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

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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 informa-tion 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
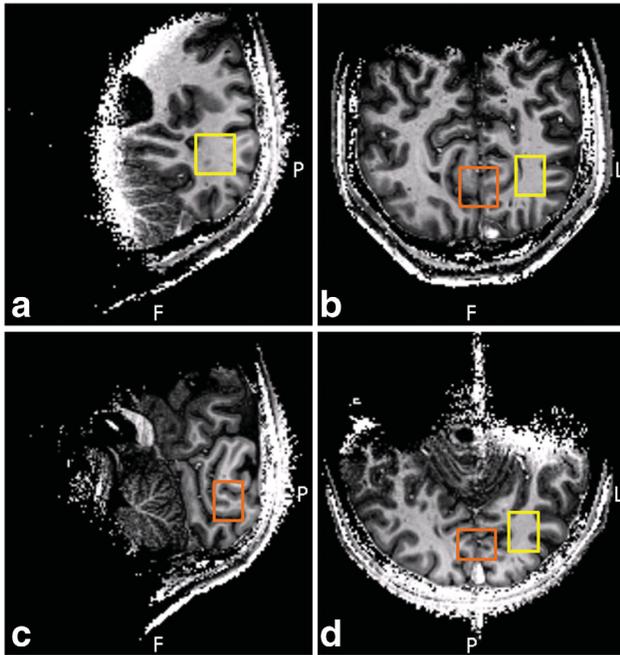
FIG. 1. $T_1$-weighted images reconstructed in the sagittal (**a, c**), coronal (**b**), and transverse (**d**) plane from the three-dimensional images acquired using MP2RAGE (TE/TR = 3.37/5000 ms, TI$_1$/TI$_2$ = 700/2200 ms, slice thickness = 1 mm, field of view = 176 × 256 mm$^2$, matrix size = 176 × 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 $^1$H 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 $T_1$s 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 × [1 − $b$ × 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 × $T_1$), 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
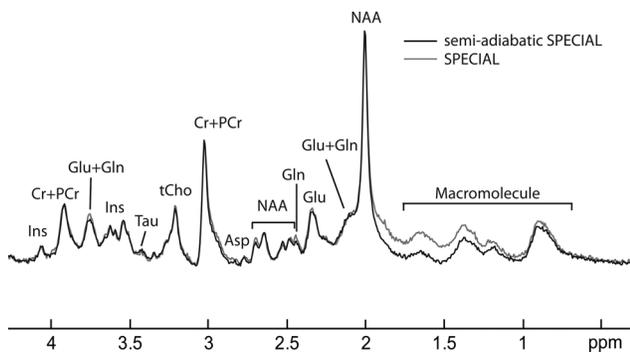
FIG. 2. In vivo $^1$H MR spectra acquired using the semi-adiabatic SPECIAL (TE/TR = 12/7500 ms, 32 averages) and SPECIAL (TE/TR = 6/7500 ms, 32 averages) localization sequences from an identical VOI (20 × 15 × 20 mm$^3$) in the occipital lobe of a healthy male volunteer (for both spectra, appodization, 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 $T_1$s 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.
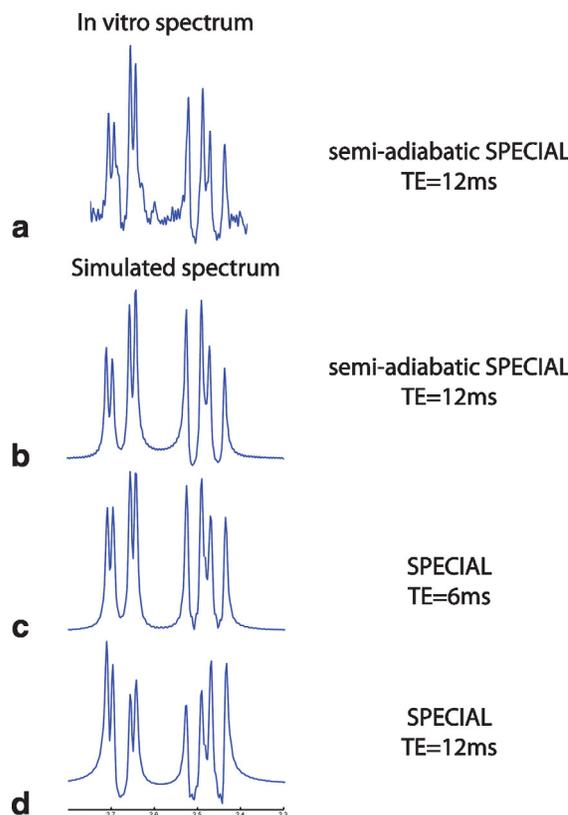


FIG. 3. In vitro $^1$H MR spectra (**a**) of the methylene group of the aspartate moiety of NAA measured using semi-adiabatic SPECIAL (TE = 12 ms, TR = 15 s, and 128 averages) and simulated spectra obtained using (**b**) semi-adiabatic SPECIAL at TE = 12 ms; (**c**) SPECIAL at TE = 6 and (**d**) 12 ms ($T_2$ 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 $\pm$ SD, $n = 6$)

| | WM (%) | GM (%) | Cerebrospinal fluid (%) |
|---|---|---|---|
| Occipital WM | 60 $\pm$ 2 | 19 $\pm$ 8 | 21 $\pm$ 9 |
| Occipital GM | 16 $\pm$ 5 | 75 $\pm$ 5 | 9 $\pm$ 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 $\pm 6\%$ 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 unreli-
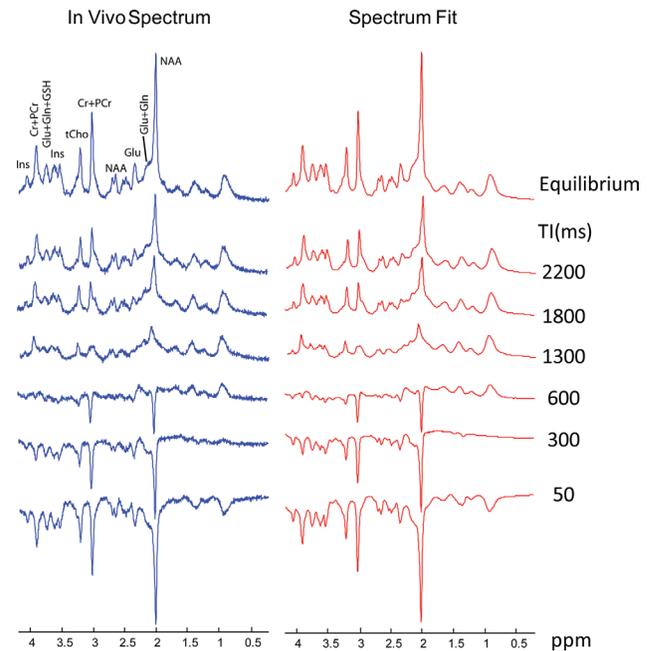


FIG. 4. A series of in vivo ^{1}H inversion-recovery MR spectra acquired using semi-adiabatic SPECIAL (VOI = 15 × 20 × 20 mm$^3$, TE/TR = 12/7500 ms, 32 averages, appodization, baseline correction, and post-water removal were all not performed) at different TIs in the occipital white-matter-rich tissue 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.]

able 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.

Table 2

$T_1$ Relaxation Times (mean $\pm$ 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 $\pm$ 0.04 | 1.74 $\pm$ 0.06 |
| tCr (3.92 ppm) | 1.10 $\pm$ 0.06 | 1.13 $\pm$ 0.04 |
| NAA (2.01 ppm)* | 1.90 $\pm$ 0.06 | 1.83 $\pm$ 0.05 |
| tCho** | 1.32 $\pm$ 0.06 | 1.51 $\pm$ 0.11 |
| Ins | 1.19 $\pm$ 0.07 | 1.28 $\pm$ 0.08 |
| Glu** | 1.75 $\pm$ 0.04 | 1.61 $\pm$ 0.09 |
| NAA(CH$_2$) | 1.19 $\pm$ 0.05 | 1.24 $\pm$ 0.05 |
| GSH | 1.06 $\pm$ 0.06 | 1.14 $\pm$ 0.18 |
| Gln | 1.74 $\pm$ 0.23 | 1.64 $\pm$ 0.07 |
| Scyllo | 1.23 $\pm$ 0.07 | 1.31 $\pm$ 0.20 |
| Tau | 2.09 $\pm$ 0.04 | 2.15 $\pm$ 0.11 |
| PE | 1.32 $\pm$ 0.30 | 1.31 $\pm$ 0.18 |
| NAAG* | 0.94 $\pm$ 0.08 | 1.21 $\pm$ 0.22 |
| Macromolecules | 0.42 $\pm$ 0.02 | 0.43 $\pm$ 0.02 |
| Water*** | 1.55 $\pm$ 0.07 | 2.00 $\pm$ 0.12 |

The differences between $T_1$ values in WM and GM were evaluated by the unpaired Student's $t$-test (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).
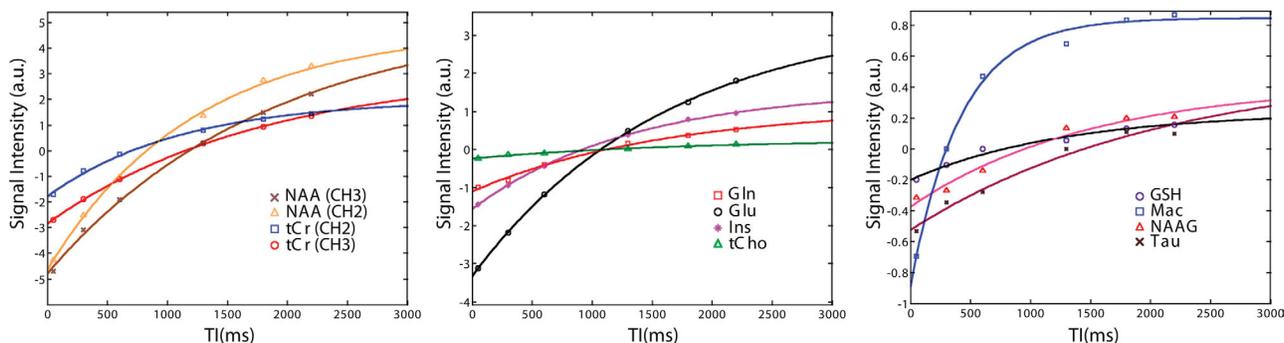
FIG. 5. Plots of the signal intensity (obtained as apparent concentrations from LCModel) and the monoexponential recovery fits of metabolite resonances as a function of TI in occipital WM. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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 $23 \pm 1\%$, $28 \pm 2\%$, and $13 \pm 4\%$. 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, $T_1$s 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 $\geq$ 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 $\geq$ 4s, the error of metabolite quantification would be less than 10% due to $T_1$ effects.

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