

# Magnetization Transfer MRI of Mouse Brain Reveals Areas of High Neural Density

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## Introduction:

*In vivo* magnetic resonance imaging (MRI) of the mouse brain at high spatial resolution allows for the identification of a large number of cerebral microstructures and offers repeated studies of the same animal. Despite the availability of excellent soft-tissue contrast in  $T_1$ - and  $T_2$ -weighted MRI, the physical nature of the underlying differences in nuclear magnetic relaxation times restricts the structural information to specific aspects of the molecular mobility of water (and lipid) protons. Complementary morphologic information may be obtained by magnetization transfer (MT) techniques. The purpose of this study was (i) to quantify MT model parameters in mouse brain *in vivo*, (ii) to optimize MRI parameters for MTC of mouse brain *in vivo*, and (iii) to examine whether MTC provides tissue-specific contrast beyond  $T_1$ - or  $T_2$ -weighted MRI.

## Materials and Methods:

Anesthetized young adult mice (C57BL/6J, intubated, 70:30  $N_2O:O_2$ , 1.0-1.5 % halothane) were examined at 2.35 T on a Bruker DBX system using a Helmholtz coil ( $\varnothing$  100 mm) for excitation and an elliptical surface coil (20 mm  $\times$  12 mm) for signal reception. In order to measure MT model parameters a 2D RF-spoiled FLASH sequence was used ( $\alpha=5^\circ$ , TR/TE=30/7.1 ms,  $156 \times 156 \times 2000 \mu m^3$  voxel resolution). Off-resonant RF irradiation was accomplished with use of Gaussian RF pulses applied once per TR. Four different power settings for off-resonant RF irradiation (100 to 400 Hz) were combined with 9 different frequency offsets ranging from 1 to 70 kHz. All high-resolution imaging protocols of murine brain were based on a resolution of  $117 \times 117 \times 117 \mu m^3$ .  $T_1$ -weighted MRI employed a 3D RF-spoiled FLASH sequence ( $\alpha=25^\circ$ , TR/TE=30/7.6 ms, measuring time 84 min).  $T_2$  contrast was achieved with use of a fast spin-echo sequence (TR/TE=3000/98 ms, measuring time 58 min). For MT-weighted MRI an off-resonant RF irradiation with a frequency offset of 5 kHz and a mean amplitude [1] of 200 Hz (corresponding to a flip angle  $1045^\circ$ ) was incorporated into a spin density-weighted 3D FLASH sequence ( $\alpha=5^\circ$ , TR/TE=30/7.6 ms, measuring time 84 min).

## Results and Discussion:

Quantitative evaluations (not shown) demonstrated a maximum MT effect with a MRI signal saturation of 58.8 %. This requires a relatively high RF amplitude of 536 Hz and a frequency offset of 11.1 kHz. However, even much lower RF amplitudes on the order of 200 Hz can lead to a significant MT effect of more than 50 % saturation, if the frequency offset is adapted to the RF amplitude.

Although the soft-tissue contrast in MT-weighted MRI appears to be similar to  $T_2$ -weighted MRI at first glance, additional morphologic information is provided by MTC. Focusing on the mouse cerebellum Fig. 1 compares MTC with  $T_1$  and  $T_2$  contrast. It turns out that the gross appearance of  $T_1$ - and  $T_2$ -weighted images is dominated by the respective low and high signal intensities of the cerebrospinal fluid (CSF). For example, when using  $T_2$  contrast, white matter (WM) is barely visible, whereas MTC reveals a clear delineation of WM structures because of their pronounced hypointensities. The bright rims most likely correspond to the glomerular layer (GL) and the Purkinje cell layer (PC) (see [2,3]) and are therefore best described as 'densely packed' gray matter (GM). The above results indicate that MTC which is based on differences in macromolecular content rather than in molecular mobility allows for a differentiation of WM (dark) and densely packed GM (bright), whereas both structures appear isointense in either  $T_1$ -weighted MRI (bright) or  $T_2$ -weighted MRI (dark).

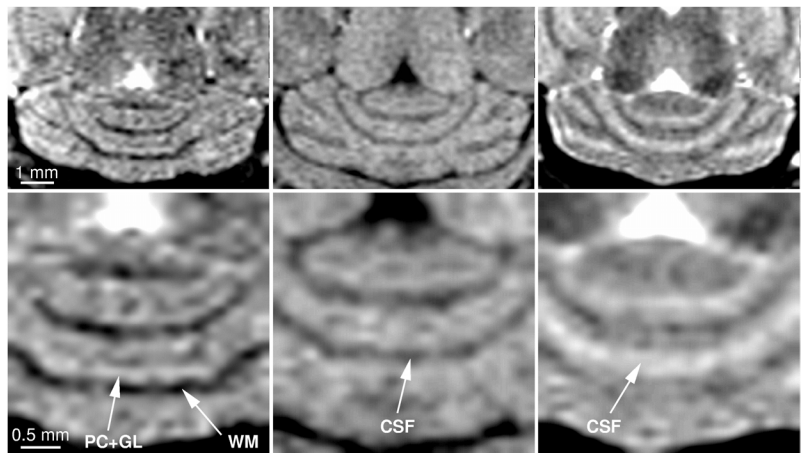
This hypothesis is further supported by a comparison of respective contrasts in the mouse hippocampus shown in Fig. 2. While  $T_1$ - and  $T_2$  weighted images depict the CA3 subfield of the hippocampus with similar signal intensity as the WM in the hippocampal fimbria or the external capsule, the MTC image clearly distinguishes the bright CA3 region from the hypointense WM. Histologic sections of the mouse hippocampus [4,5] suggest the layer of pyramidal cell bodies to be largely responsible for the bright MTC appearance of the CA3 region.

## Conclusion:

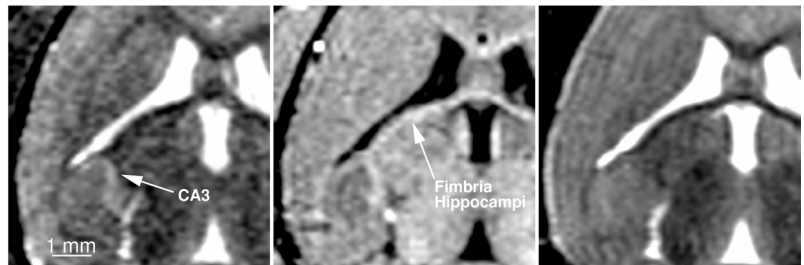
Extending the use of MTC in studies of the human central nervous system, this work provides MTC-based morphologic information of murine brain which is otherwise not accessible by conventional  $T_1$ - or  $T_2$ -weighted MRI. The novel finding that MTC allows a distinction of densely packed GM from WM makes MT-weighted MRI particularly interesting for investigations of the cerebellum and hippocampal formation in mouse models of respective brain disorders. Further studies that attempt to exploit this possibility in humans are in progress.

## References:

[1] Hua J, Hurst GC. J Magn Reson Imaging 5:113-120, 1995. [2] Yamada K, et al. J Comp Neurol 418:106-120, 2000. [3] Ozol K, et al. J Comp Neurol 412:95-111, 1999. [4] Jinno S, et al. Brain Res 814:55-70, 1998. [5] Watanabe T, et al. Magn Reson Med 48:852-8859, 2002.



**Fig. 1:** (left) MTC, (middle)  $T_1$  contrast, and (right)  $T_2$  contrast of the cerebellum of a mouse *in vivo* in (top) horizontal sections and (bottom) corresponding magnified views.



**Fig. 2:** (left) MTC, (middle)  $T_1$  contrast, and (right)  $T_2$  contrast of the right hippocampus of a mouse *in vivo* (horizontal sections).