Alterations of DTI indices in bilateral corticospinal tract following unilateral stroke in a rat model

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Introduction: Functional loss after stroke is associated with neural fiber degeneration, but neural fibers may subsequently remodel, which is a critical feature of post-stroke brain plasticity that may lead to functional recovery (1). The pattern of white matter changes after stroke is largely unresolved, despite its crucial role in loss of functional connectivity and possible subsequent recovery (2). In this study, we investigate whether it is feasible to track the corticospinal tract (CST) in rats using diffusion tensor tractography and to serially characterize changes in DTI indices within the bilateral CST after stroke.

Method: Experimental stroke was induced by transient (90 minutes) intraluminal occlusion of the right middle cerebral artery in six male Wistar rats. The rats were scanned before the insult, and 3, 6 and 8 days thereafter, on a 4.7T horizontal bore Varian Instruments MR system, using the following sequences: T2 (multiple spin echo; TR/TE = 3000/17.5 ms; echo train length = 8) and DTI (8-shot EPI; TR/TE=3000/31 ms; FOV=32x32 mm; matrix=128x128 interpolated to 256x256; 19 coronal slices with slice thickness of 1 mm; 4 images without diffusion-weighting; diffusion-weighted images in 40 directions with b=1500 s/mm Δ/δ=11/6 ms). DTI images were first processed using the software library FSL to generate fractional anisotropy (FA), mean diffusivity (MD), and eigen diffusivity and direction maps. The FA and the primary eigen vector images were converted to DTIStudio compatible format, and bilateral CST were tracked using the two-ROI approach with ROI placements in the internal capsule and caudate putamen (Fig. 1). Spurious tracts, mostly passing the corpus callosum to reach the other hemisphere, were pruned using the NOT operation in DTIStudio. The resulting tracts were converted to binary images, 1 for voxels traversed by the tract, 0 otherwise. The binary CST image was separated into the rostral and caudal parts. The mean FA, MD, $\lambda_{//}$ (the largest eigen diffusivity) and $\lambda_{\perp}$ (the mean of the second and third diffusivity)(3) were quantified for the bilateral rostral and caudal parts of the CST. Mixed effect models were used with SPSS to detect longitudinal changes of the quantified DTI indices with time point as a factor, and the heterogeneous first order autoregression, AR(1), covariance structure was used.

Results: Part of the ipsilesional CST was displaced due to the stroke lesion, and the number of fibers traced using tractography was smaller than on the contralesional side and their length was shorter (Fig. 2). Fig. 3 shows longitudinal changes of the FA, MD, $\lambda_{//}$, $\lambda_{\perp}$ in caudal and rostral parts of the ipsi- and contralesional CST. Mixed models found significant changes in FA in ipsilesional caudal and rostral CST (p=0.002, p<0.001). Pairwise comparison showed that the significant difference in FA was between the 3 post-stroke time-points and baseline scans, while there was no significant difference among FA values at 3, 6 and 8 days after stroke. Marginally significant change was found in FA in the rostral part of the contralesional CST (p = 0.054). There were significant changes in MD both in the caudal part of the ipsilesional CST (p = 0.006), and, interestingly, in the rostral part of the contralesional CST (p = 0.029). Despite the dynamics seen in Fig. 3, pairwise comparisons showed significant difference in MD only between baseline and 3, 6, 8 days post-stroke, but no significant difference among the 3 post-stroke time-points. Highly significant changes in $\lambda_{//}$ were found in the rostral and caudal parts of the ipsilesional CST (p = 0.003 and p<0.001, respectively). A trend towards significant change in $\lambda_{//}$ was found in the contralesional CST (p =0.070 and p=0.086 for rostral and caudal parts, respectively). For $\lambda_{\perp}$, a trend toward significant change was found in the rostral part of the ipsilesional CST (p = 0.083). It is noteworthy that $\lambda_{\perp}$ increased in both rostral and caudal parts of the ipsilesional CST, although these changes did not reach statistical significance.

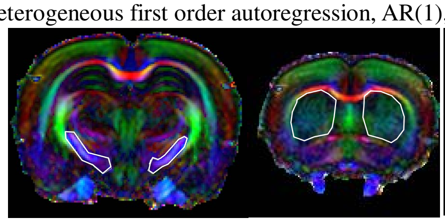

Fig.1 Placement of two ROIs for tractography on color-coded FA maps.

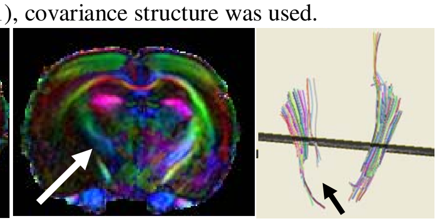

Fig. 2 Displaced ipsilesional CST (left); the number of tracked ipsilesional CST fibers was fewer and their length shorter (right).

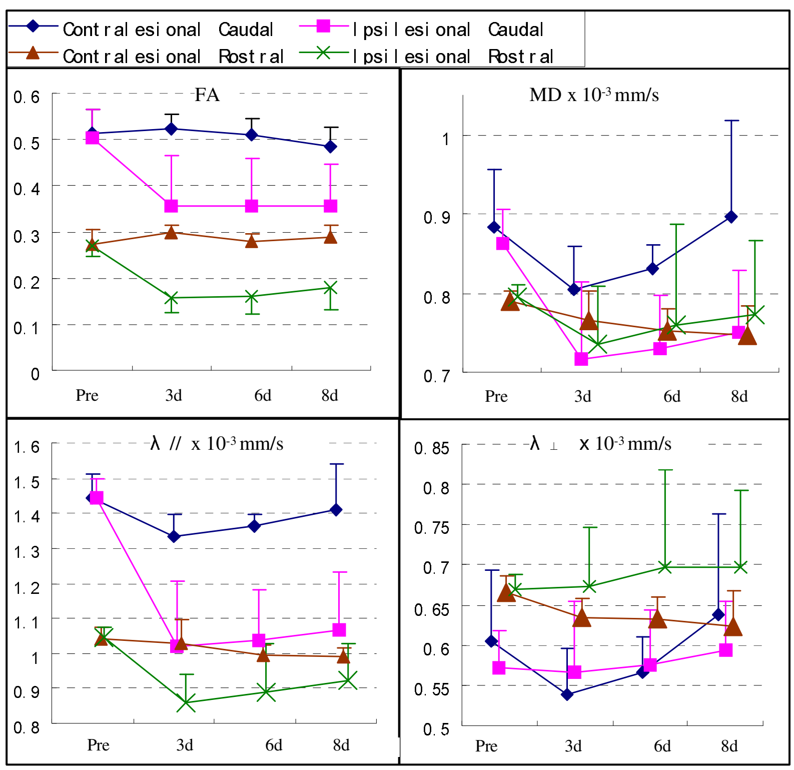

Fig.3 Longitudinal changes of the DTI indices in rostral and caudal parts of the ipsi- and contralesional CST.

Discussion: Our study demonstrates that DTI-based tractography allows explicit assessment of changes in bilateral CST in rats following unilateral stroke. We detected dynamic changes in ipsi- and contralesional DTI indices, largely driven by reductions in $\lambda_{//}$, which may be related to pathological as well as remodeling processess in white matter.

References: **1.** Carmichael SH et al. 2002. J NeuroSci. 22:6062:6070. **2**. van der Zijden JP et al. 2008. Exp Neurol. 212:217-12. **3.** Song SK et, al. 2005 NeuroImage. 26:132-40.