Quantitative MR Assessment of Spinal Cord Injury Induced Non-Invasively Using Focused Ultrasound

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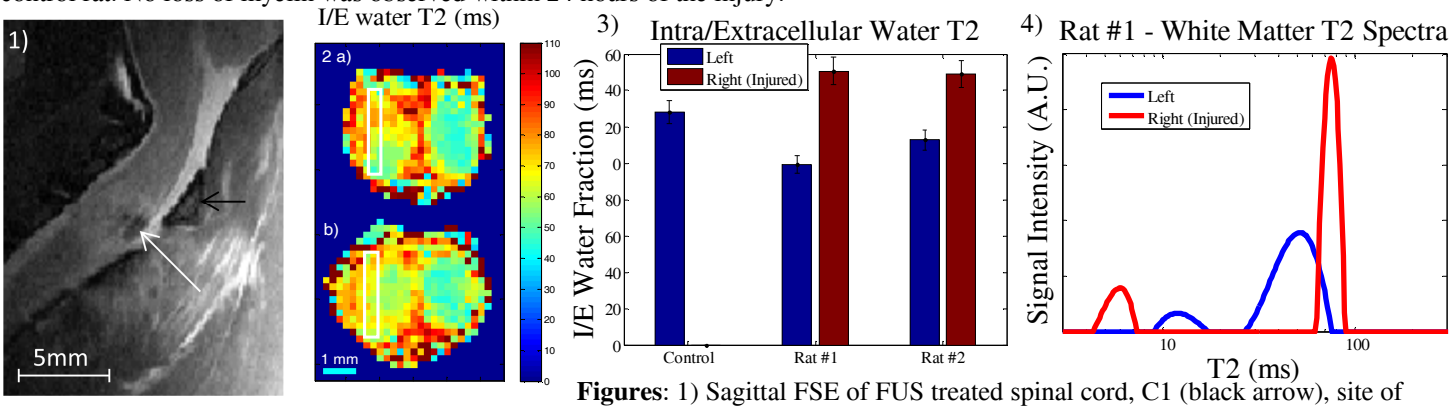
Target Audience: Those interested in spinal cord injury or quantitative MRI.

Purpose: Current preclinical models of spinal cord injury are extremely invasive and result in large amounts of unintended collateral damage to surrounding tissue. Focused Ultrasound (FUS) in combination with microbubbles has been used to transiently open the blood brain barrier in order to enhance drug delivery[1], and to create lesions in the brain[2]. The goal of this study was to assess the ability of FUS and microbubbles to create a highly localized injury of the spinal cord. This novel, non-invasive model of spinal cord injury was characterized in vivo using quantitative T2 (qT2) MRI and diffusion.

Methods: Spinal cord injuries were induced in two male Wistar rats at the C2 level of the spinal cord using FUS in combination with microbubbles, at two different power levels (1.3 or 1.6 W). The animals were anesthetized using ketamine/xylazine and secured to a platform which could be moved between the FUS treatment system and a 7T Bruker Biospin MR scanner. The location for induction of injury was prescribed using structural MR images. The right side of the spinal cord was treated with FUS (1.114 MHz, 10 ms bursts at a pulse repetition frequency of 0.5 Hz for 5 minutes, 6 sonication spots at 1mm spacing, RF driving powers of 1.3 or 1.6 W) following an injection of 0.2 ml/kg of Definity microbubbles. Quantitative MR imaging was performed immediately following FUS treatment and again at 24 hours. Anatomical images were acquired at a resolution of 0.15x0.15x1.0mm^3 using a fast spin echo sequence. QT2 measurements were made using a single slice sequence with composite refocusing pulses, TE 5ms, TR 3s, 0.2x0.2x1.0mm^3 resolution and 2 averages, lasting 20 minutes. Diffusion tensor images were acquired with an EPI sequence, 18 directions and b-value of 800s/m^2. Analysis of qT2 data was done using a non-negative least squares algorithm.

Results: 24 h after treatment both rats had evidence of swelling and reduced mobility in the back of the neck. The right hind leg of the second rat (treated with 1.6W of RF power) was paralyzed, yet was able to move when encouraged. Fractional anisotropy (FA) in the FUS treated rat was 0.56±0.05 in WM on the injured side, and 0.61±0.07 on the uninjured side, compared with 0.71±0.07 in the control rat. No loss of myelin was observed within 24 hours of the injury.



Figures: 1) Sagittal FSE of FUS treated spinal cord, C1 (black arrow), site of injury (white arrow). 2) Axial Intra/Extracellular water T2 maps of the spinal cord for FUS treated rats. Approximate location of targeted FUS treatment outlined in white. 3) Intra/Extracellular water T2 for regions of interest drawn in white matter in healthy control, and both sides of the spinal cord in FUS treated rats.4) T2 spectra of white matter in one FUS treated rat.

Discussion: It is possible to induce physical disability using a combination of FUS and microbubbles. MR visible damage was localized to the treated side of the spinal cord only. QT2 results demonstrate an increase in intra/extracellular water T2 indicative of inflammation[3], which was confirmed by histopathology. Diffusion results show a slight decrease in FA in the right (injured) side relative to the left (uninjured) side and an overall decrease in FA compared with the healthy rat.

Conclusion: This is a promising model of spinal cord injury as it causes minimal extraneous damage, and is highly localized. QT2 and diffusion MR provide *in vivo* insight into the nature and extent of the injury. Future work will look at later timepoints to determine if this injury leads to demyelination and determine the potential of this non invasive spinal cord injury model to represent clinically relevant spinal cord pathology.

References: 1. O'Reilly M, Hynynen K. Ultrasound enhanced drug delivery to the brain and central nervous system. Int.J.Hyperthermia. 2012; 28(4):386-396.

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