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WATER AND METABOLITE TRANSVERSE T2 RELAXATION TIME ABNORMALITIES IN THE WHITE MATTER IN SCHIZOPHRENIA

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Abstract

Multiple lines of evidence suggest that microstructural abnormalities in the white matter are important in the pathophysiology of schizophrenia. Diffusion MRI approaches which can provide evidence on tissue structure have been widely used to probe these abnormalities *in vivo*, but transverse relaxation times (T2) may provide additional insights since they are determined by molecule-microenvironment interactions not revealed by diffusion MRI. T2 of water – located both intra and extracellularly – and N-acetylaspartate (NAA – located intracellularly) reflect related but distinct processes due to their differential localization and interactions with other molecules. In this study, we collected water and NAA T2 data from 16 healthy subjects (HC), and 16 patients with schizophrenia (SZ) at 4 Tesla in a 9cc voxel in the right prefrontal white matter. The SZ group had longer water but shorter NAA T2 relaxation times when compared with the HC group. This pattern resulted in a statistically significant metabolite x group interaction ($F(18,1): 4.980, p=0.039$). Prolongation of water T2 and shortening of NAA T2 is consistent with an impoverishment of white matter macromolecule structures (including myelin) and abnormal intra-axonal milieu and volume in SZ.

Keywords

transverse relaxation time (T2); water; N-acetylaspartate; psychosis; myelin

INTRODUCTION

Several lines of evidence suggest that integration of activity across brain regions is as important as processing within any one brain region both for normal cognition and in the pathophysiology of schizophrenia (SZ). Related abnormalities in SZ include abnormally low correlations in resting-state BOLD fMRI signal across remote brain regions (Garritty et al.,

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2007; Whitfield-Gabrieli et al., 2009; Williamson, 2007), abnormalities in white matter (WM) integrity (Camchong et al., 2009; Kubicki et al., 2007), and in expression of myelin- and oligodendrocyte-related genes (Tkachev et al., 2003) required for WM formation and maintenance. WM abnormalities are critical to conceptualization of SZ as a dysconnection (i.e. abnormal connection) syndrome (Paus et al., 2008; Stephan et al., 2009). Diffusion MRI, and diffusion tensor imaging (DTI) in particular, have been used to probe WM abnormalities in SZ.

Magnetic resonance spectroscopy (MRS) can provide an additional window to the brain's cellular microenvironment through the measurement of transverse relaxation times (T2) of neurometabolites. Transverse relaxation is a result of nuclear spin-spin interactions reflected in MRS signal decay as echo time (TE) increases, and is sensitive to changes in molecular motion mainly through interactions of small molecules (metabolites) with structural or cytosolic macromolecules. T2 measurements convey valuable neurobiological information. For example, there is a dramatic reduction in brain water T2 during early postnatal brain development as water molecules increasingly interact with rapidly proliferating macromolecules (lipid membranes, myelin components, cytosolic proteins) (Kreis et al., 1993). T2 of major brain metabolites likewise reflect their differential tissue distribution and local molecular interactions during development and adult life (Frahm et al., 1989; Hetherington et al., 1994; Posse et al., 1995). Thus, T2 provides a glimpse into the frequency of interactions between a molecule and its microenvironment. This can be due to geometric changes within the cell (atrophy) or to the entrapment of a molecule in a larger molecular assembly (e.g. enzyme or transport molecules).

Brain water T2 relaxation times are prolonged in patients with SZ, particularly in frontal and temporal grey matter (Andreasen et al., 1991; Williamson et al., 1992), and fornix (Supprian et al., 1997). One study showed that this prolongation extends into both grey and white matter (Pfefferbaum et al., 1999). By contrast, T2 of MRS-visible intracellular metabolites such as N-acetylaspartate (NAA), Creatine (Cr), and Choline (Cho) have not been widely studied in psychiatric conditions. We recently reported reductions in T2 measures of these metabolites in bipolar disorder and schizophrenia in two grey matter regions (Ongur et al., 2010). This pattern of prolonged water T2 coupled with shortened metabolite T2 suggests that psychiatric disorders are associated with neuronal and/or glial abnormalities, specifically an impoverished macromolecule compartment and reduced cell size and density. There are currently no studies, however, that have quantified water and metabolite T2 in the same patient cohorts; this would provide compelling evidence for microstructural abnormalities in SZ.

In this study, we quantified WM water and metabolite T2 simultaneously using ^1H MRS from a new cohort of patients with chronic SZ taking medication and new healthy controls (HC) matched for age, sex, and parental socioeconomic status at 4 Tesla (4T). WM abnormalities are widely reported subjacent to the PFC in SZ and may be implicated in its pathophysiology (Camchong et al., 2009) but the microstructural basis of these abnormalities has not been fully elucidated. Therefore, we collected data from a 9cc WM voxel underlying the right prefrontal cortex (PFC). Given the design of our study, we had time to collect data from a single voxel in the white matter. We focused on the right hemisphere in order to avoid the potential for language-related variability in the left hemisphere. Based on the literature reviewed above, we hypothesized that SZ patients would have longer water and shorter metabolite T2 when compared with healthy controls. Because we report both water and metabolite data, we focused on NAA as the metabolite of interest for clarity. The Cr and Cho data were similar, as discussed below.

METHODS

Participants

Following approval by the McLean Hospital IRB, we recruited 16 healthy controls from the community and 16 participants with SZ from the clinical services at McLean Hospital. All but 2 patients were outpatients at the time of scan. Demographic and clinical characteristics of the study participants are provided in Table 1. Participants were men and women between the ages of 18 and 55; the control and SZ groups were matched for age, sex, and parental socioeconomic status (parental SES determined using the Hollingshead scale). Participants older than 55 were excluded from the study because of the higher burden of WM abnormalities starting at around this time of life (Wen et al., 2009). All participants were native English speakers and right-handed as assessed by the Edinburgh Handedness inventory. Participants were excluded if they had significant medical or neurological illness, contraindication to MR scan (including claustrophobia), or pregnancy (screened with a urine test on scan day; females of child-bearing age were using an effective contraceptive method). HC participants were screened using the SCID-IV and had no personal history of psychiatric illness including substance abuse or dependence, and no history of the same in first degree relatives. SZ participants fulfilled criteria for SZ or schizoaffective disorder (SZA) according to the DSM-IV, assessed using the SCID-IV. In this group, 4 received a diagnosis of SZA depressive subtype and another 4 a diagnosis of SZA bipolar subtype. SZA patients were included in this study if they were chronically psychotic and not currently in a mood episode – i.e. phenomenologically similar to the SZ patients. We carried out a series of exploratory t-tests for our primary measures (water and NAA T2) between the SZ, SZA depressive and SZA bipolar participants and found no significant differences between groups (not shown). None of the patients were experiencing a first episode of illness, and the group had an average duration of illness of 13.0 ± 8.8 years. Patients who met criteria for any substance abuse in the past 3 months or a lifetime diagnosis of substance dependence were excluded. Subjects who smoked tobacco were not excluded from the study but this was assessed using the Fagerstrom questionnaire. Only 5 of the SZ participants and none of the healthy controls were smokers. Among the 5, only one had a Fagerstrom score of greater than 5 (signifying more than moderate nicotine dependence). All but one patient in the SZ group was taking antipsychotic medications, and some were taking additional medications (such as benzodiazepines, lithium, or anticonvulsants). Chlorpromazine (CPZ) equivalents were calculated for antipsychotic medication dosages for all patients (Woods, 2003).

All participants completed a Consent Survey that asks 10 simple questions about the study, such as “What illness is being studied?” and “What will happen in this study?” All participants answered the questions correctly. The study visit consisted of consent procedures; a standard clinical evaluation using the SCID-IV; urine toxicology screen; urine pregnancy test if necessary; proton MRS scan at 4T; diagnostic MRI scan at 3T if one had not been obtained within one year (reviewed by a radiologist - participants with significant brain abnormalities were excluded). The following standardized scales were administered for SZ patients: Positive and Negative Syndrome Scale (PANSS); Young Mania Rating Scale (YMRS); Montgomery-Asberg Depression Rating Scale (MADRS); Edinburgh Handedness inventory; North American Adult Reading Test (NAART – an estimate of premorbid IQ); and Fagerstrom Questionnaire for Nicotine Dependence. Body mass index (BMI) was also collected for all subjects.

Magnetic Resonance Imaging and Spectroscopy

The diagnostic scan was obtained in a Siemens 3 Tesla Trio scanner (Erlangen, Germany); details as in previous publications (Ongur et al., 2008). All MRS acquisitions were

conducted on a 4T full body MR scanner (Varian/UnityInova, Varian Inc., Palo Alto, California), using a 16-rung, single-tuned, volumetric birdcage coil (Robarts Research Institute, London, Canada). First, a rapid 2D gradient-recalled echo image (12 s) was used to acquire single images in three dimensions. This permitted rapid determination of subject position and the subject was repositioned if necessary. Manual global shimming of unsuppressed water signal was then undertaken, yielding a global water linewidth of 20 Hz. High-contrast T1-weighted sagittal images (TE/TR=6.2/11.4ms, field-of-view (FOV)=24×24×8cm, readout-duration=4ms, receive bandwidth= ±32kHz, data matrix size=128×256×16, in-plane resolution=0.94×1.88mm, slice thickness=5mm, readout points=512, flip angle=11°) were acquired to serve as an anatomical guide to position the axial images and MRS voxels. T1-weighted axial images of the slab TE/TR=6.2/11.4ms, field-of-view (FOV)=24×24×8cm, readout-duration=4ms, receive bandwidth= ±32kHz, data matrix size=256×256×32, in-plane resolution =0.94×0.94mm, slice thickness=2.5mm, readout points=512, flip-angle =11°) were then acquired mid-sagittally, allowing for clear differentiation between grey and white matter. In total, imaging time including shimming was approximately 15 minutes. A 1×3×3 cm³ single WM voxel was then placed on PFC of the right hemisphere for MRS studies (Figure 1). This voxel was placed in the corona radiata, centered at the level of the genu of the corpus callosum but lateral and posterior to it (i.e. it does not include any callosal fibers). The mediolateral extent was 1cm, while anteroposterior and dorsoventral extents were 3cm. The voxel was consistently positioned in pure WM, and anchored in the same location across all participants because it abutted grey matter anteriorly.

T2 were obtained using a standard point-resolved spectroscopy (PRESS) sequence modified with 4 varying TEs (30, 90, 120 and 200 ms) and TR =3000ms; 48 repetitions for metabolite and 8 repetitions for water T2 measurements (Figure 2). Total time in the scanner including imaging and shimming was under 90 minutes. T2 data were not available from 3 subjects due to technical difficulties during the scan.

Data processing/analysis

An MR physicist (FD) examined all MRI/MRS data. Post-processing of the free-induction decays including apodization, Fourier transformation, frequency and phase correction of individual spectra as well as calculation of T2 constants were carried out using software from the Varian Console and home-grown software running on MATLAB. Although we collected Cr and Cho data along with NAA in our T2 relaxation time studies, we present only NAA data in this study. This is for two reasons: NAA is located almost exclusively in the neuronal compartment and although there is debate about the specific location of NAA synthesis within the cell, recent literature suggests this is at least partly in the cytosol (Tahay et al., 2012). Thus, NAA reflects the intracellular environment most closely; and the SNR of NAA is best, providing the highest reliability of any of our measures. In order to ensure that voxel composition was almost exclusively WM, we carried out segmentation of T1-weighted images into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) as previously described (Ongur et al., 2008). WM content was less than 5% of the voxel in all participants and there was no difference between groups in WM contribution to the voxel.

Statistical approach

All analyses were carried out using SPSS (V.17). Two-sample t-tests and chi-square tests were used to compare characteristics of the sample and signal-to-noise ratio (SNR) for the 120 ms PRESS spectrum (as an MRS data quality measure) across groups.

We first carried out a series of analyses using Pearson's R correlation coefficient to examine the relationship between T2 and age/BMI for the full dataset, and duration of illness, NAART score, CPZ equivalents, PANSS, YMRS, and MADRS for the SZ group. In addition, we carried out an ANOVA with sex as an independent variable and T2 relaxation times as dependent variables. Because of a significant finding in this analysis as described below, sex was added to all of the main analyses described below as a covariate (even though the two groups were matched for sex). We did not control for multiple comparisons in these analyses since we had *a priori* primary hypotheses (see below) and all other analyses were considered exploratory in nature.

We derived 2 linked hypotheses from the literature: that there will be a prolongation in water T2 and a shortening in metabolite T2 in SZ when compared to healthy controls. These linked hypotheses were tested using a single general linear model with water and NAA T2 relaxation times as outcomes and diagnostic group as predictor. The primary analysis involved the significance of the metabolite x group interaction term.

RESULTS

Male participants had longer water T2 than females ($F(27,1):5.259$; $p=0.030$) but NAA T2 did not differ by sex ($F(27,1):1.612$; $p=0.219$). Sex was included as a covariate in subsequent analyses.

The SZ group had longer water T2 relaxation times and shorter NAA T2 relaxation times compared to healthy controls in an analysis controlling for effects of sex (Table 2). This pattern resulted in a statistically significant metabolite x group interaction ($F(18,1):4.980$, $p=0.039$). There was also a significant main effect of metabolite indicating that NAA T2 was longer than water T2 on average ($F(18,1):610.914$, $p<0.001$); there was no main effect of group ($F(18,1):1.926$, $p=0.182$). In *post hoc* tests, the prolongation of water T2 in the SZ group approached significance ($t(27)=3.154$, $p=0.087$) but the shortening of NAA T2 in the SZ group did not ($t(27)=0.448$, $p=0.511$).

Among the correlation analyses the only significant finding was a strong and negative correlation between water T2 and PANSS scores within the SZ group ($R=-0.683$, $p=0.010$). Notably, there was no correlation between CPZ equivalents and water T2 ($R=-0.379$, $p=0.201$) or NAA T2 ($R=0.392$, $p=0.262$). In addition, there was no correlation between NAA T2 and water T2 ($R=-0.258$, $p=0.272$).

We also examined metabolite concentration differences between the two groups. There were no significant differences for any metabolite in this measure. For example, NAA levels (reported as NAA/H₂O ratio expressed in institutional units) were 0.17 ± 0.03 for both study groups.

DISCUSSION

We have observed that water T2 is prolonged and NAA T2 is shortened in SZ when compared to healthy controls in the WM underlying the PFC. Our findings suggest that non-invasive study of brain microstructure using transverse relaxation may provide useful biological information about major psychiatric illnesses.

White matter contains axons emanating from neurons in the gray matter and these are covered by myelin synthesized by oligodendrocytes. There is also fluid (mainly water) in both intracellular and extracellular compartments. T2 relaxation results from interaction of the metabolite with foreign molecules in its microenvironment. If this process is more frequent as happens when molecules are packed in a smaller space, T2 will be shorter. By

contrast, homogeneous phases promote prolongation of T2 because one nucleus is more likely to interact with another nucleus of its own kind than a foreign nucleus. Because NAA is located intracellularly and almost exclusively localized to neurons, the shortened NAA T2 suggests intra-axonal abnormalities in SZ, possibly due to increased interactions with intracellular macromolecules or to changes in cell size. This interpretation is consistent with the reported reductions in cell body size in the cerebral cortex in SZ (Chana et al., 2003; Pantazopoulos et al., 2007) since axonal sizes may correlate with cell body size. It is also possible that reported cytoskeletal abnormalities in these disorders contribute by modifying the intracellular macromolecule or organelle composition (Beasley et al., 2006). Our finding of prolonged water T2 in SZ is also consistent with reductions in cell body size since this would lead to relative expansion of the extracellular compartment. In addition, since myelin contains the overwhelming majority of macromolecules within WM (such as myelin lipids and myelin-associated proteins), this finding suggests myelin abnormalities in SZ (MacKay et al., 2006). This pattern of intraneuronal composition and cell size changes and expansion of extracellular compartment in SZ is depicted in Figure 3. Note that this graphic is consistent with our findings but we cannot specify which of these abnormalities are most pronounced in SZ based on current data.

Our findings are broadly consistent with previously reported metabolite T2 relaxation times in the healthy human brain, giving us confidence in the validity of our disease-specific findings. For example, the healthy controls in our study showed NAA T2 very similar to what has previously been reported at 4.1T (Hetherington et al., 1994) and shorter than those reported at 1.5T (Posse et al., 1995), consistent with the underlying physics. The sex effects on water T2 in our study have not been studied previously; our results suggest differences in the cellular make-up of the cerebral cortex between the sexes but more work is needed to understand fully these differences. We did not obtain evidence of multi-exponential decay in water or NAA as has been previously reported (Ke et al., 2002; MacKay et al., 2006) but our ability to detect multi-exponential decay was limited by the number of echo times used to fit the decay curve. The negative correlation between PANSS scores for SZ patients and water T2 in our study is unexpected. This suggests that as a group, SZ patients had prolonged water T2, but the more symptomatic the patient the shorter the water T2. We do not have an explanation for this finding, and it requires further study.

Our study has some limitations. One is that all patients in the study were taking medication (one was not taking antipsychotic medication but that individual was on an antidepressant). Many kinds of medication can modify tissue T2, including diuretics (Karlik, 1986) and omega-3 fatty acids (OFAs) (Hirashima et al., 2004). The effect of antipsychotic medications on metabolite T2 has not been studied. In our study there was no relationship between CPZ equivalents and metabolite T2, suggesting that the dose of antipsychotic medication did not have an effect on our measures. Nonetheless, we cannot rule out the possibility that our findings are secondary to medication effects. Another limitation is that we did not start collecting data until 30 ms. PRESS acquisitions with a TE shorter than 30msec on our system were made difficult by hardware limitations. There may be substantial information in short TE spectra and collecting data at shorter TEs may reveal multiexponential decay in metabolite signal, providing additional clues about the local compartments of water or NAA molecules, in particular the so-called myelin water fraction.

In addition to the biological significance of our findings, T2 abnormalities are relevant for data quantification in MRS studies of psychiatric conditions. T2 differences may cause MRS signal to decay faster or slower in the SZ group than in healthy controls. This may lead to artifactual abnormalities in measured patient metabolite levels, especially in longer TE studies where more differential signal decay takes place. This issue is potentially of greater concern at higher magnetic field strengths (e.g. 4T) where T2 relaxation times are short. As

a result, some of the variation in brain NAA levels seen in SZ in the literature may be due to unaccounted for relaxation effects. We suggest that quantification of metabolite T2 relaxation times should be considered in ^1H MRS studies in SZ.

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Figure 1.
Axial views of the brain from a T1-weighted image illustrating the voxel placement on 3 slices in one control subject.

Figure 2.

Representative spectra from a healthy control (top row) and a schizophrenia patient (bottom row) showing signal decay for the water resonance (left panel) and NAA resonance (right panel) with increasing TE from 30 to 200 ms. Each series is presented with spectral amplitude normalized to the first spectrum for presentation purposes.

Figure 3.

Graphic representation of potential WM changes in schizophrenia consistent with our T2 findings. The T2 of each metabolite is represented by the size of the starburst pattern. Note that in schizophrenia a reduction in myelin content would lead to prolonged water T2, while reduction in axon size as well as changes in intracellular macromolecules (represented by shading) would lead to shorter NAA T2.

Table 1
Demographic and clinical characteristics of study participants

	Healthy Control (N=16)	Schizophrenia (N=16)	Statistical Evaluation
Age (years)	31.7±7.2	34.8±10.1	F(31,1)=1.02; p=0.321
Gender	10M, 6F	11M, 5F	$\chi^2=0.139$; p=0.710
BMI	23.0±2.7	28.0±5.6	F(31,1)=9.82; p=0.004
Education *	6.7±1.0	4.2±1.7	F(31,1)=28.18; p<0.001
Parental SES	5.9±1.4	5.5±1.6	F(26,1)=0.458; p=0.505
Age at onset	--	20.2±5.2	
MADRS	--	9.8±11.0	
YMRS	--	5.8±5.9	
PANSS	--	44.6±10.1	
Lithium	--	2	
Anticonvulsants	--	2	
SGAs	--	14	
FGAs	--	1	
CPZ equivalents	--	507±525	
Benzodiazepines	--	4	

SGA: second generation antipsychotic; FGA: first generation antipsychotic. Other abbreviations as in the text. Parental SES calculated according to the Hollingshead scale.

* Education code: 3: graduated high school; 4: part college; 5: graduated 2 year college; 6: graduated 4 year college; 7: part graduate/professional school; 8: completed graduate/professional school

Table 2

Metabolite T2 (mean±SD in milliseconds)

Metabolite	Healthy Control (N=16)	Schizophrenia (N=16)
Water	60.9±2.4	65.8±5.3
NAA	209.5±23.8	189.7±23.3

All abbreviations are as in the text.