Diffusion-derived MRI Measures of Longitudinal Microstructural Remodeling Induced by Marrow Stromal Cell Therapy after TBI

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Background and Purpose: Cell transplantation after traumatic brain injury (TBI) promotes white matter reorganization which can be revealed by fractional anisotropy (FA)[1]. Diffusion entropy, a model-independent estimate, is superior to FA in identifying structural alterations[2]. However, quite limited data exist regarding the use of entropy to dynamically monitor structural changes, particularly for cell-induced neural remodeling in TBI. The objective of the present study was designed to investigate the capacity and sensitivity of FA and entropy to longitudinally detect the therapeutic effect of human bone marrow stromal cells (hMSCs) on TBI.

Materials and Methods: Male Wistar rats (300-350g, n=30) subjected to controlled cortical impact TBI were intravenously injected with 1 ml of saline (n=5 per group, at 6 hours or 1 week post-injury) or hMSCs in suspension ($3x10^6$ hMSCs, n=10 per group, at 6 hours or 1 week post-injury). *In vivo* MRI acquisitions of T2-weighted imaging (TR=4.5s, TE=15, 30, 45, 60, 75, 90ms) and diffusion-weighted imaging (Q-ball: TR=10s, TE=50ms, b=0, 1500s/mm^2, 64 directions) were performed on all animals pre-injury, 1 day and weekly for 3 weeks post-injury, and sensorimotor function was evaluated at the same time points. Maps of FA and entropy were generated and their values were monitored in the peri-contusional cortex regions where oriented and extended bundles of myelinated axons were observed histologically.

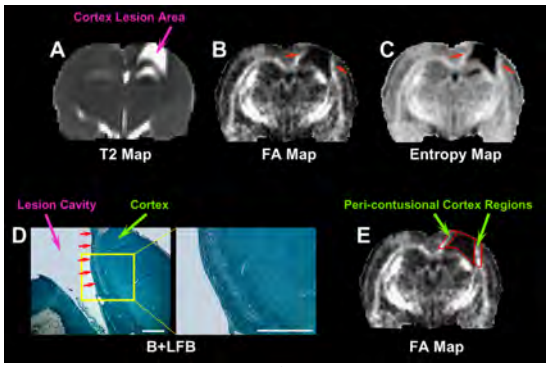

Fig. 1 Representative slice of a 6h-cell-treated animal (3 weeks post-TBI) showing white matter reorganization and ROI creation. The hyperintensities on both FA and entropy maps are detected in the cortex regions nearby the lesion (red arrows in B and C), implying microstructural changes. Tissue slice (B+LFB stain) reveals that these peri-contusional cortex regions contain oriented and extended bundles of myelinated axons (D), suggesting white matter reorganization. While T2 hyperintensities identify the lesion area (A), the 6-pixel wide ROIs immediately adjacent to the lesion encompass the lesion boundary regions with structural alterations (E).

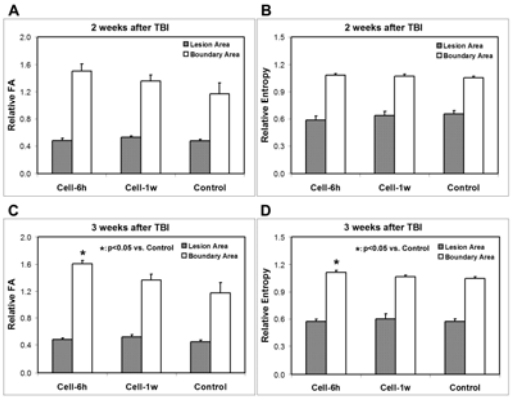

Fig. 2 Changes of FA (A, C) and entropy (B, D) values in the lesion and boundary areas. At 2 weeks after TBI, no statistical differences between three treatment groups are found for both FA and entropy values either in the lesion or in the boundary area (A-B). At 3 weeks after TBI, however, significant increased FA and entropy are detected in the boundary area only in the 6h-cell-treated animals compared to the controls (C-D).

Results: All animals with saline injection post-TBI were considered as a saline-treated group since no significant differences in MRI measurements and functional outcomes between the acute (6h) and delayed (1w) saline-treated group were detected. Administration of hMSCs after TBI led to white matter reorganization, particularly along the lesion boundary, which can be identified by both FA and entropy (**Fig. 1**). At 3 weeks post-TBI, significantly elevated FA and entropy values in this region were detected in the 6h-cell-treated animals, but not in the 1w-cell-treated animals, as compared to controls (**Fig. 2**). These MRI data were confirmed by histological estimates. While FA and entropy had similar capability to dynamically detect the microstructural changes in the tissue region with predominant orientation of fiber tracts (**Fig. 1 & 2**), entropy exhibited sensitivity, superior to FA, in probing the structural alterations in the area with crossing fibers (**Fig. 3**).

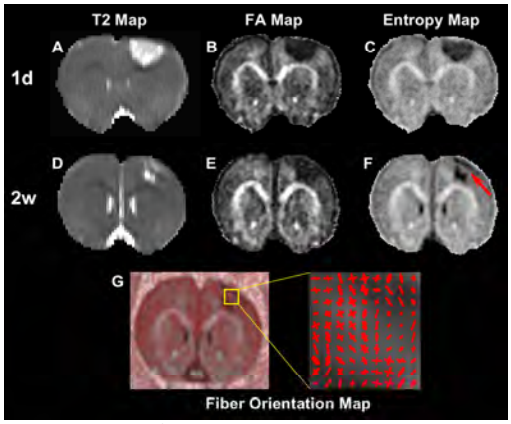

Fig. 3 A slice of a 6h-cell-treated animal longitudinally showing the sensitivity of FA and entropy to structural alteration. At 1 day (A-C) after TBI, both FA (B) and entropy (C) detect the hypointensive area in the cortex region which corresponds to the hyperintensive lesion identified on T2 (A). At 2 weeks (D-F) after TBI, the change of T2 lesion in both size and shape is apparent (compare D with A), which nicely match the evolution of structural status revealed by entropy (compare F with C). This structural alteration, however, is not reflected on FA (compare E with B). The tissue area present on entropy (red arrow in F), but absent on FA, mainly contains crossing fibers, as shown by fiber orientation map (G).

Discussion and Conclusions: Compared to delayed cell engraftment (1w) after TBI, acute cell intervention (6h) promotes structural reorganization in the injured brain, which may contribute in part to the corresponding earlier functional recovery[3]. Entropy is more sensitive than FA to longitudinally detect structural alteration, particularly in the tissue area with crossing fibers.

References:

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3. Li L, Chopp M, Ding GL, et al. MRI measurement of angiogenesis and the therapeutic effect of acute marrow stromal cell administration on traumatic brain injury. JCBFM 2012; 32: 2023-2032.