Validation of Neurite Remodeling after TBI Using MRI and Histopathology

S. Wang[1,2], M. Chopp[1,2], G. Ding[1], M-R. Nazem-Zadeh[1], S. Pourabdollah Nejad D. [1], C. Qu[3], Z. Zhang[1], A. Mahmood[3], L. Li[1], L. Zhang[1], and Q. Jiang[1,2]

[1]Neurology, Henry Ford Health System, Detroit, MI, United States, [2]Physics, Oakland University, Rochester, MI, United States, [3]Neurosurgery, Henry Ford Health System, Detroit, MI, United States

Introduction: Neurorestorative therapy which induces neurite outgrowth improves functional recovery in experimental TBI, [1]. Neurite density is an important parameter in the study of neuronal remodeling after TBI. However, MRI measurement of neurite density after TBI has not been investigated. In this study, we report for the first time that quantitative MRI neurite density can monitor neuronal remodeling after TBI and MRI measured neurite density was highly correlated with the gold standard immuno-histochemistry evaluation.

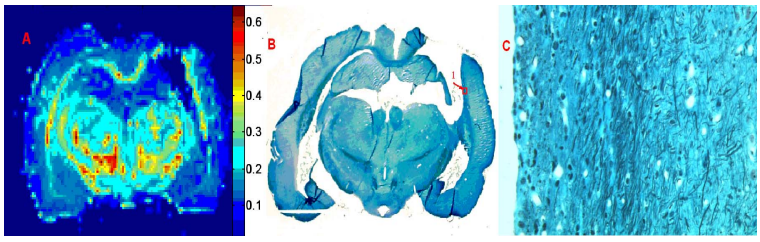

Fig.1: (A) MRI neurite density map (B) Histology image (0.5x) red arrow mark points to the axonal remodeling box area (C) Histology image (40x) from the red arrow box area in (B) shows axonal density and fiber directions.

Methods: Five male Wistar rats were subjected to a controlled cortical impact model of TBI and sacrificed at 5 weeks after being treated with approximately $3x10^6$ bone marrow stromal cells (MSCs) 5 days post-TBI. MRI measurements were performed with a Varian 7T MRI system on the ex-vivo rat brains. Multiple-shell q-space diffusion MRI was acquired using pulsed gradient spin-echo sequence with matrix size 128x128, FOV= 3.2 cm, 13 slices, TE=40ms, TR=1500ms, slice thickness 1 mm, nine averages, and 125 diffusion attenuate directions with 5 b-values: 360, 1440, 3240, 5760, 9000 s/mm^2 respectively. The q-DTI data was fit to a two-compartment water diffusion displacement model [2]. Neurite density was processed using diffusion function with spherical harmonic expansion (L=4) to extract structural parameters [3]. We also used the 3rd shell of 21 gradient directions with a b-value of 1500 s/mm^2 for the visualization of fiber crossings and fiber tracking of TBI animal data. Neurite density values were measured in external capsule, prim somatosens, dentate gyrus, globus pallidus, insular cortex, caudate putamen, corpus callosum regions. The axonal densities from the same ROIs were also measured in Bielshowski and Luxol fast blue-staining sections in rat brain.

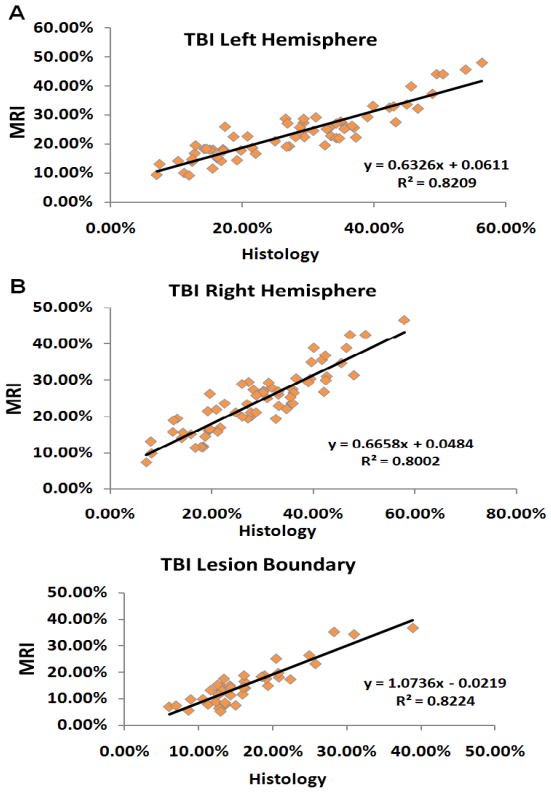

Fig.2: Correlations between neurite densities measured by MRI and histological staining in the contralateral hemisphere (A), ipsilateral hemisphere (B), and TBI lesion boundary areas (C).

Results: Neurite densities exhibited a significant correlation (r^2<0.82, p<1E-15) between MRI and immuno-histochemistry measurements in ipsilateral hemisphere (r^2=0.80, p=1.0E-23), contralateral hemisphere (r^2=0.82, p=3.3E-25), and TBI lesion boundary (r^2=0.82, p=7.7E-16). Neurite reorganization after MSC treatment of TBI is predominantly located in the extended area of the corpus callosum, where increased axonal density and change of axonal bundle orientation were confirmed by the immuno-histochemistry staining.

Discussion and Conclusion: Multiple q-space diffusion encoding technique and spherical harmonics data fitting procedure provide non-invasive approachs which directly quantitate neurite density in brain after TBI. High correlations were detected between MRI and histological neurite densities in the TBI brain. Although the MRI neurite density measurements need to be improved, our investigation provides a promising approach for the quantification of neurite density in TBI brain and this method could be potentially applied to not only TBI recovery but to other neurological diseases, such as stroke, hemorrhage, and neurodegenerative diseases.

References:

[1] Li Y, Chopp M. *Neurosci Lett*. 456:120 (2009).
[2] Y. Assaf, Magn. Res. Med. 59:1347 (2008).
[3] S.N. Jespersen, NeuroImage 34:1473 (2007).

Grant support: Supported by NINDS grants P50 NS23393, PO1 NS42345, RO1 NS48349, NS43324, and HL6476.