Original Research

^{1}H Metabolite Relaxation Times at 3.0 Tesla: Measurements of T1 and T2 Values in Normal Brain and Determination of Regional Differences in Transverse Relaxation

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Purpose: To measure ^{1}H relaxation times of cerebral metabolites at 3 T and to investigate regional variations within the brain.

Materials and Methods: Investigations were performed on a 3.0-T clinical whole-body magnetic resonance (MR) system. T2 relaxation times of N-acetyl aspartate (NAA), total creatine (tCr), and choline compounds (Cho) were measured in six brain regions of 42 healthy subjects. T1 relaxation times of these metabolites and of myo-inositol (Ins) were determined in occipital white matter (WM), the frontal lobe, and the motor cortex of 10 subjects.

Results: T2 values of all metabolites were markedly reduced with respect to 1.5 T in all investigated regions. T2 of NAA was significantly ($P < 0.001$) shorter in the motor cortex (247 ± 13 msec) than in occipital WM (301 ± 18 msec). T2 of the tCr methyl resonance showed a corresponding yet less pronounced decrease (162 ± 16 msec vs. 178 ± 9 msec, $P = 0.021$). Even lower T2 values for all metabolites were measured in the basal ganglia. Metabolite T1 relaxation times at 3.0 T were not significantly different from the values at 1.5 T.

Conclusion: Transverse relaxation times of the investigated cerebral metabolites exhibit an inverse proportionality to magnetic field strength, and especially T2 of NAA shows distinct regional variations at 3 T. These can be attributed to differences in relative WM/gray matter (GM) contents and to local paramagnetism.

Key Words: magnetic resonance, high field; magnetic resonance spectroscopy; in vivo relaxation times; brain metabolites; absolute quantification
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SEVERAL MAGNETIC RESONANCE (MR) studies performed at magnetic fields of 3 T or higher have shown that longitudinal relaxation times T1 of water protons in human brain tissue are prolonged at increasing field strength, whereas T2 of water is progressively reduced (1–5). However, until now, only a few reports on the measurement of proton T1 and T2 relaxation times of brain metabolites in vivo at magnetic fields beyond the 2 T threshold have been published. Accurate values for ^{1}H metabolite relaxation times are required for reliable and reproducible determination of absolute metabolite concentrations in cerebral tissue by MR spectroscopy (MRS).

Analogous to the observed field dependence of water T2 relaxation times, the high-field MRS studies available up to now indicate a steady decrease of ^{1}H metabolite T2 values of N-acetyl aspartate (NAA), total creatine (tCr), and choline compounds (Cho) when progressing from 1.5–3 T and up to 7 T (6–10). While these data reveal a consistent trend, detailed information at 3 T, particularly regarding variations of metabolite T2 in different cerebral areas, is still incomplete. The aim of our study was to measure ^{1}H metabolite T2 in an extended set of brain regions covering a broad range of different mixtures of white matter (WM) and gray matter (GM) and with an adequate number of samples for each localization.

High-field measurements of ^{1}H metabolite T1 have been performed at 3.0 T (6), 4.0 T (8), and 4.1 T (9). In contrast to the pronounced effects on water T1, and on water T2 and metabolite T2, no obvious influence of magnetic field strength on ^{1}H metabolite T1 values can as yet be derived from these studies considering the rather large overlying regional and interindividual variations.

A question often raised in clinical applications of MRS is whether differences in absolute metabolite signals or ratios between patients and normal controls are really due to altered tissue concentrations or rather might be attributed to changes in metabolite relaxation times. To enable clarification of this item in forthcoming MRS investigations, a further aim of our study was to set up sufficiently fast protocols for accurate metabolite T1 and T2 measurements, which are suited to also be included in patient studies. This intention should particularly profit from the gain in signal-to-noise ratio (SNR) at higher magnetic fields (7,10–12), which allows the reduction of measurement time or voxel size.

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MATERIALS AND METHODS

MR System and Study Subjects

Measurements of cerebral ^{1}H metabolite relaxation times were performed at a magnetic field of 3.0 T on a clinical whole-body MR system (Gyroscan Intera 3.0 T; Philips Medical Systems, Best, The Netherlands) equipped with 30 mT/m gradients and a transmit/receive birdcage head coil suited for MR imaging (MRI) and MRS. Forty-two healthy volunteers (22 males and 20 females, mean age = 40 ± 18 years) were included in the MRS study. T2 data sets were acquired from all participants, and in 10 cases metabolite T1 was also measured. The study was approved by the local institutional board and written informed consent was obtained from all study subjects.

MRS voxels were selected image-guided by the point-resolved spectroscopy (PRESS) localization scheme (13). The volume sizes (mean value = 15.7 cm^3, range = 10–25 cm^3) were chosen large enough to acquire high SNR spectra within measurement times sufficiently short to be also suited for patient investigations. First-order shimming of the volume of interest (VOI) resulted in spectral line widths of <0.05 ppm for parietal and occipital brain regions and <0.08 ppm in more basal localizations. MRS voxel position on the images was referenced to a frequency offset of –340 Hz from the water peak. Therefore, no chemical shift displacement of the selected volume occurred for the resonance of NAA at 2.02 ppm. For the methyl protons of tCr and Cho, the true VOI position was shifted by 9% and 10%, respectively, of its linear extension (e.g., a voxel length of 2 cm corresponding to a selection gradient amplitude of 1.8 mT/m results in a VOI position shift of 2 mm for Cho). In the occipital lobe, it was possible to place MRS voxels with sizes of 10–15 cm^3, which almost exclusively (>80%) contained WM. However, in cortical areas with predominant GM contents, e.g., the motor cortex and the cingulate gyrus, partial-volume effects with adjacent WM had to be taken into account. We selected six cerebral regions representing quite different anatomical positions and a widespread range of relative WM/GM contents to investigate the regional variability of metabolite T2 values. For each localization in the brain, spectra were obtained from 5–10 study subjects.

Metabolite T2 Determination

^{1}H metabolite T2 relaxation times of the methyl protons in NAA, tCr, and Cho, and of the CH_2 molecular group in tCr resonating at 3.93 ppm, were measured by a series of spin-echo (SE) spectra with at least five different echo delays TE. A total of 46 VOIs were placed in occipital WM (N = 10), cortical GM of the primary motor area (N = 10), basal ganglia (N = 8), fronto-lateral WM/GM (N = 7), GM of the cingulate gyrus (N = 6), and left cerebellar hemisphere (N = 5). Half-echo sampling of 512 data points at a frequency of 1500 Hz (= detection bandwidth) corresponded to a noninterpolated spectral resolution of 3 Hz/point. For water suppression with a bandwidth of 160 Hz the dual inversion technique (14) was applied with two frequency-selective inversion pulses preceding the 90° excitation pulse. In the standard protocol, TE_{1-5} = 50/120/200/280/400 msec were used with 16 signal averages each for TE = 50–280 msec, and with 32 averages for TE = 400 msec, to compensate for the SNR loss at the longest echo delay. With two start-up cycles for each TE to provide steady-state conditions and a TR of 2500 msec ensuring at least 80% recovery of longitudinal magnetization, a total measurement time of 4 minutes 30 seconds resulted. From simulations and initial testing this setting with five TE values covering a signal range of approximately 20% to 80% of total T2 decay for NAA and Cho (and 25% to 90% for tCr) was considered optimal with respect to T2 sensitivity, high SNR within tolerable measurement time, and appropriate overdetermination to yield low parameter errors in a monoexponential regression. However, to check for possible multiexponential T2 relaxation behavior of any of the investigated resonance lines, an extended protocol with TR = 2000 msec and 8–11 different TE values between 30 and 450 msec was performed in eight of the cases.

Metabolite signals were quantified by time-domain fitting using the nonlinear AMARES algorithm (15) of the MRUI software package (16,17). Preprocessing included HLSVD filtering of residual water and Lorentz-Gauss apodization (5 Hz Gaussian/–3 Hz exponential multiplication) to improve SNR, especially at long TE, and to reduce spectral overlap by converting the line shapes to a more Gaussian profile. Therefore, the four investigated singlets of NAA, tCr-CH_3, Cho, and tCr-CH_2 were fitted with Gaussian line shapes, and signal contributions from adjacent resonances of spin-coupled multiplets could be neglected at least for TE ≥ 50 msec. Finally, from the plot of the line areas S(TE) obtained by the AMARES fit vs. TE, the transverse relaxation times of the respective metabolite resonances were calculated monoexponentially using a two-parameter least-squares fit to T2 and S_0:

$$S'(TE) = S(TE)/f(T1,TR,TE) = S_0 \cdot \exp(-TE/T2)$$

with

$$f(T1,TR,TE) = 1 - 2\exp[-(TR-TE/2)/T1] + \exp(-TR/T1).$$

The slightly TE-dependent correction factor f(T1,TR,TE) for partial T1 saturation (18) (differing between shortest and longest TE by 5% at maximum for TR = 2500 msec) was applied to the measured values prior to the fit to provide linear proportionality between ln S′(TE) and the relaxation rate 1/T2.

Metabolite T1 Determination

T1 relaxation times of NAA, tCr, Cho, and of the C1/C3 and C4/C6 protons in myo-inositol (Ins), at 3.54 and 3.63 ppm, respectively, were measured in occipital WM (N = 4), motor cortex (N = 5), and fronto-lateral WM/GM (N = 3). In eight VOI measurements, T1 was determined from a series of inversion recovery spectra with TR/TE = 4000/50 msec and five or six different inversion delays TI. The frequency of the 180° pulse was centered at −300 Hz offset from the water peak, between the resonances of NAA and tCr-CH_3. An inversion

bandwidth of 500 Hz was chosen to provide spin inversion up to −50 Hz, thus extending well beyond the tCr methylene frequency, but without interacting with the Gaussian excitation prepulses used for water suppression. For six TI values with 16 signal averages each, total acquisition time was 7 minutes 12 seconds. AMARES time-domain fitting of seven Gaussian lines included the combined glutamine/glutamate (Glx) resonance at 3.76 ppm to improve quantification of tCr-CH_2 and the two Ins peaks. This was followed by a nonlinear two-parameter determination of T1 and equilibrium magnetization. Due to the increased frequency dispersion of the metabolite peaks at 3 T, we suspected less efficient inversion of resonances near the edge of the inversion bandwidth (i.e., tCr-CH_2 and Ins). Therefore, in eight cases we used progressive saturation (PS) as an alternative technique for T1 measurement. In the PS experiments, a series of six differently T1-saturated SE spectra with TR_{1-6} = 600/1000/1400/2000/3000/5000 msec covering a signal range from 30% to 95% of full T1 recovery were acquired. The minimum TR was essentially determined by the time interval required for data sampling. To obtain comparable SNR in all spectral rows, the number of signal averages was progressively reduced from 64 at shortest TR to 16 at the longest TR, resulting in a total measurement time of 5 minutes 38 seconds. Again, seven Gaussian components were used in the AMARES quantification, and T1 was determined from nonlinear least-squares fitting of two parameters to the six data points on the recovery curve of longitudinal magnetization. Although measurement time could have been shortened by using fewer TR values, a considerable increase in the parameter errors has to be expected (19), especially for the PS method with inherently lower T1 sensitivity. Altogether, a total of 16 T1 data sets were obtained by inversion recovery (IR) and PS acquisitions from 12 VOIs in 10 subjects, allowing intraindividual comparison of both techniques in four cases.

Statistical Evaluation

The SPSS software package (SPSS, Inc.) was used for statistical data analysis. Nonparametric tests were applied throughout, as the number of cases per brain region was not sufficiently high to assume normal distribution. The Mann-Whitney U-test for unmatched pairs was performed to compare metabolite T2 of the investigated cerebral regions. This test was also used to compare T1 values from IR and PS acquisitions. Differences on the $P < 0.05$ level were considered significant.

RESULTS

All 46 T2 and all 16 T1 data sets from the 42 participants were of sufficient quality to be included in the data analysis. However, only those acquisitions were used for T2 or T1 fitting where the respective metabolite resonance could be quantified in at least four rows of the spectral series. This was possible for NAA in all, and for tCr-CH_3 and Cho in 44/46 T2 sets. The less intense methylene resonance of tCr at 3.93 ppm, showing faster T2 decay than the other three components, was often not detectable at the longest echo delays. Additionally, in regions with enhanced susceptibility broadening the superposition by residual water signal or adjacent spin-coupled metabolite lines sometimes prevented reliable quantification, particularly at short TE. Nevertheless, T2 of tCr-CH_2 could be determined in 32/46 data sets. In Fig. 1 an example for metabolite T2 measurement of a 15-mL volume located in the basal ganglia is displayed, which was performed using the standard protocol with five TE values. Despite susceptibility-broadened line widths of about 8 Hz, component separation and SNR were good enough to provide an excellent match of the obtained metabolite peak areas to monoexponential relaxation curves (with regression coefficients of >0.991 and a T2 fitting accuracy of 7% for tCr-CH_2 and 2% to 3% for the other three components). While NAA and Cho reveal similar T2 values, the two tCr peaks show much faster T2 decay and have almost decreased to noise level at TE = 400 msec.

Recent observations (20) at 1.5 T indicate a biexponential T2 relaxation of the tCr methyl resonance due to different T2 values of creatine and phosphocreatine. However, at 3.0 T we found no evidence for multiexponential T2 decay for any of the investigated four metabolite singlets when applying the extended protocol with >7 TE values. In the example in Fig. 2 with eight TE values ranging from 30–400 msec in the cingulate gyrus no systematic deviations from a purely monoexponential T2 decay can be recognized apart from the elevation of the tCr-CH_2 resonance at TE = 30 msec caused by the underlying Glx-CH and macromolecular components. Applying a biexponential least-squares fit yielded no meaningful results for the enlarged set of four parameters, and the same observation was made for NAA and Cho and in all investigated brain regions. Due to contributions from the Glx-CH_2 multiplets, at TE = 30 msec the signal of the NAA methyl protons was also often raised above the regression line in the semilogarithmic plot. For this reason, 50 msec was used as the shortest TE in the standard protocol. On the other hand, exclusion of the data for the longest TE values (>280 msec) from the two-parameter fit revealed no significant change in measured T2 of any of the metabolites (<1% difference in mean T2 for NAA and Cho, 2.2% decrease for tCr-CH_3) but considerably enlarged the error limits of the fit.

In all cases where T2 of the tCr-CH_2 protons could be quantified, we also determined the equilibrium intensities S_0 relative to those of the respective methyl protons. Since this value directly reflects the proton ratio within the same molecule, it should not depend on brain region or individual, and thus can be used as an internal check of the reliability of the parameter results. The mean value was 0.64 ± 0.10, which is in good agreement with the ratio 2/3 of the proton numbers in the methylene and methyl groups. Through the application of correction factors for partial saturation at a given TR, a slight T1 dependence is introduced into the T2 determination. In the cases where metabolite T1 of the same VOI was not measured individually, the mean values of the group were used. However, as already mentioned in the Materials and Methods section, only the TE-dependent differential correction could influence the T2 results. Therefore, even an assumed T1 error of 20%

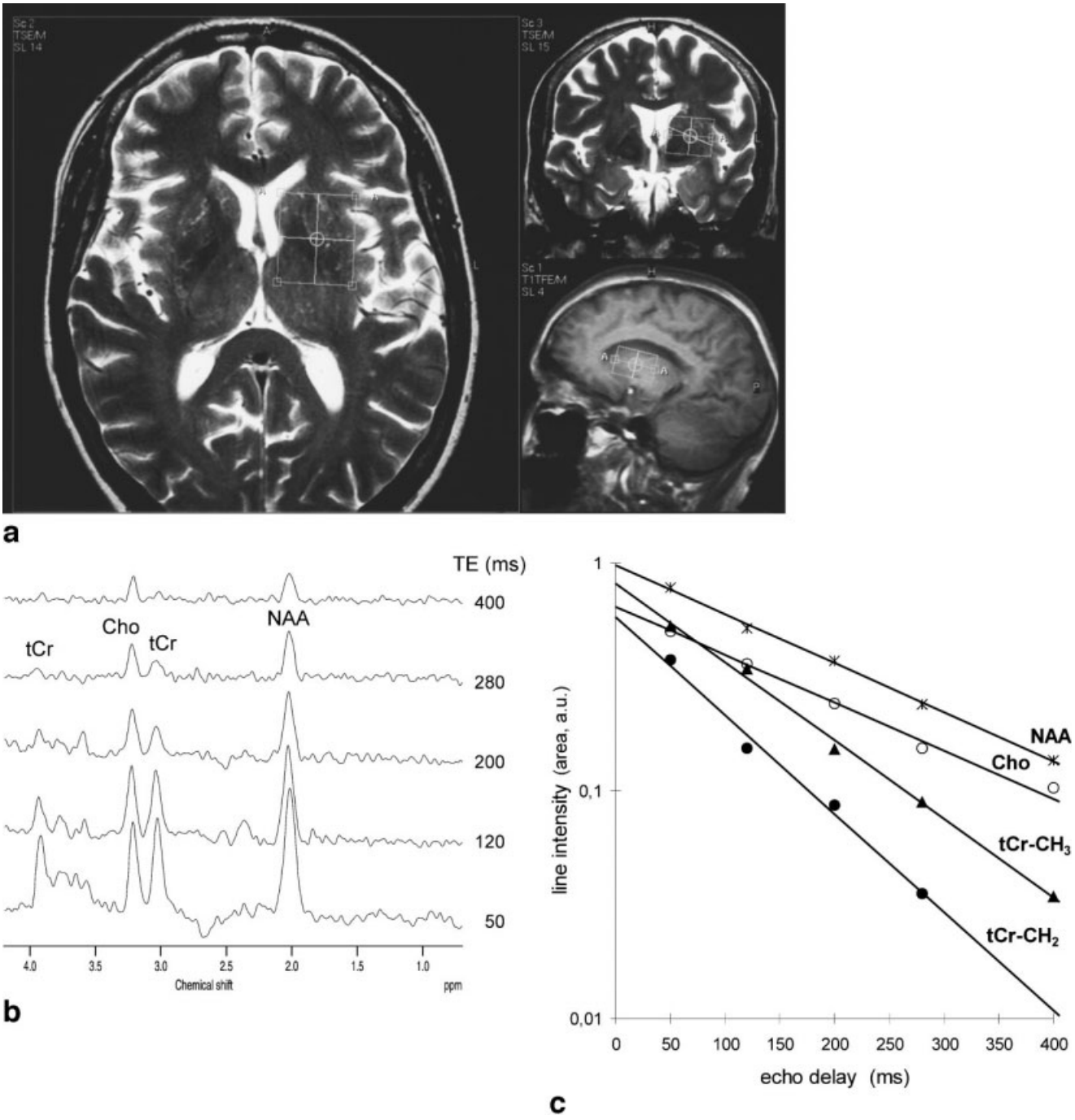

Figure 1. Metabolite T2 measurement in a 3 × 2.5 × 2 cm (anterior-posterior/left-right/cranial-caudal) volume located in the basal ganglia of a healthy volunteer. **a:** Display of image-guided VOI selection on transverse and coronal T2-weighted turbo spin echo (TSE) and on sagittal T1-weighted turbo field echo (TFE) sequences. **b:** Series of SE spectra from selected VOIs obtained with TR = 2400 msec and TE_{1-5} = 50/120/200/280/400 msec. **c:** Monoexponential fit of the metabolite line areas as determined by MRUI processing vs. echo delay TE. Linear regression curves in semilogarithmic display correspond to T2 values (± fit errors) of 202 ± 5 msec for NAA, 126 ± 4 msec for tCr-CH_3, 195 ±5 msec for Cho, and 101 ± 7 msec for tCr-CH_2.

would change the calculated T2 values by less than 1% at the used settings of TR and TE.

Table 1 lists the results of our T2 measurements at 3.0 T as regional mean values ± standard deviation (SD) for the metabolite resonances of NAA, tCr, and Cho. Relative SDs were typically 5% to 10% and exceeded this margin only for Cho in the frontal lobe and for tCr-CH_2. The T2 values of NAA ranging from 220–300 msec differed significantly from those of Cho (range = 200–280 msec) in occipital WM ($P < 0.001$) and the motor cortex ($P < 0.01$). The methylene protons in tCr exhibited 19% to 29% shorter T2 in all regions (range = 110–140 msec) than the methyl protons of the same metabolite (range = 140–180 msec). For comparison, Table 1 also includes the T2 results from earlier MRS studies of our group at 1.5 T (21 and unpublished data). These were obtained using the same technique but with TE = 50/136/272/400/550 msec adapted to longer T2 at this field strength and with

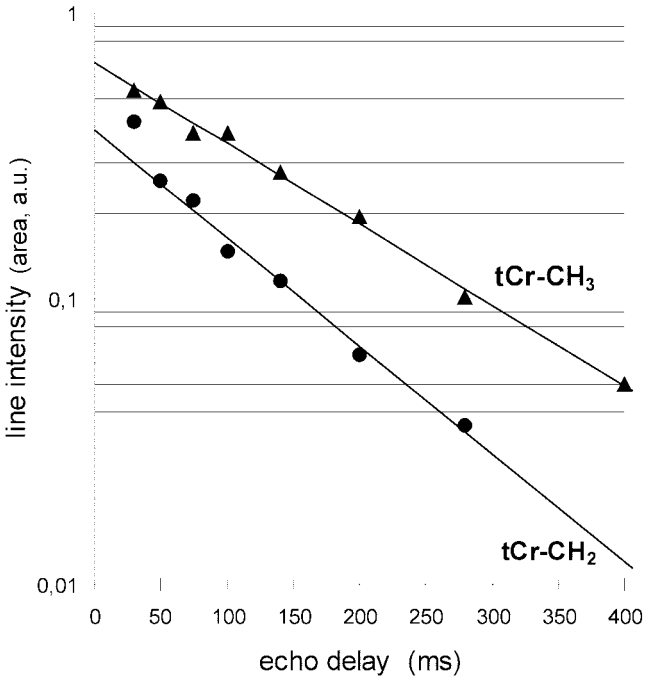

Figure 2. Semilogarithmic plot of MR spectral line areas for the methyl and methylene protons of tCr measured at eight TE values (TR = 2000 msec, 16 signal averages each) in a 22-mL VOI located in the cingulate gyrus GM of both hemispheres. The monoexponential fit yielded regression coefficients of 0.995 for tCr-CH_3 and 0.990 for tCr-CH_2. Regression lines are calculated from the T2 parameter fit results (± fit errors) of 154 ± 4 msec for tCr-CH_3 and 115 ± 6 msec for tCr-CH_2.

larger VOI (20–30 mL) due to lower SNR. Metabolite T2 relaxation times at 3.0 T were reduced by more than 15% with respect to the 1.5 T values in all investigated brain areas.

Regional comparison at 3.0 T between occipital WM and volumes with predominant GM contents (primary motor area and cingulate gyrus) by the Mann-Whitney U-test for unmatched samples revealed significantly smaller T2 values in GM for NAA ($P < 0.001$) and—less pronounced—for tCr methyl protons ($P = 0.021$ for motor cortex and $P < 0.01$ for cingulate gyrus). This correlation between T2 of these metabolites and relative WM/GM contents becomes even more obvious when including the results for the fronto-lateral volumes, which contained WM and GM in almost equal percentage, and sorting the regions with respect to GM contents (Fig. 3). From a linear extrapolation considering the partial volumes, pure GM T2 estimates were about 220 msec for NAA and about 150 msec for tCr-CH_3. Much shorter T2 values than in all other regions were observed in the basal ganglia; these results are also plotted in Fig. 3. Even for Cho, T2 was significantly reduced there ($P < 0.01$ vs. occipital WM, $P = 0.021$ vs. motor cortex). From the equilibrium intensities S_0 determined by the T2 fit, metabolite concentration ratios could also be obtained for the investigated regions. Mean concentrations relative to tCr were 1.64 ± 0.14 in occipital WM, 1.47 ± 0.28 in the motor cortex, and 1.19 ± 0.12 in the basal ganglia for NAA; and 0.31 ± 0.05 in occipital WM, 0.24 ± 0.04 in the motor cortex, and 0.28 ± 0.05 in the basal ganglia for Cho (with proton factor 3 already included).

Figure 4 shows an example of a metabolite T1 measurement performed by an IR series of spectra with six inversion delays in a 15-mL voxel positioned in fronto-lateral WM/GM. At the used TE of 50 msec, signal overlay of NAA, Ins, and tCr-CH_2 by the Glx and macromolecular resonances is already considerably reduced, thus improving quantification accuracy, especially at TI values near the zero crossing of longitudinal magnetization where a flat baseline is desired (rows 2–4 in Fig. 4b). However, the peaks from the Ins-CH protons (C1/C3 at 3.54 ppm and C4/C6 at 3.63 ppm) were already decreased at TE = 50 msec due to short T2 and showed some dephasing by spin coupling. The intensities of the two Ins components were averaged to improve the quality of the T1 fit. While in our T2 measurements regional differences exceeding 20% were observed, the metabolite T1 determinations revealed no obvious T1 variations between the examined cerebral regions. Therefore, and with respect to the smaller number of acquisitions, the T1 results were averaged over all MRS volumes in occipital WM, motor cortex GM, and fronto-lateral region of the brain. Table 2 displays the results of our ^{1}H metabolite T1 measurements

Table 1
MRS Results for ^{1}H Metabolite Relaxation Times T2 (msec) in Different Regions of the Brain

Metabolite component chemical shift (ppm)	*N*	NAA 2.02	tCr-CH_3 3.03	Cho 3.21	tCr-CH_2 3.93
3.0 T[a]					
Occipital WM	10	301 (18)	178 (9)	222 (17)	127 (13)
Motor cortex GM	10	247 (13)	162 (16)	222 (15)	121 (13)
Cingulate gyrus GM	6	254 (15)	161 (10)	265 (29)	128 (11)
Fronto-lat. WM/GM	7	279 (16)	169 (9)	242 (37)	137 (7)
Basal ganglia	8	221 (18)	143 (13)	201 (16)	112 (14)
Cerebellum	5	287 (14)	178 (13)	276 (13)	134 (16)
1.5 T[b]					
Occipital WM	15	361 (39)	215 (15)	330 (44)	
Motor cortex GM	8	317 (25)	208 (14)	300 (33)	
Fronto-lat. WM/GM	5	357 (26)	216 (14)	332 (26)	

Data are mean ± SD.
[a]This work.
[b](21), sample enlarged by unpublished results from own work

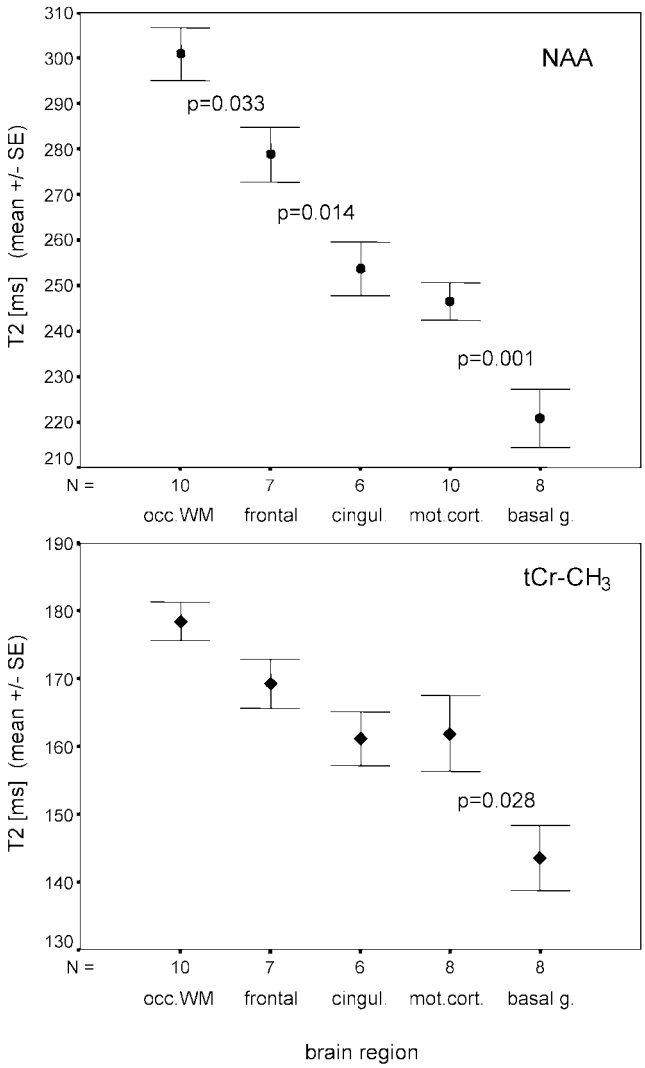

Figure 3. Plot of metabolite T2 vs. brain region, ordered with respect to increasing GM contents within the MRS volume, for the methyl resonances of NAA and tCr. Error bars correspond to standard errors of the mean; *P* values represent significance levels obtained from Mann-Whitney U-test.

by the IR technique and by PS of SE spectra at 3.0 T in comparison to our earlier 1.5-T studies (21 and unpublished data). At 1.5 T we performed IR acquisitions of ^{1}H spectra from 30-mL volumes in parietal WM/GM, including the primary motor cortex. No significant changes of metabolite T1 values were found at the two field strengths. While T1 determination by inversion and saturation techniques at 3 T yielded consistent results for NAA and Cho intra- and interindividually (intrasubject differences in T1 values were less than 0.1 second in all cases), considerable discrepancies were observed for tCr and Ins.

DISCUSSION

At present, only the studies of Mlynárik et al (6) and Barker et al (7) provide a comparison to the results of our metabolite T2 determinations at 3.0 T. For T2 of NAA our results are in perfect agreement with those of Mlynárik et al in occipital WM as well as in cortical GM, and they sufficiently match for tCr and Cho in GM (although different cortical areas were investigated). For tCr-CH_3 and Cho in WM, higher T2 values were observed in our study. However, the standard errors given by Mlynárik et al are considerably larger for the WM voxels, which is presumably due to reduced SNR for these voxels because a surface coil was used in their study. The much lower T2 value for NAA (210 ± 20 msec) in WM of the centrum semiovale obtained by Barker et al (7) may be questionable, as it is even inferior to the 4.1-T results of Hetherington et al (9). Since only four TE values between 20 and 272 msec were used in this study, signal contributions from macromolecules and coupled spins underlying the singlet resonances at the shortest TE could have led to an overestimation of their T2 decay. The stimulated echo acquisition mode (STEAM) localization scheme applied in both mentioned studies at 3 T is sensitive to spin dephasing within the mixing time (TM), yielding shorter apparent T2 for very long TM values, as has been demonstrated by Posse et al (8) at 4 T. However, the influence on T2 should be negligible at the used TM values of 14 and 60 msec, respectively. On the other hand, the comparably higher metabolite T2 values for WM observed in our study also exclude systematic errors due to enhanced spin dephasing effects caused, e.g., by susceptibility gradients or diffusion. An overestimation of T2 corresponding to slower signal decrease at long TE values (e.g., due to multiexponential T2 relaxation) could be ruled out by comparison with the results obtained when all data for TE > 280 msec were ignored.

Although we applied a lower number of signal averages per TE than the other 3-T studies to keep measurement time within limits also suited for clinical applications, the corresponding SNR loss could be fully compensated by use of slightly larger MRS volumes. Our results show that with measurement times of less than 5 minutes, an accuracy of 5% to 10% for the metabolite T2 relaxation times could be achieved at 3.0 T, which proved to be sufficiently high to resolve regional differences and should also allow detection of pathological changes. One reason for the rather low parameter errors resulting from the T2 fits (typically <5%) might be the extension of the TE values (up to 450 msec) over the full dynamic range of metabolite signal decay, thus increasing T2 sensitivity. In the other two 3-T studies, TE values of 250 and 272 msec, respectively, were used as maximum values, thus covering only 60% to 70% of total T2 decay for NAA and Cho. Inclusion of shorter TE values than 50 msec in the MRS series for T2 determination might be of benefit only for metabolite resonances with very short TE. When quantifying the peaks of NAA, tCr, and Cho at TE = 30 msec, the signal contributions from spin-coupled multiplets and from macromolecular resonances deteriorated the quality of the T2 fit, although this was only evident for NAA and tCr-CH_2. Improvements at echo delays of TE < 50 msec could possibly be achieved with smaller line widths for better component separation, but this would require much smaller VOIs and higher-order shimming. Within a TE range of 50–450 msec, our results were consistent with purely monoexponential T2 relaxation of all investigated singlet resonances. To also determine T2 values of J-coupled components is desir-

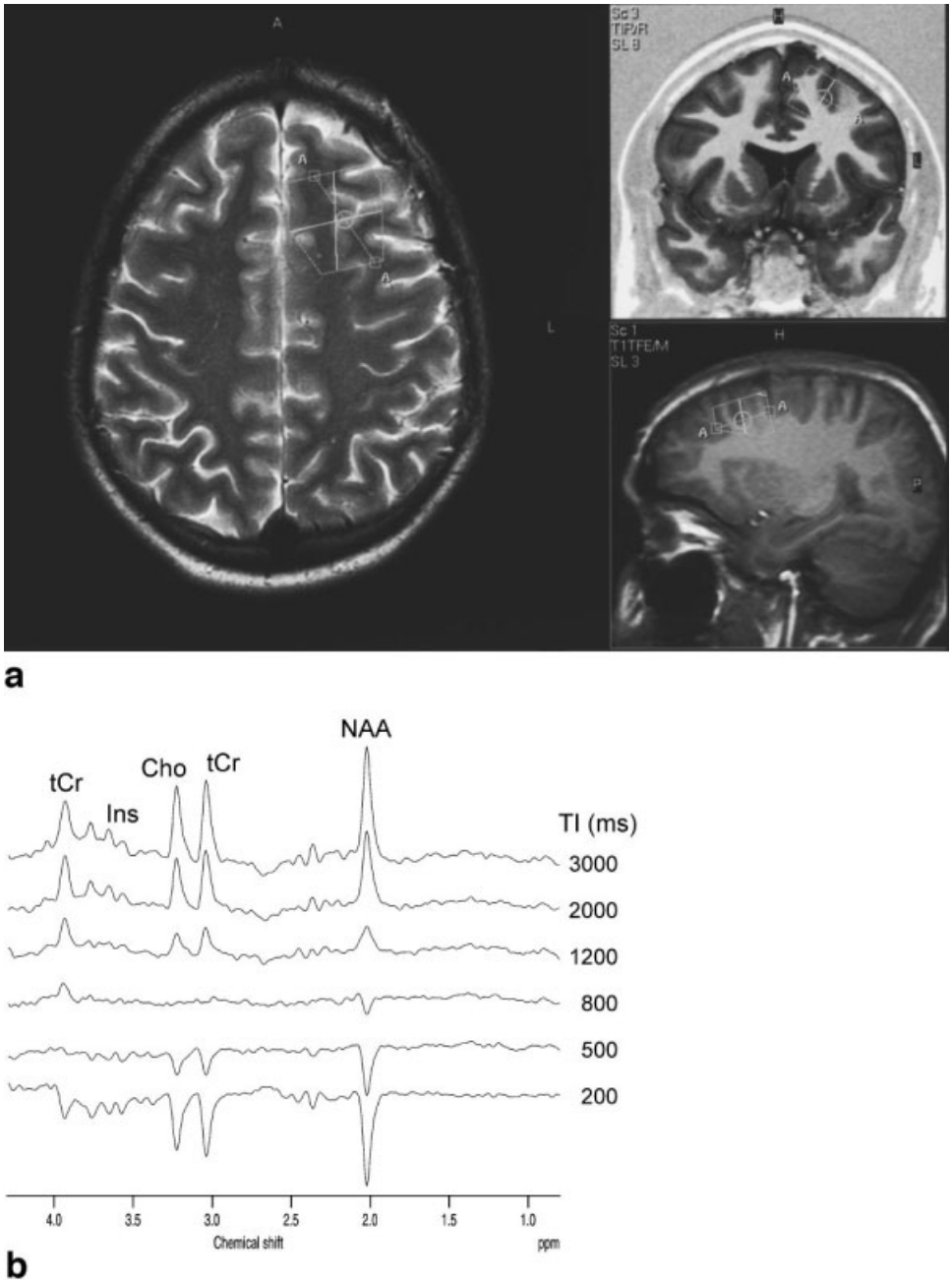

Figure 4. Metabolite T1 measurement in a 15-mL VOI located in the fronto-lateral region. **a:** Display of selected volume comprising left frontal WM and cortical GM on transverse TSE, coronal IR-TSE, and sagittal TFE images. **b:** IR series of localized spectra obtained with TR/TE = 4000/50 msec and TI_{1-6} = 200/500/800/1200/2000/3000 msec.

Table 2
MRS Results for Cerebral ^{1}H Metabolite Relaxation Times T1(s)[a]

Metabolite component chemical shift (ppm)		NAA 2.02	tCr-CH_3 3.03	Cho 3.21	Ins 3.54/3.63	tCr-CH_2 3.93
3.0 T[b]						
IR	$N = 8$	1.34 (0.08)	1.11 (0.11)	1.14 (0.07)	0.98 (0.16)	0.76 (0.13)
PS	$N = 8$	1.39 (0.03)	1.47 (0.07)	1.15 (0.04)	1.36 (0.25)	1.02 (0.13)
1.5 T[c]						
IR	$N = 10$	1.41 (0.14)	1.19 (0.18)	1.16 (0.16)	0.8–1.1 ($N = 4$)	

Data are Mean ± SD.
[a]T1 results at 3 T are pooled mean values averaged over VOI localizations in occipital WM ($N = 4$), motor cortex GM ($N = 5$), and fronto-lateral WM/GM ($N = 3$).
[b]3 T results were obtained from inversion-recovery series (IR) and by progressive saturation in spin-echo series (PS).
[c]1.5 T values were measured by IR in parietal WM/GM including the motor cortex (21, sample enlarged by unpublished own work).

able, especially for Ins, but would require editing techniques with TE adapted to the coupling constants, which was beyond the scope of this study.

The comparison to metabolite T2 relaxation times at 1.5 T measured in our earlier study and by several other groups (22–27) shows a systematic reduction of 15% to 20% for T2 of NAA and tCr at 3.0 T in WM as well as in cortical GM. An even more pronounced decrease of about 30% is observed for T2 of Cho. This leads to a distinct difference between the T2 values of the methyl protons of NAA and Cho, particularly in occipital WM, while at 1.5 T the T2 relaxation times of these metabolites are equal within their limits of error. This trend to separated T2 values for the three metabolites seems to be continued at 4 T (8,9). In general, an inverse proportionality between magnetic field strength and metabolite T2 relaxation times is observed for NAA, tCr, and Cho, corresponding to the T2 decrease of the protons in tissue water at increasing B_0.

Regional variations of metabolite T2 values have not been investigated at 3.0 T until now, except from the comparison between occipital WM and GM in the study of Mlynárik et al (6). While almost pure WM voxels could be positioned within the occipital lobe in our study, VOIs only containing cortical GM would require volume sizes unacceptably small for single-voxel MRS. Nevertheless, we observed a distinct correlation between T2 and relative WM/GM composition of the selected regions, especially for NAA and to lower degree for tCr-CH_3 (Fig. 3). Taking into account that a rather large partial volume of adjacent WM was always included in the VOI assigned as cortical GM, pure GM relaxation times of NAA and tCr-CH_3 are expected to be even shorter than the T2 values measured in these voxels. Considerable regional differences attributable to tissue composition have been ascertained for the absolute concentrations of cerebral metabolites by MRS and MRS imaging studies (28,29). In their study at 2.0 T, Pouwels and Frahm (28) also detected spatial concentration gradients within tissues of the same type, especially for Cho in cortical GM. This could be in line with our finding of significantly ($P < 0.003$) longer T2 of Cho in the anterior cingulate gyrus with respect to T2 measured in motor cortex GM (see Table 1). The missing correlation between T2 of Cho and relative WM/GM contents cannot be ascribed to the slight VOI mislocalization by chemical shift displacement, as this would affect tCr-CH_3 by almost the same amount. Also, the steep decrease of T2 in the basal ganglia for all three investigated metabolites cannot simply be explained by the tissue composition in this area. Paramagnetic relaxation enhancement caused by the local iron deposits in this cerebral region might account for the strong T2 reduction found at 3.0 T.

Comparing our metabolite T1 measurements at 3.0 T to the 1.5 T results, we could confirm the observation made by other groups (8,9) of almost unchanged ^{1}H metabolite T1 relaxation at magnetic field strengths up to 4.1 T. This is in contradiction to the known prolongation of cerebral T1 for aqueous protons in tissue. However, accurate comparison is complicated by the rather large SDs (>10%) for metabolite T1 values measured at 1.5 T (19,23–27) and by considerable discrepancies between the results of the different 1.5-T studies. Moreover, regional differences in metabolite T1 at 1.5 T have been reported by Brief et al (19), stating lower T1 values in occipital GM than in parietal and frontal WM. At 3.0 T, however, a longer metabolite T1 was found in the cortical GM of occipital brain than in the adjacent WM (6). Such regional differences might contribute to the variations in T1 results and possibly surpass a slight field-dependent effect on metabolite T1. Due to the limited number of cases for each investigated cerebral region, a tissue-selective analysis of our T1 results at 3.0 T was not statistically meaningful. Nevertheless, the low error limits of our pooled T1 data do not support a major influence from regional variability.

While spin inversion was used for metabolite T1 measurement in all high-field studies (6,8,9), progressive spin saturation at varying TR was applied in most 1.5-T investigations. In our study at 3.0 T we performed both techniques with similar measurement duration (20% longer for IR series with six TI values) and found consistent results from IR and PS acquisitions for T1 of NAA and Cho. Due to the wider dynamic range of the measured signal, T1 sensitivity is much higher in the IR experiment, which indeed was reflected in a smaller mean of the individual parameter errors of the nonlinear T1 fit (0.04 second for NAA, tCr-CH_3, and Cho vs. 0.05–0.06 second in the PS acquisitions). However, the interindividual SDs of the T1 results were lower in the PS experiments, except for Ins (see Table 2). One possible reason for this effect is the applied dynamic acquisition scheme, which compensates the lower inherent SNR at shorter TR by an increasing number of signal averages. Moreover, the saturation technique is less affected by pulse angle imperfections, which becomes an important issue, particularly in high-field studies. The smaller T1 values obtained for Ins and tCr-CH_2 from our IR measurements might indeed be caused by incomplete inversion of these resonances near the cutoff frequency of the selected inversion band. However, at present we have no conclusive explanation for the 25% shorter T1 of the tCr methyl peak (which is almost centered within the inversion bandwidth) in the IR acquisitions (20% to 27% reduction also in all intraindividual comparisons). Cross-relaxation phenomena caused by ^{1}H magnetization transfer between metabolite protons and immobile protons, e.g., of water, have been observed in particular for tCr (30–32) and may contribute to this effect.

In conclusion, in addition to the general reduction of T2 relaxation times of ^{1}H metabolites at 3.0 T, the results of our study revealed pronounced region-specific variations in normal brain. This regional dependence has to be taken into account when using these T2 values for absolute quantification of metabolite concentrations. Furthermore, when comparing metabolite ratios at varying TE values or field strengths, the differential T2 effect between NAA, tCr, and Cho has to be considered. Due to the decreased T2, MRS protocols with shorter TE values are preferable at 3 T with respect to SNR, e.g., antiphase lactate detection at TE around 140 msec instead of in-phase acquisitions. TR adjustments in MRS sets are of minor importance because of almost unchanged metabolite T1 relaxation in comparison to 1.5 T.

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