

An optimized Tract-Based Spatial Statistics pipeline in longitudinally monitoring the dynamic of white matter reorganization in primate ischemic stroke model

Huaiqiang Sun¹, Haoyang Xing¹, Chunlin Wang¹, Xianglong Li², Jin Li², and Qiyong Gong¹

¹Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China, ²Regenerative Medicine Research Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Introduction:

Ischemic stroke represents as rapid loss of brain function due insufficient blood supply to some region of brain, which will result in permanent neurological damage or even death. Diffusion tensor imaging (DTI) has become a powerful tool in investigating ischemic stroke. However, previous investigations primarily focus on the relationship between white matter damage measured by DTI in acute phase and the prognosis. Less has been paid to the effects of white matter reorganization on stroke recovery. Genetic studies have proved that injured brain is primed for potentiation of neuronal restorative processes¹. Nevertheless, the exact stroke recovery mechanisms remain incompletely understood. The Spatial and temporal characteristics of restorative process still need to be clarified. In this study, we are exploring the potential of an optimized Tract-Based Spatial Statistics (TBSS) pipeline² to longitudinally monitor the dynamic of white matter reorganization in a primate permanent ischemic stroke model.

Method:

13 male macaque rhesus (4-years old, 4.5-5.5kg bodyweight) were anaesthetized and underwent permanent right Middle Cerebral Artery occlusion (pr-MCAo). The MRI scanning was performed at 20, 35, 60, 90 days (t1-t4) post-surgery on a clinical 3T scanner with 32 channel head coil. The DTI data was acquired using a bi-polar diffusion weighted spin-echo EPI sequence (TR=8000ms, TE=110ms) with 128 x 128 matrix over a field of view of 128 x 128 mm and 25 axial slices of 2 mm thickness. Each DTI dataset included 30 images of unique diffusion directions at b=1000s/mm² and a non-diffusion image (b=0). Motion and eddy-current correction was performed using tools from FMRIB's Software Library (FSL). The non-brain tissue was removed manually and a diffusion tensor model was fit to the preprocessed data using FMRIB's Diffusion Toolbox (FDT).

For longitudinal analysis, an unbiased tensor-based image registration scheme (Fig. 1) proposed in ref 3 was integrated into conventional TBSS. The registration scheme includes two steps. First, a with-in subject template was generated from tensor images of four time points in an iteratively average-register way for each animal. The deformation field from each time point to with-in subject template was denoted by D1. Second, a study specific template was generated from each with-in subject template with same procedure. The deformation field from with-in subject template to study specific template was denoted by D2. The D1 and D2 were then combined and applied to each raw tensor image to get the final tensor images in study specific template space. All linear and non-linear registration was performed on tensor images using algorithm provided by open source software DTI-TK⁴. Fractional Anisotropy (FA) maps derived from registered tensor images were averaged to create a mean FA map. The mean FA map was subsequently skeletonized and thresholded (FA > 0.2) to create a mean FA skeleton. The nearest local FA maximums of each individual FA map were projected onto this skeleton. Voxel wise permutation-based nonparametric inference was performed using Randomize tool from FSL. Skeletonized FA data from same time point were treated as a group. The group contrasts between t1-t2, t1-t3 and t1-t4 were tested with 5000 permutations. The statistical threshold was set at p < 0.05 using the Threshold-Free Cluster Enhancement (TFCE) method to define the clusters.

In addition to DTI measurement, behavioral impairment was also quantitatively assessed at each time point based on balance, gross motor skill, defense reaction and so on.

Result:

The monkeys following pr-MCAo showed a similar infarction area at the intersection of posterior frontal lobe, anterior parietal lobe and upper temporal lobe of right hemisphere. The DTI data indicate severe white matter degeneration at right external capsule, anterior limb of internal capsule, posterior limb of internal capsule and superior corona radiate. The TBSS results indicate that there was no significant FA alteration at t2 compared with t1. FA increasing clusters first emerged at t3 in the fiber bundles connected to primary motor cortex and primary sensory cortex in ipsilesional hemisphere and bilateral superior longitudinal fasciculus. At t4, more FA increasing happens at genu and midbody of corpus callosum, anterior limb of internal capsule in non-affected hemisphere and bilateral fiber bundles that connected to primary motor cortex and primary sensory cortex (Fig. 2). Behavioral test also showed constantly motor function improvement from t1 to t4.

Discussion and conclusion:

To our knowledge, this is the first study that employs unbiased tensor-based image registration scheme to longitudinally investigate white matter changes in primate ischemic stroke model. This registration scheme avoids interpolation asymmetry induced bias and has been proved to have significant improvement in reliability and sensitivity over FA map based method³. From previous studies, the increase of FA can be interpreted as the increase of axonal density, thus the increase connectivity between nodes in residual network. Our findings suggest that white matter reorganization occurs in chronic phase of stroke and shows a dynamic pattern in restorative processes. When correlate with results from behavioral test, the connection enhancement happens in ipsilesional hemisphere has considerable contribution to functional recovery following ischemic stroke.

Reference:

[1]Cramer et al., Trends Neurosci 2000. [2]Smith et al., NeuroImage 2006 [3] Keihaninejad et al., NeuroImage 2013 [4] Zhang et al., IEEE T Med Imaging 2007

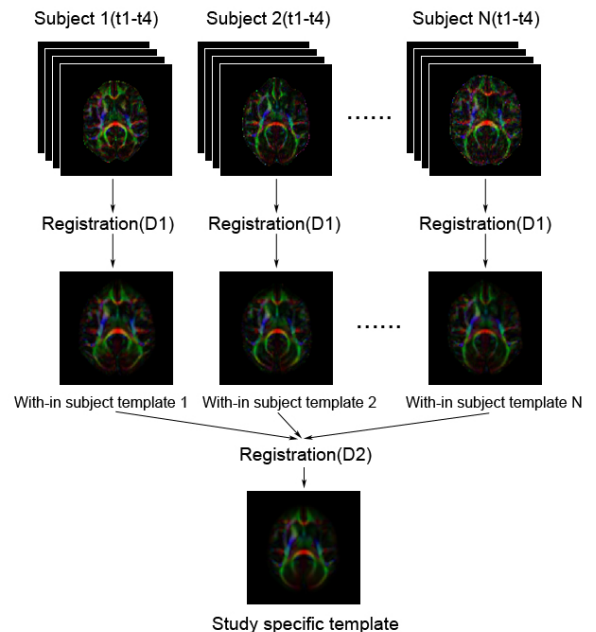


Fig. 1 The pipeline of unbiased tensor-based image registration scheme to study longitudinal white matter changes

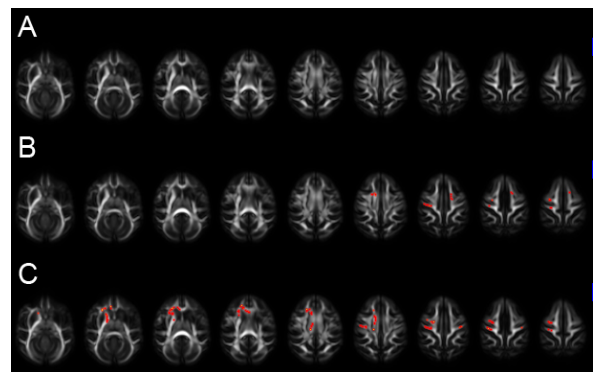


Fig. 2 The overlay of TBSS results on study specific FA map. The significant FA increasing clusters (red) in t2(A), t3(B) and t4(C) when compare with t1.