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T2-based segmentation of periventricular volumes for quantification of proton magnetic resonance spectra of multiple sclerosis lesions

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Abstract Partial volume averaging of signal from multiple sclerosis lesions influences biexponential fitting of the water T2 relaxation as used for tissue/CSF segmentation of spectroscopic volumes. Periventricular volumes-of-interest comprising CSF, lesion and normal-appearing white matter in varying proportion were studied. The relaxation of the localized water signal was measured at 12 echo times (STEAM, geometric spacing from 30 ms to 2000 ms, least-squares fit). Magnetization transfer (MT) was applied to identify contributions of tissue signal to the CSF component. The T2 of the long-lived component

($T_{2\text{long}}=433\text{--}1782$ ms) and its prolongation after MT were inversely correlated to the MT ratio. Hence, short $T_{2\text{long}}$ is associated with overestimation of CSF partial volume, and thus metabolite concentrations. A T2-correction for the CSF partial volume was suggested and applied to the quantification of MR spectra of large MS lesions. The T2 of bulk CSF (2280 ± 87 ms) and the influence of the TE sampling scheme were also studied.

Keywords T2 relaxation · Magnetic resonance spectroscopy · Quantification · Cerebrospinal fluid · Multiple sclerosis

Introduction

Segmentation of the volume-of-interest (VOI) into subvolumes of cerebrospinal fluid (CSF) and tissue is necessary for absolute quantification in single-volume MR spectroscopy (MRS) of cortical gray matter [1, 2]. The difference in relaxation times provides the basis for the separation of 'brain water' and CSF. Problems and solutions of T2-based segmentation arising from severe alterations of water content and T2 times have been reported for non-focal pathologies in children [3]. Volume segmentation is mandatory also in periventricular VOIs. These can be of interest in some degenerative white matter diseases, e.g. multiple sclerosis (MS). As a result of minimizing partial volume contributions from normal-appearing white matter (NAWM), the partial volume of CSF may show considerable variation and may exceed the CSF fraction of cortical VOIs.

Water content and T2 differ in MS lesions compared to NAWM and CSF. Some lesions contain water of intermediate T2 (200–400 ms) [4, 5, 6]. This additional component cannot be reliably detected in periventricular VOIs because time constrains the number of TE points sampled in consecutive single-echo measurements. When the biexponential tissue/CSF model is applied, the fitted components may be affected by partial volume averaging [7] and no longer represent homogeneous compartments. In particular, the CSF component will be overestimated by unknown contributions from signal of intermediate T2.

This report addresses this effect of partial volume averaging in spectroscopy VOIs of periventricular MS lesions. Because magnetization transfer (MT) is known to be absent in CSF, we used MT to identify contributions from tissue signal to the fitted long-T2 component [5]. A correction formula is suggested that utilizes an idealized T2 of CSF derived from the correlation of MT with the

shortening of $T2_{\text{long}}$. The correction was applied to the absolute quantification of proton MR spectra. In addition, we studied the T2 of bulk CSF and the influence of TE sampling scheme.

Materials and methods

The experiments were carried out on a 1.5-Tesla clinical MR system (Signa Advantage, General Electric Medical Systems, Milwaukee, Wis.) using the standard quadrature birdcage headcoil. Single scans were acquired using the implemented steamsci sequence without phase-encoding for single-volume MRS [8]. T2 relaxation of the unsuppressed localized water signal was studied by 12 consecutive single acquisitions at echo times spaced geometrically between $TE_{\text{min}}=30$ ms and $TE_{\text{max}}=2000$ ms:

$$TE_i = TE_{\text{min}} \left(\frac{TE_{\text{max}}}{TE_{\text{min}}} \right)^{\left(\frac{i-1}{n-1} \right)} \quad i = 1, 2, \dots, n = 12. \quad (1)$$

The time between two acquisitions was 15 s. The eddy current compensation was controlled regularly to avoid TE-dependent refocusing errors. The bandwidth of the excitation profile of the slice-selective radiofrequency pulses was 2367 Hz. Hence, the chemical shift difference between water and *N*-acetyl aspartate (NAA) (≈ 2.65 ppm) corresponded to 7% of the slice thickness. The localization error across the spectrum was minimized by measuring the relaxation with the carrier frequency shifted by +100 Hz. Thus, the water signal represented a chemical shift of about 3.0 ppm, the centre between the acetyl resonance of NAA (3%) and the methylene resonance of creatine (-3%).

Two exponential components were fitted to the data points (Fig. 1) as described in [5]. The quantification procedure combined the external reference method, to account for coil filling, match/tune errors, and long-term signal changes, with the reciprocity method, to account for sensitivity differences between

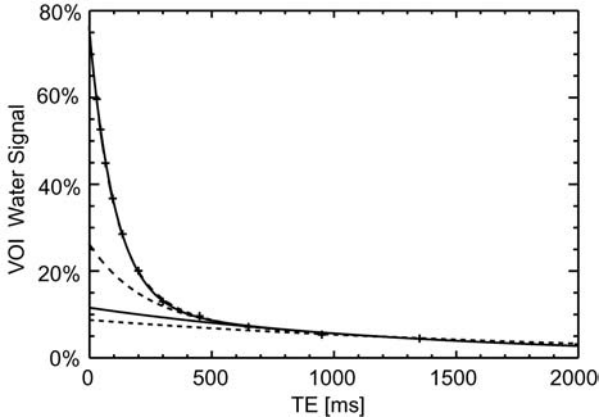


Fig. 1 Two exponential components fitted to a 12-point relaxation measurement of a periventricular multiple sclerosis (MS) lesion (*bold curves*: $T2_{\text{long}}=1388$ ms, $T2_{\text{short}}=107$ ms, $\beta_{\text{MR}}=71.7\%$, $\chi^2=0.147$). Also shown is the long-T2 component. In this example, an unconstrained least-square fit of three components converged (*dashed curves*: $T2_{\text{long}}=1980$ ms, $T2_{\text{int}}=218$ ms, $T2_{\text{short}}=88$ ms, $\beta_{\text{tot}}=74.0\%$, $\chi^2=0.099$), but the decrease in χ^2 was not significant. The F(8,6) distribution yielded $p=0.32$. In general, the intermediate component could not be reliably detected, which was in part due to subject motion, CSF flow, and the limited number of sampled TE points

phantom and VOI due to inhomogeneity of the radiofrequency field [9]. After scaling by volume and correcting for variations of sensitivity, component amplitudes (s_{short} , s_{long}) were expressed relative to the T2-corrected water signal obtained from the calibration experiment, which served as a reference for 100% water content in the VOI. Assuming 100% water content of CSF, the amplitude of the long-lived component (s_{long}) was used as a measure for the CSF partial volume. Division of the short-lived component (s_{short}) by $1-s_{\text{long}}$ yielded the ‘MR water content’ of tissue [1]:

$$\beta_{\text{MR}} = s_{\text{short}} / (1 - s_{\text{long}}). \quad (2)$$

We also tried to fit three exponentials to the relaxation data by constraining $T2_{\text{long}}$ of the CSF component to 2 s. If components of short and intermediate T2 (s_{short} , s_{int}) could be successfully fitted, the ‘total water content’ of tissue was calculated:

$$\beta_{\text{tot}} = (s_{\text{short}} + s_{\text{int}}) / (1 - s_{\text{long}}). \quad (3)$$

The present study comprises 26 adult patients with MS and one healthy subject. It was compiled from three different projects that were conducted in compliance with the ethical guidelines of the local human subject protection board.

1. Detection of partial volume averaging

Contributions of tissue signal to the long-lived component due to partial volume averaging were assessed by MT. Nine MS patients participated in this part after a clinical examination involving the injection of a paramagnetic contrast agent (gadodiamide, Nycomed, Norway, single dose of 0.1 millimol per kg body weight). The 15 periventricular VOIs comprised T2-hyperintense lesions without contrast enhancement and variable fractions of CSF and NAWM.

A chain of selective off-resonance radiofrequency pulses was implemented as modification of the water-suppression part of the sequence. Single-lobe pulses (hamming-filtered sinc-mainlobe) of 12 ms duration and 1440° nominal flip angle were applied 1 kHz off-resonance with a repetition period of 30 ms. Coherent transverse magnetization was ‘spoiled’ by permutation of gradient directions. Forty saturation pulses were applied, which was the maximum number compatible with system restrictions, yielding a total saturation time of 1.2 s [5]. The fitted parameters (with and without MT) were compared using a two-sided paired *t*-test. Magnetization transfer ratios (MTR) were calculated from the amplitudes of the long-lived component:

$$MTR_{\text{long}} = 1 - s_{\text{long}}^{\text{MT}} / s_{\text{long}}^{\text{ref}}. \quad (4)$$

In the biexponential fit, the long-T2 component is mainly determined from the data points where the short-T2 component is zero. The remaining lesion signal shortens the T2 of CSF due to minimization of χ^2 . This contribution is expected to change with and without MT, shortening $T2_{\text{long}}$ to different degrees. Thus, partial volume averaging will result in concomitant changes in amplitude and transverse relaxation. For comparison with MTR_{long} , the relative change in relaxation rates was calculated from $T2_{\text{long}}$, $T2_{\text{short}}$:

$$\Delta R_{2\text{long}} = T2_{\text{long}}^{\text{ref}} / T2_{\text{long}}^{\text{MT}} - 1. \quad (5)$$

The amplitude, s_{long} , can be regarded as an exponential extrapolation of the CSF signal to zero TE by the fitted $T2_{\text{long}}$. In other words: after the lesion signal has decayed, the fitted component describes the CSF signal. In order to counterbalance the effect of $T2_{\text{long}}$ on MTR_{long} , the MTR of the long-lived component at a certain time (τ) was calculated by weighting s_{long} exponentially by $T2_{\text{long}}$ before applying Eq. 3:

$$s_{\text{long}} \rightarrow s_{\text{long}} \cdot \exp(-\tau / T2_{\text{long}}). \quad (6)$$

Since fitted s_{long} and $T_{2\text{long}}$ are correlated, weighting reduced the influence of other sources of variation in $T_{2\text{long}}$ [5]. In repeated relaxation measurements, the weighted signal showed better reproducibility than the amplitude [10]. As previously observed in cortical VOIs [5], the value of τ that yielded an average of zero MTR_{long} (τ_{CSF}) was chosen as TE, where the fitted long-lived components typically represented CSF.

The effect of partial volume averaging (shortened $T_{2\text{long}}$ and increased amplitude s_{long}) was accounted for by taking the signal of the fitted $T_{2\text{long}}$ component at τ_{CSF} and re-calculating the amplitude by exponential extrapolation to zero TE with the T2 of CSF, $T_{2\text{CSF}}$. From the assumption of zero MTR in CSF, we determined $\tau_{\text{CSF}}=1050$ ms and $T_{2\text{CSF}}=1780$ ms (see Results). The signal of CSF (or partial volume) was approximated by the formula:

$$s_{\text{CSF}} = s_{\text{long}} \cdot \exp\left(1050\text{ms} \cdot \left(1/1780\text{ms} - 1/T_{2\text{long}}\right)\right). \quad (7)$$

Assigning the difference $\Delta s = s_{\text{long}} - s_{\text{CSF}}$ to tissue water, the MR water content of tissue was corrected to:

$$\beta_{\text{MR}}^{\text{corr}} = (s_{\text{short}} + s_{\text{long}} - s_{\text{CSF}}) / (1 - s_{\text{CSF}}). \quad (8)$$

2. Volume correction of absolute concentrations

To test the impact of the corrected CSF estimate (Eq. 7) on absolute quantification of proton MR spectra, 21 periventricular MS lesions filling more than 50% of the VOI were selected from a previous MRS study (11). The spectra were acquired at short echo time (30 ms) and long repetition time (6 s), individually phase corrected for motion effects (12) prior to averaging, and evaluated using a linear combination of model spectra (LCModel, [13,14]). Absolute tissue concentrations of the main metabolites were estimated using s_{long} and the corrected s_{CSF} for the CSF partial volume.

3. T2 of bulk CSF

T2 of bulk CSF was measured in seven patients with enlarged ventricles for comparison with $T_{2\text{long}}$. The VOIs were placed in the trigonum area of a lateral ventricle, excluding the plexus choroideus and any tissue by a margin of 5 mm. A modified nine-point protocol was used (TE=30, 100, 200, 400, 700, 1000, 1300, 1600, 2000 ms) with delays of 20 s to provide full T_1 relaxation in CSF. No quantification was performed, and a single exponential was fitted. The effect of contrast agent on the T2 of CSF was studied in a single patient by measurements before and approximately 10 min after the injection of a single dose of contrast agent. Care was taken to avoid regions of inhomogeneous pulsative flow, as indicated on fluid-attenuated inversion recovery images or by signal loss in singular TE points. These were observed at turbulent in-flow from the foramen monroi and along the septum. VOIs reaching far into the ventricles were more prone to flow artefacts than those including only a few percent of CSF from the vicinity of the tissue.

4. Influence of the sampling scheme

The influence of the sampling scheme was studied using previously published 32-point relaxation measurements in periventricular white matter [5]. TE_{min} was increased from 451 ms ($n=12$ points) to 1332 ms ($n=4$) to exclude tissue signal, and a single CSF component was fitted. TE_{max} was reduced from 2000 ms ($n=32$) to 451 ms ($n=20$) by consecutively omitting the longest TE value, and the biexponential tissue/CSF model was fitted.

Results

1. Detection of partial volume averaging

The heterogeneous character of the long-lived T2 component was indicated by marked MT attenuation of the amplitude ($MTR_{\text{long}}=24\pm 17\%$) and significant prolongation of $T_{2\text{long}}$ (from 1136 ± 518 ms to 1359 ± 469 ms, $p=0.00013$ of a paired two-sided t -test). Contributions from lesion signal resulted in a significant inverse correlation between MTR_{long} and $T_{2\text{long}}$, as well as between MTR_{long} and $\Delta R_{2\text{long}}$ (Fig. 2, see caption for details). In Fig. 2A, linear regression yielded $T_{2\text{CSF}}=1778$ ms as x -intercept for zero MTR. In eight of 15 VOIs, $T_{2\text{long}}$ values were more than four standard deviations below the average in healthy controls [5]. The six points with the lowest $T_{2\text{long}}$ (<800 ms) showed particularly large MTR_{long} of about 40%. Since these VOIs contained only little CSF, the high MT indicated that the long-lived component was dominated by lesion signal. Hence, the errors in s_{long} and thus in quantification can be severe. In the scatter plot of MTR_{long} and $\Delta R_{2\text{long}}$ (Fig. 2B), some of these points deviated from the otherwise excellent linear correlation (Pearson's coefficient of correlation $r=0.97$). In such cases, the fitted parameters and MTRs probably reflect the properties of the individual lesion rather than the proportion between CSF and lesion signal. The short-T2 component assigned to tissue water was also affected by partial volume averaging and did not represent a homogeneous compartment. Similar to the long-lived component, $T_{2\text{short}}$ increased in the MT experiment (from 102 ± 16 ms to 109 ± 19 ms, $p = 0.0096$) and MT ratios calculated from s_{short} (41–70%, mean 54%) were inversely correlated with $T_{2\text{short}}$ ($r=-0.71$).

When weighting the amplitude with the individual $T_{2\text{long}}$ (Eq. 6), zero-average MTR_{long} was found for $\tau_{\text{CSF}}=1050$ ms. Again, the VOIs dominated by the six lesions showed the largest deviation from zero ($>10\%$), but exclusion of these yielded a consistent average MTR of zero. Thus, the water signal at $TE>1,050$ ms appears to be due to CSF alone, which was in accordance with findings in cortex and the intermediate T2 times observed in MS lesions [4,5].

The correction formula corrects for the overestimation of partial volume by s_{long} by replacing individual values of $T_{2\text{long}}$ for a typical value, $T_{2\text{CSF}}$. Thus the difference to s_{CSF} , Δs , depends on $T_{2\text{long}}$. For smaller $T_{2\text{long}}$, differences amounted up to 10% of VOI size, but were generally smaller than 3% for longer $T_{2\text{long}}$. However, only minor increases in $\beta_{\text{MR}}^{\text{corr}}$ ($73.7\pm 4.6\%$) were observed when compared to β_{MR} ($72.6\pm 4.7\%$).

This correction does obviously not account for errors in s_{short} . A third component of intermediate T2 could be fitted in nine of the 15 lesion VOIs, when constraining $T_{2\text{long}}$ to 2 s. The CSF amplitude obtained from the three-component fit showed an excellent correlation with

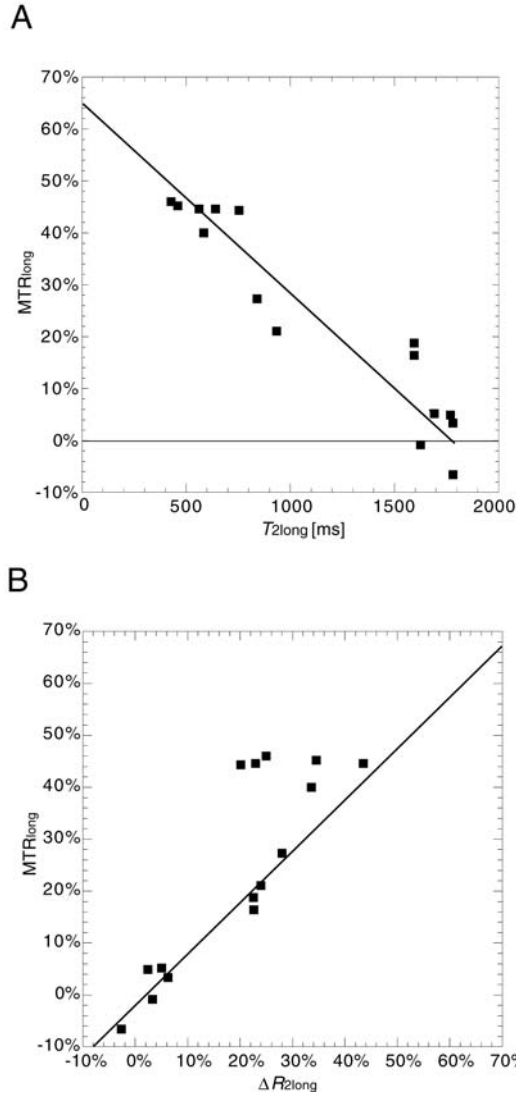


Fig. 2 Magnetization transfer ratios (MTR) of the heterogeneous ‘CSF’ component due to partial volume averaging. **A** Inverse correlation between MTR and T2 of the long-T2 component, assigned to CSF. The regression line is given as $MTR = 65\% - 36.5\% \text{ s}^{-1} T_{2\text{long}}$ (errors $\pm 4\%$ and $\pm 3\% \text{ s}^{-1}$, Pearson’s $r=0.95$, $p<0.001$). Note that the x-intercept of the regression line (for zero MTR_{long}) at 1,778 ms corresponds well to the T2 of the CSF observed after gadolinium injection. **B** MTR_{long} was correlated to the relative change in relaxation rates $\Delta R_{2\text{long}} = T_{2\text{long}}^{\text{ref}}/T_{2\text{long}}^{\text{MT}} - 1$ ($r=0.84$, $p<0.001$). The points showing MTR_{long} of about 40% were dominated by lesion signal. Here, the large variation in $\Delta R_{2\text{long}}$ may be due to lesion heterogeneity. Shown is the linear correlation in the other data points ($MTR_{\text{long}} < 30\%$), where CSF dominated the long-T2 component as indicated by lower MT ($r=0.97$). For zero $\Delta R_{2\text{long}}$, the y-intercept of the regression line of -2% was consistent with the absence of MT in CSF

the corrected s_{CSF} (Pearson’s $r=0.999$). The fitted values of $T_{2\text{short}}$ (84 ± 9 ms) and $T_{2\text{int}}$ (228 ± 46 ms) and the corresponding MTRs were consistent with previous findings in chronic T_1 -hypointense MS lesions embedded in NAWM [5]. The total water content, β_{tot} , of the short and

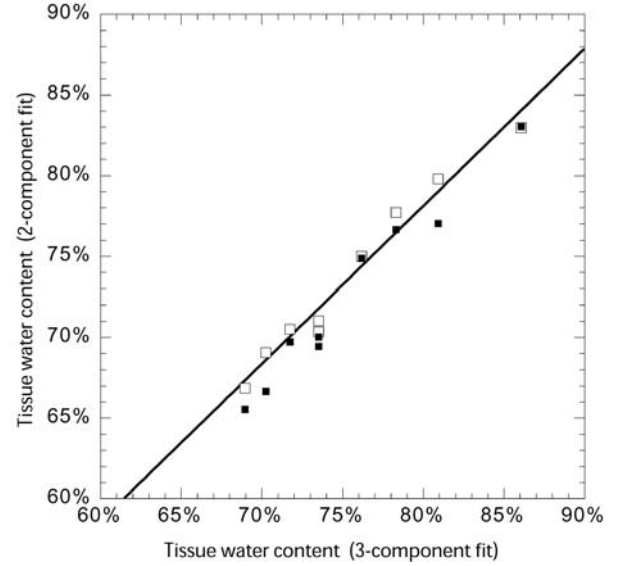


Fig. 3 Tissue water content β_{tot} derived from biexponential tissue/lesion model (Eq. 7) plotted versus the tissue water content β_{MR} derived from the atrophy model (Eq. 2, squares) and $\beta_{\text{MR}}^{\text{corr}}$ corrected to $T_{2\text{CSF}}=1778$ ms (Eq. 6, open squares, regression line $\beta_{\text{MR}}^{\text{corr}} = 0.0\% + 0.95\beta_{\text{tot}}$, errors: $\pm 5\%$ and ± 0.06 , $r=0.984$)

intermediate components (Eq. 3) was $75.5 \pm 4.3\%$. This was significantly higher than β_{MR} and $\beta_{\text{MR}}^{\text{corr}}$ ($p < 0.001$ of a two-sided paired t -test). However, β_{MR} and $\beta_{\text{MR}}^{\text{corr}}$ were strongly correlated with β_{tot} (Fig. 3, see caption for details). Though far from representing the ‘true’ tissue water content due to exclusion of ‘myelin water’ [14], the ‘MR water content’ derived from the biexponential tissue/CSF model may be used as a measure for the average water content in NAWM and MS lesion.

2. Volume correction of absolute concentrations

In these 21 lesions, the long-lived component s_{long} was in the range of 5.2–43.6% (mean 22.3%). Uncorrected concentration estimates of total NAA (tNAA), total creatine, and choline compounds were inversely correlated with s_{long} at the $p < 0.05$ level. The concentration estimates are summarized in Table 1. The corrected s_{CSF} was between 3.2% and 43.7% (mean 16.4%). The mean concentrations reflected the mean difference in s_{long} and s_{CSF} , respectively.

The fitted $T_{2\text{long}}$ was between 406 ms and 2090 ms, but more evenly distributed than in previous section. The concentration estimates for tNAA are plotted against $T_{2\text{long}}$ in Fig. 4. As mentioned above, the correction of s_{long} was particularly important when an excess of lesion signal over CSF signal resulted in short $T_{2\text{long}}$ and high amplitudes. In particular, singular high estimates for tNAA (>10 mM) were reduced when using s_{CSF} instead

Table 1 Estimates of absolute tissue concentration^a in periventricular multiple sclerosis lesions

Volume correction:	None ^b	by $(1-s_{\text{long}})$	by $(1-s_{\text{CSF}})$
CSF fraction (%)	–	22.3 ± 8.6 (5.2–43.6) ^c	16.4 ± 9.0 (3.2–43.7) ^d
Tissue water (%)	59.2 ± 6.7 (44.1–73.5) ^e	76.1 ± 3.4 (68.8–84.9) ^f	77.8 ± 3.1 (70.3–85.5) ^g
Total NAA	6.0 ± 0.9 (3.7–7.9)	7.8 ± 1.0 (5.2–10.8)	7.3 ± 1.0 (5.0–9.8)
Total creatine	5.0 ± 0.9 (3.4–7.3)	6.4 ± 0.9 (4.5–8.2)	6.0 ± 0.8 (4.5–7.8)
Cholines	1.5 ± 0.5 (0.7–2.6)	1.9 ± 0.4 (0.9–2.8)	1.8 ± 0.4 (0.8–2.7)
Myo-inositol	6.6 ± 1.3 (4.2–10.4)	8.6 ± 1.6 (4.7–12.7)	8.1 ± 1.7 (4.4–12.7)

^a Values of mean \pm SD (range) given in mmol/l

^b Concentrations refer to the nominal volume of the VOI

^{c,d} Values given correspond to s_{long} , and s_{CSF} , respectively

^{e,f,g} Values given correspond to s_{short} , β_{MR} , and $\beta_{\text{MR}}^{\text{corr}}$, respectively

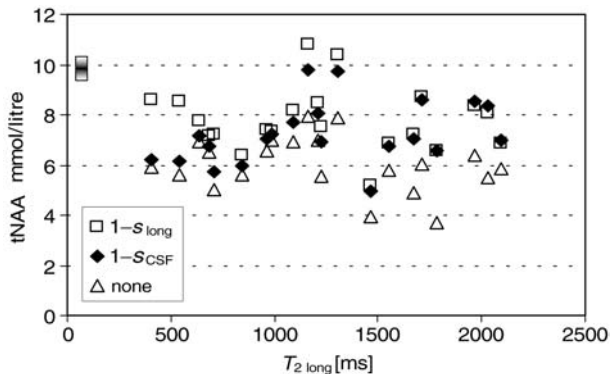


Fig. 4 Scatter plot of absolute concentrations of tNAA versus the fitted $T_{2\text{long}}$. \triangle Uncorrected concentrations per volume-of-interest (VOI) volume, \square volume correction by $(1-s_{\text{long}})$, \blacklozenge volume correction by $(1-s_{\text{CSF}})$. The shaded box indicates the mean \pm SD interval of the control group [10]. Note the 2 mmol/l difference between \blacklozenge and \square for short $T_{2\text{long}}$

of s_{long} for volume correction. Only minor differences were seen when s_{long} was in the normal $\pm 2\text{SD}$ range of controls (1400–2072 ms).

3. T2 of bulk CSF

T2 in bulk CSF was between 2157 ms and 2410 ms (mean \pm SD: 2280 \pm 87 ms). In the presence of contrast agent, T2 was reduced from 2200 ms (± 39 ms, four measurements) to 1770 ms (± 6 ms, two measurements). The increase in the T2 relaxation rate by 0.111 s⁻¹ corresponded to a gadolinium concentration of 0.021 mmol/l in CSF, which is about one-fifth of the applied dose. The transverse relaxivity of gadodiamide of 5.3 s⁻¹mmol⁻¹ was determined in vitro (M. Karlsson, Stockholm, personal communication).

4. Influence of the sampling scheme

When fitting a single exponential to the last data points, increasing TE_{min} resulted in a steady increase of the fit-

ted $T_{2\text{long}}$ from 2050 ms to 2370 ms in this periventricular VOI. On the other hand, $T_{2\text{long}}$ decreased steadily from 2050 ms to 1222 ms in a biexponential fit when reducing TE_{max} successively from 2000 ms to 451 ms. The deviations in $T_{2\text{long}}$ were larger than 5% for $\text{TE}_{\text{max}} < 1000$ ms. The non-linear least-square fit enforced concomitant deviations in the other parameters. A parallel decrease in $T_{2\text{short}}$ (from 75.7 ms to 70.3 ms) was linearly correlated to $T_{2\text{long}}$ (Pearson's coefficient of linear $r=0.999$). Since this increased s_{long} and decreased s_{short} , the water content changed by only 0.3%, which was well below the error of the quantification [9], and may hence be neglected.

Discussion

The key aspect of this study was the effect of partial volume averaging in spectroscopy VOIs of periventricular MS lesions when using the two-component tissue/CSF model of Ernst et al. [1]. Signal of intermediate T2 originates from hypocellular regions in the MS lesion [4]. The correlation between MT and the fitted T2 indicated the influence of tissue signal on the shortened relaxation component attributed to CSF. The fitted $T_{2\text{long}}$ will depend on the proportions between CSF and the size and hypocellularity of the lesion. Values of $T_{2\text{long}}$ below 500 ms were observed, and the CSF compartment may be severely overestimated. We have suggested a correction formula for the biexponential fit (Eq. 6).

Increasing TE in consecutive acquisitions is straightforward, but time constraints limit the number of sampled values in clinical applications. Based on our experience, the simple biexponential fit converges even for a small number of TE points once the VOI contains CSF and some TE-points are sampled after the tissue signal has relaxed. This is probably because of the inherent correlation between the fitted parameters, which reduces the degrees of freedom as demonstrated in this study (see Influence of the sampling scheme) or by more sophisticated programs, such as DISCRETE (courtesy of S. Provencher, [16]).

As an alternative, one may consider the complete characterization of transverse relaxation by multi-echo

techniques and a continuous T2 distribution [17]. In the presence of CSF, however, this requires a sufficient length of the echo train or the correct assumptions regarding the T2 of CSF. Systematic reduction of TE_{\max} indicated that the relaxation should be sampled at TE times longer than 1 s if CSF is present. However, such long TE are incompatible with gated acquisition. Pulsative motion of up to 2 mm/s in the lateral ventricle is observed during approximately 20% of the cardiac cycle [18], thus affecting about one in five points in ungated single-echo measurements. The 12-point sampling scheme (Eq. 1) provided five points of $TE \geq 450$ ms to determine the CSF component for improved robustness against flow. During the course of the T2 measurement, the CSF partial volume may change due to subject movement, especially in periventricular VOIs. The suggested correction method implies that s_{CSF} mainly reflects on the CSF signal at the end of the experiment (points #10–12).

Notwithstanding the increased sensitivity of single-echo to diffusion in local field gradients, the T2 of bulk CSF (section 3 in Results) may be used as an upper limit for the inversion of multi-echo experiments onto a grid of T2 values [17]. Diffusion weighting by the sinusoidal crusher gradients (10 mTesla/m peak amplitude) was independent of TE, since their duration (10 ms) and spacing (13.7 ms TM interval) were kept constant. The T2 of bulk CSF was found to be close to that of de-gassed water at 37 °C ($T2=2460 \pm 50$ ms, unpublished data). This was significantly longer than values obtained from segmentation of gray and white matter VOIs [5]. This can be explained by relaxation of additional components arising from diffusion to the tissue boundary that is acting as a ‘relaxation sink’ [19] or random motion in local field gradients at the tissue boundary. While the nature of this effect has yet to be explored, it appears to be stronger when the volume-boundary-ratio of the CSF compartment is smaller, as in gray-matter VOIs. The CSF signal is particular sensitive due to the small transverse relaxation rate and high self-diffusion of CSF and the use of single-echoes. On the other hand, the T2 of CSF from the compact sub-volume at the border of the lateral ventricle (see Influence of the sampling scheme) was consistent with measurements in bulk CSF (see T2 of bulk CSF).

Because the apparent relaxation of CSF depends on the geometry of the CSF subspace, it is, strictly speaking, not possible to assign a certain T2 value to CSF. Temporal changes of contrast agent may also induce variable shortening of the T2 of CSF. In a particular patient, the shortened T2 of bulk CSF after contrast administration was still consistent with $T2_{\text{CSF}}$ determined from the MT/T2-correlation in this study (see Detection of partial volume averaging) or the $T2_{\text{long}}$ found in normal controls [5]. Results from ‘Detection of partial volume averaging’ were applied in another part of this study (see

Volume correction of absolute concentrations), because the clinical protocols were consistent as the research examination started approximately 10 min after contrast application. Besides flow artefacts, subject motion, and lesion heterogeneity, variable T2 may be one reason why segmentation of tissue signal into short and intermediate components could not be reliably achieved by constraining $T2_{\text{long}}$. Of course, the assumption of a typical T2 for CSF in the correction formula is a major point of critique. However, the corresponding differences between s_{long} and the corrected s_{CSF} are small. Across the ± 2 SD range of controls ($1400 \text{ ms} < T2_{\text{long}} < 2072 \text{ ms}$) the error Δs is between 17% and –8% of s_{long} . The corresponding deviations in partial volume were less than 3%, which is smaller than the typical error of the LCModel evaluation [14]. On the other hand, the size of the effect for the smallest $T2_{\text{short}}$ was considerable (up to 2 mM difference in tNAA, Fig. 4), demonstrating the necessity for a correction.

Fitting the CSF component with ‘fixed’ values of $T2_{\text{long}}$ resulted in similar correlations between the $T2_{\text{long}}$ and the fitted parameters as seen in the section ‘Influence of the sampling scheme’. The amplitude s_{long} decreased with increasing $T2_{\text{long}}$, while s_{short} increased with little change in β_{MR} . Fitting a component with the T2 of bulk CSF would result in a systematic underestimation of the CSF partial volume. In the presence of considerable lesion signal, χ^2 minimization with fixed $T2_{\text{long}}$ yielded CSF components that tended to be higher than the signal at $TE > 1000$ ms even when using $T2_{\text{CSF}}$.

It may be of practical relevance that the ‘MR water content’ derived from the biexponential fit [1] is quite robust against errors of the biexponential fit. The similarity of $\beta_{\text{MR}}^{\text{corr}}$ and β_{MR} becomes clear when Eq. 8 is rewritten as an expansion of Eq. 6:

$$\beta_{\text{MR}}^{\text{corr}} = (s_{\text{short}} + \Delta s) / (1 - s_{\text{long}} + \Delta s) \quad (8a)$$

where the correction terms Δs partially cancel. In this equation, Δs may describe any error introducing similar, but opposite deviations in s_{long} and s_{short} . Such errors may be due to contributions from signal of intermediate T2 (studied by MT) or due to the inherent coupling between the fitted parameters inherent to the fit (studied by the TE_{\max} dependence). However, the tissue water component, s_{short} , and thus β_{MR} , are influenced by the effect of residual short-time eddy currents on $T2_{\text{short}}$ (shown by correlation, unpublished results). β_{MR} may further depend on errors in the signal correction for absolute quantification [11], and on TE_{\min} determining potential contributions from fast-relaxing ‘myelin water’ in white matter [7].

Conclusion

Partial volume averaging of signal of intermediate T2 from MS lesions in the biexponential tissue/CSF relax-

ation model results in a shorter fitted $T_{2\text{long}}$, which is inversely correlated to the MTR of the component. Severe over-estimation of the CSF partial volume (up to 20% of total VOI size) may occur if $T_{2\text{long}}$ is short (around 500 ms). Such errors in the long-T2 component may be reduced by a T2-correction of the amplitude to a typical T2 of CSF. Conversely, the 'MR water content' derived from the biexponential tissue-water/CSF

relaxation model [1] is robust against errors in long-T2 component.

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References

- Ernst T, Kreis R, Ross BD (1993) Absolute quantification of water and metabolites in the human brain. I. Compartments and water. *J Magn Reson* B102:1–8
- Kreis R, Ernst T, Ross BD (1993) Absolute quantification of water and metabolites in the human brain. II. Metabolite concentrations. *J Magn Reson* B102:9–19
- Danielsen ER, Ros BD (1995) Problems and solutions of quantitative MRS in diseased brain. In: 3rd Proc Intl Soc Magn Reson Med, San Francisco, p. 256
- Barnes D, Munro PMG, Youl BD, Prineas JW, McDonald WI (1991) The longstanding MS lesion. A quantitative MRI and electron microscopy study. *Brain* 114:1271–1280
- Helms G, Piringer A (2001) Magnetization transfer of water T2 relaxation components in human brain: Implications for T2-based segmentation of spectroscopic volumes. *Magn Reson Imaging* 19:803–811
- Helms G (2001) Volume correction for edema in single volume proton MR spectroscopy of contrast enhancing multiple sclerosis lesions. *Magn Reson Med* 46:256–263
- Whittall KP, MacKay AL, Li DKB (1999) Are mono-exponential fits to a few echoes sufficient to determine T2 relaxation for in human brain? *Magn Reson Med* 41:1255–1257
- Webb PG, Sailatsuta N, Kohler SJ, Raidy T, Moats RA, Hurd RE (1994) Automated single-voxel proton MRS: Technical development and multisite verification. *Magn Reson Med* 31:365–373
- Helms G (2000) A precise and user-independent quantification technique for regional comparison of single volume proton MR spectroscopy of the human brain. *NMR Biomed* 13:398–406
- Piringer A. , M.Sc. Thesis, Stockholm University, 1998
- Helms G, Stawiarz L, Kivisäkk P, Link H (2000) Regression analysis of metabolite concentrations estimated from localized proton MR spectra of active and chronic multiple sclerosis lesions. *Magn Reson Med* 43:102–110
- Helms G, Piringer A (2001) Restoration of motion-related signal loss and line-shape deterioration of proton MR spectra using the residual water as intrinsic reference. *Magn Reson Med* 46:395–400.
- Provencher SW (1993) Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med* 30:672–679
- Helms G (1999) Analysis of 1.5 Tesla proton MR spectra of human brain using LCMoDel and an imported basis set. *Magn Reson Imag* 17:1211–1218
- MacKay A, Whittall K, Adler J, Li D, Paty D, Graeb D (1994) In vivo visualization of myelin water in brain by magnetic resonance. *Magn Reson Med* 31:673–677
- Provencher SW (1976) An eigenfunction expansion method for the analysis of exponential decay curves. *J Chem Phys* 64:2772–2777
- Whittall KP, MacKay AL, Graeb DA, Nugent RA, Li DKB, Paty DW (1997) In vivo measurements of T2 distributions and water content in normal human brain. *Magn Reson Med* 37:34–43
- Greitz D, Wirestam R, Franck A, Nordell B, Thomsen C, Ståhlberg F (1992) Pulsatile brain movement and associated hydrodynamics studies by magnetic resonance phase imaging. *Neuroradiology* 34:370–380
- Brownstein KR, Tarr CE (1979) Importance of classical diffusion in NMR studies of water in biological cells. *Phys Rev A* 19:2446–2449