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T_2 relaxation effects on apparent N-acetylaspartate concentration in proton magnetic resonance studies of schizophrenia

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Abstract

Over the past two decades, many magnetic resonance spectroscopy (MRS) studies reported lower N-acetylaspartate (NAA) in key brain regions of patients with schizophrenia (SZ) compared to healthy subjects. A smaller number of studies report no difference in NAA. Many sources of variance may contribute to these discordant results including heterogeneity of the SZ subject populations and methodological differences such as MRS acquisition parameters, and post-acquisition analytic methods.

The current study reviewed proton MRS literature reporting measurements of NAA in SZ with a focus on methodology.

Studies which reported lower NAA were significantly more likely to have used longer echo times (TEs), while studies with shorter TEs reported no concentration difference. This suggests that NAA quantitation using MRS was affected by the choice of TE, and that published MRS literature reporting NAA in SZ using a long TE is confounded by apparent differential T_2 relaxation effects between SZ and healthy control groups.

Future MRS studies should measure T_2 relaxation times. This would allow for spectral concentration measurements to be appropriately corrected for these relaxation effects. In addition, as metabolite concentration and T_2 relaxation times are completely independent variables, this could offer distinct information about the metabolite of interest.

Keywords

T2 relaxation; NAA; schizophrenia; MRS

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1 INTRODUCTION

Spatially resolved magnetic resonance spectroscopy (MRS) has proven to be a powerful and non-invasive tool for the investigation of the neurochemistry of the working healthy and pathological brain. MRS has been used as an investigational tool in schizophrenia (SZ) research following the development of spatially selective pulse sequences and water suppression techniques in the late 1980's which enabled the *in vivo* detection of brain metabolite resonances.

One brain metabolite commonly examined in MRS studies is N-acetylaspartate (NAA). NAA is a free amino acid that is biosynthesized in neuronal mitochondria. It is found almost exclusively in neurons, including axons and dendrites, and is considered a marker for neuronal viability and integrity. Changes in NAA concentrations could be caused by changes in neuronal density or neuronal dysfunction (such as changes in glucose metabolism or mitochondrial function). A number of proton MRS (^{1}H-MRS) studies have reported reduced NAA in the frontal and temporal lobes and other structures of patients with SZ. However, a lesser number of studies report no difference in NAA between patients with SZ and healthy controls (HCs). What are the possible origins of the disparate findings? There are many potential sources of variance which may contribute to these conflicting results including differences in clinical and demographic characteristics (such as medication status or duration of illness), and also the choice of specific MRS acquisition parameters, techniques, and analytic methods (Sanches et al., 2004).

The fundamental principle underlying proton MRS is that for each MRS visible metabolite, the fundamental frequency at which the nucleus of each hydrogen atom (proton) resonates is shifted by a small amount (measured in parts-per-million, ppm) from the basic resonant frequency of a single, isolated, proton. Chemically identical hydrogen nuclei within an MRS visible metabolite experience similar local magnetic fields and nuclear spin-spin interactions and therefore have a characteristic chemical shift along the resonance frequency axis, which results in a spectral peak that is a chemical signature of that group of protons within that metabolite. The peak intensity or area under the spectral peak is proportional to the number of nuclei contributing to that peak, which is determined by the concentration of that metabolite within a selected volume of interest (voxel) (Jansen et al., 2006).

As discussed below, several MRS acquisition parameters and subject tissue characteristics ultimately affect the measured spectral peak area. When these myriad factors are properly accounted for, or held constant, a "raw" peak integral (area under the peak) is obtained which is proportional to the concentration of the metabolite of interest. These raw spectral measurements reflect absolute metabolite concentrations which may then be further normalized into conventional units or expressed as dimensionless concentration ratios to some within-subject reference metabolite such as creatine (Cr). The use of metabolite (or water) ratios does correct for differences in excitation within a voxel of interest. However, when using this method, if a change in normalized data is observed, it is impossible to tell whether the numerator (the metabolite of interest) or the denominator (the reference metabolite, often Cr) is changing (Jansen et al., 2006). In early MRS studies, the creatine spectral peak (Cr-PCr) was commonly chosen as the reference metabolite as it was hypothesized to be constant and comparable between brain regions or participant populations; however it has been demonstrated that this assumption does not always hold, even in healthy individuals. In fact, coefficients of variation are higher in ratio studies than in absolute quantification studies (Schirmer and Auer, 2000; Li et al., 2003). The assumption of uniform concentration of a reference metabolite is even more unreliable in abnormal populations such as patients with SZ (Ongur et al., 2010b). Therefore, although the use of a reference metabolite such as Cr was commonly used in the early MRS literature, in recent

years this practice has diminished in favor of absolute concentration measures with the caveat that normalization to the absolute water reference peak is still common practice as discussed below.

However, there are a number of other methodological considerations that affect spectral quantification as well, including radiofrequency coil properties, calibration procedures, spectral fitting methods, voxel corrections for fractional cerebral spinal fluid (CSF)/gray matter/white matter content, macromolecule suppression, and spectral editing techniques (Jansen et al., 2006). The acquisition of a spatially resolved spectroscopic signal for a metabolite of interest requires the selection of a significant number of spectrometer acquisition parameters. Each of these parameters has an impact on the characteristics of the spectrometer signals used to excite the specific brain region being analyzed, and in the resultant spectrum obtained from the excitation echoes. The conversion of an integrated area under a spectral peak for a specific resonance line to a metabolite concentration requires a number of approximations. A general expression for this relationship between signal intensity I and metabolite concentration [M] is:

$$I = c_1 \cdot N \cdot [M] \cdot V \cdot B_1(r) \cdot L \cdot \sin(\theta) \cdot \exp(-\mathrm{TE}/T_2*) \cdot (1-\exp(-TR/T_1)) \quad [1]$$

where I = signal intensity, c_1 = constant, N = number of equivalent atoms per molecule, [M] = metabolite concentration, V = volume, B_1(r) = reception field distribution, L = function of radiofrequency coil loading, θ = RF excitation tip angle, TE = acquisition delay or echo time (depending upon method), T_2* = spin-spin transverse relaxation time including static field effects, TR = pulse repetition time, and T_1 = spin-lattice relaxation time.

The goal in MRS experiments is to hold values of c_1, N, V, B_1(r), and θ constant, to the extent possible, or, when necessary, to correct for variations. For example, L (the amount of power necessary to transmit the signal) and the signal to noise ratio (SNR) is dependent on the volume of the object near the coil (ie. the size and tissue composition of the head being examined) and by the electrical impedance of the coil when “loaded” with a subject’s head. Larger, denser objects require more transmitted power to achieve a constant flip angle θ. As the size of the participant’s head cannot be controlled, this is a source of variability, although some experimenters attempt to control for this by measuring the power received by the coil and the SNR and calculating the volume of the head (Jansen et al., 2006). T_1 is assumed to be constant, and in most proton MRS experiments, T_1 variability is considered to have a negligible effect especially at a longer TR. Saturation of longitudinal magnetization due to repeated pulses in standard MRS pulse sequences also tend to reduce T_1 effects. Most TRs for these experiments range from 1500–3000ms, and the T_1 for NAA at 1.5 and 3T is ~1300–1400 ms (Rutgers and van der Grond, 2002; Traber et al., 2004). This review does assume that T_1 is not variable between groups, however this could be an interesting topic of a future study, especially one focused on phosphorus MRS findings as the variability would manifest as a TR-dependence (long vs. short) in the observed MRS signal.

Thus, after eliminating all other terms of the above equation as sources of variance, this review will focus on the possibility that differential NAA concentration measurements between experiments could be due to the selection of long versus short TEs during signal acquisition because long TE experiments are more sensitive to any differences in T_2 relaxation times between HC and SZ groups. The T_2 relaxation time reflects the mean decay time of the MR signal or free-induction decay (FID) for a given metabolite, and different metabolites have different T_2 relaxation times. Mobile molecules will have longer T_2 times (longer FIDs) than less mobile molecules. Therefore, if the local micro-environment in which the metabolite of interest resides is altered, then relaxation times (and therefore measures of metabolite concentrations) may also be affected. This is especially important

when normalizing metabolites that are intracellular only (ie NAA) to molecules which are found in both the intracellular and extracellular space (ie Cr) as changes in the relaxation times of metabolites in these two compartments could be differentially affected by an abnormal environment. Studies that normalize to water rather than Cr do not avoid this problem either, as previous studies have found schizophrenia-related changes in water proton relaxation times (Andreasen et al., 1991; Williamson et al., 1992; Supprian et al., 1997; Pfefferbaum et al., 1999; Aydin et al., 2007; Ongur et al., 2010b). For instance, some studies have found that within groups of patients with SZ, T_2 relaxation times of intracellular metabolites (Cr + phosphocreatine, choline containing compounds) are reduced compared to that of HC subjects (Ongur et al., 2010b). The authors suggest that this could be due to a decrease in neuronal cell volumes and/or increased macromolecule concentrations resulting in increased metabolite-macromolecule interactions and more rapid loss of transverse magnetization (decreased T_2 relaxation time) (Ongur et al., 2010b).

The existence of significant discrepancies in MRS research literature examining SZ has motivated this review of these assumptions and analysis of the published results. These questions were tangentially addressed in an insightful review and meta-analysis by Steen et al., (2005) which concluded that some of the inconsistency in findings on NAA within the literature are due to many of these studies being underpowered. The present review focuses instead on published proton MRS literature reporting proton MRS measurements of NAA in SZ research with a focus on the choice of TE. These analyses reveal evidence that certain analytic assumptions may not hold in comparisons of quantitative spectroscopic data between patients with SZ and HCs.

2 METHODS

A pubmed search was performed with the keywords schizoph*, spectroscopy, “magnetic resonance”, brain, and limited to English language articles on humans with an abstract available. This search resulted in 351 articles. Of these, 239 were excluded. For exclusion details, see Table 1. In addition, three more articles were found in reference lists (Renshaw et al., 1995; Bertolino et al., 1998; Deicken et al., 1999) resulting in 115 journal articles. A table of data from all studies included in the analysis can be found in Table 2. Studies were not examined for details of patient selection such as matching to control participants by age, sex, symptom profiles, or for duration of illness. Only peer reviewed, published reports were included in the analysis. Subjects who meet diagnostic criteria for schizophrenia comprise a very heterogeneous population, and the studies included in the analysis, in the aggregate, reflect this diversity reporting results from study populations that span different age ranges, illness durations, and symptom severity.

Reported results for NAA concentration in patients with SZ and HC participants, the spectrometer acquisition parameter TE, normalization technique (the ratio of NAA to Cr versus examination of absolute concentration of NAA), and region of interest were recorded for each study. The regions of interest included: Anterior Cingulate (ACC), Basal Ganglia, Cerebellum, Frontal Lobe (including dorso-lateral Prefrontal Cortex, Orbitofrontal Cortex, and Prefrontal Cortex), Hippocampus/Temporal Lobe, Thalamus/Putamen, Occipital lobe, Parietal Lobe, and other (including Centrum, Pons, Insular Cortex, Cingulate Gyrus, Centrum Semiovale, Dentate Nucleus, gray matter (whole brain) and white matter (whole brain). When more than one region of interest was examined, each region was counted as a separate experiment. The goal of this analysis is to test for acquisition parameter dependence of published results and since the regional distribution of NAA T_2 abnormalities is unknown each separate experiment was considered independent. This assumption is not required for the region specific results reported. Also, when more than one population was examined (ie. different medication groups, or participants with and without deficit syndrome), each

population was counted as a separate experiment. A cut off of 40 ms was used to differentiate long TE from short TE methods. This choice of 40 ms was driven by a natural partition in the data set with the vast majority of studies having either a TE over 100 ms or ≤ 40 ms. In fact, of all 115 journal articles included in the current analyses, only 4 studies had a TE between 40 and 100 ms (Table 2).

A statistical test for TE dependence of the published NAA results was performed using the 1-sided Fisher's Exact Test with TE (short versus long) and NAA finding (decrease versus no change) as the variables of interest in a 2×2 table. For details of breakdown of analysis groups see Table 3. All N's refer to the number of experimental results (all regions, both normalization methods, and all studies), rather than the number of subjects. First, data from all studies (both those using normalization to Cr and those quantifying absolute concentrations) were broken down by region. As discussed in the introduction, normalization to an internal "reference metabolite" may create additional confounds due to possible reference metabolite variation between subjects, so experiments were then broken down into two groups: studies normalizing to Cr (n=200) and studies which yielded absolute concentrations of NAA (n=186). Finally, data both Cr normalization and absolute concentration studies and all regions of interest were tested (n=333). Studies which included both normalization techniques were included in each individual data set (when they were segregated into studies which normalized to Cr versus studies which yielded absolute concentrations), however only absolute concentration data for these studies were included in the "all studies, all regions" analysis).

3 RESULTS

See Table 2 for a complete list of studies, study findings, regions of interest in each study, and TE used in each study. The first analysis included data normalized to Cr as well as data which quantified absolute concentrations (Figure 1A). The comparison of NAA findings between long and short TE studies was significant within the thalamus and putamen (Figure 1A; Fischer's Exact Test p=0.039). All other comparisons were not significant, although there was a trend level change within the hippocampus and temporal cortex (Figure 1A; Fischer's Exact Test p=0.053). The second analysis included only data from studies which quantified absolute concentrations of NAA (Figure 1B). The comparison of NAA findings between long and short TE studies was significant within the thalamus and putamen (Figure 1B; Fischer's Exact Test p=0.023), as well as the hippocampus and temporal cortex (Figure 1B; Fischer's Exact Test p=0.007). In a final analysis, only regional data from studies which used metabolite ratios normalized to Cr were included, and all comparisons were not significant (Figure 1C).

Because the field strength at which the experiment was conducted affects metabolite specific T1 and T2 relaxation rates, there may be an enhancement or minimization of the T2 effect when different field strengths are used. Therefore, we also conducted the analyses, including only studies that were conducted at 1.5T. When this analysis included data which normalized to Cr as well as data which quantified absolute concentration, the comparison of NAA findings between long and short TE studies was significant within the thalamus and putamen (Fischer's Exact Test p=0.042. When this analysis included only data from studies which quantified absolute concentrations of NAA, the comparison of NAA findings between long and short TE studies was significant within the thalamus and putamen (Fischer's Exact Text p=0.043), as well as the hippocampus and temporal cortex (Fischer's Exact Test p=0.013). When this analysis included only data normalized to Cr, all comparisons were not significant.

Finally, data from all regions of interest were examined. Although there are a number of limitations associated with this analysis, such as combining data from assessments of both gray and white matter, these analysis are meant to assess findings within the literature as a whole, rather than only assessing findings from regions of interest that have attracted sufficient attention to merit several publications. In this all-inclusive analysis, there was a significant difference in comparison of NAA finding between long and short TE studies when only data from studies which quantified absolute concentration were included in the analysis (Figure 2; Fischer's Exact Test p=0.024). Comparisons which included only data normalized to Cr, and comparisons including both Cr normalization and absolute concentrations were not significant (Figure 2). For the same rational mentioned above, we repeated this analysis including only studies that were conducted at 1.5T. When we included only data only from studies which quantified absolute concentrations of NAA, the comparison of NAA findings between long and short TE studies decreased to a trend level of significance (Fischer's Exact Test p=0.057).

4 DISCUSSION

The analyses in the current study provide evidence that the published literature to date on MRS studies of schizophrenia is partially confounded by T_2 effects. Studies with one set of acquisition parameters (long TE) were much more likely to report lower concentrations of NAA in patients with SZ, while studies with different acquisition parameters (short TE) were likely to report no change. Previous publications have also noted this possibility (Olson et al., 2003; Sanches et al., 2004; Tunc-Skarka et al., 2009), however the current study uses a much larger data set to confirm this bias. Several MRS studies have now reported metabolite and water T_2 relaxation differences in some brain regions of schizophrenic subjects, further supporting the assertion that T_2 effects have likely been confounding measurements reported in the MRS schizophrenia literature for decades (Tunc-Skarka et al., 2009; Ongur et al., 2010b).

Even so, these studies do also confirm reduced NAA concentrations in patients with schizophrenia. Indeed, one caveat to our analysis is that our use of the χ^2 technique necessitated that we treat each study with equal weight, regardless of sample size. A meta-analytic approach to the same data may yield different results, perhaps showing reduced NAA even at longer TEs. In addition, it is important to note that Tunc-Skarka et al report NAA T_2 findings in relatively homogeneous white matter voxels whereas Ongur et al, and other studies reporting T_2 relaxation times in NAA and other brain metabolites in gray matter voxels are subject to partial volume effects including both concentration and relaxation rate differences for NAA (and other metabolites) in white vs. gray matter. While partial volume corrections are routinely done for fractional gray vs. white voxel composition, they are rarely, if ever, done for differential relaxation rates. As discussed below, between group water proton T_2 relaxation differences also contribute to the list of potential confounds.

So what does this mean for future MRS studies? It should be noted that long TE methods were originally used because early gradient systems on MRI scanners had significant difficulties with eddy currents that made short TE spectra difficult to interpret. Hardware advances, driven by explosive interest in the use of echo-planar MRI largely resolved this issue. This advance, coupled with the growing awareness of the potential confounding effects of long TE MRS acquisition (with resultant T_2 effects on spectral quantification), has allowed for a shift away from longer echo times in the published MRS literature since 2004 (Figure 3). While short TE MRS studies minimize T_2 weighting, the advantages of measuring metabolite T_2 times should not be overlooked.

For example, when metabolite T_2 times are measured, absolute metabolite concentrations may be properly corrected for residual T_2 weighting – even at short echo times. This would be especially important in instances when T_2 effects on the MRS signal may oppose and partially or completely obscure changes due to concentration. As one hypothetical example: if NAA concentration within a voxel is increased due to increased neuronal cellular packing density, but NAA T_2 is decreased (due to decreased neuronal cell volume and increased spin-spin interactions with macromolecules causing more rapid signal dephasing), these factors would tend to cancel each other out, and the (uncorrected) concentration acquired by a simple single TE MRS experiment could indicate that NAA concentration is not changing when it is actually increased. However, if the experimenter were to measure the NAA T_2 relaxation time as well as the T_2 corrected NAA concentration, both important changes within the microstructural environment could be identified. Choice of normalization technique also introduces complex T_2 considerations. Even the preferred water normalization method, which uses the unsuppressed water signal as a normalizing factor can be affected by between group differences in tissue water concentration and water proton T_2 differences. Higher water proton T_2 relaxation times have been reported in schizophrenia (Tunc-Skarka et al., 2009; Ongur et al., 2010b). Using water as a reference denominator, we can predict that higher water T_2 would artificially lower the normalized NAA concentration measurement in the context of unchanged or reduced NAA T_2. This would have increased the likelihood of reporting lower NAA for studies at longer TE which did not correct for T_2 relaxation effects.

In addition, metabolite concentration and T_2 relaxation times are completely independent variables which offer distinct and complimentary information about the metabolite of interest. Changes in T_2 relaxation times reflect changes in the metabolite-specific compartment of interest which is different for each metabolite. NAA T_2 relaxation occurs primarily within the intra-neuronal cytosolic compartment, and changes in T_2 relaxation times in individuals with SZ may correlate with specific changes within neurons. Decreased NAA T_2 (reflecting more rapid NAA MRS signal dephasing due to spin-spin interactions with macromolecules in the cytosol) is consistent with smaller cell volume rather than complete loss of neurons. In this case, the suggestion that some component of decreased NAA may be due to T_2 relaxation effects would be an encouraging finding as it might suggest a potentially reversible pathologic change, whereas complete neuronal loss is more problematic. Decreased NAA T_2 is also consistent with the observed reduced gray matter volume, increased packing density, smaller cell size, and the relatively preserved number of neurons reported in the post-mortem literature for subjects with schizophrenia (Olson et al., 2003; Ongur et al., 2008; Ongur et al., 2010b; Ongur et al., 2010a). Similarly, T_2 relaxation time measurements of other commonly studied MRS visible metabolites may yield additional insight into metabolite-specific micro-environments. For example, the portion of choline that is visible using MRS is the free component (non-bound) both within neurons, myelin, and in the extracellular compartment. Changes in choline T_2 contrasted with changes in choline concentration can answer questions that concentration data alone cannot address.

In the future, experiments should be designed such that spectra are acquired at multiple TEs to provide an estimate of the individual T_2 relaxation times for each metabolite. A study by Tunc-Skarka et al. (2009) took just this approach. Using a protocol including 30 ms, 80 ms, 200 ms, 300 ms, and 420 ms TEs, they scanned 23 patients with SZ and 29 HCs. They found a trend for reduced NAA concentrations at the lowest TE, which became significant in all longer TE experiments. They also found shortened NAA T_2 relaxation times in the patients, and conclude that this is consistent with changes in microstructural white matter in patients with SZ. They found no changes in concentration or T_2 relaxation time in any other metabolites, including glutamate, choline, and creatine. Although it does take additional

time, designing experiments using this or a similar method will allow accurate metabolite concentrations to be calculated which take into account changes in metabolite T_2 relaxation times in addition to metabolite concentration. This will avoid potential errors in concentration measurements as well as provide new and complimentary information about the local micro-environment of each metabolite species.

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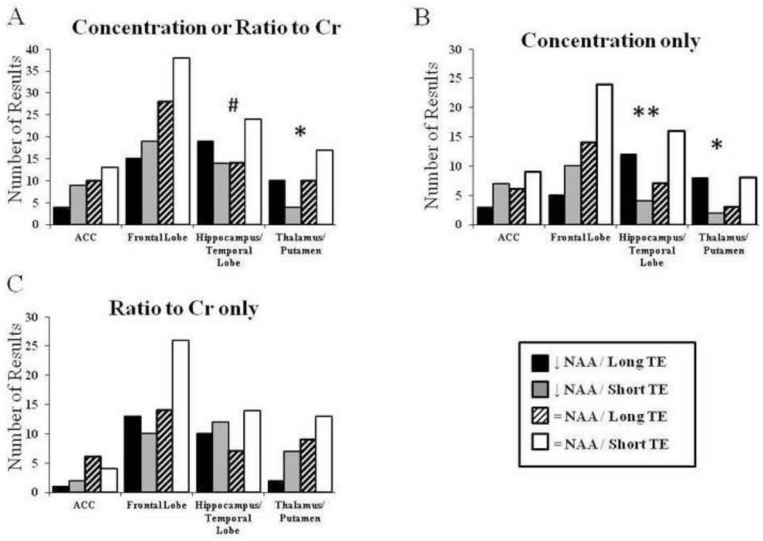

Figure 1.

Count of results organized by NAA concentration finding and TE methodology. This includes studies quantifying absolute NAA concentration for each region of interest from both quantification methods:-- normalizing to Cr or quantifying absolute NAA concentration (A), data from studies which only quantified absolute NAA concentration (B), and studies which only normalized to Cr (C). Data are separated by brain region. Data are expressed as a number of results. # = $p < 0.10$, * = $p < 0.05$, ** = $p < 0.01$

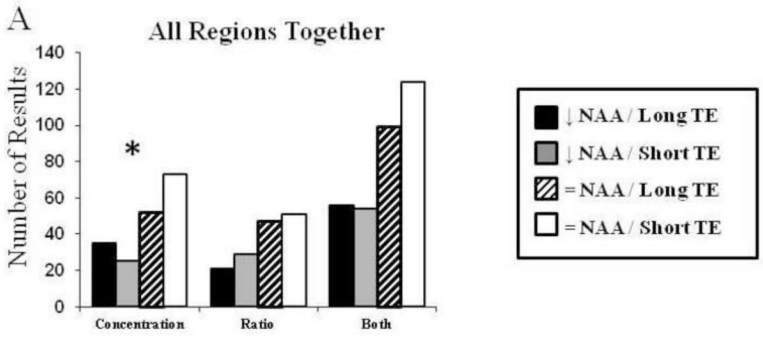

Figure 2.
Count of results organized by NAA concentration finding and TE methodology. This includes studies quantifying absolute NAA concentration for all brain regions assessed.

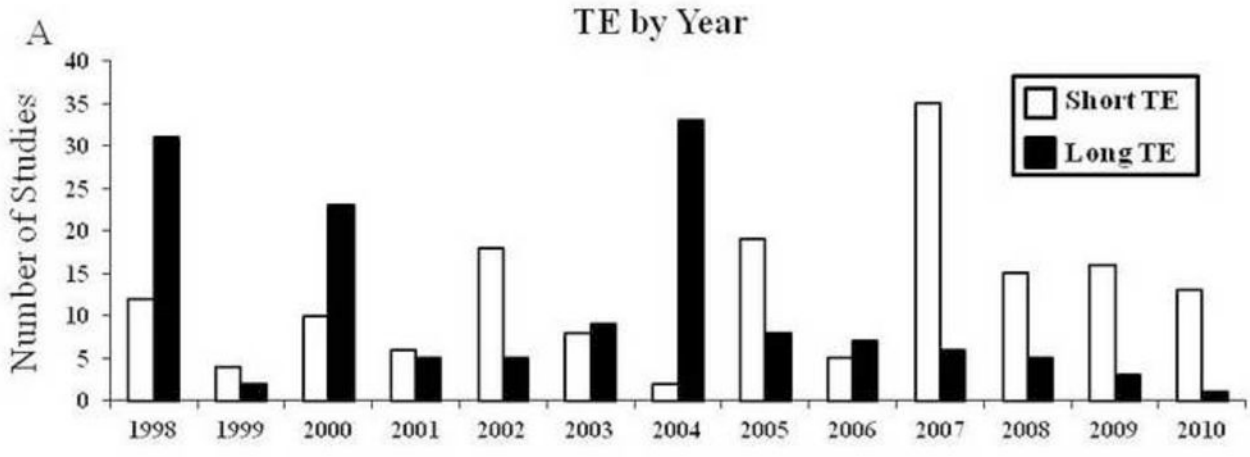

Figure 3.
Number of studies with long versus short TE organized by year. Data are expressed as a count of studies.

Table 1

Articles excluded from the final analysis

N	Reason for exclusion
58	Non-MRS methodology
57	Review articles with no new data
55	Phosphorus MRS only
29	Methods only/no new statistics/correlational only
25	No separate healthy control or patient groups
8	Postmortem/cerebrospinal fluid/serum study
2	Spectral normalization to choline
2	N > 5
2	Did not report TE
1	Not in humans

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TABLE 2

Data from all studies included in the analysis

Finding	TE	N	Brain Region	Normalization	Citation
=	40ms	7 SZ; 7 HC	BG	Cr	(Ando et al., 2002)
=	35ms	32 SZ; 17 HC	Parietal WM; Thal	Concentration	(Auer et al., 2001)
↓ in FE = in chronic	30ms (multi-TE)	12 FE; 16 chronic; 15 HC	Genu of Corpus Callosum	Concentration	(Aydin et al., 2007)
↓	30ms (multi-TE)	14 SZ; 15 HC	Genu of Corpus Callosum	Concentration	(Aydin et al., 2008)
=	20ms	10 SZ; 10 HC	mPFC	Concentration	(Bartha et al., 1997)
= in GM	20ms	11 FE SZ; 11 HC	Left mesial-TL	Concentration	(Bartha et al., 1999)
↓	171ms	10 SZ; 10 HC	dlPFC, HP	Cr	(Bertolino et al., 1996)
↓	272ms	10 SZ; 10 HC	dlPFC, HP	Cr	(Bertolino et al., 1998a)
↓	272ms	14 SZ; 14 HC	dlPFC, HP	Cr	(Bertolino et al., 1998c)
↓ in dlPFC & HP = in others	272ms	12 SZ; 12 HC	dlPFC, HP, Thal, superior temporal gyrus, ACC, PCC, Occip, OFC, PFC WM, centrum semiovale	Cr	(Bertolino et al., 1998b)
↓	272ms	13 SZ; 13 HC	Bilateral dlPFC	Cr	(Bertolino et al., 2000)
↓	272ms	24 SZ; 24 HC	HP, dlPFC	Cr	(Bertolino et al., 2003)
↓ in HP = in others	272ms	17 SZ; 17 HC	dlPFC, HP, Thal, superior temporal gyrus, ACC, PCC, Occip, OFC, PFC WM, centrum semiovale, putamen, inferior temporal gyrus, superior cingulate,	Cr	(Blasi et al., 2004)
=	272ms	25 SZ; 19 HC	BG, FL	Cr	(Block et al., 2000)
=	30ms	11 SZ; 15 HC	TL	Concentration	(Bluml, 1999)
↓	136ms	16 SZ; 12 HC	FL	Cr	(Brooks et al., 1998)
=	68ms	28 SZ; 20 HC	TL, FL	Concentration	(Buckley et al., 1994)
↓ haloperidol = clozipine	40ms BG; 30ms FL	38 SZ; 21 HC	BG, FL	Concentration	(Bustillo et al., 2001)
=	40ms	11 SZ; 11 HC	BG	Concentration	(Bustillo et al., 2002a)
↓ FL medicated = in others	40ms	20 SZ; 10 HC	FL, Occip	Concentration	(Bustillo et al., 2002b)
=	40ms	32 SZ; 21 HC	FL, Occip, caudate, cerebellar	Concentration	(Bustillo et al., 2008)
↓	20ms	14 SZ; 10 HC	ACC	Concentration	(Bustillo et al., 2010)
↓ in H = in others	272ms	47 SZ; 66 HC	HP, ACC, posterior cingulate, centrum semiovale, Occip, FL WM, Thal, putamen, OFC, dlPFC, superior temporal gyrus	Cr	(Callicott et al., 1998)

Finding	TE	N	Brain Region	Normalization	Citation
↓ in HP & PFC = in others	272ms	13 SZ; 18 HC	ACC, putamen, PFC, HP, Thal	Cr	(Callicott et al., 2000b)
=	272ms	36 SZ; 73 HC	Centrum semiovale, superior temporal gyrus, OFC, ACC, posterior cingulate, Occip, FL WM	Cr	(Callicott et al., 2000a)
↓	21ms dlPFC; 19 ms midTL	10 SZ; 14 HC	dlPFC, midTL	Cr	(Cecil et al., 1999)
= Occip ↓ in others	30ms	23 SZ; 22 HC	FL (L and R), TL (L and R), Occip	Concentration	(Chang et al., 2007)
↓	20ms	23 SZ; 10 HC	FLWM	Cr	(Choe et al., 1994)
↓	20ms	34 SZ; 20 HC	PFC (L and R)	Cr	(Choe et al., 1996)
↓	135ms	24 SZ; 15 HC	FL (L)	Concentration	(Deicken et al., 1997b)
↓	135ms	26 SZ; 16 HC	ACC (R and L)	Concentration	(Deicken et al., 1997a)
↓	135ms	30 SZ; 28 HC	HP (R and L)	Concentration	(Deicken et al., 1998)
↓	135ms	23 SZ; 18 HC	HP (L and R)	Concentration	(Deicken et al., 1999)
↓	135ms	17 SZ; 10 HC	Thal (L and R)	Concentration	(Deicken et al., 2000)
↓	135ms	20 SZ; 15 HC	CB	Concentration	(Deicken et al., 2001)
↓ with deficit syndrome = in all together	30ms	17 SZ; 5 deficit syndrome; 22 HC	mPFC (L and R)	Cr	(Delamillieure et al., 2000b)
=	30ms	27 SZ; 24 HC	Thal (L and R)	Cr	(Delamillieure et al., 2000a)
=	30ms	17 SZ; 14 HC	mPFC, Thal, HP	Cr	(Delamillieure et al., 2002)
↓ pons = cerebellum	30ms	12 SZ; 8 HC	Cerebellum, pons	Cr	(Eluri et al., 1998)
↓	135ms	19 SZ; 16 HC	Anterior cingulate gyrus	Concentration	(Ende et al., 2000)
↓	135ms	15 SZ; 15 HC	Bilateral Thal	Concentration	(Ende et al., 2001)
↓ Thal & HP = putamen	135ms	13 SZ; 15 HC	Putamen, HP, Thal	Concentration	(Ende et al., 2003)
= pons, dentate nucleus ↓ in others	135ms	14 SZ; 14 HC	Pons, CB, cerebellar cortex, dentate nucleus	Concentration	(Ende et al., 2005)
↓ non-med. HP = in others	35ms	32 SZ; 18 HC	BG, PFC, HP	Cr	(Fannon et al., 2003)
=	135ms	13 SZ; 12 HC	BG (L and R)	Cr	(Fujimoto et al., 1996)
↓ medial TL; = FL	135ms	15 SZ; 15 HC	Medial TL (L), FL (L)	Cr	(Fukuzako et al., 1995)
↓	60ms	64 SZ; 51 HC	Medial TL (L)	Cr	(Fukuzako et al., 1996)
↓	60ms	40 SZ; 40 HC	Medial TL (L)	Cr	(Fukuzako et al., 1999)
=	35ms	15 short prodromal; 15 long prodromal; 19 HC	FL (L), TL (L), Thal (L)	Cr	(Galinska et al., 2009)

Finding	TE	N	Brain Region	Normalization	Citation
= FL ↓ others	68ms	18 SZ; 18 HC	BG (L), frontal, parieto-Occip	Cr	(Goto et al.)
=	270ms	13 SZ; 13 HC	Frontal cortex (L and R), Thal (L and R)	Cr	(Hagino et al., 2002)
=	30ms	18 SZ; 31 HC	BG, FL, Thal (L and R), TL	Cr	(Heimberg et al., 1998)
↓	126ms	12 SZ; 13 HC	Frontal (L)	Cr	(Hendren et al., 1995)
↓	135ms	22 SZ; 22 HC	Thal (L and R)	Concentration	(Jakary et al., 2005)
= TL ↓ in others	272ms	21 SZ; 31 HC	ACC, FL, TL	Cr	(Jessen et al., 2006)
=	20ms	10 SZ; 10 HC	HP	Cr	(Kegeles et al., 2000)
=	20ms	11 high risk; 12 HC	ACC	Cr	(Keshavan et al., 1997)
↓	30ms	40 SZ; 46 HC	Caudate	Concentration	(Keshavan et al., 2009)
↓	80ms	29 SZ; 44 HC	HP (L)	Concentration	(Klar et al., 2010)
= GM ↓WM	144ms	10 SZ; 9 HC	PFC, TL, PL, Occip	Concentration	(Lim et al., 1998)
↓ in left = right	135ms	25 SZ; 32 HC	HP (L and R)	Concentration	(Maier et al., 1995)
=	135ms	26 SZ; 38 HC	HP (L and R)	Concentration	(Maier and Ron, 1996)
=	135ms	26 SZ; 38 HC	HP (R)	Concentration	(Maier et al., 2000)
↓	272ms	49 SZ; 37 HC	Thal (L and R)	Cr	(Martine z-Granados et al., 2008)
↓ in SZ w/GS = in SZ w/o GS	30ms	15 SZ w/GS; 15 SZ w/o GS; 15 HC	BG (L), CV?, HP (L)	Cr	(Miyaoka et al., 2005)
= in recent onset ↓ in chronic	136ms	16 recent onset; 19 chronic; 20 HC	dlPFC (L and R)	Cr	(Molina et al., 2005)
↓ dlPFC (R) in chronic = others	136ms	17 FE SZ; 17 chronic SZ; 20 HC	dlPFC (L and R)	Cr	(Molina et al., 2006)
↓	136	11 SZ; 10 HC	dlPFC (L and R)	Cr	(Molina et al., 2007)
↓ on right	50ms	11 SZ; 11 HC	HP/amygdala	Concentration	(Nasrallah et al., 1994)
=	40ms	10 SZ; 10 HC	BG	Concentration	(Ohara et al., 2000)
↓	20ms	15 FE; 20 chronic	Left dlPFC	Concentration	(Ohrmann et al., 2007)
↓ dlPFC = ACC	32ms	43 SZ; 37 HC	ACC, dlPFC	Concentration	(Ohrmann et al., 2008)
↓ Thal = FL	136ms	20 SZ; 18 HC	FL, Thal	Cr	(Omori et al., 2000)
=	272ms	11 pediatric; 11 SZ; 20 HC	ACC (inferior and superior; L and R), Putamen, caudate, frontal WM (L and R), frontal cortex (L and R), Occip (L and R), parietal WM (L and R), parietal (L and R), Thal (L and R)	Concentration	(O'Neill et al., 2004)
=	30ms (multi-TE)	21 SZ; 19 HC	ACC, POC	Concentration	(Ongur et al., 2008)
↓ ACC = POC	30ms (multi-TE)	17 SZ; 21 HC	ACC, POC	Concentration	(Ongur et al., 2010a)

Finding	TE	N	Brain Region	Normalization	Citation
↓	20ms	24 SZ; 20 HC	FL (L and R)	Cr	(Pae et al., 2004)
↓	35ms	30 SZ; 15 HC	Dorsal ACC	Concentration	(Premkumar et al., 2010)
=	20ms	15 SZ; 14 HC	Medial FL	Concentration	(Purdon et al., 2008)
=	80ms	26 SZ; 23 HC	Bilateral dorsal ACC	Cr	(Reid et al., 2010)
↓	30ms	13 SZ; 15 HC	TL (L and R)	Cr	(Renshaw et al., 1995)
=	35ms	10 w/deficit syndrome; 10 w/o; 11 HC	Middle PFC (L), inferior parietal (L)	Concentration	(Rowland et al., 2009)
=	30ms	29 SZ; 31 HC	dlPFC (L), HP	Concentration	(Rusch et al., 2008)
=	35ms	14 SZ; 15 HC	Cingulate gyrus	Cr	(Sarramea Crespo et al., 2008)
=	28.5ms	4 SZ; 9 HC	BG, Occip	Cr	(Sharma et al., 1992)
↓PCG? = temporal	144ms	19 SZ; 18 HC	PCG??, TL	Cr	(Shimizu et al., 2007)
=	135ms	21 SZ; 21 HC	BG	Concentration	(Shioiri et al., 1996)
=	102ms	19 SZ; 18 HC	Medial PFC Cortex	Concentration	(Shirayama et al., 2010)
=	136ms	25 SZ; 26 HC	dlPFC (L and R)	Concentration	(Sigmundsson et al., 2003)
=	20ms	32 SZ; 24 HC	FL	Concentration	(Stanley et al., 1996)
↓ early onset = others	20ms	8 early onset; 10 late onset; 34 HC	dlPFC	Concentration	(Stanley et al., 2007)
=	145ms	10 SZ; 10 HC	FL (L and R)	Concentration	(Steel et al., 2001)
↓ Thal = others	30ms	27 SZ; 27 HC	HP (L), ACC, Thal (L)	Concentration	(Stone et al., 2009)
=	35ms	106 SZ (separated by med); 21 HC	FL, TL, Thal	Concentration	(Szulc et al., 2007)
↓	30ms	14 SZ; 13 HC	FL (L)	Concentration	(Tanaka et al., 2006)
↓ medial TL = others	30ms	42 SZ; 40 HC	Medial TL (L and R) frontal (L and R) Occip (L and R)	Concentration	(Tang et al., 2007)
↓ ACC = BG	18ms	31 SZ; 26 HC	ACC, BG	Concentration	(Tayoshi et al., 2009)
=	5ms	13 SZ; 3 HC	ACC	Concentration	(Terpstra et al., 2005)
=	20ms	21 SZ; 28 HC	ACC (L), Thal (L)	Concentration	(Theberge et al., 2002)
=	20ms	21 SZ; 21 HC	ACC (L), Thal (L)	Concentration	(Theberge et al., 2003)
↓ FL = OC	20 ms	13 SZ; 12 HC	FL, OC	Cr	(Thomas et al., 1998)
=	120ms	12 SZ; 12 HC	CB	Cr	(Tibbo et al., 2000)
=	30ms	21 SZ; 33 HC	dlPFC (L), HP (L)	Concentration	(van Elst et al., 2005)
=	30ms	29 SZ; 24 HC	ACC (L and R), HP (L and R)	Concentration	(Venkatraman et al., 2006)

Finding	TE	N	Brain Region	Normalization	Citation
↓	135ms	15 SZ; 15 HC	HP	Concentration	(Weber-Fahr et al., 2002)
=	30ms	22 SZ; 41 HC	Frontal cortex	Cr	(Wobrock et al., 2008)
↓ dlPFC = others	135ms	56 SZ; 21 HC	dlPFC (L), medial TL (L)	Cr	(Wood et al., 2003)
↓	30ms	15 SZ; 14 HC	Dorsal ACC (L and R), rostral ACC (L and R)	Concentration	(Wood et al., 2007)
=	30ms	34 SZ; 19 HC	HP (L and R)	Concentration	(Wood et al., 2008)
=	35ms	15 SZ; 14 HC	ACC	Cr	(Yamasue et al., 2002)
= Thal w/o GS ↓ others	30ms	15 w/GS; 15 SZ w/o; 20 HC	ACC (L), insular cortex, Thal	Cr	(Yasukawa et al., 2005)
↓ Thal = others	140ms	22 SZ; 22 HC	ACC, dlPFC, Thal	Concentration	(Yoo et al., 2009)
↓	20ms	16 SZ; 14 HC	TL (L and R)	Cr	(Yurgelun-Todd et al., 1996)
↓ dlPFC (L) = dlPFC (R)	136ms	8 SZ; 33 HC	dlPFC (L and R)	Concentration	(Zabala et al., 2007)

ACC=anterior cingulate cortex; BG=basal ganglia; CB=cerebellar vermis; dlPFC=dorso-lateral prefrontal cortex; FL=frontal lobe; HP=hippocampus;Occip=occipital lobe; PCC=posterior cingulate cortex; PL=parietal lobe; Thal=thalamus; TL=temporal lobe

HC=healthy control; SZ=schizophrenic; L=left; R=right

TABLE 3

Details of breakdown of analysis groups

Analysis Set	Total N*	Lower NAA, TE ≥ 40 ms	Lower NAA, TE < 40ms	Unchanged NAA, TE ≥ 40 ms	Unchanged NAA, TE < 40 ms
All brain regions					
Cr normalization and NAA concentration	333	56	54	99	124
Cr normalization only	195	28	37	52	78
NAA concentration only	185	35	25	52	73
Region of interest analysis; Cr normalization and NAA concentration					
Frontal Cortex	100	15	19	28	38
Occipital Lobe	15	0	0	7	8
Parietal Lobe	11	1	1	4	5
Hippocampus and Temporal Lobe	71	19	14	14	24
Thalamus and Putamen	41	10	4	10	17
ACC	36	4	9	10	13
Basal Ganglia	31	0	4	12	15
Cerebellum	8	4	0	2	2
“Other”	20	3	3	11	3
Region of interest analysis; Cr normalization only					
Frontal Cortex	63	13	10	14	26
Occipital Lobe	8	0	0	4	4
Parietal Lobe	3	1	1	0	1
Hippocampus and Temporal Lobe	43	10	12	7	14
Thalamus and Putamen	31	2	9	13	4
ACC	13	1	2	6	4
Basal Ganglia	18	0	2	4	12
Cerebellum	2	0	0	1	2
“Other”	14	1	3	7	3
Region of interest analysis; NAA concentration					
Frontal Cortex	53	5	10	14	24
Occipital Lobe	9	0	0	3	6

Analysis Set	Total N*	Lower NAA, TE ≥ 40 ms	Lower NAA, TE < 40ms	Unchanged NAA, TE ≥ 40 ms	Unchanged NAA, TE < 40 ms
Parietal Lobe	8	0	0	4	4
Hippocampus and Temporal Lobe	39	12	4	7	16
Thalamus and Putamen	21	8	2	3	8
ACC	25	3	7	6	9
Basal Ganglia	16	0	2	8	6
Cerebellum	6	4	0	1	1
“Other”	8	3	0	5	0

*N refers to the total number of experiments, not the total number of participants or studies. Please see the Methods section for more details.