Mapping of Cellular Layers in Mouse Brain and Spinal Cord Using Magnetization Transfer and Manganese

T. Watanabe[1], J. Frahm[1], and T. Michaelis[1]
[1]Biomedizinische NMR Forschungs GmbH am MPI für biophysikalische Chemie, Göttingen, Germany

Introduction

In the central nervous system, cell bodies are often densely packed to yield functional units in the form of cellular layers or nuclei. T1-weighted (T1W) MRI can be used to identify such assemblies, because of their short T1 due to the reduced contribution of extracellular water and the predominance of intracellular water (high ion content, intermolecular relaxation). However, their delineation is sometimes hampered by adjacent white matter also presenting with a short T1 due to its high myelin content. Magnetization transfer (MT) can be used to saturate mobile water protons by off-resonance irradiation of highly immobilized protons bound to macromolecules (for review see [1]). Therefore, the white matter is expected to be efficiently saturated by MT, leaving the cell body assemblies less affected. This contrast may be further improved by delivering manganese (Mn^{2+}) (for review see [2]), because this T1-shortening ion is expected to accumulate in the intracellular fluid and thus predominantly in the cell body assemblies. The purpose of this work is to examine the effects (i) of MT on T1W MRI of the brain in living mice, and (ii) of the systemic administration of Mn^{2+} on respective images.

Methods

Animals. Six female mice (NMRI, 8-12 weeks, 30-38 g) were used. Each mouse received manganese chloride (0.12 mmol/kg body weight) via subcutaneous injection. The mice were returned to a chamber with unlimited access to food and water.

MRI. Before and 3 days after Mn^{2+} injection, MRI measurements were carried out at 2.35 T (Magnex Scientific, Abingdon, UK). Radiofrequency (RF) excitation and signal reception were accomplished with the use of a Helmholtz coil (inner diameter 100 mm) and an elliptical surface coil (inner diameter 20×14 mm), respectively. An off-resonance RF irradiation with a frequency offset of 5 kHz and a mean amplitude of 200 Hz (flip angle 1045°) [3] was incorporated into a T1W gradient-echo MRI sequence (RF-spoiled 3D FLASH, TR/TE 30/7.6 ms, α 25°) at 117 µm isotropic resolution unless otherwise stated. The MT ratio was obtained from acquisitions with and without off-resonance RF irradiation. For evaluation of signal intensities, regions-of-interest were chosen in the neuron-rich tissue (hippocampal formation, habenula, cerebellar cortex), cerebral cortex, and in the white matter (corpus callosum, cerebellar white matter).

Results and Discussion

As shown in Figs. 1 and 2, off-resonance RF irradiation effectively suppresses the signal of the white matter, while the signal of the cellular layers is much less affected. This differential effect well complements the contrast induced by Mn^{2+} administration. Fig. 3 shows the application of both MT and Mn^{2+} to the mapping of the Purkinje cell layer in the cerebellum.

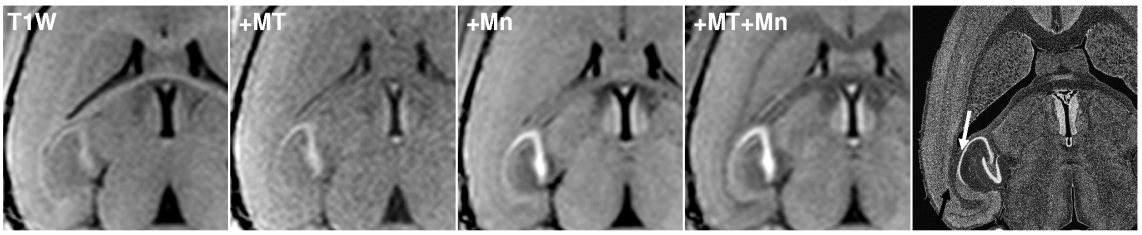

Fig. 1 T1W images of a mouse brain (horizontal section), with MT, after Mn^{2+} injection, and with MT after Mn^{2+} injection, in comparison with (right) histological staining of the cell bodies (highlighted) [4]. The pyramidal cell layer (highlighted, white arrow) of the hippocampal formation is better delineated from adjacent white matter (black arrow) by using MT and Mn^{2+}.

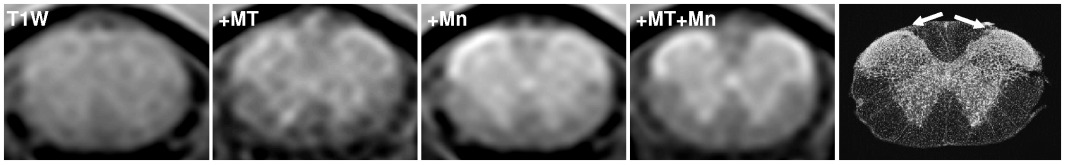

Fig. 2 T1W images of the cervical spinal cord of a mouse (axial section) as shown in Fig. 1. The cellular layers of the Rexed lamina II (highlighted, white arrows) of the gray matter are better delineated from adjacent tissue by using MT and Mn^{2+}.

A quantitative evaluation (Table) confirms these qualitative findings. MT increases the CNR between the neuron-rich tissue and the white matter from 0.24 to 5.5, while the Mn^{2+} injection alone increased the CNR to 13.7. The best CNR of 19.0 was achieved using both MT and Mn^{2+}. Furthermore, after Mn^{2+} injection, the SNR increased to a much greater degree when combined with MT. For example, the SNR of the neuron-rich tissue increased by 75% from its basal value (rather than by 54 % without MT). This indicates that MRI with MT is more sensitive to the local Mn^{2+} concentration, which may be exploited for the elucidation of regional activity or for a reduction of Mn^{2+} dosage to minimize toxicity.

In conclusion, MT supports the delineation of neuron-rich tissues as well as the detection of local Mn^{2+} concentrations in the nervous system.

Table. MT Ratio, SNR, and CNR of Brain Tissue Using T1W MRI Before and 3 Days After $MnCl_2$

		Before Mn (n = 5)		After Mn (n = 5)	
		MT (-)	MT (+)	MT (-)	MT (+)
MT Ratio	Neuron-Rich Tissue	0.28 ± 0.01		0.22 ± 0.02	
	Cerebral Cortex	0.29 ± 0.01		0.25 ± 0.03	
	White Matter (WM)	0.40 ± 0.01		0.35 ± 0.02	
SNR	Neuron-Rich Tissue	43.8 ± 3.4	32.0 ± 2.7	67.0 ± 3.8 (+54%)	55.8 ± 4.9 (+75%)
	Cerebral Cortex	37.9 ± 3.2	26.7 ± 2.0	53.1 ± 3.7 (+37%)	42.3 ± 3.9 (+53%)
	WM	43.5 ± 2.9	26.5 ± 1.6	53.3 ± 1.7 (+23%)	36.9 ± 2.3 (+39%)
CNR (Neuron-Rich Tissue–WM)		**0.24 ± 1.1**	**5.5 ± 1.3**	**13.7 ± 2.2**	**19.0 ± 2.7**

Values are given as mean ± SD, Values in parentheses: % change from Before Mn, CNR: contrast-to-noise ratio.

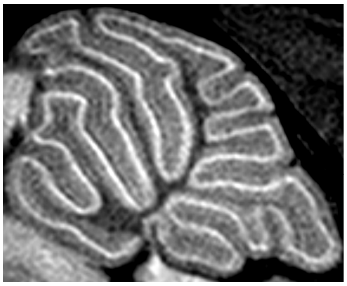

Fig. 3 The Purkinje cell layer (highlighted) of the cerebellum (40×40 µm² in-plane resolution).

References

[1] Henkelman RM et al. *NMR Biomed* 2001;14:57-64. [2] Koretsky AP, Silva AC. *NMR Biomed* 2004;17:527-31. [3] Natt O et al. *Magn Reson Imaging* 2003;21:1113-20. [4] Mikula S et al. *Neuroimage* 2007;35:9-15.