Cell-based Treatment Induced White Matter Reorganization after Traumatic Brain Injury Measured by Gaussian, Q-space DTI, and Histology

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INTRODUCTION: Cell-based treatment of traumatic brain injury (TBI) promotes brain remodeling and functional recovery[1]. Neuroplasticity, such as white matter (WM) reorganization is associated with functional recovery after TBI[1]. However, dynamic monitoring of treatment induced WM reorganization is a challenge. In the current study, we evaluated the effects of cell-based treatment of TBI on WM reorganization using MRI. We demonstrate that FA and fiber tracking from Gaussian DTI can correctly identify white matter reorganization in the brain tissue with a preponderance of single oriented fibers after TBI. However, Q-space DTI, such as standard deviation (SD)[2] and q-ball need to be employed to detect WM reorganization if fiber crossing is present in the recovery tissue.

MATERIALS AND METHODS: Male Wistar rats (n=17) were subjected to a controlled cortical impact model of TBI and sacrificed at 6 weeks after being treated with scaffolds+MSC (collagen scaffolds impregnated with bone marrow stromal cell, MSC, n=8) or without (n=9) at 1 week after TBI. The MSCs were labeled by superparamagnetic particles using Ferrumoxide-protamine sulfate complex labeling method[3]. MRI measurements were performed two days, and weekly for 7 consecutive weeks after TBI. Rats were sacrificed after the last MRI measurements. MRI measurements were performed with a 7 T, 20 cm bore, Magnex superconducting magnet equipped with a 20 G/cm, 12 cm bore gradient insert. T_1, T_2, FA, radial ($\lambda_\perp$) and axial ($\lambda_\parallel$) diffusivity, fiber orientation, q-ball, and SD were used to characterize biophysical changes of white matter reorganization after TBI. T_1 was measured using a Look-Locker (L-L) sequence[4]. Q-ball and SD analyses were run on data from a spherical acquisition scheme with 128 diffusion directions. To detect white matter reorganization, brain sections were stained using Bielshowsky (axons, black) and Luxol fast blue (myelination, blue) immunoreactive staining.

RESULTS: Cell-based treatment promotes WM reorganization, confirmed by an increase in axons (black in C, D, and G of Fig 1) and myelination (blue in C, D, and G of Fig 1), which reflected elevated FA ($p<0.01$ at 6 weeks) in the TBI recovery region, decreased T_2 ($p<0.01$ at 2, 3, and $p<0.05$ at 4, 6 weeks) in TBI core, and improved functional recovery ($p<0.05$, ≥ 2 weeks) compared with untreated animals after TBI. WM reorganization after cell-based treatment of TBI is predominantly located in the extended area of the corpus callosum (arrows in Fig 1B-FA and Fig 1D). The fiber tracking map (Fig 1B, FT) revealed connections between white matter reorganized regions separated by the TBI lesion (circular color lines, arrow heads), and these connections correspond visually with the white matter reorganized region in the coronal FA map (Fig 1B, coronal FA, arrow heads). Although Gaussian DTI exhibited promising results in detecting WM reorganization in the recovery regions where the fiber orientation map exhibited more single oriented fibers than crossing fibers, FA did not detect the increase in axons in the bottom of the TBI lesion (yellow arrow in Fig 1D) where fiber crossing was detected by the q-ball orientation map (Fig 1B, q-ball, FD). In contrast with FA, the SD map exhibited increased SD (Fig 1B, SD, yellow arrows) in the WM remodeling region with more crossing fibers (Fig 1B, q-ball, yellow arrows), which is consistent with histological confirmation of increased axonal density(Fig 1D, yellow arrow heads and 1F, red arrow heads).

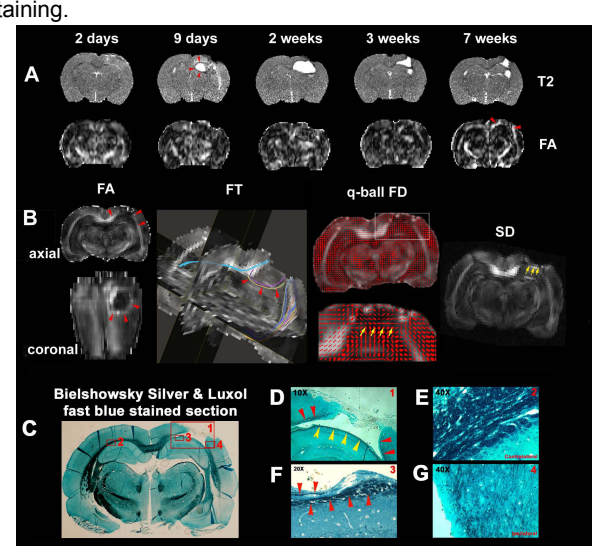

Fig. 1 The evolution of in-vivo (A) T2 and FA maps and corresponding ex-vivo (B) FA, Fiber tracking, q-ball fiber orientation, and SD maps, and the Bielshowsky and Luxol fast blue immunoreactive staining images (C-G) measured from the fixed animal brain. The images in D to G are high magnification images from the box areas in panel C as indicated the numbers in the up right corner in the images of D to G.

DISCUSSION: Our data suggests that MRI can detect white matter reorganization and reconnection after cell-based treatment of TBI. White matter reorganization after cell-based treatment of TBI is predominantly located in the extended area of corpus callosum. Although FA shows promise in differentiating white matter reorganized brain tissue from other TBI damaged tissues, FA does provide error information if crossing fibers are predominant in the white matter reorganized region. Since crossing axons are dominant during the early stage of WM reorganization, our data suggest that we may provide information about the stage of white matter remodeling in the injured brain, with increased SD alone (without FA elevation) representing an early recovery stage of fiber crossing, while the increased FA identifies more mature linear fibers.

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