QMT Estimated Pool Size Ratio and DTI Derived Radial Diffusivity Reflect the Integrity of Myelin Sheath in Mice

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Introduction

A selective inversion recovery quantitative magnetization transfer (SIR-QMT) technique was employed to quantify the ratio of pool sizes of the bound and free water in ex vivo mouse brains. The goal is to determine the pool size ratio sensitivity to myelin. Fixed brains from both shiverer mice and control littermates were imaged. The pool size ratio in the corpus callosum of shiverer mice was substantially lower than that in the control mice, while there was no distinguishable difference in the pool size ratio in the gray matter. These results correlate well with diffusion tensor imaging (DTI) derived radial diffusivity which reflects myelin integrity. Histological study reveals the presence of myelin in control mice white matter and the absence of myelin in shiverer mice white matter, supporting the QMT and DTI results. Our findings support the view that the SIR-QMT method can be used for estimating myelin integrity.

Methods

Four shiverer and four control mice were euthanized and perfused with phosphate-buffered saline (PBS) followed by 10% formalin/PBS solution. The mice brains were kept in 10% formalin/PBS solution and stored at 4°C for one week, then transferred to PBS solution before imaging. Fixed brains were placed in a 1cm inner diameter solenoid coil, and data from the mid-sagittal slice of each brain were acquired in a 4.7T Varian UNITY INOVA spectrometer. A fast spin echo sequence with an inversion pulse was used for the QMT experiments. 18 images with the inversion times ranging from 5ms to 7.9s were obtained with 2s constant pre-delay[1], 8 averages, 16 echoes, 10ms echo spacing time, 25mm by 25mm field of view, 0.8mm thick slice, and 256x256 data matrix. Data were fitted to a bi-exponential function of the inversion times to determine the pool size ratio pixel by pixel. A diffusion weighted spin echo pulse sequence with 1s repetition time, 38ms echo time, 13ms time between gradient pulses, 4ms diffusion gradient duration, b value of 1.879 $ms/\mu m^2$, diffusion sensitizing gradients along six directions (1,1,0)(0,1,1)(1,0,1)(-1,1,0)(0,-1,1)(1,0,-1), and the same spatial resolution as in the QMT experiments was used to acquire data to determine the axial and radial diffusivities of each sample. Myelin basic protein (MBP) immunostaining was performed on a $3\mu m$ thick midsagittal slice of one shiverer and one control mouse brain to provide histological comparison.

Results

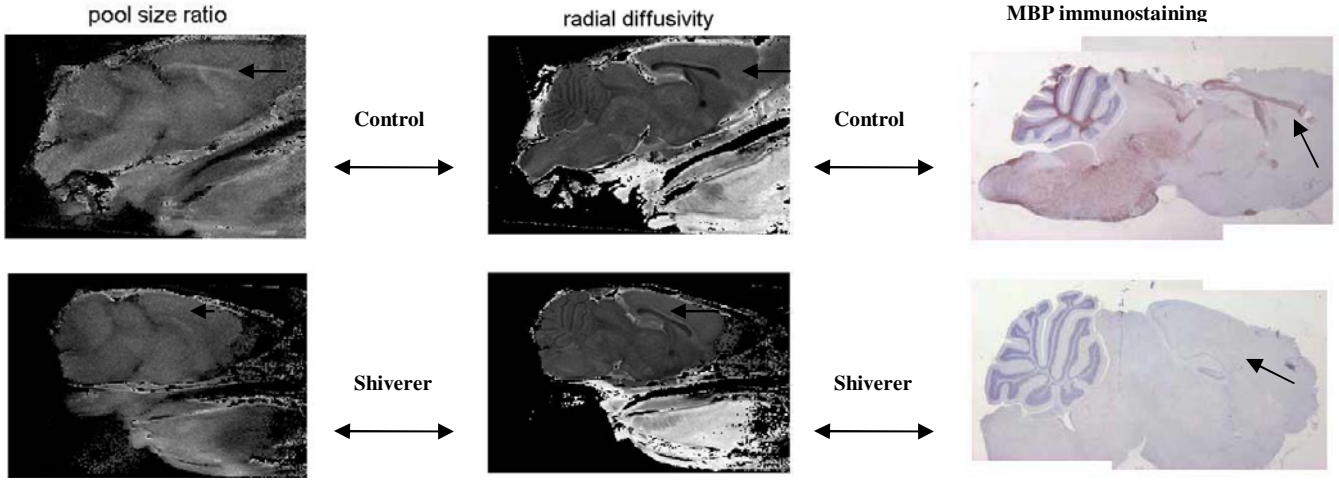

Fig.1: The pool size ratio maps (left), the radial diffusivity maps (center), and the MBP staining maps (right) for control and shiverer mice. The black arrow inside each image points to the corpus callosum in the mouse brain.

	Pool size ratio		Radial diffusivity ($\mu m^2/ms$)		Axial diffusivity ($\mu m^2/ms$)	
	White matter	Gray matter	White matter	Gray matter	White matter	Gray matter
Control mice	0.10±0.01	0.07±0.01	0.09±0.02	0.23±0.01	0.38±0.05	0.30±0.01
Shiverer mice	0.07±0.01	0.08±0.01	0.12±0.01	0.23±0.02	0.40±0.02	0.30±0.02

Discussion

Shiverer mouse is known as an animal model of dysmyelination[2]. We argue that the SIR-QMT is a valid technique for non-invasive evaluation of myelin integrity. The pool size ratio in the control mice white matter (corpus callosum) is about 40% higher than that in gray matter, reflecting the effect of the presence of myelin sheath in the white matter. The pool size ratio in the shiverer mice white matter is about the same as that in gray matter, likely reflecting the lack of myelin in the white matter. These results correlate well with those from diffusion measurements, where the radial diffusivity in the shiverer mice white matter is about 33% higher than that in the control mice white matter. There is no distinguishable radial diffusivity difference in the gray matter between the control and shiverer mice. There is, however, a difference between the gray and white matter radial diffusivity in the shiverer mice, indicating that radial diffusivity is not sensitive to only myelin. The similar extent of change in radial diffusivity and pool size ratio of shiverer mice white matter also supports the notion that diffusion anisotropy and magnetization transfer in white matter mainly originate from the same axonal myelin sheath microstructures. The axial diffusivity, which reflects the axonal fiber integrity, is about the same for both shiverer and control mice. The MBP immunostaining results clearly show the presence of myelin in the control mice but not in the shiverer mice, supporting our non-invasive MRI findings.

References

1. Gochberg DF et al, Magn Res Med (2006), in press. 2. Song SK et al, NeuroImage 17, 1429-1436 (2002)