Direct Detection of Myelin Using Zero-Echo Time (ZTE) Imaging in Lamb Spinal Cord

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Introduction: Myelin is an essential biomaterial responsible for electrically insulating axons and thus ensuring efficient neural current transport. Image-based quantification of myelin has the potential to reveal central nervous system (CNS) abnormalities such as multiple sclerosis and enhance our understanding of neurological diseases. Most current MRI methods for detection of myelin abnormalities use magnetization transfer (MT) imaging[1] and T_2 relaxometry[2] based on water's interaction with myelin. Both methods are indirect, i.e. providing surrogate measures of myelin content, rather than detecting myelin itself, and the underlying biophysical mechanisms are not well understood. Direct detection of myelin would remove the complications of indirect methods. Our previous work demonstrated that myelin extract and intact rat spinal cord myelin can be imaged on a laboratory 9.4T spectrometer with ultra-short echo time (UTE) imaging[3]. However, the extremely short T_2 values (ranging from 1-100μs) and relatively low proton density pose significant challenges given clinical systems' hardware limitations. Here, we evaluated the performance of zero-echo time (ZTE) imaging in reconstituted myelin and lamb spinal cord at 9.4T as well as on a 3T whole-body scanner.

Methods: *Myelin Sample Preparation*: Myelin was first extracted from bovine spinal cord by a sucrose gradient technique[4]. The purified extract was then suspended in 99.9% D_2O to achieve 14% concentration matching that of myelin in white matter. The ^1H spectrum of the purified myelin extract was recorded at 9.4T to ensure that the lipid bilayer structure was preserved[3]. A 10-mm NMR tube of this myelin-D_2O suspension was imaged at 3T along with two other 10-mm tubes containing H_2O-saline and 99.9% D_2O, and also at 9.4T.

Lamb Spinal Cord Preparation: Two 36-mm segments of cervical spinal cord were dissected from the neck of a lamb slaughtered 2 weeks prior. Before imaging, one segment was D_2O-exchanged in 4 passes of 12 mL D_2O-saline each over the course of 44 hours, and one was stored in 12 mL of H_2O-phosphate buffered saline.

Hardware Configuration: At 9.4T, scans were performed using a 15-mm linearly-driven birdcage RF coil in a 1,000 mT/m 3-axis gradient set. 3T imaging was performed with a custom-built 4.5 cm-diameter, 8 cm-long, 3-turn transmit/receive solenoid RF coil constructed using fully ^1H-free materials, with 40 mT/m maximum gradient strength.

Image Acquisition: The myelin extract and D_2O-exchanged lamb spinal cord were scanned at 9.4T using a commercial ZTE sequence with the following parameters: *TR*=2 ms, FA=4.1°, 2 μs pulse duration, 3.2 μs dwell time, G=245 mT/m, 80,892 half projections, 188×188×375μm^3 resolution, scan time ~21 mins. To provide reference anatomic images, the H_2O buffered lamb spinal cord was scanned with a turbo-RARE sequence at 51×51×400 μm^3 voxel size. At 3T, the myelin sample was imaged with a ZTE-PETRA sequence developed in house with the following parameters: *TR*=7 ms, FA=8.3°, 32 μs pulse duration, 16 μs dwell time, 25,000 half-projections, 1×1×1mm^3 voxel size, 4 averages, scan time~13mins. To evaluate the feasibility of long-T_2 suppression, the myelin phantom was scanned with an IR-ZTE sequence in which 7 ZTE acquisitions were performed after each adiabatic inversion with TR=300 ms and TI=120 ms (scan time ~18 min). The D_2O-exchanged lamb spinal cord was imaged using the same protocol as myelin extract imaging.

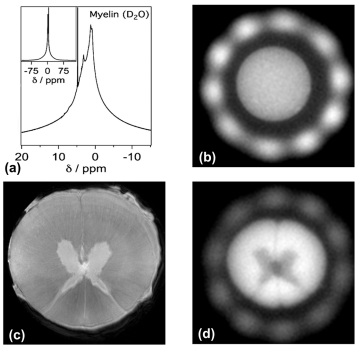

Fig. 1: 9.4T results: (a) spectrum; (b)ZTE image of myelin extract in D_2O; (c) High-resolution RARE image of lamb spinal cord; (d) ZTE of D2O exchanged spinal cord

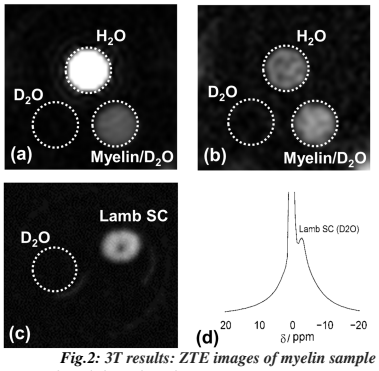

Fig.2: 3T results: ZTE images of myelin sample (a) with and (b) without long-T2 suppression; (c) ZTE image and spectrum of D_2O-exchanged lamb spinal cord

Results: The ^1H spectrum of myelin extract-D_2O suspension at 9.4 T in **Fig. 1a** shows a broad resonance with relatively narrow components centered at lipid frequency, consistent with dipolar broadened liquid-crystalline lipid system as reported previously[3]. **Fig. 1b** shows the 400 MHz myelin extract image at SNR~50. The signal surrounding the sample originates from the RF coil's plastic support. **Figs. 1c** and **d** show the RARE image of the native tissue sample and ZTE image of the same lamb spinal cord specimen after D_2O-exchange, respectively. The white matter region shows higher signal intensity than gray matter in the ZTE image, consistent with the notion that myelin content is higher in white matter. Myelin extract images at 3T are shown in **Figs. 2a** and **b**. Image SNR of the myelin sample was ~20 and whereas the signal of D_2O was virtually at noise level, demonstrating that over 99% of the signal in the myelin suspension arose from myelin rather than from residual HDO. More than 90% of the water signal was suppressed in **Fig. 2b** while the myelin extract signal was attenuated by 15%, resulting higher signal level in myelin sample than water. **Fig. 2c** shows the image of D_2O-exchanged lamb spinal cord with SNR~20. Due to the low gradient strengths available on clinical scanners and the very short T_2 of myelin, point-spread function blurring is severe; nevertheless, the central low-signal intensity gray matter is clearly visible. The spectrum in **Fig. 2d** further confirms that the measured signal in **Fig. 2c** arises from myelin.

Conclusions: SNR achieved with ZTE for both myelin extract and D_2O-exchanged spinal cord at 9.4T was superior to that reported in previous work by UTE imaging[3], suggesting ZTE to be a better choice for direct myelin imaging. The images of myelin extract and spinal cord acquired at 3T suggest feasibility of myelin imaging on a clinical scanner. Future work will focus on the combination of an optimized long-T_2 suppression module preceding ZTE readout for direct myelin quantification in native spinal cord at 3T.

References: 1. Dousset V. et al. Radiology 1992;182:483–491. 2. Whittall K, Mackay A (1989) MRM 1989;84:134–152. 3. Wilhelm M.J. et al. PNAS 2012;109:9605-9610. 4. Norton W.T. et al.. Methods Enzymol 1974;31:435-444.

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