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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 T in a 9 cm^3 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 × 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.

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1. 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 (Garrity et al., 2007; Williamson, 2007; Whitfield-Gabrieli et al., 2009), abnormalities in white matter (WM) integrity (Kubicki et al., 2007; Camchong et al., 2009), 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 gray matter (Andreasen et al., 1991; Williamson et al., 1992), and fornix (Supprian et al., 1997). One study showed that this prolongation extends into both gray 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 gray matter regions (Ongur et al., 2010). This pattern of prolonged water

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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 ^{1}H 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 (4 T). 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 9 cm^3 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.

2. Methods

2.1. 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 4 T; diagnostic MRI scan at 3 T 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.

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	10 M, 6 F	11 M, 5 F	$\chi 2 = 0.139$; $p = 0.710$
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.

2.2. 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 4 T 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 = 6.2/11.4 ms, field-of-view (FOV) = 24 × 24 × 8cm, readout-duration = 4 ms, receive bandwidth = ± 32 kHz, data matrix size = 128 × 256 × 16, in-plane resolution = 0.94 × 1.88 mm, slice thickness = 5 mm, 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 = 6.2/11.4 ms, field-of-view (FOV) = 24 × 24 × 8cm, readout-duration = 4 ms, receive bandwidth = ± 32 kHz, data matrix size = 256 × 256 × 32,

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