MRI Monitoring of Neural Precursor Cell Transplantation Therapy in a Rat Spinal Cord Injury Model

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Introduction: Spinal cord injury (SCI) is a devastating event with major social and economic implications. Present treatment options for SCI provide only modest therapeutic benefits. Recent advancements in stem and progenitor cell biology, tissue engineering, nanotechnology, and magnetic resonance imaging (MRI) have increased the likelihood that a therapeutic strategy leading to meaningful functional repair following SCI will soon be realized. Given the complexity and heterogeneous pathobiological nature of SCI, the discovery of promising therapies will require the development of quantitative magnetic resonance imaging approaches capable of assessing treatment efficacy in-vivo. Neural precursor cell (NPC) transplantation has shown benefit in rodent models of SCI, however the underlying mechanisms leading to functional recovery are not fully understood. In this study we optimize a series of quantitative MR methods for spinal cord imaging. These methods are suitable for monitoring NPC transplantation therapy in-vivo. This should result in an improved ability to report on efficacy of the treatment.

Methods: Moderate clip-compression injuries were performed at the T7 bony level of female Wistar rats. Two weeks after the injury, rats were randomized to no treatment (n=7), or to NPC transplantation (n=6). BBB motor testing was performed weekly on all animals. MR imaging was performed 7 weeks post injury on a Bruker BioSpec 7T system, using the 112mm gradient insert, 72mm linear transmit coil, and 4 channel phased array for signal detection. DTI (10 directions b=1000 multi-shot EPI), CPMG (128 echoes TE~5.5ms), and inversion recovery fast spin echo were used to generate quantitative MR parameter maps. An automatic clustering algorithm was used to segment the tissue into healthy, cyst and lesional. Animals were sacrificed 8 weeks post injury. Animals were perfused and their axial spinal cord sections were stained with luxol fast blue as well as hematoxylin and eosin to delineate gray matter, white matter, cyst and lesional tissue. *Image J* was used to quantify these regions every 360 microns. A modification of the Cavalieri method was subsequently used to quantify volumes of these tissue types and correlation to quantitative MR measures was performed.

Results: There was a decrease in average cord T1 in treated animals, suggesting a decrease in CSF infiltration and inflammation at the site of the SCI. Automatically segmented MR ROIs, based on diffusion parallel and perpendicular to the spinal cord, T2, and T1 are visually well correlated to manually segmented histology ROIs. All spinal cord histology sections experienced a reduction in total area of ~12% as compared to MR, possibly due to tissue fixation and cutting compression. This resulted in an underestimation of cyst and lesional tissue by histology. Total neural tissue (TNT) as measured by MR proved to be a good marker for functional recovery, as measured by the BBB score, showing a significant difference in preserved tissue between plain injured and injured treated animals. The TNT measure by MR and TNT measured by histology had a statistically significant correlation of 0.63.

Discussion: NPC transplantation is associated with preservation of grey and white matter suggesting that neuro-protection may contribute to functional recovery as measured by the BBB score. At the resolution and SNR available of the acquired images DTI, T2 or T1 are not capable of quantitatively detecting changes in the cord during NPC transplantation treatment. By combining the information from the quantitative maps we are able to monitor tissue sparing *in-vivo*, as demonstrated by the correlation of MR measures with functional recovery and histology

References: 1. Wachowicz K and Snyder RE, Magn.Reson.Med, 2002. 47: p. 239-245. 2. Beaulieu C, et al., Magn.Reson.Med, 1996. 36: p. 627-631. 3. Kozlowski, P., et. al.. Magn Reson Med 59, 796-802 (2008). 4. Kozlowski, P., et al., J Neurotrauma 25, 653-676 (2008). 5. Laule, C., et al.,J Neurol 251, 284-293 (2004).

Figure 1: Representative plain Injured and NPC transplanted animal histological sections from the imaged region of each spinal cord are shown in comparison to MR images taken from the same region.

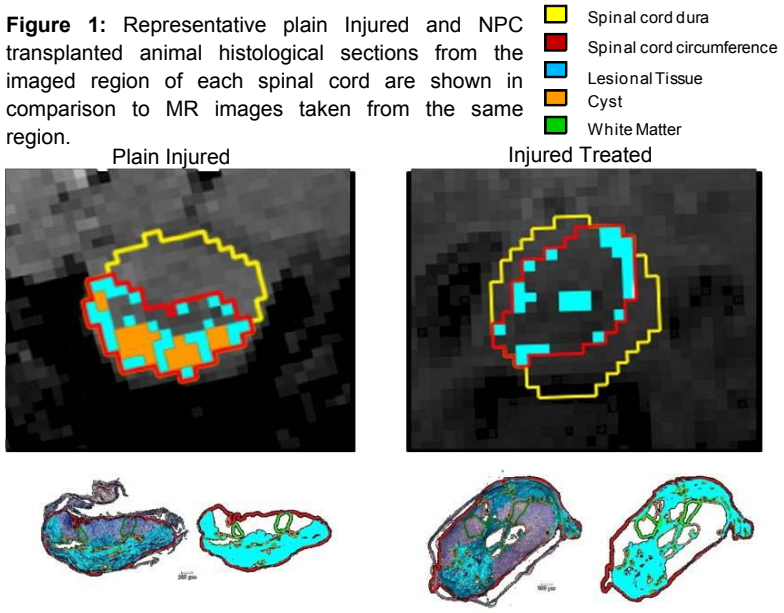

Figure 2. Healthy Neural Tissue as Measured by Automatic Segmentation of MR Data Demonstrates Tissue Sparing in NPC Transplanted Animals ($p<0.01$)

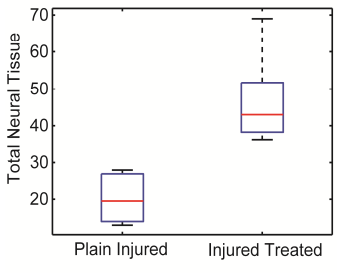

Figure 3. Comparison of Total Neural Tissue (TNT) as measured by MR and Histology