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Perspective

Measurement of Brain Metabolites by ^{1}H Magnetic Resonance Spectroscopy in Patients with Schizophrenia: A Systematic Review and Meta-Analysis

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A systematic review of the literature identified 64 published English-language papers that used proton (^{1}H) magnetic resonance spectroscopy to measure *N*-acetylaspartate (NAA) concurrently in healthy controls and in patients with a diagnosis of schizophrenia (SZ). A total of 1209 controls and 1256 patients have been evaluated, with 88% of studies carried out at 1.5 T field strength, and 77% of studies focused on patients with chronic SZ. There is consistent evidence that NAA is reduced in a broad range of tissues in the SZ brain. Broad consensus ($\geqslant$10 studies) is emerging that NAA levels are reduced $\geqslant$5% in hippocampus and in both cortical gray matter (GM) and white matter (WM) of the frontal lobe. There is no evidence to support a hypothesis that relative NAA levels are reduced to a different degree in frontal lobe GM and WM, nor is there robust evidence of a difference in NAA levels between patients with first-episode and chronic SZ. Study reliability may be a problem, as most studies appear to be underpowered. With simple assumptions about the inherent difference in NAA levels between patients and controls, it can be calculated that a minimum sample size of approximately 39 patients and 39 controls is required for acceptable statistical power. Only three of 64 studies included enough subjects to have 80% power to detect a 10% NAA reduction in patients, and no studies were adequately powered to detect a 5% NAA reduction with 80% power.

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INTRODUCTION

Proton (^{1}H) magnetic resonance spectroscopy (MRS) of the human brain *in vivo* makes it possible to measure the pool size of certain chemical constituents presumed to be metabolically important, including amino acids (eg *N*-acetylaspartate or NAA), amines, sugars, and bioenergetic metabolites (Martin *et al*, 2001). The promise inherent to measuring metabolites in the living brain has made MRS methodology very attractive to investigators interested in psychiatric illness. However, it is not yet clear whether the method has sufficient precision and accuracy to detect differences from normal that may be quite subtle in psychiatric patients.

The most abundant metabolite visible by MRS in the healthy human brain is NAA, which is present almost exclusively in the nervous system (Birken and Oldendorf, 1989), and which is hypothesized to be a marker of the number of viable neurons (Meyerhoff *et al*, 1993). Consistent with this hypothesis, levels of NAA in the brain are reduced in a broad range of pathological states, with dramatic reductions seen in patients with tumor or stroke (Zimmerman and Wang 1997; Taylor *et al*, 1998). Owing to its abundance, NAA can usually be measured with greater precision than any other compound of interest, and many studies have examined NAA levels in the brain of patients with schizophrenia (SZ).

Nevertheless, it is still controversial as to whether brain NAA is reduced in patients with SZ. While some studies have reported a reduction of NAA in certain brain tissues, other studies have failed to replicate such findings or have documented a reduction in other brain tissues, leading to confusion in the literature. To shed light on whether NAA is indeed reduced in patients with SZ, we have systematically reviewed all published English-language reports about NAA in the SZ brain. We also present meta-analyses to determine whether NAA is reduced to an equivalent degree in both gray matter (GM) and white matter (WM), and in both first-episode (FE) and chronic SZ patients. In addition, we discuss levels of other metabolites in the brain of patients with SZ.

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METHODS

Study Inclusion and Exclusion Criteria

Relevant studies of SZ patients were identified in several ways. The primary search used PubMed and the key words 'schizophrenia and spectroscopy and magnetic resonance and brain', in various combinations. The search was limited to articles in English, with abstracts, relating to research in human subjects. This search yielded 169 articles whose abstracts were read, to identify studies that used proton (^{1}H) MRS on patients with either FE or chronic SZ. All studies that met these broad inclusion criteria were identified as primary references, and the full paper was obtained.

After the primary references were obtained, a secondary search was undertaken, using each of the primary references as a source. The bibliography of each primary reference was searched for additional references that had been missed by the PubMed search. In addition, the bibliographies of several key review articles were searched (Kegeles *et al*, 1998; Bertolino and Weinberger, 1999; Lyoo and Renshaw, 2002), for papers relating specifically to ^{1}H MRS in SZ patients. Finally, current journals were reviewed to find references too new to have been included in the PubMed search.

Studies are included in the present analysis if brain MRS data were reported for a population of SZ patients and for a population of healthy control subjects evaluated concurrently. Studies were excluded if patients had psychosis without a primary diagnosis of SZ, or if a concurrent control group was not evaluated. We also excluded studies that did not include data on NAA, or did not report data in a format that enabled us to calculate patient metabolite levels as a percentage of control metabolite levels, in an individual brain region.

Data from all eligible studies were entered into a spreadsheet that tabulated study details, including a brief description of the study and the demographics of the study population. Each line of the database tabulated a particular metabolite in a certain brain structure in a specific study (eg NAA in hippocampus in Buckley *et al*, 1994). Data were also entered summarizing the percent difference in metabolite levels, relative to controls, and whether this difference was statistically significant, according to the analysis presented in the original reference. The final database was 22 columns wide and 155 lines long, and contained approximately 3410 cells.

Data Analysis

We sought to tabulate NAA levels in a way that would enable us to compare between studies. This meant that we wanted to ignore the units used in individual studies, which can be NAA concentration (usually in arbitrary units) or NAA expressed as a ratio to various other metabolites (eg NAA/creatine (Cr) or NAA/Cho). We therefore calculated patient NAA levels as a proportion of control NAA levels, irrespective of the units in which NAA was expressed in the original paper, assuming that control NAA levels are comparable across all studies. In most cases, if separate values were reported for each hemisphere, we calculated separate ratios, and then averaged the ratios, since the hypothesis of interest is not related to hemispheric laterality.

Our approach of calculating ratios of patient NAA to concurrently collected control NAA offers the advantage that it should be insensitive to artifacts of the particular data collection parameters used in each individual study. This approach should also be relatively insensitive to partial volume problems that are unique to each study, as long as volumes of interest are placed in equivalent positions in patients and controls. We tested the validity of this approach by comparing NAA levels in various studies of the hippocampus, as a function of the units in which NAA was expressed in the original reference.

We also performed a meta-analysis of the hippocampal data. It is not possible to use proportions in a meta-analysis, since proportions are not normally distributed. Thus, for each component study in the meta-analysis, we abstracted information about sample properties (mean and standard deviation (SD)) from the original paper, and then randomly generated a data set whose sample properties were identical to those reported for each component study. We then pooled all studies and analyzed the pooled data set for significance, using typical parametric statistics.

We then sorted the database by brain structure, to determine where metabolite changes had been sought. Brain metabolite changes in SZ patients are summarized, with respect to controls, on a structure-by-structure basis. We then focused on frontal lobe metabolite levels, to determine whether there is a difference in NAA levels between GM and WM. Finally, we contrasted patients with FE SZ and patients with chronic SZ, by tabulating NAA levels in the prefrontal cortex for both groups.

We did not attempt to do a formal meta-analysis in every case for several reasons. Papers often publish insufficient information to enable one to do a meta-analysis, since some measure of data scatter (SD, standard error (SE)) is required, and such a measure is missing from many papers. In addition, there are several other issues: a meta-analysis requires that many studies use essentially identical patient populations, methods, and end points, which is often not the case in MRS studies of the brain; publication bias (the tendency not to publish negative or nonsignificant results) can be an unseen but intractable problem; and multiple published studies often seem to be derived from overlapping sets of subjects, which would lead to an artifactually high p-value, if the effect size were calculated.

In our final analysis, we summarized the coefficient of variation (CV) in all studies that measured NAA levels in frontal lobe, to address the question of whether studies were adequately powered to detect a difference between patients and controls. The NQuery Advisor program (SAS) was used to calculate the power of each individual study to detect an effect of the size reported in that study. This calculation used the reported patient and control sample sizes, and the pooled SDs for patients and controls, to calculate *post hoc* power.

RESULTS

Overview of Studies

Of the 169 articles that were identified in the original PubMed search, 112 were excluded for any of several

reasons. A total of 48 articles presented results from some type of spectroscopy other than proton (^{1}H) MRS (46 articles were on ^{31}P MRS and two were on ^{19}F MRS), and another 27 articles were reviews that did not present new data. Other reasons for study exclusion were: no values for NAA were tabulated (11 studies excluded); patients had a primary diagnosis other than SZ (11 studies excluded); data presented were not from MRS (10 studies excluded); study was performed either *ex vivo* or *in vitro* (three studies excluded); study published data that appeared to be completely duplicative (one study excluded); or no control data were presented (one study excluded). This left a total of 57 articles, which were used in the secondary search.

The secondary search, in which the reference section of each primary reference was searched for relevant references, yielded an additional seven articles that had not been found by the PubMed search. Thus, the PubMed search was 89% successful (57/64) in identifying relevant references.

The final total of 64 articles that were evaluated (Table 1) includes 1256 patients and 1209 healthy controls. However, some of these tabulated studies probably include an overlapping set of patients or controls; therefore, the total subject number of 2465 may be an overestimate. The average number of subjects per study was 19.6 patients and 18.9 controls, but 72% of studies (46 of 64) had fewer than the average number of patients or controls. In fact, 53% of studies (34 of 64) had fewer than the average number of both patients and controls. Roughly 88% of all published studies (56 of 64) were performed at a magnetic field strength of 1.5 T.

Table 1 Total Studies Evaluated

Author (year)	Tesla	Cts	Pts	Patient type
Ando *et al* (2002)	1.5	7	14	Chronic
Auer *et al* (2001)	1.5	17	32	Chronic
Bartha *et al* (1997)	1.5	10	10	FE
Bartha *et al* (1999)	1.5	11	11	FE
Bertolino *et al* (1996)	1.5	10	10	Chronic
Bertolino *et al* (1998a)	1.5	14	14	Childhood onset (FE?)
Bertolino *et al* (1998b)	1.5	12	12	Chronic, drug free
Bertolino *et al* (1998c)	1.5	10	10	Chronic
Bertolino *et al* (2000)	1.5	13	13	Chronic??
Bertolino *et al* (2003)	1.5	24	24	FE
Block *et al* (2000)	1.5	54	38	Chronic
Brooks *et al* (1998)	1.5	12	16	Childhood onset (FE)
Buckley *et al* (1994)	1.5	20	28	Chronic
Bustillo *et al* (2001)	1.5	21	38	Chronic
Bustillo *et al* (2002a)	1.5	10	10	Drug-naïve FE
Bustillo *et al* (2002b)	1.5	11	11	Drug-naïve FE
Callicott *et al* (1998)	1.5	66	47	Chronic
Callicott *et al* (2000)	1.5	73	36	Chronic
Cecil *et al* (1999)	1.5	24	18	Drug-naïve FE
Choe *et al* (1994)	1.5	10	23	Chronic (drug naïve)
Choe *et al* (1996)	1.5	20	55	Chronic
Deicken *et al* (1997a)	1.5	16	26	Chronic
Deicken *et al* (1997b)	1.5	15	24	Chronic
Deicken *et al* (1998)	1.5	18	30	Chronic
Deicken *et al* (1999)	1.5	18	23	Chronic
Deicken *et al* (2000)	1.5	10	17	Chronic
Deicken *et al* (2001a)	1.5	15	20	Chronic
Delamillieure *et al* (2000)	1.5	21	22	Chronic??
Delamillieure *et al* (2002)	1.5	14	17	Chronic
Eluri *et al* (1998)	1.5	8	12	Chronic
Ende *et al* (2000)	1.5	16	19	Chronic
Ende *et al* (2001)	1.5	15	15	Chronic
Ende *et al* (2003)	1.5	15	13	Chronic
Fannon *et al* (2003)	1.5	18	33	FE
Fujimoto *et al* (1996)	2	12	14	Chronic
Fukuzako *et al* (1995)	2	15	15	Chronic
Fukuzako *et al* (1999)	2	40	40	Chronic
Fukuzako (2000)	2	51	64	Chronic
Gimenez *et al* (2003)	1.5	11	11	FE
Hagino *et al* (2002)	1.5	13	13	Chronic
Heimberg *et al* (1998)	1.5	39	24	Chronic
Kegeles *et al* (2000)	1.5	10	10	Chronic
Lim *et al* (1998)	1.5	9	10	Chronic
Maier *et al* (1995)	1.5	32	25	Chronic
Maier and Ron (1996)	1.5	38	26	Chronic
Moore *et al* (2002)	1.5	20	20	Chronic
Nasrallah *et al* (1994)	1.5	11	11	Chronic
Ohara *et al* (2000)	1.5	10	10	Chronic
Omori *et al* (2000)	1.5	16	20	Chronic
O'Neill *et al* (2004)	1.5	20	11	Childhood onset (FE)
Renshaw *et al* (1995)	1.5	15	7	FE
Sharma *et al* (1992)	1.5	9	4	Chronic
Shioiri *et al* (1996)	1.5	21	21	Chronic
Sigmundsson *et al* (2003)	1.5	26	25	Chronic
Spaniel *et al* (2003)	1.5	1	1	Chronic
Stanley *et al* (1996)	1.5	24	11	Drug-naïve FE
Steel *et al* (2001)	2	10	10	Chronic
Theberge *et al* (2002)	4	21	21	Drug-naïve FE
Theberge *et al* (2003)	4	21	21	Chronic
Thomas *et al* (1998)	1.5	12	12	FE children and adolesc.
Tibbo *et al* (2000)	3	12	12	Chronic
Weber-Fahr *et al* (2002)	1.5	15	15	Chronic
Yamasue *et al* (2002)	1.5	13	15	Chronic
Yurgelun-Todd *et al* (1996)	1.5	14	16	Chronic
	Total # subjects	1209	1256	
	Average subjects/ study	18.9	19.6	

FE = first episode; adolesc. = adolescent; Cts = controls; Pts = patients.

Most studies (77% or 49 of 64) focused on patients with chronic SZ, as there have been only 14 studies of FE patients, of which four studies were of patients with juvenile-onset SZ. In total, only 167 adolescent or adult FE patients have been studied; therefore, relatively little is known about whether the brain of a typical newly diagnosed patient is different from normal.

Brain Metabolite Levels

To determine whether the approach of normalizing patient values to control values is a valid way to compare between studies, we tabulated patient hippocampal NAA levels measured in arbitrary units of NAA concentration *vs* as a ratio of NAA/Cr (Table 2). This comparison was carried out in hippocampus because this tissue is of relevance in SZ; therefore, there have been a fairly large number of studies that focus on hippocampus. The apparent equivalence of patient NAA levels after normalization to control levels, whether patient NAA levels were originally expressed as [NAA] or NAA/Cr, suggests that normalization to control values is a valid way to compare across studies. As this approach references patient values to concurrently collected control values, this should even make it possible to compare between different field strengths. Results suggest that hippocampal NAA is reduced about 10% in patients compared to controls. These results appear to be robust, as most studies (80% or 12 of 15) report a significant reduction in NAA among patients (Table 2).

The question of whether normalizing patient values to control values is a valid approach to compare between studies is crucial to our purpose; therefore, we also did a meta-analysis of these data (Figure 1). In evaluating studies which presented NAA as a raw value, there was a significant reduction in NAA in patient hippocampus compared to control hippocampus ($p<0.0001$), although there was significant heterogeneity between studies ($p<0.0001$). The least-squares (LS) mean NAA in patients was 15.37 U (95% confidence interval (CI): 14.64–16.10 U), whereas the LS mean NAA in controls was 18.18 U (95% CI: 17.45–18.90). Thus, the ratio of patient to control NAA by LS mean raw values was 84.5%.

In evaluating studies that presented NAA as a ratio of NAA/Cr, there was also a significant reduction in NAA/Cr in patient hippocampus compared to control hippocampus ($p<0.0001$), although there was again significant heterogeneity between studies ($p<0.0001$). The LS mean NAA/Cr ratio in patients was 1.47 U (95% CI: 1.39–1.54 U), whereas the LS mean NAA/Cr ratio in controls was 1.70 (95% CI: 1.63–1.77). The ratio of patient to control NAA by LS ratios was thus 86.5%, which is similar to the ratio by raw values (Figure 1).

There is consistent evidence that NAA is reduced in a broad range of tissues in the SZ brain (Table 3). The extent of reduction of NAA in GM is generally comparable to the extent of reduction of NAA in WM. However, this comparison of GM to WM is confounded by what appears to be regional variation in the extent of brain NAA

Table 2 Metabolite Measurements made in Hippocampus of Schizophrenic Patients at 1.5 T

NAA in patients (relative to controls)				Reported values for [NAA] or NAA/Cr					
[NAA]	NAA/Cr	Author (year)	Reported *p*-value	Patient (mean)	Patient (SD)	Pt (*n*)	Control (mean)	Control (SD)	Ct (*n*)
85	—	Deicken *et al* (1998)	0.002	33.80	6.20	30	39.60	6.80	18
85	—	Deicken *et al* (1999)	0.005	33.20	6.00	23	39.20	6.60	18
92	—	Ende *et al* (2003)	0.004	11.80	1.00	13	12.90	0.80	15
79	—	Maier *et al* (1995)	0.009	6.44	2.05	25	8.18	2.77	32
80	—	Maier and Ron (1996)	—	6.40	2.04	26	8.00	2.71	38
94	—	Weber-Fahr *et al* (2002)	0.013	1.63	0.12	15	1.74	0.11	15
—	85	Bertolino *et al* (1996)	0.03	1.71	0.23	10	2.02	0.26	10
—	90	Bertolino *et al* (1998a)	0.05	1.70	NR	14	1.90	NR	14
—	86	Bertolino *et al* (1998b)	0.02	1.80	0.40	12	2.10	0.20	12
—	83	Bertolino *et al* (1998c)	0.003	1.71	NR	10	2.05	NR	10
—	87	Bertolino *et al* (2003)	0.003	1.71	0.34	24	1.97	0.29	24
—	84	Callicott *et al* (1998)	0.00001	1.60	0.30	47	1.90	0.50	66
—	111	Delamillieure *et al* (2002)	—	1.26	0.29	11	1.14	0.16	14
—	84	Fannon *et al* (2003)	0.0002	0.81	0.13	11	0.96	0.10	14
—	89	Kegeles *et al* (2000)	—	1.52	0.28	10	1.70	1.02	10
85.8	**88.8**								
6.1	**8.7**								

Both [NAA] and NAA/Cr are reported for patients as a percentage of the values reported for controls in the same study, to normalize across studies. Values to the right of the vertical bar were used to perform a meta-analysis contrasting the two methods of reporting NAA levels. If left and right hippocampus were separately reported, only the left hippocampus values are analyzed here. Papers by Bertolino (1998a, c) were excluded from the meta-analysis because sample standard deviation (SD) was not reported (NR) in the original paper.

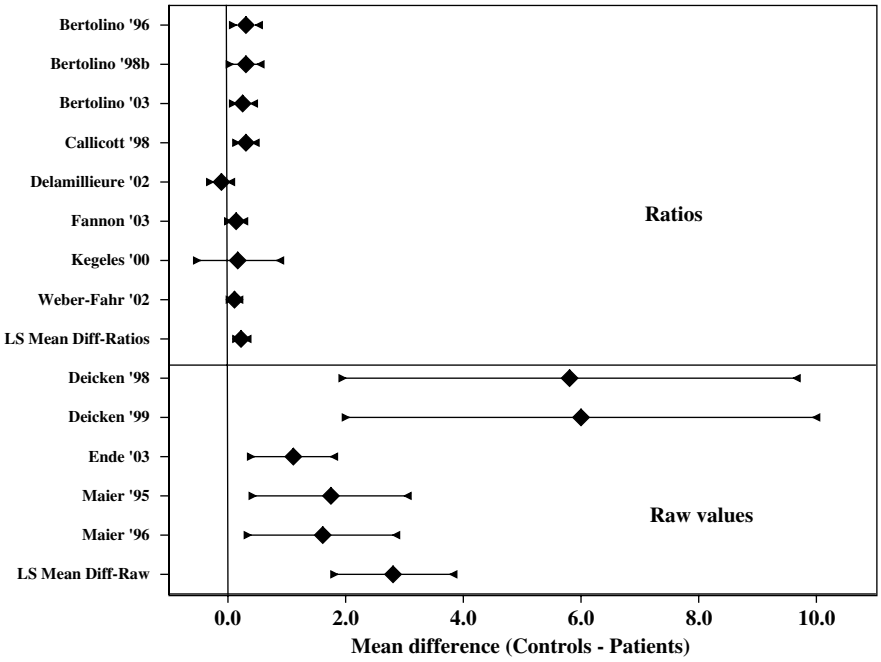

Figure 1 Visual summary of a meta-analysis of NAA levels in the hippocampus of patients with schizophrenia (SZ) compared to healthy controls (data from Table 2). NAA levels expressed in ratios are shown separately from NAA levels expressed in raw values. There is no apparent trend difference, depending upon how NAA levels were expressed in the original paper, suggesting that calculating patient NAA values as a proportion of control NAA values is a valid way to compare between studies.

reduction in patients. For example, NAA levels do not appear to be reduced in SZ patients in basal ganglia, caudate, occipital cortex, posterior cingulate, putamen, centrum semiovale, or parietal WM. However, levels of NAA do appear to be substantially reduced (>5%) in the cerebellum, frontal cortex, hippocampus, parietal cortex, temporal cortex, frontal WM, and temporal WM. At least 10 published studies provide evidence that there is a substantial (>5%) and often significant reduction in levels of NAA in the hippocampus, and in both the cortical GM and WM of the frontal lobe. However, because NAA levels in all GM tissues and all WM tissues were combined (Table 3), without considering regional variation in NAA (Auer *et al*, 2001), a direct comparison of GM to WM may be confounded. Nevertheless, we note that there is no compelling evidence to suggest that NAA is significantly elevated in any brain tissue in patients with SZ (Table 3).

To explore further whether NAA levels in patients are reduced to an equivalent degree in GM and in WM, NAA levels in the frontal lobe are tabulated separately for the two tissue types (Table 4). This comparison suggests that NAA is reduced to a comparable degree in frontal lobe GM and frontal lobe WM, despite some findings to the contrary (Bertolino *et al*, 1996, 1998a, b). Furthermore, although the data are quite sparse, there is no convincing evidence that levels of choline (Cho) or Cr differ in GM or WM of the frontal lobe. We note that this analysis does not mean that levels of NAA (or Cr or Cho) are equivalent in healthy gray and WM, but rather that levels of NAA are reduced to an equivalent degree in both gray and WM of the SZ brain.

We undertook a meta-analysis of the data in Table 4, to test further whether frontal lobe GM and frontal lobe WM show a significant reduction in NAA (Figure 2). In frontal lobe GM, there was a significant reduction in patient NAA compared to control frontal lobe GM ($p<0.0008$), although there was significant heterogeneity between studies ($p<0.0001$). The LS mean NAA in patients was 4.12 U (95% CI: 4.03–4.21 U), whereas the LS mean NAA in controls was 4.31 U (95% CI: 4.23–4.39 U). Thus, the ratio of patient to control NAA in frontal lobe GM was 95.6% by LS mean raw values.

In frontal lobe WM, there was also a significant reduction in patient NAA, as compared to control frontal lobe WM ($p<0.0001$), with significant heterogeneity between studies ($p<0.0001$). The LS mean NAA in patients was 5.98 U (95% CI: 5.79 to 6.16 U), whereas the LS mean NAA in controls was 6.48 U (95% CI: 6.30–6.66 U). Thus, the ratio of patient to control NAA in frontal lobe WM was 92.3% by LS mean raw values. These results may mean that there was greater reduction of NAA in WM than GM. However, the degree of heterogeneity between studies precludes a direct meta-analytic comparison of GM to WM in frontal lobe.

To determine whether FE patients are comparable to patients with chronic SZ, NAA levels in the prefrontal cortex (excluding anterior cingulate) were tabulated separately for each patient group (Table 5). Given the small sample size of FE patients, this comparison does not provide convincing evidence of a difference in NAA levels between patients as a function of disease duration. The trend towards lower NAA in FE patients is not convincing, yet it seems clear that NAA levels are probably not lower in chronic patients, as was expected. Nevertheless, there is a robust reduction of NAA in prefrontal cortex. When this type of analysis was also undertaken for anterior cingulate and temporal lobe (data not shown), there was likewise no convincing evidence for a difference between FE and chronic patients.

Table 3 Summary of NAA Levels in all Studies, Separated by Tissue Type and Brain Region

	Patient NAA (as % of control)	
Brain region	**Total *n* studies evaluated**	**Mean across *n* studies**
Gray matter (GM)		
Anterior cingulate GM	12	95.9
Basal ganglia	6	98.5
Caudate	3	100.3
Cerebellum	3	92.3
Frontal cortex	25	94.2
Hippocampus	17	88.9
Lenticular nucleus	2	104.5
Occipital cortex	8	102.8
Parietal cortex	1	94.0
Post cingulate	5	100.0
Putamen	7	100.6
Striatum	1	112.6
Temporal cortex	5	94.0
Thalamus	19	96.5
Total # comparisons	114	
GM average across comparisons		95.5
White matter (WM)		
Centrum semiovale	5	100.2
Frontal lobe WM	18	94.8
Occipital WM	1	96.0
Parietal WM	2	99.0
Temporal WM	8	87.3
Total # comparisons	34	
WM average across comparisons		94.2

The total number of comparisons is larger than the number of studies because some studies reported more than one comparison. All studies for a given tissue are combined without weighting for sample size. For example, there are 12 studies that report NAA levels in GM of the anterior cingulate; each study was treated as a 'vote' and the mean across all 12 votes was calculated, irrespective of sample size in each study.

We summarize the CV of measured NAA levels in all studies of the frontal lobe (Table 6), to address the question of study reliability. We elected to do this analysis in frontal lobe because ROIs in the frontal lobe tend to be rather large (by comparison to the hippocampus, for example); therefore, measurements made in the frontal lobe should be more reliable than those made in many other parts of the brain. This tabulation shows that the average CV for both patients and controls is about 14% across all studies. Studies with a CV smaller than 14% are more likely to detect small differences between patients and controls, and so would be expected to have a greater likelihood of having statistically significant findings. Conversely, studies with a CV larger than normal are less likely to report significant findings. Therefore, a study with a large CV that also has a low associated *p*-value is more likely to be reporting spurious findings.

We show the results of *post hoc* power calculations, to address whether MRS studies were adequately powered to detect the NAA differences that they report (Table 6). Power calculations in general are imprecise estimates, based on estimates of variation and effect size that are of uncertain accuracy. *Post hoc* power calculations estimate the power of a completed study to reject the null hypothesis, given the sample size used in the study. These calculations assume that the population effect size is equal to the sample effect size, that the population variance is equal to the sample variance, and that all statistical tests were two sided. The average statistical power of all measurements across the 16 tabulated studies was 37%. If adequate power is assumed to be at least 80%, then only four measurements in three studies had adequate power. Overall, 12 of 16 studies reported at least one comparison with less than 50% power to detect a difference of the magnitude reported (Table 6). If one were to assume an *a priori* hypothesis that NAA is reduced in patients, relative to healthy controls, one could argue that a one-sided statistical test is appropriate. With such an assumption, the power of the statistical tests would increase, because of the implied directionality of change. However, while a one-sided test may be appropriate now, it was probably not appropriate when most of these studies were carried out, since there was no *a priori* reason to assume that NAA was reduced in patients.

Required sample sizes for adequate power can be calculated if we assume that NAA levels in controls are 13.4 ± 2.0 U SD, which is approximately the mean and SD of all studies tabulated in Table 6 (data not shown). We further assume that patient NAA levels are 10% lower than control NAA levels (Tables 2, 3, and 5), and that the SD in patients and controls is equal. If 80% power to detect a 10% difference in NAA is the goal, then a minimum sample size of 39 patients and 39 controls is needed. If either the desired statistical power is increased or the actual difference in NAA between patients and controls is decreased, then required sample sizes would increase accordingly. For example, if the goal was to have 80% power to detect a 5% difference in NAA, will all other assumptions remain the same, then a minimum sample size of 130 patients and 130 controls would be required.

This analysis confirms that most studies performed to date are underpowered. For example, only three of 64 studies (Table 1) were large enough to have 80% power to detect a 10% NAA difference between patients and controls, and only one study was large enough to have 90% power to detect such a 10% NAA difference. No studies were adequately powered to detect a 5% difference in mean NAA between patients and controls.

DISCUSSION

Evidence is accumulating to suggest that there are MRS differences between controls and SZ patients, although these differences may be rather subtle (Table 3). At least 10 published studies provide evidence that there is a substantial ($>5\%$) and often significant reduction in NAA

Table 4 Metabolite Levels in Frontal Lobe, as a Function of Tissue Type (GM and WM)

	Patient values (relative to controls)				Reported values for [NAA] or NAA/Cr					
Tissue	**NAA (%)**	**Cho (%)**	**Cr (%)**	**Author (year)**	**Patient (mean)**	**Patient (SD)**	**Patient (*n*)**	**Control (mean)**	**Control (SD)**	**Control (*n*)**
Frontal lobe GM										
Medial PFC	97	103	109	Bartha *et al* (1997)	13.30	2.20	10	13.70	1.30	10
Dorsolateral PFC	87	103	—	Bertolino *et al* (1996)	2.44	0.27	10	2.80	0.28	10
Orbitofrontal C	100	97	—	Bertolino *et al* (1996)	2.60	NA	10	2.60	NA	10
Anterior cingulated	104	110	—	Bertolino *et al* (1996)	2.90	NA	10	2.80	NA	10
Dorsolateral PFC	87	92	—	Bertolino *et al* (1998a)	2.60	NA	14	3.00	NA	14
Orbitofrontal C	104	105	—	Bertolino *et al* (1998a)	2.80	NA	14	2.70	NA	14
Anterior cingulate	100	106	—	Bertolino *et al* (1998a)	2.70	NA	14	2.70	NA	14
Dorsolateral PFC	81	92	—	Bertolino *et al* (1998b)	2.50	0.60	12	3.10	0.30	12
Orbitofrontal C	96	97	—	Bertolino *et al* (1998b)	2.70	0.60	12	2.80	0.30	12
Anterior cingulate	100	96	—	Bertolino *et al* (1998b)	2.70	0.50	12	2.70	0.40	12
Dorsolateral PFC	86	96	—	Bertolino *et al* (1998c)	2.45	NA	10	2.86	NA	10
Dorsolateral PFC	88	—	—	Bertolino *et al* (2003)	2.05	0.38	24	2.32	0.51	24
Inferior frontal C	96	—	—	Bertolino *et al* (2003)	2.10	NA	24	2.20	NA	24
Anterior cingulated	100	—	—	Bertolino *et al* (2003)	2.00	NA	24	2.00	NA	24
Dorsolateral PFC	96	98	98	Callicott *et al* (1998)	2.60	0.30	47	2.70	0.30	66
Orbitofrontal C	96	99	100	Callicott *et al* (1998)	2.50	0.50	47	2.60	0.40	66
Anterior cingulated	96	96	103	Callicott *et al* (1998)	2.50	0.50	47	2.60	0.40	66
Dorsolateral PFC	55	118	—	Cecil *et al* (1999)	0.93	0.09	18	1.70	0.90	24
Medial PFC (L)	105	106	—	Delamillieure *et al* (2000)	1.42	0.23	17	1.35	0.21	21
Anterior cingulate (L)	100	104	—	Delamillieure *et al* (2002)	1.36	0.15	17	1.36	0.15	14
Medial PFC	99	99	—	Fannon *et al* (2003)	1.04	0.08	12	1.05	0.11	18
Inferior frontal C (L)	87	110	—	Hagino *et al* (2002)	1.44	0.23	13	1.66	0.37	13
Frontal GM	104	100	103	Lim *et al* (1998)	10.66	1.11	10	10.27	1.22	9
Inf. ant. cingulate (L)	95	119	116	O'Neill *et al* (2004)	5.70	2.20	11	6.00	1.60	20
Frontal C (L)	103	117	102	O'Neill *et al* (2004)	8.00	0.50	11	7.80	1.60	20
Dorsolateral PFC (L)	96	103	108	Sigmundsson *et al* (2003)	13.30	1.80	25	13.90	1.70	26
Anterior cingulated	68	87	—	Thomas *et al* (1998)	1.08	0.28	13	1.59	0.35	12
Average	93.6	102.2	104.9							
SD	11.3	8.3	5.8							
Frontal lobe WM										
PF WM	97	99	—	Bertolino *et al* (1996)	3.30	NA	10	3.40	NA	10
PF WM	91	103	—	Bertolino *et al* (1998a)	3.20	NA	14	3.50	NA	14
Frontal WM	91	94	—	Bertolino *et al* (1998b)	3.10	0.70	12	3.40	0.60	12
Frontal WM	96	—	—	Bertolino *et al* (2003)	2.40	NA	24	2.50	NA	24
Frontal WM	87	87	—	Brooks *et al* (1998)	1.67	0.22	16	1.92	0.31	12
Frontal WM	92	110	102	Buckley *et al* (1994)	39.40	9.20	28	42.80	7.40	20
Frontal WM	89	96	92	Bustillo *et al* (2001)	11.10	1.80	31	12.50	1.60	18
Frontal WM	102	100	96	Bustillo *et al* (2002a)	10.50	0.80	10	10.30	0.70	10
Frontal WM	94	99	98	Callicott *et al* (1998)	2.90	0.60	47	3.10	0.70	66
Frontal WM	84	83	—	Choe *et al* (1994)	1.33	0.28	23	1.58	0.32	10
Frontal WM (L)	84	103	115	Deicken *et al* (1997b)	32.00	6.90	24	37.90	7.30	15
Frontal WM	104	102	—	Fukuzako *et al* (1995)	1.69	0.37	15	1.63	0.29	15
Frontal WM	102	94	—	Heimberg *et al* (1998)	1.30	0.19	13	1.28	0.17	14
Frontal WM	93	105	104	Lim *et al* (1998)	8.15	0.42	10	8.80	0.58	9
Frontal WM	97	93	—	Omori *et al* (2000)	2.28	0.24	20	2.36	0.22	16
Frontal WM (L)	99	99	98	O'Neill *et al* (2004)	7.20	1.50	11	7.30	1.50	20
Frontal WM (L)	87	—	—	Steel *et al* (2001)	1.03	0.21	10	1.18	0.19	10
Average	**93.5**	**97.8**	**100.7**							
SD	**6.2**	**6.9**	**7.4**							

PFC = prefrontal cortex; PF = prefrontal; WM = white matter; NA = not available; C = cortex.
Data to the right of the vertical line was used in the meta-analysis.
Cells containing a dash indicate that the data were not presented in the original paper.

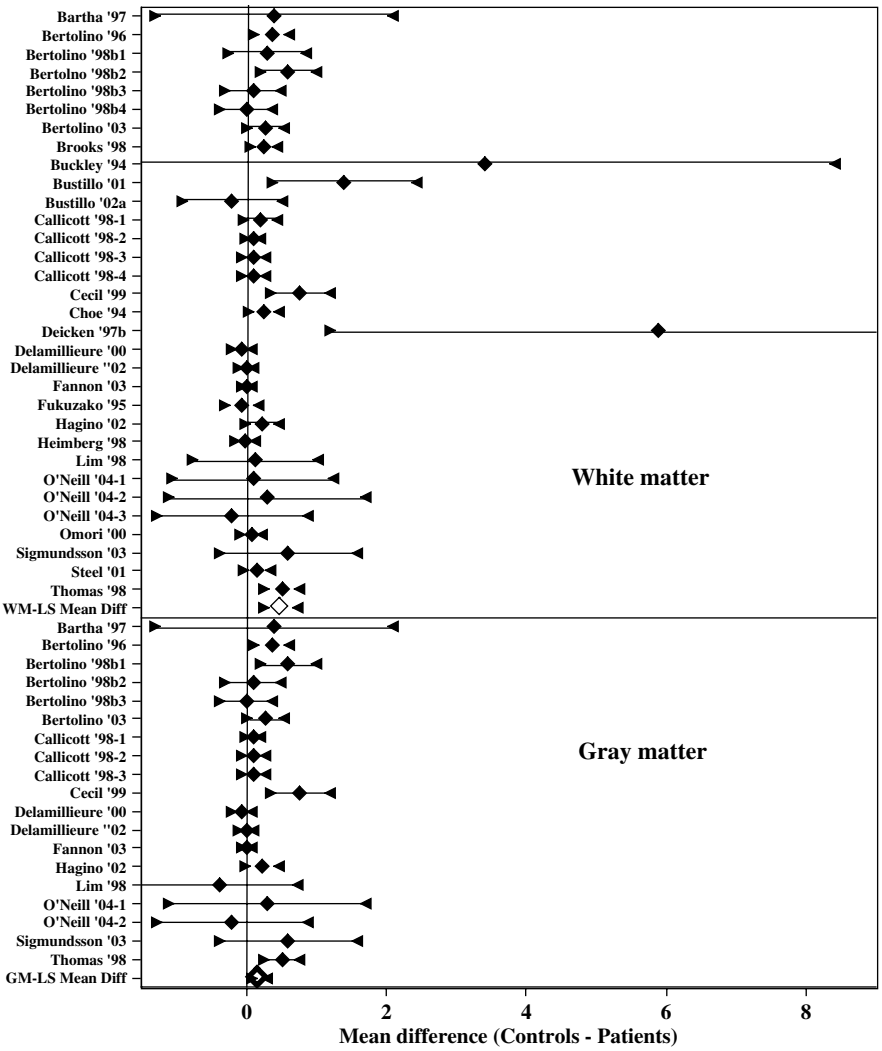

Figure 2 Visual summary of a meta-analysis of NAA levels in WM of the frontal lobe and in GM of the frontal lobe of patients with schizophrenia (SZ) compared to healthy controls (data from Table 4). There is no apparent difference between patient WM and patient GM, in the extent of reduction of NAA levels.

levels in hippocampus and in cortical GM and WM of the frontal lobe. No other tissues show as well corroborated or convincing a reduction of NAA in SZ patients (Table 3). There is little evidence to support a hypothesis that GM and WM differ in relative NAA levels (Table 4), or that chronic patients have a lower level of NAA than FE patients (Table 5).

Most (eight of 15) published studies of the hippocampus report a highly significant ($p<0.01$) reduction of NAA in patients, with an average difference of 10% (Table 2). Our meta-analysis confirms that the reduction of NAA in patients is significant, whether NAA is characterized as a raw value ($p<0.0001$) or as the ratio of NAA/Cr ($p<0.0001$). This is somewhat surprising, given that power calculations suggest that only one of these studies had 80% power to detect a reduction of NAA of 10% in patients. This suggests that there may be a publication bias in the literature, such that studies which report a significant difference between patients and controls are more likely to be published than are studies that report no such differences. More work will be needed to determine whether the differences in hippocampal NAA that have been reported between patients and controls are real and meaningful.

A potential weakness of our analytic approach is that simply measuring NAA levels provides little or no specificity as to the disease process inherent to SZ, since brain NAA is reduced in a broad range of illnesses. Extensive evidence confirms that NAA levels are lower than normal in patients with tumor or stroke (Zimmerman and Wang 1997; Taylor *et al*, 1998), but recent evidence shows that NAA is also reduced in traumatic brain injury (Ariza *et al*, 2004), multiple sclerosis (Gadea *et al*, 2004; Tartaglia *et al*, 2004), epilepsy (Bernasconi *et al*, 2003; Vermathen *et al*, 2003), vascular dementia (Schuff *et al*, 2003), Alzheimer disease (Dixon *et al*, 2002; Valenzuela and Sachdev, 2001), Huntington disease (Sanchez-Pernaute *et al*, 1999), spinocerebellar ataxia (Guerrini *et al*, 2004), perinatal asphyxia (Pavlakis *et al*, 1999), transposition of the great arteries (Miller *et al*, 2004), mood disorder (Cecil *et al*, 2003), gliomatosis cerebri (Galanaud *et al*, 2003), focal cortical dysplasia (Vuori *et al*, 2004), and radiation necrosis

Table 5 Findings in Prefrontal Cortex (Excluding Anterior Cingulate) of FE and Chronic SZ Patients

		Reported values for [NAA] or NAA/Cr						
Author (year)	**NAA (%)**	**Original (*p*-value)**	**Patient (mean)**	**Patient (SD)**	**Patient (*n*)**	**Control (mean)**	**Control (SD)**	**Control (*n*)**
FE patients								
Bertolino *et al* (1998a)	86	0.009	2.54	NR	14	2.97	NR	14
Bertolino *et al* (2003)	99	—	2.14	NR	24	2.17	NR	24
Brooks *et al* (1998)	87	0.02	1.67	0.22	16	1.92	0.31	12
Cecil *et al* (1999)	57	0.0006	0.96	0.38	18	1.70	0.34	24
Total					72			74
Average	82.3							
SD	17.8							
Chronic patients								
Bertolino *et al* (1996)	87	0.03	2.43	NR	10	2.78	NR	10
Bertolino *et al* (1998b)	82	0.004	2.53	0.61	12	3.09	0.26	12
Bertolino *et al* (1998c)	86	0.001	2.45	NR	10	2.86	NR	10
Block *et al* (2000)	94	—	2.75	0.28	25	2.93	0.35	19
Buckley *et al* (1994)	92	—	39.40	9.20	20	42.80	7.40	15
Callicott *et al* (1998)	97	—	2.65	0.36	47	2.74	0.41	66
Hagino *et al* (2002)	87	—	1.44	0.23	13	1.66	0.37	13
Sigmundsson *et al* (2003)	96	—	13.30	1.80	25	13.90	1.70	26
Total					162			171
Average	90.1							
SD	5.4							

SD = standard deviation; *n* = sample size; NR = not reported.

(Dowling *et al*, 2001). As NAA reduction is characteristic of such an extraordinarily broad range of diseases, the abundance of NAA in the brain offers little or no insight into the disease process inherent to SZ.

A second potential weakness of our analytic approach is that we have treated NAA as if it was the only information available by MRS, and this is not true (Omori *et al*, 1997). In fact, measurement of NAA alone is clearly not sufficient to make a clinical diagnosis, since the spectra acquired from patients with a broad range of brain diseases are often quite similar in having low NAA. There are other abundant brain metabolites, such as Cho and Cr, which are clearly visible in patient spectra, and there are additional metabolites, including lipid, lactate, glutamate, GABA, and inositol, which are in still lower abundance and can be very hard to discern in patient spectra. To understand disease processes in the brain, investigators must analyze these other resonances, in addition to NAA (Richards, 1991). Nevertheless, the analysis presented here (Table 6) suggests that even NAA is seldom measured with enough precision to provide a clear picture of disease processes. Resonances other than NAA, because they are less easily resolved by MRS, are measured with substantially less precision than is possible for NAA (Mullins *et al*, 2003). The only way to overcome the problems inherent to an insensitive methodology such as MRS is to improve the precision of the measurement or to accrue a large number of subjects. We note that it is especially important to validate the precision of MRS methodology in any study that involves data collection at multiple sites (Komoroski *et al*, 2004).

A third potential weakness of our analytic approach is that we assume that all studies are of equal validity, and this also is not true. Studies with large sample sizes have greater statistical power than small studies, even if the *p*-values are similar (Table 6). Yet, some studies with a reasonable sample size could still be weakened by inadequate methodology. We have not attempted to discern which studies are more likely to be methodologically robust, for several reasons: firstly, it is essentially impossible to determine methodological rigor from the brief description of methods that is typically published in a nonspecialty journal; secondly, in the absence of an objective way to determine which studies are rigorous, it would be wrong to rely upon hearsay evidence as to which studies are flawed; and finally, older studies are more likely to be methodologically flawed than are newer studies, but they are also more likely to be seminal or published by senior researchers. We believe that criticizing a study for being formative would be foolish. As an example of the increased methodological rigor that is characteristic of more recent

Table 6 CV of NAA (Units of [NAA] or NAA/Cr) and Study Power in Frontal Lobe at 1.5 T

CV of NAA and power calculation for each study

Author (year)	Patients	Controls	Region studied	Pt CV	Ct CV	Power (%)
Block *et al* (2000)	38	54	Frontal lobe	10.2	11.9	92
Buckley *et al* (1994)	28	20	L frontal lobe	23.4	17.3	26
Bustillo *et al* (2001)	17	17	L frontal (cloz.)	9.7	13.3	7
Bustillo *et al* (2001)	18		L frontal (haloper.)	14.7		53
Bustillo *et al* (2002a)	10	10	L frontal WM	7.6	6.8	8
Deicken *et al* (1997a)	26	16	R ant. cingulate	16.8	9.5	88
Deicken *et al* (1997a)	As above		L ant. cingulate	18.1	14.5	84
Deicken *et al* (1997b)	24	15	R frontal lobe	19.4	17.4	12
Deicken *et al* (1997b)	As above		L frontal lobe	21.6	19.3	69
Delamillieure *et al* (2000)	22	21	L medial PFC	16.2	15.6	5
Delamillieure *et al* (2000)	As above		R medial PFC	17.3	12.0	5
Delamillieure *et al* (2002)	17	14	L PFC	11.0	11.0	5
Delamillieure *et al* (2002)	As above		R PFC	16.2	9.9	5
Ende *et al* (2000)	19	16	Ant. cingulate	13.8	6.6	79
Fannon *et al* (2003)	21	18	Frontal cortex	11.4	10.3	5
Fannon *et al* (2003)	12		Frontal cortex	7.7		73
Hagino *et al* (2002)	13	13	L inf. frontal cortex	16.0	22.3	64
Hagino *et al* (2002)	As above		R Inf. frontal cortex	20.5	19.0	12
Heimberg *et al* (1998)	13	14	L frontal lobe	14.6	13.3	5
Omori *et al* (2000)	20	16	L frontal lobe	10.5	9.3	30
O'Neill *et al* (2004)	11	20	Frontal cortex	6.4	20.0	42
Sigmundsson *et al* (2003)	25	26	R frontal lobe	14.5	8.8	5
Sigmundsson *et al* (2003)	As above		L frontal lobe	13.5	12.2	22
Thomas *et al* (1998)	12	12	Frontal cortex	25.9	22.0	91
Average study *n*	19.2	18.9	Average	14.9	13.7	37.0

Pt = patient; ct = control; L = left hemisphere; R = right hemisphere; WM = white matter; Inf. = inferior; *n* = sample size; PFC = prefrontal cortex.
This tables includes only papers that tabulated means and standard deviations (SD) of data. Power of each study to detect the difference reported was calculated with NQuery using patient and control means and the pooled SD calculated from the patient and control standard deviations.

studies, we note that many early studies did not properly match patients to controls by demographics; it would be problematic to match patients to controls by NAA levels, if they were not properly matched by age.

Nevertheless, the analysis we present can offer some unique insights. If NAA reduction is localized, this can potentially provide a clue as to the locus of brain injury. For example, NAA appears to be reduced in the thalamus of patients with idiopathic generalized epilepsy (Bernasconi *et al*, 2003), and a significant negative correlation was found between thalamic NAA/Cr and the duration of epilepsy, whereas NAA was not reduced in any other brain region examined in such patients. This finding argues that progressive thalamic neuronal dysfunction may be involved in idiopathic generalized epilepsy (Bernasconi *et al*, 2003). If we extend this argument, by asking if there are specific loci of brain abnormality in patients with SZ, the answer is less clearcut (Table 3). The only tissues for which there are well-replicated and robust findings of NAA reduction are the frontal lobe, including both cortical GM and WM, and the hippocampus. Evidence of NAA reduction is weaker in tissues of the basal ganglia, in brain lobes other than the frontal lobe, or in the midbrain (Table 3). Therefore, the evidence of NAA deficit is fairly strong in the same tissues for which evidence of a volumetric deficit in patients is strong (Shenton *et al*, 2001). Some reports suggest that there is no relationship between NAA reduction and volumetric loss (Deicken *et al*, 1999), but it seems reasonable nonetheless, to propose that frontal lobe and hippocampus are key loci of brain injury or abnormality in SZ.

There is recent evidence that treatment with antipsychotic medication can have an effect on NAA levels in SZ patients (Fannon *et al*, 2003; Bertolino *et al*, 2001). Patients treated with atypical antipsychotics had higher levels of NAA in hippocampus than did patients treated with haloperidol (Fannon *et al*, 2003). A longitudinal within-subjects design was used to evaluate 23 chronic SZ patients, first when they were drug free (either drug naïve or off medication for at least 2 weeks), then again after they had been stably medicated for at least 4 weeks. Spectra acquired by spectroscopic imaging were analyzed for relative changes in NAA, with 11 brain regions assessed. Patient NAA levels increased significantly in as little as 4 weeks in the dorsolateral prefrontal cortex (DLPFC), but in none of the

other 10 brain regions. As the experimental design of this study used each patient as their own control, relatively small changes in NAA were potentially significant (Bertolino *et al*, 2001). Another study, which did not use a within-subjects design, also reported that NAA levels were higher among patients on atypical antipsychotics (clozapine or risperidone) than among patients on typical antipsychotics (Braus *et al*, 2001, 2002). Furthermore, the longer patients had been treated with atypical antipsychotics, the higher were levels of NAA in the anterior cingulate, suggesting that atypical antipsychotics may reverse the NAA decrease seen in chronic SZ (Braus *et al*, 2001, 2002). These results, while preliminary, suggest that NAA levels can change acutely, in response to medication, over a fairly short period of time. This would tend to argue against the current conception of NAA as a marker of neuronal viability (Meyerhoff *et al*, 1993).

The NAA peak has been hypothesized to be a marker of the number of viable neurons in brain tissue (Meyerhoff *et al*, 1993), but evidence is beginning to accumulate against this simple hypothesis. For example, a case report of a child with mild mental retardation showed no NAA resonance at all in the brain (Martin *et al*, 2001). The NAA peak can decrease transiently after acute brain injury (de Stefano *et al*, 1995), and NAA can show stable increases after therapy for moya–moya (Shimizu *et al*, 1997), amyotrophic lateral sclerosis (Kalra *et al*, 1998), or Wernicke encephalopathy (Mascalchi *et al*, 2002). The finding that NAA deficits can be reversed over a relatively short period of time argues strongly that NAA is not a reliable marker of neuronal loss (Barker, 2001). Furthermore, NAA can be chronically elevated in certain disease states that are not known to be associated with neuronal proliferation, including Asperger syndrome (Murphy *et al*, 2002), sickle cell disease (Steen and Ogg, 2005), Pelizaeus–Merzbacher disease (Takanashi *et al*, 2002), Canavan disease (Matalon *et al*, 1995), and familial bipolar I disorder (Deicken *et al*, 2001b). These results are not consistent with the proposed role of NAA as a neuronal marker (Bertolino and Weinberger, 1999; de Stefano *et al*, 1995; Barker, 2001; Steen and Ogg, 2005); thus, NAA reduction in SZ patients cannot be interpreted as suggesting neuronal depletion in disease.

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