Proton T_1 Relaxation Times of Metabolites in Human Occipital White and Gray Matter at 7 T

Lijing Xin,[1]* Benoît Schaller,[2] Vladimir Mlynarik,[2] Huanxiang Lu,[3] and Rolf Gruetter[1,2,4]

Proton T_1 relaxation times of metabolites in the human brain have not previously been published at 7 T. In this study, T_1 values of CH_3 and CH_2 group of *N*-acetylaspartate and total creatine as well as nine other brain metabolites were measured in occipital white matter and gray matter at 7 T using an inversion-recovery technique combined with a newly implemented semi-adiabatic spin-echo full-intensity acquired localized spectroscopy sequence (echo time = 12 ms). The mean T_1 values of metabolites in occipital white matter and gray matter ranged from 0.9 to 2.2 s. Among them, the T_1 of glutathione, scyllo-inositol, taurine, phosphorylethanolamine, and *N*-acetylaspartylglutamate were determined for the first time in the human brain. Significant differences in T_1 between white matter and gray matter were found for water (−28%), total choline (−14%), *N*-acetylaspartylglutamate (−29%), *N*-acetylaspartate (+4%), and glutamate (+8%). An increasing trend in T_1 was observed when compared with previously reported values of *N*-acetylaspartate (CH_3), total creatine (CH_3), and total choline at 3 T. However, for *N*-acetylaspartate (CH_3), total creatine, and total choline, no substantial differences compared to previously reported values at 9.4 T were discernible. The T_1 values reported here will be useful for the quantification of metabolites and signal-to-noise optimization in human brain at 7 T. **Magn Reson Med 69:931–936, 2013. © 2012 Wiley Periodicals, Inc.**

Key words: T_1 relaxation time; human brain; metabolites; occipital lobe; white matter; gray matter; 7 T

INTRODUCTION

In vivo ^{1}H magnetic resonance spectroscopy of human brain at high magnetic field strength (7 T and above) provides increased sensitivity and spectral resolution, which allows noninvasive measurement of the neurochemical profile including a large number of metabolites (1,2). However, to measure the neurochemical information within a clinically acceptable time, studies at high magnetic field strength are usually performed at a short repetition time (TR) (3). Therefore, knowledge of T_1 relaxation times of metabolites is essential for the optimization of measurement parameters and for the accurate quantification of metabolites in single voxel MR spectroscopy and spectroscopic imaging. In addition, T_1 relaxation times are useful for investigating changes in the cell microenvironment induced by physiological and pathological processes (4).

Previous studies have measured T_1 relaxation times of singlet resonances of *N*-acetylaspartate (NAA), total creatine (tCr), total choline (tCho), and proton resonances of myo-inositol (Ins) at 3.57 ppm in different brain regions at 1.5, 2, 3, 4, and 9.4 T in the human brain (2,5–9). However, proton T_1 relaxation times of metabolites in the human brain have not been previously reported at 7 T. Furthermore, the overlap of metabolite resonances was a limiting factor in measuring T_1 values of most metabolite peaks, such as glutamate (Glu), glutamine, glutathione (GSH), etc. Therefore, the aim of this study was to measure T_1 relaxation times of the CH_3 and CH_2 group of NAA and tCr and mean T_1 relaxation times of other brain metabolites, i.e., tCho, Ins, Glu, glutamine, GSH, taurine (Tau), scyllo-inositol (Scyllo), phosphorylethanolamine (PE), *N*-acetylaspartylglutamate (NAAG) as well as macromolecules and water in occipital white and gray matter (GM) in the healthy human brain at 7 T.

METHODS

Subjects

Ten healthy volunteers (8 males, 2 females, 20–28 years old), who gave informed consent prior to the study, were recruited for 12 measurements of T_1 values in volume of interests (VOIs) located in occipital white matter (WM) ($n = 6$) and GM ($n = 6$).

Pulse Sequence

The spin-echo full-intensity acquired localized spectroscopy (SPECIAL) sequence (10,11) achieves localization by applying a slice-selective adiabatic full-passage pulse on alternate scans (one-dimensional image selected in vivo spectroscopy scheme) followed by a slice-selective spin-echo sequence. In the original implementation, an asymmetric 90° pulse (bandwidth (BW) = 5.3 kHz, T_{pulse} = 1.28 ms, $\gamma B_1/2\pi$ = 1.3 kHz) and the Mao refocusing pulse (BW = 1.8 kHz, T_{pulse} = 3.2 ms, $\gamma B_1/2\pi$ = 1.7 kHz) were used. To minimize the chemical shift displacement introduced by the narrow-band Mao pulse at 7 T, a semi-adiabatic SPECIAL sequence was designed by replacing

[1]Department of Radiology, University of Lausanne, Lausanne, Switzerland.
[2]Laboratory of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland.
[3]Institute of Surgical Technologies and Biomechanics, University of Bern, Bern, Switzerland.
[4]Department of Radiology, University of Geneva, Geneva, Switzerland.

Grant sponsor: SNSF; Grant number: 3100A0-131087; Grant sponsors: Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, and EPFL and the Leenaards and Jeantet Foundations

*Correspondence to: Lijing Xin, Ph.D., Ecole Polytechnique Fédérale de Lausanne (EPFL), EPFL-SB-IPSB-LIFMET, Station 6, CH-1015 Lausanne, Switzerland. E-mail: lijing.xin@epfl.ch

Received 9 February 2012; revised 2 May 2012; accepted 4 May 2012.
DOI 10.1002/mrm.24352
Published online 30 May 2012 in Wiley Online Library (wileyonlinelibrary.com).

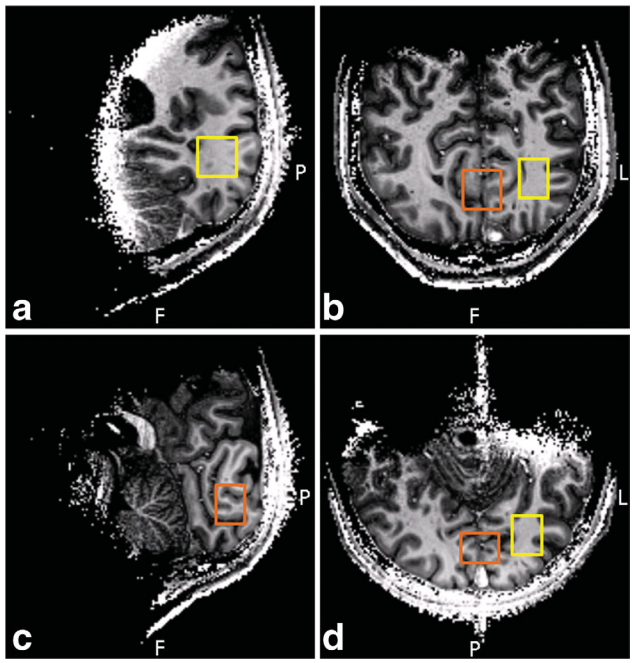

FIG. 1. T_1-weighted images reconstructed in the sagittal (**a, c**), coronal (**b**), and transverse (**d**) plane from the three-dimensional images acquired using MP2RAGE (TE/TR = 3.37/5000 ms, TI_1/TI_2 = 700/2200 ms, slice thickness = 1 mm, field of view = 176 × 256 mm^2, matrix size = 176 × 256) indicating typical VOI in occipital WM (yellow) and GM (orange) for T_1 measurements. Labels in the images: F (feet), P (posterior), and L (left).

the Mao refocusing pulse by two broadband adiabatic pulses (hyperbolic secant, $R = 28$, BW= 7.4 kHz, T_{pulse} = 3.5 ms, $\gamma B_1/2\pi$ = 1.6 kHz) (12) with a minimum echo time (TE) of 12 ms. To determine T_1 relaxation times, a nonselective hyperbolic secant full-passage pulse (BW = 3.9 kHz, T_{pulse} = 5.12 ms, $\gamma B_1/2\pi$ = 1.4 kHz) was inserted and interleaved with outer volume suppression and water suppression with variable-pulse power and optimized relaxation delays (13) prior to the localization sequence.

Magnetic Resonance Spectroscopy Protocol

Magnetic resonance spectroscopy experiments were performed on a 7 T/68 cm MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a home-built ^1H quadrature surface coil (10-cm diameter circular loops). Three-dimensional anatomical images acquired using MP2RAGE (14) (TE/TR = 3.37/5000 ms, TI1/TI2 = 700/2200 ms, slice thickness = 1 mm, field of view = 176 × 256 mm^2, and matrix size = 176 × 256) were used to position the VOI and to determine the tissue content of the voxel. B_0 field inhomogeneities were minimized in the occipital GM (VOI = 20 × 15 × 20 mm^3) and WM (VOI = 15 × 20 × 20 mm^3) (Fig. 1) using first- and second-order shims with FAST(EST)MAP (15,16), thus achieving water linewidth of 12.8 ± 0.6 Hz (mean ± standard deviation [SD]). T_1 measurements were made using an inversion-recovery method. Six inversion time (TI) intervals (50, 300, 600, 1300, 1800, and 2200 ms) were chosen, and equilibrium signals were obtained from spectra acquired without an inversion pulse (TE/TR = 12/7500 ms, T_{acq} = 512 ms, number of acquisition = 2 × 16 blocks/TI, spectral BW = 4 kHz, 2048 data points). Spectra acquired without water suppression were used to calculate T_1s of water.

Data Analysis

A home-written segmentation tool (17) was used to determine WM, GM, and cerebrospinal fluid content percentage in the VOI selected for T_1 measurements based on the MP2RAGE image. Water suppressed in vivo spectra acquired at each TI were analyzed using LCModel (18) with a simulated metabolite basis set (19,20), combined with an experimentally measured macromolecule baseline. Because of the faster recovery of macromolecules relative to metabolites, the basis set for TI = 600 ms comprises macromolecules and metabolites with opposite phase. To determine the T_1 values of separate chemical groups of metabolites, creatine (Cr) and phosphocreatine (PCr) CH_2 (3.92 ppm) and CH_3 (3.03 ppm), NAA (CH_3) singlet (2.01 ppm), and its aspartate moiety (CH_2) resonances were simulated separately and included in the basis sets. The quantification accuracy is expressed using Cramér–Rao lower bounds. Signal intensities were fitted by a three-parameter monoexponential function $a \times [1 - b \times \exp(-TI/T_1)]$ using the curve-fitting toolbox in Matlab (Version R2009b; The MathWorks, Inc., Natick, MA). Values obtained at equilibrium without an inversion pulse were included in the fit assuming a TI = 20,000 ms ($\sim 10 \times T_1$), which should provide 99.995% of the signal intensity obtained at equilibrium. The quality of the fit was evaluated by the coefficient of determination (R^2) and visual inspection. An unpaired two-tailed Student's t-test was used to compare the T_1 values in occipital WM and GM.

RESULTS

To improve the localization of metabolites at high magnetic fields, the semi-adiabatic SPECIAL sequence was implemented at 7 T. In contrast to the original SPECIAL sequence (10,11), two broadband adiabatic full-passage pulses were used for the refocusing of coherences in the semi-adiabatic SPECIAL sequence. A reduction of chemical shift displacement error from ±25% to ±6% in Z direction for the chemical shift range of 3 ppm was achieved. By the careful placement of outer volume suppression bands, high quality and artifact-free spectra were obtained from VOIs in occipital WM and GM with a signal-to-noise ratio of 52 ± 4 and 65 ± 3 (relative to NAA singlet at 2.01 ppm, $n = 6$, mean ± standard error of the mean, 32 averages), respectively, which allowed the quantification of 14 metabolites including NAA, Cr+PCr, glutamine, Glu, Ins, PE, tCho with Cramér–Rao lower bounds <10%, NAAG, Lac, GSH, Asp, Tau with Cramér–Rao lower bounds <20%, and Scyllo, γ-aminobutyric acid with Cramér-Rao lower bounds <30%.

Although the use of two adiabatic full-passage pulses prolonged the minimum TE to 12 ms, it substantially suppressed the phase distortion of signal due to J-evolution, showing a minor difference of spectral appearance

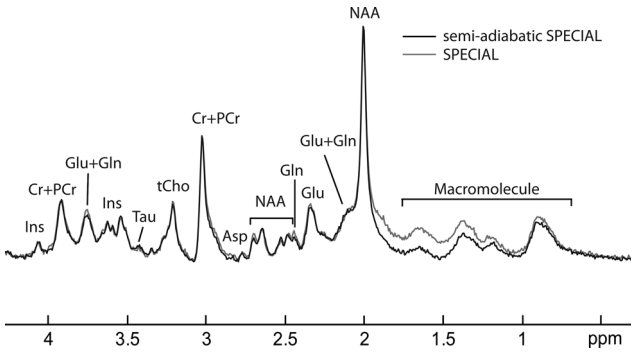

FIG. 2. In vivo ^{1}H MR spectra acquired using the semi-adiabatic SPECIAL (TE/TR = 12/7500 ms, 32 averages) and SPECIAL (TE/TR = 6/7500 ms, 32 averages) localization sequences from an identical VOI (20 × 15 × 20 mm^3) in the occipital lobe of a healthy male volunteer (for both spectra, appodization, baseline correction, and post-water removal were all not performed).

between spectra acquired by semi-adiabatic SPECIAL at TE = 12 ms and those obtained by SPECIAL at TE = 6 ms (Fig. 2). The in vitro signal of the methylene group of the NAA aspartate moiety measured using semi-adiabatic SPECIAL with TE = 12 ms (Fig. 3a) and simulated under the same experimental condition (Fig. 3b) showed a spectral pattern similar to that simulated with a single spin-echo at 6 ms (Fig. 3c). When comparing the single spin-echo spectral pattern simulated for this group at TE = 12 ms (Fig. 3d) with that obtained using semi-adiabatic SPECIAL at the identical TE (Fig. 3b), the effect of J-evolution was apparent. Furthermore, due to the short T_2 of macromolecules, signals in the upfield region acquired by semi-adiabatic SPECIAL were lower than those obtained using SPECIAL (Fig. 2).

VOIs for T_1 measurement were positioned in the occipital lobe and contained predominantly WM or GM as shown in Fig. 1. To determine voxel composition, three-dimensional MP2RAGE images were segmented, providing on average 76% WM and 82% GM signal contribution in the WM and GM VOIs, respectively (Table 1). The spectra in WM-rich tissue and GM-rich tissue resulted in mean concentration ratios of tCr/tCho of 6.0 for occipital WM-rich tissue and 8.6 for GM-rich tissue, respectively. By linear extrapolation of tCr/tCho concentration ratios versus fraction of GM, the tCr/tCho values of 4.9 and 9.0 were obtained in pure WM and GM, respectively.

To determine T_1 relaxation times, an inversion pulse was applied prior to the localization sequence. A series of spectra obtained at different TIs from VOI in the occipital WM-rich tissue are shown in Fig. 4. Because of the short T_1 relaxation time, the macromolecule signal was minimized at TI = 300 ms and showed a positive amplitude at TI = 600 ms, while metabolite resonances were still displaying negative amplitude for these TIs (Fig. 4 left). At TI of 1300 ms, metabolites and macromolecule resonances both recovered with positive signals. The tCr (CH_2) resonance at 3.92 ppm and the tCr (CH_3) resonance at 3.03 ppm demonstrated a difference in T_1 that can be observed from the null signal intensity of tCr (CH_2) at TI of 600 ms, while the tCr (CH_3) peak was still negative. The LCModel fits of spectra at individual TIs mimicked the in vivo spectral pattern (Fig. 4 right). Note that the spectral shapes in simulated basis sets were further validated by the similar spectral pattern of methylene group of aspartate moiety of NAA in vitro (Fig. 3a,b).

T_1 values were determined for tCr (CH_3), tCr (CH_2), NAA (CH_3), NAA (CH_2), and nine other metabolites (Table 2), and the representative fits were illustrated in Fig. 5. High R^2 values (i.e., 0.974–0.999) for all T_1 fits demonstrated the good quality of the fits. The fits of tCr (CH_2) and tCr (CH_3) in Fig. 5 reflected a shorter T_1 of tCr (CH_2) compared to that of tCr (CH_3) as previously demonstrated in Fig. 4. In addition, T_1 of Macromolecules was much shorter than T_1s of metabolites.

The mean T_1 values of metabolites in occipital WM and GM ranged from 0.9 to 2.2 s (Table 2), with Tau having the longest T_1, followed by the NAA singlet, tCr (CH_3), Glu, glutamine, and the other metabolites. The T_1 relaxation times of water and Macromolecules were 1.55 s and 0.42 s in WM, and 2.00 s and 0.43 s in GM, respectively. A statistically significant difference was found between T_1 of water in WM and that in GM (P = 0.0003). The T_1 values of tCho (P = 0.007) and NAAG (P = 0.028) were significantly shorter in WM than in GM, whereas T_1 values of NAA (CH_3) (P = 0.047) and Glu (P = 0.008) were longer in WM than in GM.

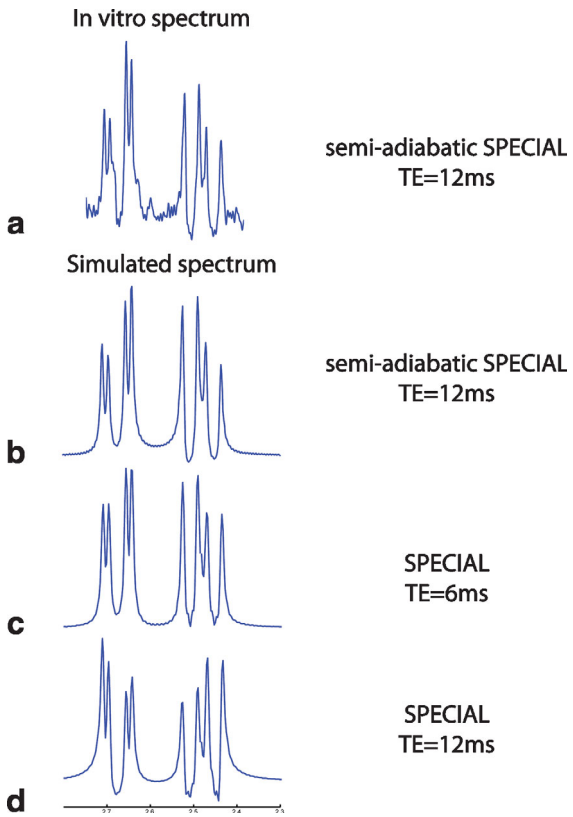

FIG. 3. In vitro ^{1}H MR spectra (**a**) of the methylene group of the aspartate moiety of NAA measured using semi-adiabatic SPECIAL (TE = 12 ms, TR = 15 s, and 128 averages) and simulated spectra obtained using (**b**) semi-adiabatic SPECIAL at TE = 12 ms; (**c**) SPECIAL at TE = 6 and (**d**) 12 ms (T_2 relaxation was neglected for the simulation). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1
Tissue Composition of VOIs for Measurements of T_1 Relaxation Times (Mean ± SD, $n = 6$)

	WM (%)	GM (%)	Cerebrospinal fluid (%)
Occipital WM	60 ± 2	19 ± 8	21 ± 9
Occipital GM	16 ± 5	75 ± 5	9 ± 2

DISCUSSION

In this study, T_1 relaxation times of tCr (CH_3), tCr (CH_2), NAA (CH_3), NAA (CH_2), plus nine additional metabolites, the macromolecular baseline and water were measured in occipital WM and GM of the human brain at 7 T. In particular, T_1 values of GSH, Scyllo, Tau, PE, and NAAG were reported for the first time in the human brain. The measurement was based on the implementation of a semi-adiabatic SPECIAL sequence by replacing the refocusing pulse with two broadband adiabatic pulses to minimize the chemical shift displacement error to ±6% over 3 ppm.

Spectra acquired with semi-adiabatic SPECIAL demonstrated similar spectral quality to those obtained with short-TE SPECIAL (Fig. 2), while benefiting from the suppressed J-evolution during radiofrequency pulses even at a TE of 12 ms, and from longer apparent T_2 relaxation times relative to those in the standard SPECIAL sequence, due to spin-locking effect of adiabatic full-passage pulses (21). In general, the metabolite concentrations determined in the occipital lobe using the semi-adiabatic SPECIAL sequence (data not shown) were in good agreement with those reported in previous studies at 7 T (11,22).

Although the preliminary implementation of semi-adiabatic SPECIAL in this study was performed using a surface coil, the use of a volume transceiver coil with a more limited maximum B_1 should be feasible by either increasing TE, or using gradient-modulated adiabatic pulses with low peak B_1 (23,24), or by local B_1 shimming (22).

As a proton resonance in a molecule may have a distinct T_1, the reported T_1 relaxation times corresponded to a weighted mean over different proton groups in a molecule. In addition, the T_1 value of tCho is likely dominated by the nine protons of the methyl group. For metabolites with overlapping resonances such as tCr (PCr and Cr) or tCho (PCho and GPC), the T_1 values corresponded to weighted mean values of the metabolites contributing to the specific resonances.

Because of the differences in T_1, some metabolite peaks were positive while others were negative at intermediate TIs. As a result, spectra acquired at those TIs would display a complicated pattern due to the variable phases of the peaks. In such cases, quantification using LCModel would be challenging due to the unknown prior knowledge for the spectral phase of metabolites. Therefore, TIs were carefully selected such that peaks of metabolites had the same polarity (either all negative or all positive), thus omitting an unfavorable TI range from 600 to 1300 ms. In addition, metabolite peak intensities were close to zero in this range of TI, resulting in unreliable metabolite quantification. Thus, the standard LCModel basis set was used to analyze spectra acquired at most TIs. However, due to the fast recovery of macromolecules relative to metabolites, a special basis set with the phase of macromolecules opposite to that of metabolites was used at TI = 600 ms.

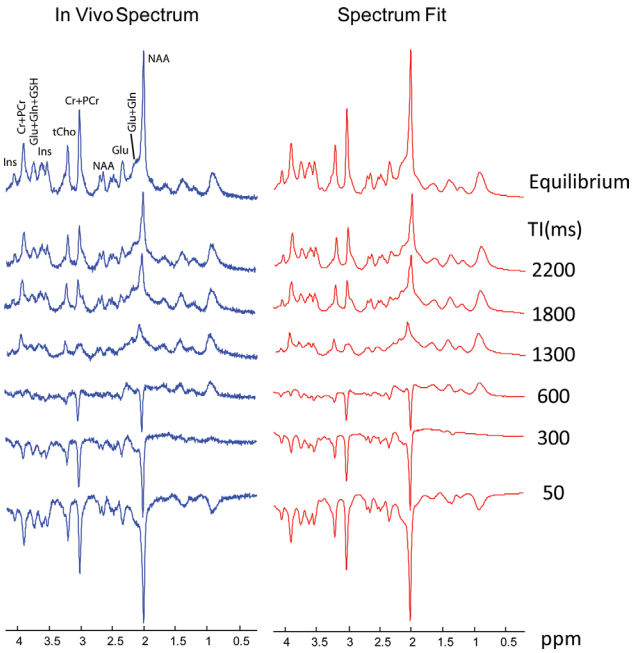

FIG. 4. A series of in vivo ^{1}H inversion-recovery MR spectra acquired using semi-adiabatic SPECIAL (VOI = 15 × 20 × 20 mm^3, TE/TR = 12/7500 ms, 32 averages, appodization, baseline correction, and post-water removal were all not performed) at different TIs in the occipital white-matter-rich tissue of a healthy volunteer and the corresponding fits obtained from LCModel analysis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 2
T_1 Relaxation Times (mean ± SD, $n = 6$) of Cerebral Metabolites, Macromolecule Baseline, and Water in Occipital White and GM In Vivo at 7 T

T_1 (s)	WM	GM
tCr (3.03 ppm)	1.78 ± 0.04	1.74 ± 0.06
tCr (3.92 ppm)	1.10 ± 0.06	1.13 ± 0.04
NAA (2.01 ppm)*	1.90 ± 0.06	1.83 ± 0.05
tCho**	1.32 ± 0.06	1.51 ± 0.11
Ins	1.19 ± 0.07	1.28 ± 0.08
Glu**	1.75 ± 0.04	1.61 ± 0.09
NAA(CH_2)	1.19 ± 0.05	1.24 ± 0.05
GSH	1.06 ± 0.06	1.14 ± 0.18
Gln	1.74 ± 0.23	1.64 ± 0.07
Scyllo	1.23 ± 0.07	1.31 ± 0.20
Tau	2.09 ± 0.04	2.15 ± 0.11
PE	1.32 ± 0.30	1.31 ± 0.18
NAAG*	0.94 ± 0.08	1.21 ± 0.22
Macromolecules	0.42 ± 0.02	0.43 ± 0.02
Water***	1.55 ± 0.07	2.00 ± 0.12

The differences between T_1 values in WM and GM were evaluated by the unpaired Student's t-test (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

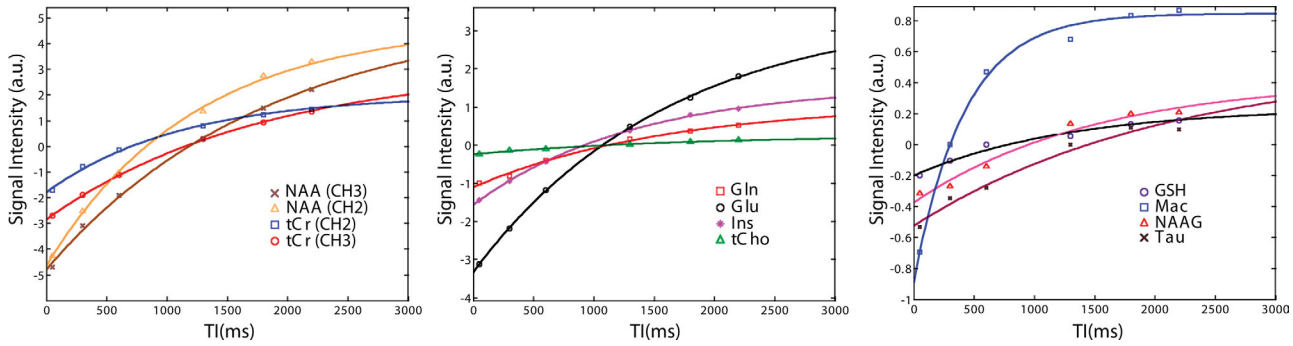

FIG. 5. Plots of the signal intensity (obtained as apparent concentrations from LCModel) and the monoexponential recovery fits of metabolite resonances as a function of TI in occipital WM. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Previous studies of T_1 relaxation were restricted to a few major resonances (e.g., tCr, NAA, tCho) in human brain at field strengths below 7 T (5–7,25). In this study, T_1 relaxation of a larger number of metabolites at 7 T was measured in occipital WM and GM (Table 2). When compared with reports from GM and WM in the occipital lobe at 3 T and 1.5 T (5,7), T_1 values of NAA (2.01 ppm), tCr (3.03 ppm), and tCho appear to be increased at 7 T by 23 ± 1%, 28 ± 2%, and 13 ± 4%. On the other hand, no differences (within experimental error) were observed when comparing with values measured at 9.4 T (2), suggesting a minimal T_1 increase beyond 7 T. Note that in the human brain T_1 of Tau is the longest among metabolites, followed by NAA (2.01 ppm) and tCr (3.03 ppm), as previously observed in rodent brain (26,27).

T_1 of water in the GM VOI was similar to values measured by MP2RAGE (14), whereas longer T_1 in WM was ascribed to a 20% signal contribution from cerebrospinal fluid within VOIs. Consistent with previous reports (14), T_1 of water in WM was much shorter compared to that in GM. Furthermore, T_1s of water in both regions were prolonged at 7 T relative to those at 1.5, 3, and 4 T (28), which was in accordance with field-dependent relaxation properties of aqueous protons (29).

Relaxation times are typically sensitive to the microenvironment, which might show tissue-dependent properties. We noticed that the T_1 relaxation time was shorter for tCho (14%) and NAAG (29%) in WM than in GM, whereas those of NAA methyl group (4%) and Glu (8%) were longer in WM. Previous studies at 3 T reported either no significant difference in T_1 relaxation times between the occipital WM and GM (7) or small changes for Cr (3.03), Cho (3.22), and Ins (3.57) (5).

The quantification of metabolites using magnetic resonance spectroscopy may be affected by differences in T_1, in particular when using a short TR. For example, according to measured T_1 values reported here and using tCr as an internal reference, the bias of metabolite concentration at TR = 4 s and 3 s would be between −2 and +10%, and between −7 and +18%, respectively. Therefore, a TR ≥ 4 s is expected to have minor effects on metabolite quantification.

We conclude that T_1 values of tCr (CH_3), tCr (CH_2), NAA (CH_3), NAA (CH_2), and nine other metabolites were measured in vivo in the human brain at 7 T including for the first time those of GSH, Tau, Scyllo, PE, and NAAG. They ranged from 0.9 s (NAAG) to 2.2 s (Tau), suggesting that when using a TR of ≥ 4s, the error of metabolite quantification would be less than 10% due to T_1 effects.

ACKNOWLEDGMENTS

The authors thank Dr. Arthur Magill for proof reading the manuscript.

REFERENCES

1. Tkac I, Andersen P, Adriany G, Merkle H, Ugurbil K, Gruetter R. In vivo 1H NMR spectroscopy of the human brain at 7 T. Magn Reson Med 2001;46:451–456.
2. Deelchand DK, Van de Moortele PF, Adriany G, Iltis I, Andersen P, Strupp JP, Vaughan JT, Ugurbil K, Henry PG. In vivo 1H NMR spectroscopy of the human brain at 9.4 T: initial results. J Magn Reson 2010;206:74–80.
3. Boer VO, Siero JC, Hoogduin H, van Gorp JS, Luijten PR, Klomp DW. High-field MRS of the human brain at short TE and TR. NMR Biomed 2011;24:1081–1088.
4. Bottomley PA, Hardy CJ, Argersinger RE, Allen-Moore G. A review of 1H nuclear magnetic resonance relaxation in pathology: are T1 and T2 diagnostic? Med Phys 1987;14:1–37.
5. Mlynarik V, Gruber S, Moser E. Proton T (1) and T (2) relaxation times of human brain metabolites at 3 Tesla. NMR Biomed 2001;14: 325–331.
6. Hetherington HP, Mason GF, Pan JW, Ponder SL, Vaughan JT, Twieg DB, Pohost GM. Evaluation of cerebral gray and white matter metabolite differences by spectroscopic imaging at 4.1T. Magn Reson Med 1994;32:565–571.
7. Ethofer T, Mader I, Seeger U, Helms G, Erb M, Grodd W, Ludolph A, Klose U. Comparison of longitudinal metabolite relaxation times in different regions of the human brain at 1.5 and 3 Tesla. Magn Reson Med 2003;50:1296–1301.
8. Choi CG, Frahm J. Localized proton MRS of the human hippocampus: metabolite concentrations and relaxation times. Magn Reson Med 1999;41:204–207.
9. Brief EE, Whittall KP, Li DK, MacKay A. Proton T1 relaxation times of cerebral metabolites differ within and between regions of normal human brain. NMR Biomed 2003;16:503–509.
10. Mlynarik V, Gambarota G, Frenkel H, Gruetter R. Localized short-echo-time proton MR spectroscopy with full signal-intensity acquisition. Magn Reson Med 2006;56:965–970.
11. Mekle R, Mlynarik V, Gambarota G, Hergt M, Krueger G, Gruetter R. MR spectroscopy of the human brain with enhanced signal intensity at ultrashort echo times on a clinical platform at 3T and 7T. Magn Reson Med 2009;61:1279–1285.

12. Tannus A, Garwood M. Adiabatic pulses. NMR Biomed 1997;10: 423–434.
13. Tkac I, Starcuk Z, Choi IY, Gruetter R. In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time. Magn Reson Med 1999;41:649–656.
14. Marques JP, Kober T, Krueger G, van der Zwaag W, Van de Moortele PF, Gruetter R. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. Neuroimage 2010;49:1271–1281.
15. Gruetter R, Tkac I. Field mapping without reference scan using asymmetric echo-planar techniques. Magn Reson Med 2000;43: 319–323.
16. Gruetter R. Automatic, localized in vivo adjustment of all first- and second-order shim coils. Magn Reson Med 1993;29:804–811.
17. Van Leemput K, Maes F, Vandermeulen D, Suetens P. Automated model-based bias field correction of MR images of the brain. IEEE Trans Med Imaging 1999;18:885–896.
18. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30:672–679.
19. Xin L, Gambarota G, Mlynarik V, Gruetter R. Proton T2 relaxation time of J-coupled cerebral metabolites in rat brain at 9.4 T. NMR Biomed 2008;21:396–401.
20. Govindaraju V, Young K, Maudsley AA. Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed 2000;13: 129–153.
21. Michaeli S, Garwood M, Zhu XH, DelaBarre L, Andersen P, Adriany G, Merkle H, Ugurbil K, Chen W. Proton T2 relaxation study of water, N-acetylaspartate, and creatine in human brain using Hahn and Carr-Purcell spin echoes at 4T and 7T. Magn Reson Med 2002;47:629–633.
22. Emir UE, Auerbach EJ, Moortele PF, Marjanska M, Ugurbil K, Terpstra M, Tkac I, Oz G. Regional neurochemical profiles in the human brain measured by (1) H MRS at 7 T using local B(1) shimming. NMR Biomed 2011;25:152–160.
23. Steinseifer IK, Mekle R, Gruetter R, Scheenen TW, Heerschap A. Implementation of GOIA-Wurst pulse in a SPECIAL localization sequence at 7T. In: Proceedings of the 10th Annual Meeting of ISMRM, Montreal, Canada; 2011. p1431.
24. Andronesi OC, Ramadan S, Ratai EM, Jennings D, Mountford CE, Sorensen AG. Spectroscopic imaging with improved gradient modulated constant adiabaticity pulses on high-field clinical scanners. J Magn Reson 2010;203:283–293.
25. Kreis R, Ernst T, Ross BD. Development of the human brain: in vivo quantification of metabolite and water content with proton magnetic resonance spectroscopy. Magn Reson Med 1993;30:424–437.
26. de Graaf RA, Brown PB, McIntyre S, Nixon TW, Behar KL, Rothman DL. High magnetic field water and metabolite proton T1 and T2 relaxation in rat brain in vivo. Magn Reson Med 2006;56: 386–394.
27. Cudalbu C, Mlynarik V, Xin L, Gruetter R. Comparison of T1 relaxation times of the neurochemical profile in rat brain at 9.4 Tesla and 14.1 Tesla. Magn Reson Med 2009;62:862–867.
28. Rooney WD, Johnson G, Li X, Cohen ER, Kim SG, Ugurbil K, Springer CS Jr. Magnetic field and tissue dependencies of human brain longitudinal 1H2O relaxation in vivo. Magn Reson Med 2007; 57:308–318.
29. Bloembergen N, Purcell EM, Pound RV. Relaxation effects in nuclear magnetic resonance absorption. Phys Rev 1948;73:679–712.