

Longitudinal evaluation of white matter injury in a macaque model of ischemic stroke with DTI

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Target audience: MRI scientists and researchers on stroke study.

Introduction: Stroke is the leading cause of long-term disability in the United States. Many stroke patients benefit from the FDA-approved drug recombinant tissue plasminogen activator (rtPA). However, only ~5% stroke patients receives the rtPA treatment as it has very limited treatment time window (3-4.5 hours) and high risk of hemorrhage. Recent rodent studies suggest the neuro-restorative treatments in the subacute or chronic phase can improve the functional recovery after stroke [1-2]. Also, the spontaneous functional recovery and white matter reorganization have been observed in stroke animals [3]. In comparison with rodent model which has little white matter, non-human primates (NHPs) resemble most aspects of human in brain vascular structure and functionality and have unparalleled advantages in the study of neuronal and vascular remodeling after brain injury. In the present study, longitudinal alteration of white matter with stroke lesion was evaluated in a macaque model of ischemic stroke by using diffusion tensor imaging (DTI).

Materials and Methods: Permanent middle cerebral artery occlusion (MCAo) was induced in adult rhesus monkeys (n = 3, 10-16 years old) using minimally invasive interventional approach [4]. Stroke lesion was observed in the cortical regions of each animal. After occlusion, animals were moved into a 3T MRI scanner immediately and scanned for 7 hours, then re-scanned for 3 hours 48 hours and 96 hours later, respectively. Animals were sacrificed immediately after the last scan to harvest brains for histology, except one was sacrificed after the first scan. DTI was acquired with a single-shot EPI sequence with the parameters: TR = 5000 ms / TE = 87 ms, b-value = 0, 1000 s/mm², 30 gradient directions, 1.5 mm isotropic resolution. Also, MR angiography, FLAIR, T1-weighted, T2-weighted images were acquired for validation purpose (not shown). DTI data were processed with DTI-Studio for calculating mean diffusivity (MD), fractional anisotropy (FA), and fiber tracking. The white matter bundles in or adjacent to the infarct territory were selected as region of interest (ROI) for fiber tracking. The contralateral side in the brain of each animal was used as control for comparison purpose. FA, diffusion-weighted imaging (DWI) and T2-weighted images were used as reference to define the ROIs for fiber tracking. The fiber numbers and mean fiber lengths from the ROIs in both lesion and control sides were obtained, respectively. MD and FA values in the fiber tract-based ROIs were calculated. The MD, FA, fiber number and mean fiber length values in the lesion side and their corresponding contralateral side were compared with paired T-test at each time point.

Results: As shown in Fig 1a, MD of white matter with stroke lesion decreased in the acute phase and increased since 48 hours. Significant difference of MD between the lesion side and the contralateral side was observed at 48 hours post surgery. FA remained unchanged in acute phase and decreased in chronic phase, and significant difference was observed at 96 hours post surgery (Fig. 1b). Similarly, the fiber number and mean fiber length remained unchanged in the acute phase, but decreased obviously in the chronic phase (Fig 1c and 1d), consistent with that seen in Fig. 2, in which the fiber tracking results in one of the monkeys is illustrated.

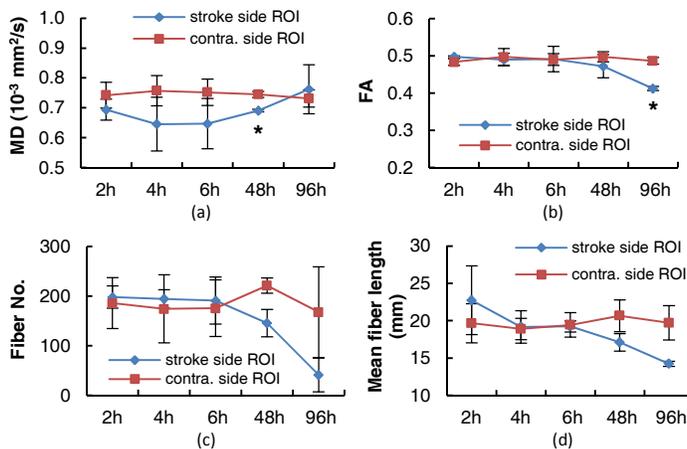


Fig. 1 The changes in (a) MD, (b) FA, (c) fiber number and (d) mean fiber length from the fiber tract-based ROI analysis on the white matter bundle in or adjacent to the infarct region vs. their corresponding contralateral control ROI. The error bars are the standard deviations. *: p < 0.05.

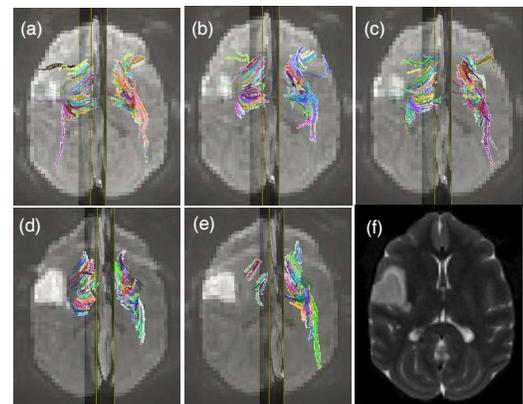


Fig. 2 Fiber tracking results in one stroke monkey scanned at (a) 2 hours, (b) 4 hours, (c) 6 hours, (d) 48 hours and (e) 96 hours post surgery. (f) Corresponding T2-weighted image.

Discussion and conclusions: The DTI fiber tracking and fiber tract-based ROI analysis results demonstrated that the white matter tissues in or adjacent to the infarct region were injured due to the MCA occlusion, as seen in FA, MD and the fiber changes in quantity and average length. The results indicate that white matter demyelination is still in progress in 96 hours after stroke injury in the primate model. Also, temporal changes of MD and FA in the white matter fiber bundle adjacent to the infarct region showed similar pattern as that in the infarct region, but the scale of the changes was reduced which may be due to the hypoperfusion effect (data not shown). The longitudinal changes of MD and FA are in agreement with those seen in previous stroke studies in the acute and subacute stages after stroke [5-7]. The pilot results indicate that DTI with fiber tract-based ROI analysis is sensitive to characterize the white matter injury in ischemic stroke model of primates and could be a robust means to access the white matter damage and reorganization after stroke.

References: [1] Chopp et al, Stroke, 2007; 38:827-831; [2] Jiang et al, Stroke, 2010; 41:S112-S113; [3] Po et al, PLOSone, 2012; 9:e45629; [4] Crespigny et al, J of stroke & cerebrovascular diseases, 2005; 14(2):80-87; [5] Bhagat et al, MRI, 2008; 26:683-693. [6] Pitkonen et al, Brain Research, 2012; 1445(103-110). [7] Liu et al, Stroke, 2006; 38:138-145.