White Matter Reorganization after Stroke Measured by Gaussian DTI, q-ball, and PAS MRI

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INTRODUCTION: Neurorestorative treatment of stroke promotes brain remodeling and functional recovery[1]. Although the mechanism of neurorestorative treatment of stroke has been primarily focused on angiogenesis and neurogenesis[1], white matter reorganization is important for functional recovery after stroke[2]. In the current study, we evaluated the effects of neurorestorative treatment of stroke on white matter reorganization using MRI. We demonstrate that MRI fractional anisotropy (FA) identifies tissue with white matter reorganization, fiber orientation of axonal projection from Gaussian DTI, ODF in q-ball, and PAS MRI detects the changes of axonal orientation in the ischemic boundary region after stroke.

MATERIALS AND METHODS: Male Wistar rats (n=21) were subjected to embolic stroke and sacrificed at 5-6 weeks without (n=10) and with sildenafil treatment (n=11) starting at day 1 and daily for an additional 6 days after stroke. MRI measurements were performed one day, and weekly for 5-6 consecutive weeks after stroke. 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, and fiber orientation were used to characterize biophysical changes of white matter reorganization after stroke. T_1 was measured using a Look-Locker (L-L) sequence[3]. Q-ball and PAS MRI reconstructions 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. The ischemic damaged areas were determined by using the threshold T_2 value of mean + 2 standard deviations from T_2 value measured in the contralateral hemisphere on T_2 maps after stroke. The ischemic recovery regions were identified by subtracting the ischemic core areas obtained 5-6 weeks after stroke from the ischemic area in T_2 maps obtained 1 day after stroke. The relative changes of MR measurements in ischemic core and recovery ROIs (ischemia/contralateral ischemia) were used to detect the regional and group differences. The diffusion MRI data were analyzed using Camino software[4].

RESULTS: White matter reorganization, confirmed by an increase in axons (black in A and B of Fig 1) and myelination (blue in A and B of Fig 1), was coincident with increases of FA ($p < 0.05$) for the treated and control groups after stroke, and coincident with decreases of relative T_1, T_2, ($p < 0.05$) in the ischemic recovery regions compared to that in the ischemic core region in both treated and control groups. After stroke, the treated group shows a large increase in FA ($p<0.05$) in the ischemic recovery regions compared with the control group. Also, the Bielshowsky and Luxol fast blue immunoreactive staining showed that axonal projections emanating from individual parenchymal neurons exhibited an overall orientation parallel to lesion areas after stroke. White matter reorganization after neurorestorative treatment of stroke is predominantly located in the extended area of the corpus callosum in the ipsilateral striatum (red arrows in FA and A of Fig 1). The fiber orientation maps derived from Gaussian DTI, ODF, and PAS MRI revealed similar orientation patterns in the axonal remodeling area in the extended area of the corpus callosum in the ipsilateral striatum. Both the PAS and ODF clearly show two consistent pairs of peaks in the crossing fibers (white arrows in E and F of Fig 2) in the layer between corpus callosum and cortex as demonstrated by 3D laser scanning confocal microcopy (LSCM) in the panel I and G (bright green lines are axons) in Fig 2 from a transgenic mice expressing yellow fluorescent protein in pyramidal neurons. However, the crossing fiber orientation is less clear in the ODF compared with the PAS plot. Although PAS and ODF showed promise in detecting crossing fibers, further studies need to be performed to reduce effect of noise on crossing fiber evaluation in ischemic region.

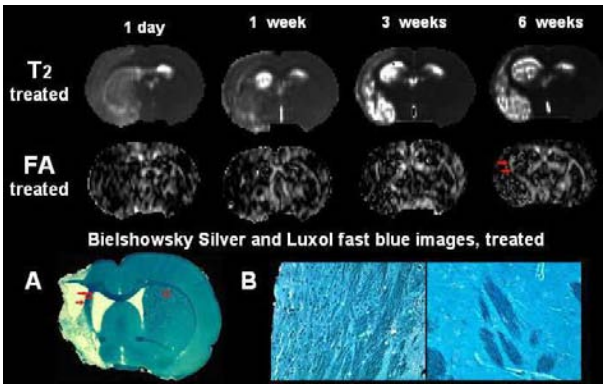

Fig. 1 The evolution changes in T_2 (top row) and FA (middle row) maps after sildenafil treatment and corresponding Bielshowsky Silver and Luxol fast blue stained coronal section (A, B) from the same rat. The left image in B is a higher magnified image from the box area in panel A and the corresponding contralateral area (right image in B).

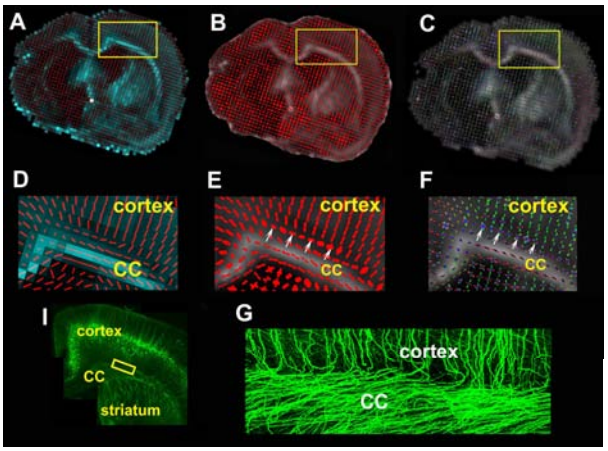

Fig. 2 Panels A, B, and C show fiber directions from Gaussian DTI (A), q ball (B) and PASMRI (C) superimposed on the FA maps from a sildenafil treated rat 6 weeks after stroke. Panels D, E, and F are magnified images from boxes in A, B, and C. Panel I and G are the axonal projections (green lines) in LSCM images. G is magnified LSCM image from the box in I. CC, corpus callosum.

CONCLUSION: Our data suggest that MRI can detect white matter reorganization after neurorestorative treatment of stroke. White matter reorganization after neurorestorative treatment of stroke is predominantly located in the extended area of corpus callosum in the striatum. FA differentiated white matter reorganized brain tissue from other ischemic damaged tissues. PAS and ODF provide crossing fiber information and requires further validation.

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