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Metabolite Proton T_2 Mapping In The Healthy Rhesus Macaque Brain At 3 T

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Abstract

The structure and metabolism of the rhesus macaque brain, an advanced model for neurological diseases and their treatment response, is often studied non-invasively with MRI and ^1H -MR spectroscopy (^1H -MRS). Due to the shorter transverse relaxation time (T_2) at the higher magnetic fields these studies favor, the echo-times used in ^1H -MRS subject the metabolites to unknown T_2 -weighting, decreasing the accuracy of quantification which is key for *inter*- and *intra*-animal comparisons. To establish the “baseline” (healthy animal) T_2 values we mapped them for the three main metabolites’ T_2 s at 3 T in four healthy rhesus macaques; and tested the hypotheses that their mean values are similar (*i*) among animals; and (*ii*) to analogs regions in the human brain. This was done with 3D multivoxel ^1H -MRS at $(0.6 \times 0.6 \times 0.5 \text{ cm})^3 = 180 \mu\text{L}$ spatial resolution over a $4.2 \times 3.0 \times 2.0 = 25 \text{ cm}^3$ (~30%) of the macaque brain in a two point protocol that optimizes T_2 precision per unit time. The estimated T_2 s in several gray and white matter regions are all within 10% of those reported in the human brain (mean $\pm$ standard error of the mean): *N*-acetylaspartate = 316 ± 7 , creatine = 177 ± 3 and choline = 264 ± 9 ms, with no significant gray versus white matter differences.

Keywords

Animal Models; Brain Metabolites; High Magnetic Field; MR Spectroscopic Imaging; Rhesus Macaque; Transverse Relaxation Time

Introduction

The biochemical, morphological and functional similarities between the human brain and its non-human primate counterpart has lead to extensive use of the latter as an advanced model for studies of neurological diseases and their treatment (1–4). Due to cost, complexity and frequent serial nature, these studies often favor non-destructive modalities: MRI for morphology and function and proton MR spectroscopy (^1H -MRS) to probe the metabolism. The latter can monitor neuronal cells, cell energetics and membrane turnover through

quantitative assessment of the *N*-acetylaspartate (NAA), creatine (Cr) and choline (Cho) - their surrogate markers (5,6).

Quantitative ^1H -MRS requires accounting for various parameters that influence the signals of these metabolites. Some, *e.g.*, the echo- and repetition-times (TE and TR) or the voxel size, are always known. Other instrumental factors, such as the static ($\mathbf{B}_0$) and radio-frequency (RF, $\mathbf{B}_1$) fields inhomogeneity can be estimated by field mapping (7) and internal water referencing (8). The molecular environment however, requires either knowledge of the longitudinal (T_1) and transverse (T_2) relaxation times (5); or to minimize their influence with long $TR \gg T_1$ and short $TE \ll T_2$. Since the flatter baseline, simpler peak structure and milder demands on the hardware of longer- TE spectra are often preferred (5), the ability to distinguish true metabolite levels from mere changes in relaxation times (quantification accuracy) depends on knowledge of T_2 (9,10).

This knowledge is especially pertinent to animal models since the stronger $\mathbf{B}_0$ s that enable the higher spatial resolution needed for their smaller brains come at a cost of shorter T_2 , exacerbating the weighting per given TE (11). To establish the “baseline” T_2 values (of healthy animals) in order to correct for this weighting, we measured the T_2 s of NAA, Cho and Cr at 3 T in several brain regions of four healthy rhesus macaques in order to test the following two hypotheses: (i) That these regional T_2 s are similar among animals, *i.e.*, are characteristic; and (ii) that they are also similar to analogous regions of the human brain, rendering macaques good model systems with respect to T_2 . To maximize spatial coverage and T_2 precision this was done with three-dimensional (3D) ^1H -MRS at 180 μL spatial resolution in over 30% of that brain using a two-point protocol optimized for T_2 precision per unit time (6,12).

Materials and Methods

Non Human Primates

Four healthy female adult (3 – 5 years old, 3.9 – 6 kg weight) rhesus macaques (*Macaca mulatta*) were studied. Each was tranquilized with 15 – 20 mg/kg intra-muscular ketamine hydrochloride and intubated to ensure a patent airway during the experiment (no mechanical ventilation was needed). Intravenous injection of 0.4 mg/kg atropine was administered to prevent bradycardia. Continuous infusion of 0.25 mg/kg/min propofol was maintained throughout via catheter in a saphenous vein. Heart rate, oxygen saturation, end-tidal CO_2 , respiratory rate and temperature were monitored continuously and a water blanket used to prevent hypothermia. Animals were under constant veterinary supervision and the protocol was approved by the Harvard Medical School and Massachusetts General Hospital IACUCs.

Instrumentation and MRI

All experiments were done in a 3 T imager (Magnetom TIM Trio, Siemens AG, Erlangen, Germany) with its standard circularly-polarized transmit-receive knee coil. To guide the ^1H -MRS volume of interest (VOI) sagittal, coronal and axial turbo spin echo MRI ($TE/TR=15/10000$ ms, 512×512 matrix, 140×140 mm² field of view (FOV), 1 mm slice thickness) were acquired.

^1H -MRS

A $4.2 \times 3.0 \times 2.0$ cm³ anterior-posterior $\times$ left-right $\times$ inferior-superior (AP $\times$ LR $\times$ IS) VOI was image-guided onto the anatomy of interest and aligned along the splenium-genu axis of the corpus callosum, as shown in Fig. 1. The manufacturer's automatic shim procedure adjusted the first and second order currents to consistent 26 ± 1 Hz full-width-at-half-maximum (FWHM) VOI water linewidth. The VOI was excited using PRESS ($TR=1820$ ms, TE s see

below) with two second-order Hadamard encoded slabs (4 slices) interleaved within every TR for optimal signal-to-noise-ratio (SNR) and duty-cycle (13). Interleaving also allowed us to apply a *very* strong, 18 mT/m, Hadamard slice select gradient to reduce the chemical shift displacement between NAA and Cho to 0.2 mm, 4% of the slice width (14). The 9.2 ms numerically-optimized PRESS 180°s were pulsed under 3.2 and 4.4 mT/m (AP×LR), leading to ~1 mm displacement (15%) at the VOI edge. The 4 slices were 16×16 chemical-shift-imaging (CSI) encoded over a 96×96 mm² (AP×LR) FOV to yield 140 voxels (0.6×0.6×0.5 cm)³ each in the VOI. The MRS signals were digitized for 256 ms with 512 points at ±1 kHz bandwidth. The 16×16×4 scan took 15.4 min.

Choice of TE and acquisition strategy

The conflicting desire for high spatial resolution *and* T_2 precision in noisy MRS experiments makes for long acquisitions. To maximize their efficiency we employed two strategies: (i) 3D ¹H-MRS to cover a larger volume at the same SNR per given time as single-voxel methods (13); and (ii) a two-point acquisition scheme that adjust the two TE s and the number of averages, N_1 and N_2 , at each for the best T_2 precision per unit-time (12,15). Using $T_2^0=185$ as the “initial guess” for the T_2 s led to $TE_1=30$ ms (minimum in our setup), $N_1=4$, $TE_2 = TE_1 + 1.25T \times T_2^0 = 260$ ms, $N_2=12$, resulting in a 4 hour protocol: 62 min. at TE_1 and 184 at TE_2 . (12). The choice of $T_2^0 = 185$ ms, just above the $T_2=172$ ms obtained for Cr in the *human* brain with this method (16), was influenced by: (i) the error in the resultant T_2 s that are worse for values below than above it; and (ii) the error remains similar over -25% to +40% about T_2^0 , as shown in Fig. 2 of Ref. (9).

¹H-MRS Post-processing

The ¹H-MRS data were processed off-line with our in-house software. The data was voxel-shifted to align the CSI grid with the NAA VOI, Fourier transformed in the time, LR and AP directions and Hadamard transformed in the IS dimension. Automatic frequency and zero-order phase corrections were done in reference to the NAA peak in each voxel. The relative i -th metabolite (i =NAA, Cr or Cho) levels, S_{1i} at TE_1 and S_{2i} at TE_2 were estimated from their peaks' area using the SITools-FITT parametric modeling and least-squares optimization software (17). The models comprised NAA, Cho, Cr, glutamate, glutamine, taurine and *myo*-inositol at $TE_1=30$ ms, and just NAA, Cr and Cho at $TE_2=260$ ms.

Metabolite T_2 determination

Proton T_{2i} relaxation times of the =NAA, Cr or Cho were assessed *in vivo* in each voxel using,

$$T_{2i}=(TE_2 - TE_1)/\ln(S_{1i}/S_{2i}), \quad [1]$$

Six different structures were examined: caudate, thalamus, putamen and cingulate gyrus in gray matter (GM); splenium of the corpus callosum and centrum semiovale in white matter (WM). Each was outlined manually on the axial MRI (*cf.* Fig. 2), our software then zero-filled the MRS to 256×256 and averaged the T_2 s in all voxels that fell entirely or partially within the outline. [Although zero-fill adds no new information to the data, it provides overlapping voxels that can increase the effective spatial resolution and reduce GM/WM partial volume (18)].

Results

The SNR and spectral resolution obtained from the 180 μ L voxels at both TE s, are shown in Fig. 1. Voxel SNRs (defined as peak-height divided by the root-mean-square of the noise) were 29.7 ± 4.0 , 23.4 ± 4.0 and 14.8 ± 4.8 for NAA, Cr and Cho [mean $\pm$ standard deviation (SD)] at TE_1 . The metabolites' linewidth, $\Delta\omega$, of 4.0 ± 0.2 Hz at TE_1 and 3.9 ± 0.1 Hz FWHM at TE_2 represent T_2^* s ($=1/\pi\Delta\omega$ assuming Lorentzian shapes) of 80 ± 4 and 82 ± 2 ms. The scaling of these $\Delta\omega$ from the 26 ± 1 Hz in the VOI approximately as the cube root of its ratio to the voxel volume ($25 \text{ cm}^3/180\mu\text{L}$)^{1/3} indicates that macroscopic susceptibility dominates T_2^* in the former (19).

Examples of the short and long TE spectra shown in Figs. 1 and 2 demonstrate the substantial T_2 -weighting incurred at longer TE s. The mean $\pm$ standard error of the mean (SEM) global T_2 s among in the 560 voxels in the VOIs of the four macaques were: NAA= 316 ± 7 , Cr= 177 ± 3 and Cho= 264 ± 9 ms. These are all within 10% of the average corresponding values reported recently in the human brain (9,10,16). Their histograms from all 140 voxels in each of the four macaques, are shown in Fig. 3. The histograms overall similar shape characterized by peak position and half-width-at-half-height (mean $\pm$ SEM): NAA= 79 ± 2 , Cr= 32 ± 1 and Cho= 71 ± 2 ms, indicate excellent *inter-animal* reproducibility. The NAA, Cr and Cho T_2 s from the regions shown in Fig. 2 are compiled in Table 1, showing similar GM and WM values in these structures.

Discussion

Metabolite T_2 s are essential to determine optimal acquisition protocols (13), and for reliable quantification at intermediate and long TE s (5,10). It is surprising, therefore, that despite studies showing *in vivo* T_2 s to shorten as B_0 is increased (11,20), only few report their values or spatial variation at 3 T, the current *de facto* clinical high field. Moreover, despite the growing use of non-human primates as models for neurological disorders and treatment (1–4), their metabolites T_2 s or their *inter-* and *intra-animal* variations at 3 T, were hereto unknown. This limited both the accuracy of quantification as well as optimal comparisons between human and macaque ^1H -MRS observable metabolism - the underlying motivation for the use of animal models.

Combining higher field 3D ^1H -MRS with an efficient two-point protocol enabled us to map the T_2 s at 180 μ L spatial resolution and at the optimal precision for the given measurement time over an extensive, 25 cm^3 ($\approx 30\%$) portion of the $\sim 80 \text{ cm}^3$ macaque brain *in vivo* (6,12). This allowed us to establish the global and regional T_2 s values in several animals in order to ascertain: (i) the *inter-animal* reproducibility and spatial variations; and (ii) their similarity to the respective values in analogous regions of the human brain at the same magnetic field strength.

The *inter-animal* reproducibility is reflected by the similar histograms' peak positions and shape (see Results and Fig. 3) as well as the less than 5% SEM of the T_2 s for each metabolite. They combine to support the first hypothesis: that these mean T_2 s may be characteristic of healthy macaques. The less than 10% variation in T_2 among different GM or WM regions for NAA, Cr and Cho (*cf.* Table 1) will lead to under 7% metabolite level variations when obtained with short or intermediate (TE s 144 ms) ^1H -MRS at this B_0 [See Appendix in Ref. (9)]. It is noteworthy that even for larger variations, of the order of the $\sim 20\%$ half-widths of the histograms in Fig. 3, use of the mean T_2 would lead to a quantification error of less than 15% for Cr and under 7% for NAA at $TE=144$ ms. These variations will decrease proportionally at shorter TE s.

The few percent differences between the T_2 s estimated here and the 265–343, 152–172 and 200–248 ms ranges reported for NAA, Cr and Cho in the *human* brain at 3 T (9,10,16,21,22), also validate the second hypothesis. They establish a “threshold” necessary to consider the healthy macaque brain as a model for its human counterpart with respect to this “metabolic environment” parameter. In addition, the less than 10% T_2 variations between WM and GM in these animals indicates that for the purpose of metabolic quantification use of the mean value for each metabolite is sufficient as long as $TE < T_2$.

Although time and cost preclude a test-retest study to quantify *intra*-animal T_2 reproducibility (precision), their coefficient of variation (CV)=SD/mean can nevertheless be estimated from the *intra*-animal performance. Given the $3.6/\text{SNR}_{16}$ theoretical limit on the optimal CV obtainable with this approach [achieved when $T_2 \equiv T_2^0$, as shown in Fig. 2 of (9); and SNR_{16} is that obtained if all the time is spent for $4+12=16$ averages at TE_1], places a lower limit on the instrumental noise contribution, CV_{inst} (9,12). Since our $T_2^0=185$ ms is close to the Cr T_2 , its $\text{SNR}_4=23.4$ at TE_1 extrapolates to $\text{SNR}_{16}=\text{SNR}_4 \times (16/4)^{1/2}=46.8$ that limits its CV_{inst} to $3.6/\text{SNR}_{16} \approx 8\%$.

The actual upper limit on CV_{inst} and the variations that are due to the biological noise, CV_{biol} , combined, CV_{tot} , is estimated from the histograms in Fig. 3 at $\sim 20\%$. Assuming that these two noise sources are independent and therefore, add in quadrature:

$$\text{CV}_{\text{tot}}^2 = \text{CV}_{\text{biol}}^2 + \text{CV}_{\text{inst}}^2, \quad [2]$$

leads to an *intra*-animal voxel T_2 CV_{biol} of $\sim 18\%$. Averaging adjacent voxels can improve CV_{tot} via two mechanisms: First, it will increase the SNR (compare the voxel spectra in Fig. 1 with regional averages in Fig. 2), *i.e.*, reduce CV_{inst} . Second, the regional variations in CV_{biol} will be smaller than in the whole VOI. The confluence of both effects is reflected in the 3 – 7% regional CV_{tot} in Table 1, that are sufficiently small for the T_2 s to be considered characteristic and suggest that more T_2 measurements on healthy animals, *e.g.*, at each study’s inception, are unnecessary in that they are unlikely to yield significantly different results.

Finally, we note that although more metabolites can be quantified at the short TE , *e.g.*, the *myo*-inositol, glutamine and glutamate (see Fig. 2), we focused only on the T_2 s of the three major singlets. This is due to our choice of $T_2^0=185$ ms for optimal precision over the 140–260 ms range (that suit Cr and Cho best) but which also requires a 230 ms delay between TE_1 and TE_2 . During the consequent $TE=260$ ms, all shorter T_2 (and J -coupled) species signals decay (or dephase) severely, as shown in Fig. 2 (23). The relationship between the precision and SNR (12), and an already long protocol motivated us to optimize for just one cluster of T_2 values.

Conclusion

Combining 3D ^1H -MRS with an optimized two-point acquisition protocol makes for the most efficient use of time to map the T_2 distribution of some of the observable neuro-metabolites in rhesus macaques. These regional T_2 values are similar among animals indicating that they may be characteristic and are also in excellent agreement with reported values in humans at 3 T, as expected from a model-system. The T_2 s and their variations between WM and GM structures indicate that for the purpose of metabolic quantification at 3 T the use of one T_2 value for each metabolite is sufficient for intermediate or long TE ^1H -MRS across both humans and macaques.

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Fig. 1.

Left: Axial (a) sagittal (b) and coronal (c) T_2 -weighted MRI and position of the $4.2 \times 3.0 \times 2.0$ cm³ VOI (frame) and Hadamard slices (arrows) in the ~ 80 cm³ macaque brain.

Right: Axial matrices of the real part of the spectra from the VOI over slice a, at the short $TE_1 = 30$ ms, $N_1 = 4$ data set (d); and the long $TE_2 = 260$ ms, $N_2 = 12$ (e). All spectra are on a 3.8 – 1.8 ppm scale but the long TE spectra are on a $\times 2.5$ smaller vertical scale than the short TE . Note the spectral resolution and SNR from these 180 μ L voxels.

Fig. 2.

Left: Axial T_2 -weighted images showing the regions where the voxels' T_2 were averaged (solid lines). In GM: cingulate gyrus (a) caudate (d), putamen (e) and thalamus (f); and in the WM: (b) centrum semiovale, (c) splenium of the corpus callosum.

Right: Real part of the averaged spectra from the corresponding regions at both TE s (black lines) with the model functions used for T_2 estimation superimposed (gray lines) on common 3.8 – 1.8 ppm and vertical scales. Note the quality of the fit at either TE , the improved SNR of regional averages versus voxel spectra (Fig. 1) and the T_2 -weighting between the two TE s, underscoring the need for T_2 values for accurate quantification.

Fig. 3. Histograms of the NAA, Cr and Cho T_2 s from all 140 voxels in the VOI for each of the four macaques. Note the inter-animal similarity of the histograms for each metabolite, indicating that: (i) a global T_2 value for each would lead to less than 15% variation in quantification for Cr (7% for NAA) at $TE=144$ ms and proportionally less at shorter echo times; and (ii) these distributions are probably characteristic in this brain. Note the histograms' similarity of the peak positions to the corresponding T_2 s reported in the human brain, making the macaque a good model system with respect to this parameter.

Table 1

Mean $\pm$ SEM proton T_2 relaxation times (milliseconds) at 3 T of the *N*-acetylaspartate (NAA), creatine (Cr) and choline (Cho) in the various GM and WM brain regions shown in Fig. 2, from the $N=4$ macaques studied.

		T_2 (ms)		
		NAA	Cr	Cho
GM	Caudate	323 $\pm$ 18	178 $\pm$ 8	261 $\pm$ 13
	Thalamus	337 $\pm$ 5	175 $\pm$ 10	289 $\pm$ 8
	Putamen	338 $\pm$ 16	179 $\pm$ 5	283 $\pm$ 13
	Cingulate gyrus	304 $\pm$ 7	178 $\pm$ 8	264 $\pm$ 15
	GM Average	325$\pm$8	178$\pm$2	274$\pm$7
WM	Splenium of the l CC	308 $\pm$ 6	181 $\pm$ 1	248 $\pm$ 7
	Centrum semiovale	316 $\pm$ 7	182 $\pm$ 4	263 $\pm$ 9
	WM Average	311$\pm$4	181$\pm$1	255$\pm$8
WM+GM average		316$\pm$7	177$\pm$3	264$\pm$9

l CC – corpus callosum.