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Motor recovery and microstructural change in rubro-spinal tract in subcortical stroke ☆

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ARTICLE INFO

ABSTRACT

The mechanism of motor recovery after stroke may involve reorganization of the surviving networks. However, details of adaptive changes in structural connectivity are not well understood. Here, we show long-term changes in white matter microstructure that relate to motor recovery in stroke patients. We studied ten subcortical ischemic stroke patients who showed motor hemiparesis at the initial clinical examination and an infarcted lesion centered in the posterior limb of internal capsule of the unilateral hemisphere at the initial diffusion-weighted magnetic resonance imaging scan. The participants underwent serial diffusion tensor imaging and motor function assessments at three consecutive time points; within 2 weeks, and at 1 and 3 months after the onset. Fractional anisotropy (FA) was analyzed for regional differences between hemispheres and time points, as well as for correlation with motor recovery using a tract-based spatial statistics analysis. The results showed significantly increased FA in the red nucleus and dorsal pons in the ipsi-lesional side at 3 months, and significantly decreased FA in the ipsi-lesional internal capsule at all time points, and in the cerebral peduncle, corona radiata, and corpus callosum at 3 months. In the correlation analysis, FA values of clusters in the red nucleus, dorsal pons, midbody of corpus callosum, and cingulum were positively correlated with recovery of motor function. Our study suggests that changes in white matter microstructure in alternative descending motor tracts including the rubro-spinal pathway, and interhemispheric callosal connections may play a key role in compensating for motor impairment after subcortical stroke.

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1. Introduction

Stroke is the leading cause of adult-onset disabilities, and hemiparesis is among the strongest predictors of later activity of daily life (Veerbeek et al., 2011). Accumulating evidence shows that patients can make a significant recovery from motor disabilities during the initial 3 months after the onset of stroke (Duncan et al., 1992; Kelly-Hayes et al., 1989). Neuroimaging studies have recently elucidated part of the mechanism

that accounts for functional recovery after stroke (see Grefkes and Ward, in press); however, details of reorganization by the surviving network are not fully understood. In animal studies, the extrapyramidal descending tract (EPT) including rubro-spinal and reticulo-spinal pathways (Lemon, 2008), a phylogenetically old corticofugal system, plays a role in recovering motor function after pyramidal tract (PT) injury (Belhaj-Saïf and Cheney, 2000; Lawrence and Kuypers, 1968; Zaaimi et al., 2012). However, in humans, there is sparse evidence for anatomical and functional significance of the EPT system (Baker, 2011; Lemon, 2008), or for its role in motor recovery.

Diffusion tensor imaging (DTI) allows us to estimate micro-architectural changes of the white matter and neuronal fiber bundles (Basser et al., 1994). Obtained DTI measures are able to quantitatively detect experimental degeneration of white matter tracts (Hayashi et al., 2013) and are also associated with the degree of motor dysfunction in stroke (Lindenberg et al., 2010; Stinear et al., 2007). Recently, Lindenberg et al. (2010) suggested that the outcome of motor impairment in stroke can be better predicted by microstructural changes of the PT and EPT together than changes of the PT alone. Additionally, others reported increased fractional anisotropy in the rubro-spinal

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pathway, part of the EPT system, in chronic stroke patients (Rüber et al., 2012; Yeo and Jang, 2010). However, these cross-sectional studies cannot evaluate longitudinal changes in the EPT system or motor function.

In the present study, we hypothesized that 1) microstructure of the regional white matter would change across time and hemispheres after stroke, and 2) if microstructural change was present, increase in fractional anisotropy would be associated with recovery of motor function. We show longitudinal changes of the white matter microstructure in subcortical stroke patients during a 3-month period, which are correlated with serially improved motor function.

2. Materials and methods

2.1. Patients

Ten patients with acute ischemic stroke, admitted to the Stroke Care Unit at the National Cerebral and Cardiovascular Research Center, were enrolled in this study. On admission the patients presented with minor to moderate impairment varying from 3 to 11 (median = 4.5) on the National Institute of Health Stroke Scale (NIHSS) and fulfilled the following inclusion criteria: (1) aged 20 years or more; (2) first-ever stroke of supratentorial pyramidal tract infarction; (3) presence of hemiparesis; and (4) clinically stable and first magnetic resonance imaging (MRI) scan acquired within 2 weeks of onset. Exclusion criteria were the presence of any cortical ischemic lesion and previous infarcted lesion involving pyramidal tracts in the initial MRI scan, disturbance of consciousness, neurological symptoms suggesting a cortical lesion (hemispatial agnosia or neglect, aphasia, apraxia), or the presence of other neurological and psychiatric disorders. We also assessed the initial T2-weighted MRI image for chronic white matter lesions using the Fazekas grade of periventricular and deep white matter hyperintensity (Fazekas et al., 1987). The study protocol was approved by the Institutional Review Board (M19-12), and was conducted in accordance with the Declaration of Helsinki and all patients gave written informed consent to participate in this study.

Each patient underwent serial examinations for neurological symptoms as well as for diffusion tensor MR imaging at 3 time points: within 2 weeks (Scan 1), at 1 month (Scan 2), and at 3 months (Scan 3) following stroke onset. Neurological motor symptoms were scored on the Fugl-Meyer Motor Scale (FMMS) (Gladstone et al., 2002), which has a range of 0 (complete hemiplegia) to 100 (normal performance) and consists of scores for upper extremities (= 66) and for lower extremities (= 34), during a comprehensive neurological examination by a board-certified neurologist (Y.T.). During the follow-up, all patients received standard medical treatment and rehabilitation, and no patient received thrombolysis, thrombectomy, or experimental treatment.

2.2. MR data acquisition

MR images were acquired with a 3 T whole-body MRI scanner (Signa3.0, GE Healthcare, Milwaukee, WI, USA) using a 16-channel phased-array head coil. Participants were placed on the scanner gantry in a head-first supine position with their ears plugged and heads secured by a plastic holder to minimize movements. The DTI data were obtained with a single-shot echo-planar imaging sequence [repetition time (TR)/echo time (TE) = 16,000/72.1 ms; flip angle = 90°; field of view (FOV) = 256 mm; matrix size = 128 × 128; slice thickness = 2 mm; 70 contiguous axial slices covering the entire brain], which consisted of 81 volumes with non-collinear diffusion gradient directions and a b-value of 1000 s/mm^2, and 9 volumes with a b-value of 0 s/mm^2. We also obtained T1- and T2-weighted MRI scans for structural information and lesion localization, as well as a gradient-echo type field map for correcting distortion in the DTI data.

The entire scanning session took around 60 min and was tolerated by all subjects.

2.3. Data preprocessing

MRI data were analyzed using FMRIB Software Library (FSL) 4.1.8 (http://www.fmrib.ox.ac.uk/fsl) (Jenkinson et al., 2012), developed by the Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK. The DTI data were preprocessed for brain extraction, distortion corrected using the field map data, eddy-current distortion corrected with an affine transformation, and analyzed by fitting a diffusion tensor model (Basser et al., 1994) to generate a fractional anisotropy (FA) image. The FA images were fed into statistics across sessions and patients by a voxel-based spatial statistics method, as well as by a region-of-interest (ROI) method as described below.

2.4. Tract-based spatial statistics (TBSS)

Voxel-based statistical analysis of FA images was carried out using Tract-Based Spatial Statistics (TBSS), part of FSL (Smith et al., 2006). All subjects' FA maps were non-linearly warped to generate an averaged symmetric FA image in the Montreal Neurological Institute (MNI) space using a non-linear image registration tool (FMRIB's Non-linear Image Registration Tool, FNIRT). To avoid shrinkage of the lesion area during the warping process, we used an infarcted lesion area map (generated as described below) as a mask to exclude from warping. The values in the warped FA images were projected onto the FA skeleton, which represents the centers of fiber bundles (Smith et al., 2006). Before this projection, warped FA images for the patients who were affected in the right hemisphere (patients 3, 4, 7, and 8, see Table 1) were right-to-left flipped to align the lesion side to the contralateral to allow us to use voxel-based statistics across all the subjects. The resulting data in the FA skeleton of the MNI space were fed into voxel-wise statistics for cross-scan and cross-subject analyses. We performed three statistical analyses using FA data as a dependent variable for (1) within-subject interhemispheric difference using a paired t-test for each time point separately (Scans 1–3); (2) the effect of time by a paired t-test between a pair of three sessions; and (3) correlation with FMMS scores. For analyzing interhemispheric differences [analysis (1)], we performed a right–left flip for all the warped images and compared between non-flipped and flipped images. In the correlation analysis [analysis (3)], we used FA data from all sessions, and the FMMS score at the corresponding point, with scores demeaned within subjects. Statistics were performed with a nonparametric permutation test using 5000 Monte Carlo simulations. The statistical threshold was set at a family-wise error corrected $p < 0.05$, based on the threshold-free cluster enhancement (TFCE) method (Smith and Nichols, 2009). The anatomical locations of significant clusters were denominated based on the atlas of JHU ICBM-DTI-81 White Matter Labels, part of the FSL atlas tools (Mori and Crain, 2005), and on Witelson's callosal atlas (Witelson, 1989).

We also performed a ROI analysis for significant clusters found in the TBSS to look at the details of FA change. Our interest was in each of the clusters in the TBSS analysis and in its corresponding mirrored region, both in the standard space. We obtained FA values of ROIs from each subject's image in the native space, and tested for the effect of hemisphere and scan session using a repeated measure analysis of variance (ANOVA), as well as for the correlation with FMMS scores. ROIs in the standard space were warped to the subject's native space by inverting the nonlinear registration. For the cluster in the corona radiata (CR), ROIs in the native space obtained as above were overlapped with infarcted areas (see described below) in some subjects, thus we obtained FA values only from voxels that did not include the infarcted area.