls, while the remaining study used intra-subject comparisons. The results of the latter study showed an increase of the NAA/Cr ratio during anti-psychotic medication, as compared to a period without medication[22]. Among the 26 studies that have included healthy volunteers as controls, eight did not evidence a significant difference between the groups, concerning NAA, 13 found NAA decrease in patients, as compared to healthy controls; the remaining five evidenced NAA changes in subgroups of patients, only.

The alterations most often found in the overall comparison of patients with healthy volunteers were a decrease of the NAA/Cr ratio[17-18, 23-29] and of the NAA absolute value[19, 30,31]. Regarding subgroup comparisons, Heimberg et al.[32], Bustillo et al.[33] and Ende et al.[34]found NAA differences between schizophrenics treated with atypical anti-psychotics as compared to schizophrenics under typical neuroleptics, and between each subgroup and its control. Buckley et al.[4] evidenced NAA decrease in male schizophrenics as compared to normal controls and to female schizophrenics. Dellamillieure et al.[24] demonstrated NAA decrease in schizophrenics with deficit syndrome, as compared to patients without such deficit and to controls.

Clinical and Demographic Characteristics

Age

It is important to control age because there are suggestions showing that NAA decreases with aging[35-36]. Therefore, NAA alterations could be due to age differences in non-paired groups. In the studies presently reviewed there were no significant differences concerning age between patients and controls, indicating methodological rigor in most of them.

Thomas el al.[28], Brooks et al.[27] and Bertolino et al.[18] did not find any correlation between age and NAA levels. Such findings disagree with the results reported by Omori et al.[37], Ende et al.[34] and Block et al.[38] who observed negative correlation between age and NAA in schizophrenic patients.

Ende et al.[34], suggest that the negative correlation between NAA concentration and age may be due to increased partial volume of cerebrospinal fluid (CSF) in the voxel and or to decreased neuronal density. According to the same author, a possible explanation for such correlation is the progressive character of schizophrenia, leading to cortical atrophy and resulting NAA decrease.

When the studies showing NAA alteration (G+) were compared with those not evidencing such alteration (G-), no significant difference in age was found (29.87 and 33.54 years of age, respectively).

Sex

One of the evidences supporting a possible effect of gender on schizophrenia is given by the study by Buckley et al.[4]. In their results, male schizophrenic patients presented significant NAA decrease, as compared to male controls and to female patients. Such results are consistent with neuroimaging findings, in which alterations in brain morphology are more frequent in male than in female schizophrenics. It has been suggested that these findings are due to a greater vulnerability among men to neurodevelopmental types of schizophrenia[39-40].

Fukuzako et al.[41] state that a factor that may have contributed to the lack of NAA decrease in schizophrenics shown by their results is the predominance of females in their sample (11 women and 4 men).

As a conclusion we can say that though gender cannot be considered a

Table 1 - Studies of proton spectroscopy in the frontal lobe of schizophrenic patients showing NAA decrease.

Study	Subjects	N (M/F)	Age ±SD	Neuro-leptics	Site	Predomi-nace WM/GM	VOXEL (ml)	SV / MRSI	TE (Ms)
Bertolino et al. (2001)	Without MED SCHZ	23(ND)	36.9 + 8.1	No	DLPFR,	GM and WM	1.4	MRSI	272
	With MED SCHZ	23(18/5)	36.9 + 8.1	Yes (13 ATYP)	anterior and posterior cingulate				
Bertolino et al. (1998)	SCHZ	14 (11/3)	16.4 ± 1.7	Yes	DLPFR,	GM and WM	1.4	MRSI	272
	CONT	14 (11/3)	16.1 ± 2.1		anterior and posterior cingulate.				
Bertolino et al. (1996)	SCHZ	10 (8/2)	37.4 ± 8.6	Yes (6 ATYP)	DLPFR,	GM and WM	1.4	MRSI	272
	CONT	10 (ND)	33.1 ± 5.4		anterior and posterior cingulate				
Block et al. (2000)	*SCHZ+EQZA	25(18/7)	35.6 ± 8.3	Yes	DLPFR	GM and WM	30	SV	272
	MIX DIAG	13 (6/7)	45.4 ± 15						
	CONT FAMILIAL	35(19/16)	49.2 ± 15.4						
	CONT	19 (7/12)	40.2 ± 5.3						
Brooks et al. (1998)	SCHZ+SCHZT	16(9/7)	11 ± 1.68	10 with ANTP	Frontal pole	WM	8	SV	136
	CONT	12(6/6)	10.8 ± .72						
Buckley et al. (1994)	SCHZ+SCHF	20(ND)	ND	Yes	Frontal pole	GM and WM	11	SV	68
	CONT	15(ND)	ND						
Bustillo et al. (2001)	SCHZ+EQZA clozapine	15 (ND)	ND	Yes	DLPFR	WM	12.6	SV	30
	*SCHZ+EQZA haloperidol	16 (ND)	ND	Yes					
	CONT	18 (ND)	ND						
Bustillo et al. (2002)	SCHZ	10 (8/2)	27.2 ± 8.1	Yes	Frontal pole	WM	12.6	SV	40
	CONT	10 (8/2)	26.8 ± 5.9						
Callicott et al. (2000)	SCHZ	36(30/6)	34 ± 8	(15ATYP,	DLPFR,	GM and WM	1.4	MRSI	272
	CONT	73(45/28)	32.2 ± 8.1	6 without MED)	anterior and posterior cingulate.				
Cecil et al. (1999)	SCHZ+SCHF	8 (6/2)	26.4 ± 6.6	No	DLPFR	WM	8	SV	21
	CONT	14 (9/5)	27.7 ± 6.8						
Choe et al. (1996)	*SCHZ without	55(25/30)	17 – 57	No	Frontal pole	ND	8	SV	20
	SCHZ with med	34(17/17)							
	CONT	20(10/10)	24-35	Yes					
Choe et al. (1994)	SCHZ	23(10/13)	17-45	No	Frontal pole	WM	8	SV	30
	CONT	10(5/5)	24-35						
Deicken et al. (1997-a)	SCHZ	24(21/3)	35.7 ± 12	Yes	ND	ND	1.3	MRSI	135
	CONT	15(11/4)	36.6 ± 6.8						
Deicken et al. (1997-b)	SCHZ	26 (22/4)	37.3 ± 10.7	(8 ATYP,	Anterior	GM	1.1	MRSI	135
	CONT	16 (12/4)	35.8 ± 7.3	Yes 2 without)	cingulate.	GM and WM	8	SV	30
Dellamillieure et al. (2000)	* DEFICIT- SCHZ	5(ND)	ND	Yes	Anterior				
	N-DEFICIT SCHZ	17(ND)		Yes	cingulate.				
	CONT	21(ND)							
Ende et al. (2000)	*SCHZ TYP	9 (ND)	36.9 ± 6.4	Yes	Anterior	GM	2.4	MRSI	135
	SCHZ ATYP	10(ND)	32.5 ± 11	Yes	cingulate.				
	CONT	16 (11/5)	34.9 ± 13.6						
Hagino et al. (2002)	SCHZ	13(11/2)	23.7 ± 5	Yes	DLPFR	GM and WM	6	SV	270
	CONT	13(11/2)	20.9 ± 2.3						
Heimberg et al. (1998)	SCHZ+SCHZA	13(13/0)	ND	Yes	Frontal pole	GM	8	SV	30
	CONT	14(ND)	ND	(2ATYP)					
Thomas et al. (1998)	CHILD-SCHZ	12(ND)	ND	Yes (10)	Anterior	GM	8	SV	20
	CONT	12 (6/6)	11 ± 3		cingulate.				

SCHZ=schizophrenics; CONT=healthy controls; SCHF=schizophreniforms; SCHZT=schizotypicals; SCHZA=schizoaffectives; CHILD-SCHZ=childhood-onset schizophrenia; MIX DIAG=mixed psychiatric diagnoses; ±SD=standard deviation; SV= single voxel. MRSI=functional spectroscopy. TE=echo time; DLPFR=dorsolateral prefrontal region; WM=white matter; GM=gray matter. ND=not described. *=NAA statistical difference as compared to control group. ANTP=anti-psychotics. ATYP=atypical anti-psychotics. TYP=typical anti-psychotics. MED=medication

determinant factor in the results presented, it seems that male schizophrenics are more likely to present decrease in the NAA levels.

Medication

The strongest evidence of NAA decrease is found in chronic schizophrenic patients. One reason, already discussed, is the possible negative correlation between NAA and age. Another possibility is that chronic patients generally have a history of prolonged use of anti-psychotics, although the consequences of such treatment on neuronal functioning are unknown. Some studies have concentrated on that variable, such the mentioned intra-subject study by Bertolino et al.[22], which found a NAA/Cr increase in medicated schizophrenic

Table 2 - Studies of frontal lobe proton spectroscopy in schizophrenic patients who did not show NAA decrease.

Study	Subjects	N (M/F)	Age ± SD	Neuro-leptics	Site	Predomi-nace WM/GM	VOXEL (ml)	SV / MRSI	TE (Ms)
Bartha et al. (1997)	SCHZ	10 (8/2)	26.3 ± 6.4	No	Cingulate	GM	4.5	SV	20
	CONT	10 (8/2)	24.4 ± 5.1						
Bertolino et al. (2000	SCHZ	8(ND)	40.1 ± 8.7	No	DLPFR	GM	1.4	MRSI	272
	CONT	7 (5/2)	36.4 ± 7.3						
Callicott et al. (1998)	SCHZ + SCHZA	47 (43/4)	34.2 ± 8.8	8 without	DLPFR,	GM and			
	CONT	66 (42/24)	32.9 ± 8.2		anterior and posterior cingulate	WM	1.4	MRSI	272
Fukuzako et al. (1995)	SCHZ	15(4/11)	39.3 ± 7.6	Yes	Frontal pole.	ND	27	SV	135
	CONT	15(4/11)	38.8 ± 7.8						
Omori et al. (2000)	SCHZ	20 (12/8)	23–43	Yes	Frontal pole.	WM	8	SV	136
	CONT	16 (10/6)		(5 ATYP, 2 without)					
Sigmundsson et al. (2003)	SCHZ	25 (24/1)	34.9 ± 8	Yes	DLPFR.	WM	2	SV	136
	CONT	26 (22/4)	31.8 ± 6.7						
Stanley et al. (1996)	SCHZ	13(11/2)	26 ± 7	No	DLPFR.	WM (70%)	8	SV	20
	SCHZ	12(10/2)	26 ± 7	Yes acute		GM (30%)			
	SCHZ	12(11/1)	41 ± 5	Yes chronic					
	CONT	24(24/0)	32 ± 11						
Steel et al. (2001)	SCHZ	10 (5/5)	34 ± 14	Yes	Frontal pole.	WM	15	SV	145
	CONT	10 (4/6)	35 ± 7						

SCHZ=schizophrenics; CONT=healthy controls; SCHZA=schizoaffectives; ±SD=standard deviation; SV= single voxel. MRSI=functional spectroscopy. TE=echo time; DLPFC=dorsolateral prefrontal cortex; DLPFR=dorsolateral prefrontal region; WM=white matter; GM=gray matter. ATYP=atypical anti-psychotics.

patients. Nevertheless, several limitations were pointed out in this study by Bustillo et al.[33]: it is a naturalistic, non-controlled study; used NAA/Cr ratio, and the NAA change observed was only 9%, which can be seen as a normal variation, although reaching statistical significance in the dorsolateral pre-frontal cortex (DLPFC). In their own results, Bustillo et al.[33] reported NAA decrease in schizophrenics treated with haloperidol, as compared to controls and patients taking clozapine, raising the hypothesis of an association of typical anti-psychotics with neuronal toxicity.

Two other studies have analyzed if the type of anti-psychotic drug may interfere with the NAA levels. Omori et al.[37] did not find any differences in the frontal lobe, when they compared typical anti-psychotic drugs (n=13) to atypical ones (n=5). In contrast, Heimberg et al.[32] reported NAA/Cr increase in patients taking atypical anti-psychotic drugs (n=2), as compared to schizophrenics taking typical neuroleptics (n=4). Nevertheless, the last result should be seen with caution, due to the small number of subjects participating in the study.

Still about the effects of anti-psychotic drugs on NAA, this review found five well-designed studies. Three of them used schizophrenic patients under no medication and, two of the studies were longitudinal. Cecil et al.[25] and Choe et al.[17] studied non-medicated patients and found NAA/Cr decrease. However, Bartha et al.[42] did not find any NAA alteration in non-medicated schizophrenics. In a longitudinal follow-up study, Choe et al.[29] observed that schizophrenic patients (n=55) had decreased levels of NAA/Cr, even though such levels did not change with anti-psychotic drugs during a treatment period of up to six-months (n=34). The comparison of this study with the other longitudinal investigation reviewed (Bertolino et al.[22]) is questionable, because of critical methodological differences. In another longitudinal study, Bustillo et al.[31] found NAA decrease during the second scan (after the use of anti-psychotic drugs).

It is noteworthy that five studies[4,24,27,34,43] have reported no significant differences in NAA levels between subgroups of non-medicated and medicated patients. Accordingly, the results obtained by Callicott et al.[23], Bertolino et al.[18,26], Deicken et al.[19,30] and Fukuzako et al.[41] did not show any correlation between NAA concentration and dosage of anti-psychotic drug.

Because of the difficulty in performing experiments with non-medicated schizophrenic patients and the diversity of results found, the query about the real interference of medication on the NAA levels is still to be answered.

Experimental Design

Sample Size

Studies in schizophrenic patients using spectroscopy are generally carried out with a small number of patients. There are several reasons for that, from the difficulty of recruiting patients and the high costs of the procedure to the time spent in each examination. Because of that, a question raised about such studies is whether

the number of subjects used is enough to minimize type II errors[44]. Steel et al.[45] and Bertolino et al.[46] admit that the lack of significant NAA decrease observed in their studies may be due to the small number of subjects used, 10 and 8 respectively.

Considering the difficulties in performing such kind of study in large number of subjects, the ones, which achieve bigger samples, should be appreciated.

Voxel Size and Location

Even though spectroscopy has many advantages, there are some shortcomings to be surmounted, such as for example, its low anatomical definition. By using the 1.5 Tesla magnetic field, H^1 MRS gets a good resolution, with voxels measuring from one to eight ml. When compared to P^{31} MRS, H^1 MRS allows the selection of smaller voxels, because proton sensitivity is fifteen times larger than that of phosphorus. As far as the intensity of magnetic fields can be increased, voxels with still smaller volumes would be selected. The advantage of small voxels is the decrease of the partial volume effect, such as the ratio of white/gray matter or CSF. On the other hand, smaller voxels decrease the signal-to-noise ratio and thus, the spectrum quality is lowered[43].

A pertinent query is whether NAA changes observed in some studies are due to decrease of the volume of the structure, with resulting presence of CSF, white matter (WM) or gray (GM) from neighboring structures. Several authors [4,22,32,41-42,45] raise the possibility of the influence of results by adjacent areas. Stanley et al.[43] for instance, admit that the lack of change in metabolites shown by their results may be explained by the fact that 70% of the voxel was composed by WM, bearing in mind that the differences in metabolites only can be found in the GM.

Among the articles reviewed, there was a considerable variation in size among the voxels selected, ranging from 1.1 ml to 30 ml.

In addition, there was large variation in the localization of voxels, even though they were all inside the frontal lobe. Table 3 shows the distribution of studies by voxel localization in the frontal lobe (dorsolateral prefrontal region, frontal pole, cingulate). In the reviewed studies, NAA decrease was found in the three sub-regions, as pointed out before[18].Taking into consideration that NAA changes are not limited to a specific region, it is even more necessary to be able to decrease voxel size without impairing the signal-to-noise ratio. Moreover, with the development of techniques for separating WM from GM and to minimize CSF interference in the voxel, more reliable results will certainly be obtained.

Laterality

Some spectroscopy studies reviewed in this article (N=11) did not evaluate the frontal region bilaterally. Among 16[18-19,22-26,28-30,34,44-48] articles that have evaluated bilateral frontal lobe, in ten[18-19,22-26,28-29,34] the abnormalities were the same bilaterally and in two[30,47] studies NAA differences were found only on the left side. In the other four[44-46,48] studies no differences were found. When only one side was selected, the left frontal lobe was clearly preferred for investigation (N= 10[4,27,31-33,37-38,41-43]) as compared to the right frontal lobe (N=1[17]). There were NAA abnormalities in 18[4,18-19,22-34,38,47] (69%) out of 26 articles that evaluated the left side, whereas NAA differences occurred in 11[17-19,22-26,28-29,34] (64%) out of 17 articles that studied the right side. Therefore, these results suggest that the NAA abnormalities in the frontal lobe are not influenced by brain laterality.

MRS Parameters

The variation of acquisition parameters in spectroscopy, as well as the physicochemical proprieties of the measured substances may distort the results obtained. Several authors[30,41,43] admit the possibility of interference of the relaxation times T1 and T2 in their results. T1 is the time the atom nucleus takes to return to its low energy basal state, which is more stable, while T2, transversal relaxation time, is the time the nucleus takes to become out of phase (such as clocks from several countries, winding in the same frequency, but showing different times). Times T1 and T2 are determined by the molecular environment around the atom nucleus.

Table 3 - Distribution of proton spectroscopy studies in schizophrenic patients paired with healthy controls among the frontal lobe sub-regions.

Frontal pole	Cingulate	DLPFR
*Brooks et al. 1998	*Dellamillieure et al. 2000	*Bustillo et al. 2001
*Buckley et al. 1994	*Deicken et al. 1997-b	*Bertolino et al. 2001
*Bustillo et al. 2002	*Ende et al. 2000	*Block et al. 2000
*Choe et al. 1994	*Thomas et al. 1998	*Bertolino et al. 1998
*Choe et al. 1996	Bartha et al. 1997	*Bertolino et al.1996
*Heimberg et al 1998	Bertolino et al. 2001	*Callicott et al. 2000
Fukuzako et al. 1995	Bertolino et al. 1998	*Cecil et al. 1999
Omori et al. 2000	Bertolino et al. 1996	*Hagino et al. 2002
Steel et al. 2001	Callicott et al. 2000	Bertolino et al. 2000
		Callicott et al. 1998
		Sigmundsson et al. 2003
		Stanley et al. 1996

DLPFR =dorsolateral prefrontal region; *indicates change in NAA concentration.

Other parameters previously defined by the authors, such as: Echo Time (TE – the time between the 90 degree pulse and the maximum in the echo in a spin-echo sequence), use or not of metabolite ratio, and predominance of white or gray matter made it difficult the comparison of the results obtained.

The definition of TE depends on the metabolite of interest and so, a short TE is preferable when the focus is in substances such as glutamate. However, if NAA is the center of attention, the NAA peak definition improves with a longer TE.

Block et al.[38] found NAA/Cho decrease in schizophrenics, only when they used 272 ms TE. With 30 ms there was no difference, probably due to higher standard deviations. Fukuzako et al.[41] reported that the NAA/Cr ratio decreases when TE drops from 135 ms to 50 ms.

It can be seen that nine[4,17,24-25,28-29,31-33] of the 19 studies that found NAA decrease used a short TE, indicating that TE is not the only determinant of the results obtained.

The best way to determine the brain concentration of a substance is its absolute value, but as such measurement is highly complex, the results are not always reliable. The determination of NAA ratio with other substances (NAA/Cr, NAA/Cr+Cho, NAA/Cho) is, on the other hand, easily obtainable, does not vary with the relaxation times T1 and T2, and is not affected by CSF influence. The disadvantage is that the result is a function of both the denominator and the numerator.

Even when the quantification in absolute value is used, the technique employed in this situation, also uses a kind of "ratio". For instance, in Heimberg et al.'s[32] study, the water concentration was used as a reference for the quantification of metabolites of interest, assuming that the magnetic characteristics of the water do not change in pathological situations.

As many as 17[17-18,22-29,32,37-38,41,44,46-47] from the 27 articles reviewed, used "ratio" instead of absolute values. Among them, 13[17-18,22-29,32,38,47] studies found decrease in the NAA ratio. From the eight studies that did not find NAA changes, two[42-43] have been criticized by Bertolino and Weinberger[20]. They argued that the use of absolute values based on previous knowledge of metabolite concentration is unreliable, because measurements obtained in different sessions are hard to replicate.

CONCLUSION

The main difficulty in analyzing these 27 articles resulted from the great variation in the methodological variables discussed above. None of those aspects, by themselves, was able to predict the results obtained in the studies.

Though the studies were rigorous in many ways, few reached satisfactory criteria, both in respect to the clinical and demographic characteristics, and in the parameters of image acquisition. Small subject group sizes, samples with a high proportion of female schizophrenics, large voxel volume and short TE are factors likely to impair the detection of NAA change. Taking into account the number of patients studied (> 20), the predominance of male patients (>80%), the TE (≥ 135 ms), the voxel size (≤ 2 ml), six well designed studies can be selected. Four out of these six best-designed studies[19,22-23,30] showed a decrease in the NAA levels in the frontal lobe of schizophrenics; and two[44,48] reported negative findings.

Thus, the results of the present review show that it is not clear if there is an association between NAA abnormalities in the frontal lobe and schizophrenia. Since many aspects of this disorder are heterogeneous, standardization of spectroscopic methodology and a more judicious selection of subjects are likely to generate more reliable evidence concerning the role of NAA in schizophrenia.

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RESUMO

SANCHES RF e col. Espectroscopia de Próton por ressonância magnética de lobo frontal em esquizofrênicos – Revisão crítica da metodologia. **Rev. Hosp. Fac. Med.S. Paulo 59**(3):145-152, 2004

Pacientes esquizofrênicos submetidos à espectroscopia de próton por ressonância magnética demonstram alterações nos níveis de N-acetilaspartato em diversas regiões cerebrais, suportando a hipótese de disfunção neuronal nestas áreas. Objetiva-se apresentar uma revisão da literatura, sobre os principais estudos de espectroscopia de próton por ressonância magnética na região frontal em esquizofrênicos. Utilizou-se o indexador MEDLINE, no

período entre 1991 e março de 2004, com o cruzamento dos termos spectroscopy, schizophrenia, proton e frontal. Foram selecionados 27 artigos originais, cujos resultados mostram-se discordantes quanto à alteração nos valores de N-acetilaspartato (19 artigos apresentaram alterações nos níveis de N-acetilaspartato e oito estudos não apresentam alterações). A presente revisão sugere que esta diversidade de resultados pode ser atribuída aos seguintes fatores: 1-número de participantes; 2- variação nas características clínicas e demográficas dos grupos; 3- pouca padronização dos parâmetros de aquisição dos espectros. Os artigos que satisfazem os critérios metodológicos mais rígidos sugerem diminuição de NAA no lobo frontal de esquizofrênicos do sexo masculino.

UNITERMOS: **Espectroscopia. Próton. Frontal. Esquizofrenia. Revisão.**

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