Correlations of Structural and Functional Connectivity Alterations in Primary Motor Cortex in a Macaque Model of Ischemic Stroke

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TARGET AUDIENCE

Neuroscientists, clinicians, and MRI physicists working on stroke.

INTRODUCTION

Structural and functional alterations in primary motor cortex (PMC) are generally seen in patients and animal models with middle cerebral artery occlusion (MCAo) [1, 2]. However, the temporal correlation between the alterations is not completely understood. By using diffusion MRI and resting-state functional MRI (rsfMRI), the correlation between the ipsilateral structural damage and interhemispheric functional alteration in primary motor cortex was evaluated with a macaque model of ischemic stroke.

METHODS

Permanent MCAo was induced in adult macaque monkeys (n = 4, 15.8 ±3.9 years old) by using a minimally invasive interventional approach [3]. Animals were scanned with a 3T Siemens Trio MRI scanner before stroke surgery, on the surgery day (0 day), and 2 days and 4 days post-stroke. Diffusion tensor MRI was acquired with a single-shot spin-echo EPI sequence with the parameters: TE/TR = 87 ms/5000 ms, b value = 0, 1000 s/mm2, 60 directions, 1.5 mm isotropic resolution. For rsfMRI data acquisition, a single-shot gradient-echo EPI was applied with TE/TR = 25 ms/2060 ms, 1.5 mm isotropic resolution, the total scan time = 5 minutes. Data were processed with FSL (FMRIB, Oxford) and custom-made MATLAB (Mathworks, Natick, MA) scripts. Mean diffusivity (MD) or apparent diffusion coefficient (ADC) maps were calculated and nonlinearly registered to a template and skeletonised (green color in Fig. 1) with TBSS toolbox in FSL. FMRI analysis was conducted with image distortion correction, intra-modal motion correction, slice timing correction, spatial smoothing and low/high-pass temporal filtering. ROI for ipsilateral primary motor cortex (PMC, in the lesion side) was selected from a high-resolution T_1-weighed monkey brain template and registered to the rsfMRI raw images for each animal. The functional connectivity (FC) map was then calculated with the brain-wide correlation analysis, followed by a Fisher r-to-z transform and transformed back to the monkey brain template space. One-way ANOVA with repeated measures was applied to test voxelwise the differences in pre-scan, day 0, and 2, 4 days post-stroke for both diffusion and rsfMRI data with FSL (significant level = 0.01, uncorrected). The voxels with significant ADC difference within the ipsilateral PMC, and those with significant FC difference within the contralateral PMC, were selected for partial correlation analysis between ADC values and z scores with age as a control variable and a significant level < 0.05.

RESULTS

Significant changes in ADC of the ipsilateral PMC and interhemispheric PMC functional connectivity were observed (as indicated in the contralateral PMC) by comparing the data scanned in pre-scan (baseline) and the days post-stroke (Fig. 1). Trends of decreased ADC in the ipsilateral PMC and reduced interhemispheric PMC FC were observed from preoperative condition to 4 days after stroke insult. The z scores of interhemispheric PMC FC significantly correlated with ADC values in the ipsilateral PMC (Fig. 2).

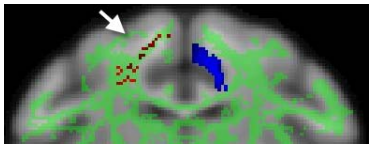

Figure 1. Changes of ADC (red color) in the ipsilateral PMC (lesion side, white arrow) and interhemispheric PMC functional connectivity (blue color), overlaid on a monkey brain template.

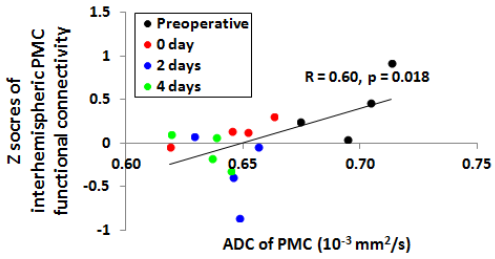

Figure 2. Interhemispheric PMC functional connectivity correlates with ADC values of ipsilateral PMC, from preoperative condition (baseline) to 4 days after stroke insult.

DISCUSSIONS AND CONCLUSIONS

Focal ischemic brain injury results in brain structural damage, functional network impairment, and behavioral deficits in stroke patients. The longitudinal ADC evolution in the macaque model of ischemic stroke agrees well with that seen in prior human stroke studies in which ADC reduction could last up to 96 hours [4]. Declining interhemispheric PMC FC after stroke insult was observed, consistent with the previous findings in motor cortex in acute stroke patients [2, 5]. In particular, the significant correlation between the ADC reduction and interhemispheric FC change during acute and subacute stroke suggests the close association between altered ADC and FC during early stroke lesion development and implication of prognosis and clinical outcome.

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