T1 relaxation in mouse brain at 9.4 and 17.6 Tesla

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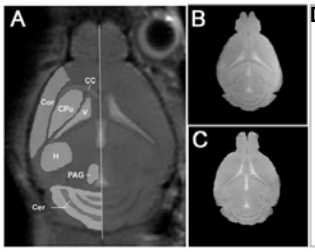
Introduction - Increasing knowledge of the mouse nervous system and the availability of a large number of transgenic models has made the mouse a very popular species to study neurological disorders. MRI has shown great potential to study brain pathology in these models. However, the small size of the mouse brain has considerable implications for obtaining images comparable to those generally obtained with MRI in patients. To obtain acceptable spatial resolution and signal to noise ratios (SNR), higher magnetic field strengths (up to 17.6 Tesla) are used. The application of higher field strengths requires knowledge of the relaxation rates at these field strengths for proper adjustment of image acquisition parameters. Reports on T_1 relaxation times for mouse brain are limited mainly to systems up to 9.4 T [1,2]. Also, with increasing field strength, chaotic spin dynamics may interfere with intrinsic relaxation. Therefore we first validate quantitative T_1 imaging at high fields using phantoms. We provide the first *in vivo* T_1 relaxation maps of mouse brain at 17.6 T and compare those with measurements at 9.4 T. The results are discussed in terms of SNR and contrast.

Methods - *Phantom tubes* containing different concentrations of Gd[DOTA] (Dotarem, Guerbet, Netherlands) in phosphate buffered saline were prepared. To validate the MRI method, T_1 relaxation times were determined both by MRI and by high resolution NMR at field strengths of 9.4 and 17.6 T.
In vivo imaging was performed on 6 female C57BL/6Jico mice aged 3 months (Charles River, Maastricht, the Netherlands). Mice were anaesthetized with 4% isoflurane in air (50%) and O_2 (50%) and maintained with ~1.5% isoflurane during all procedures. The respiratory rate was monitored via an air-pressure cushion connected to a laptop using Biotrig software (Bruker, Rheinstetten, Germany).
MRI: The experiments were performed on two vertical 89-mm-bore magnets (Bruker BioSpin, Rheinstetten, Germany) with field strengths of 9.4 T and 17.6 T. A Bruker Mini0.5 gradient system of 200 mT/m and a transmit/receive birdcage radiofrequency coil with an inner diameter of 38 mm was used on both systems. Bruker ParaVision 3.0 software was used for image acquisition. T_1 data were acquired with a saturation recovery method with variable repetition time (TR). Slice excitation and refocusing were accomplished by three-lobed sinc pulses of 1.0 and 0.81 ms, respectively. Imaging parameters were: echo time (TE)= 3.5 ms; TR-array at 9.4T = 0.1, 0.12, 0.15, 0.3, 0.5, 0.9, 1.5, 3, 6, 12 and 20 s; TR-array at 17.6T = 0.1, 0.12, 0.15, 0.3, 0.5, 0.9, 1.5, 3, 6, 10 and 30 s; matrix = 128 × 128; FOV = 25.6 mm; slice thickness = 1 mm. All images were acquired as single slices to avoid interslice modulation effects, and unwanted stimulated echoes were suppressed by spoiler gradients in the slice direction. The slice was positioned through the centre of all phantom tubes or dorsally through the middle of the cerebellum and rostrally through the olfactory bulb (Fig. 2).
High resolution NMR: To keep experimental conditions as equal as possible to the MRI experiments, the same phantoms and magnets were used and experiments were performed on the same day. Radiation damping was minimised by using a restricted sample volume in untuned, low Q probes at both field strengths. A broadband 5-mm solution-state NMR probe with a 1.20-mm sample tube insert was used at 9.4 T, while a triple-tuned magic angle spinning probe with a 4.00-mm sample holder was used at 17.6 T. T_1 was measured using an inversion recovery (IR) sequence with a 90 degree pulse length of 25 μs.
Data processing: Eight regions of interest (ROIs) for cortex, corpus callosum, caudate putamen, hippocampus, periaqueductal gray, ventricle and cerebellar gray and white matter were defined for each individual mouse (Fig. 1A). Phase correction was performed on the entire complex data matrix before image reconstruction. For the T_1 fits, eleven TR values with a fixed TE of 7 ms (second echo) were used. The T_1 values of the various ROIs were determined using a three-parameter fit function $M(t) = M_0 \exp(1 - 2\alpha \exp(-t/t1))$. All fits were performed using a non-linear least square algorithm provided by the Image Sequence Analysis (ISA) tool of ParaVision 3.02 (Bruker, Rheinstetten, Germany). T_1 maps were generated on a pixel-by-pixel basis. Signal-to-noise ratios (SNR) were calculated on images with TE/TR = 3.5/6000 ms, using SNR = SI/SD_{noise}. Contrast (C) of gray and white matter (cortex and corpus callosum) was calculated from ROI mean signal intensities (SI) as $C_{g,w} = \frac{|SIg - SIw|}{SIg + SIw}$



D ROI	9.4 T	17.6 T	Factor increase
CC	1750 ± 45	1832 ± 86	1.05
Cor	1886 ± 122	2027 ± 106	1.07
H	1821 ± 47	1901 ± 77	1.04
PAG	1700 ± 65	1842 ± 108	1.08
CPu	1746 ± 31	1824 ± 101	1.04
V	2449 ± 150	2772 ± 235	1.13
CerG	1814 ± 118	2038 ± 63	1.12
CerW	1651 ± 28	1888 ± 112	1.14

Figure 1. T_1 relaxation times of mouse brain at 9.4 and 17.6 T. ROIs were selected in a 1-mm-thick horizontal slice (A). CC, corpus callosum; CerG; cerebellum grey matter; CerW, cerebellum white matter; Cor, cortex; CPu , caudate putamen; H, hippocampus; PAG, periaqueductal grey; V, ventricle. T_1 maps at 9.4 T (B) and 17.6 T (C) were generated. The table (D) shows the T_1 values of the different ROIs and their relative changes with field strength.

Results - Measurement of phantoms showed that at 17.6 T the imaging method yields T1 relaxation times consistently 10% shorter than the high resolution NMR method. Despite these differences, a plot of $1/T_1$ *vs.* concentration Gd[DOTA] for the five phantoms with physiologically relevant T_1 values yields straight lines with comparable slopes for the two methods, validating our T_1 imaging method at high magnetic fields. The T_1 relaxation times of eight mouse brain regions in six 3-month-old wildtype C57BL/6Jico mice were determined *in vivo* at 9.4 and 17.6 T. Figure 1D shows the T_1 average relaxation times for each ROI. Additionally, T_1 maps were generated on a pixel-by-pixel basis (Fig. 1B,C). The results show that T_1 times continue to increase with magnetic field strength, and the white matter T_1 remains consistently longer than the gray matter value, as at lower fields. The SNR increases by a factor of 2.05 between 9.4 and 17.6T, which is in good agreement with the theory that SNR increases linearly with field strength. The gray/white matter T1 difference is reduced at high fields, and this leads to inversion of the apparent T_{1w} image contrast. Even with optimised TE/TR, the observed image contrast is dominated by proton density (Fig. 2).

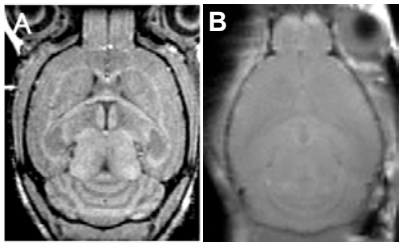


Figure 2. Gray and white matter contrast of T_1-weighted images becomes low at high field. A. T_1-weighted image at 2.35 T (courtesy of T. Michaelis). B. T_1-weighted image at 17.6 T. TE/TR = 3.5/1500 ms.

Discussion - Here we provide for the first time T_1 relaxation times of mouse brain at 17.6 T. In addition, data at 9.4 T are extended. Although the increase in SNR is one of the most important advantages of high field MRI, due to the increasing dependence of T_{1W} signal intensity on proton density and the resulting change in gray/white matter contrast, one has to take caution when interpreting T_1-weighted high field images. Special sequences such as MDEFT may be of use to regain part of the T_1 contrast.

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