Supplementary Methods

Participants

Twenty-one participants with acute ischemic stroke and visual field defect (VFD) were chosen from a previous study of 32 individuals.[1] Selection criteria included consistent diffusion tensor imaging (DTI) acquisition parameters across three visits and with those of other patients. Patients with acute ischemic stroke within 1 week of symptom onset between September 2011 and December 2014 were enrolled in this study.

The inclusion criteria were as follows: (1) aged 20 years or more; (2) acute ischemic stroke in a unilateral posterior cerebral arterial territory within the previous 1 week (confirmed by magnetic resonance imaging) as the first stroke episode; (3) VFD such as homonymous hemianopia or quadrantanopia; (4) did not undergo thrombolytic therapy for the purpose of investigating patients with natural course; (5) DTI data for three visits per each patient and identical DTI acquisition parameters within- and between-patients; (6) reliable Humphrey Visual Field tests; (7) no life threatening medical conditions; and (8) willing to participate in the study. The patients who developed neurologic events such as recurrent stroke or hemorrhagic transformation during the follow-up period and those with different DTI acquisition parameters with other visits and other patients were excluded from the final analysis. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Declaration of Helsinki.

Assessment of visual field defect

Light detection performance was used to assess the VFD of each eye using a Humphrey Field Analyzer (HFA 750i; Zeiss-Humphrey, San Leandro, CA, USA). The total deviation scores on the decibel (dB) scale, representing light detection performance relative to age-matched normal values at each tested retinal point, were obtained using the central 30-2 threshold Swedish Interactive Threshold Algorithm (SITA)-Fast protocol of the HFA. The mean total deviation (MTD) score was calculated by averaging the total deviation scores in the affected hemifield of both eyes (e.g., the affected hemifield was the left hemifield for patients with left quadrantanopia or hemianopia).

Acquisition of magnetic resonance imaging

High-resolution T1-weighted images and DTI data were collected using a 3.0 T Philips (Philips Achieva; Philips Medical Systems, Amsterdam, the Netherlands) magnetic resonance imaging scanner. High-resolution T1-weighted images were obtained using magnetization-prepared rapid acquisition with a gradient echo (MPRAGE) sequence. The acquisition parameters were as follows: repetition time/echo time, 9.9/4.6 ms; flip angle, 8°; voxel size, 1×1×1 mm^3. DTI images were obtained using the following acquisition parameters: 32 diffusion directions; repetition time/echo time, 9,732/70 ms; b factor=0, 1,000 s/m^2; and voxel size, 1×1×2 mm^3.

Analysis of diffusion tensor imaging

DTI data were preprocessed using the Pipeline for Analyzing BraiN Diffusion imAges (PANDA) software version 1.3.1 implemented in MATLAB.[2] DTI images were skull-stripped and corrected for eddy current distortion and motion artifacts through affine registration to b0 images using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Diffusion Toolbox (FDT; http://www.fmrib.ox.ac.uk/fsl). The DTIfit tool in FDT was used to compute voxelwise fractional anisotropy (FA) and mean diffusivity (MD) values.

The T1-weighted images were skull-stripped and resampled (1 mm space). As the network nodes, the brain regions were parcellated into 90 cortical and subcortical regions (45 regions per hemisphere) using the Automated Anatomical Labeling (AAL) atlas.[3]

Individual FA and MD maps, which were co-registered to the corresponding T1-weighted structural images, were then nonlinearly registered to the Montreal Neurological Institute (MNI)–International Consortium for Brain Mapping (ICBM) 152 template (2 mm space). Using the inverse matrix of the above-mentioned two-step registration method, the structural nodes defined using the AAL atlas in the stand space were inversely registered to the subject-specific FA and MD maps of the native DTI space.

The edges between nodes were defined by deterministic fiber tracking based on fiber assignment using a continuous tracking (FACT) algorithm. Tracking was interrupted when fulfilling either of the following conditions: (1) when the FA values were less than 0.2; (2) when the tracking angle between two adjacent voxels was greater than 45°. A network edge was defined as at least three fiber bundles between two adjacent brain regions.

As a result, 20 white matter tracts were defined in the native space based on the white matter tract probability map by performing deterministic fiber tracking on 28 normal subjects.[4] Among these, nine white matter tracts connecting the visual cortex were selected as the regions of interest (Supplementary Figure 1). FA and MD values extracted from the nine tracts were used for subsequent analyses.

The infarct location of the patients with VFD was matched to the location on the right hemisphere by inverting the magnetic resonance imaging scans along the x-axis for those with infarction in the left hemisphere (n=9 of 21 patients). Therefore, the right hemisphere was considered the ipsilesional hemisphere and the left hemisphere was considered the contralesional hemisphere.

Statistical analysis

Temporal changes in the MTD scores in the affected hemifield (four time points: 1 week, 1 month, 3 months, and 6 months after onset) and the FA and MD values of the nine white matter tracts connecting the visual cortex (three time points: 1 week, 1 month, and 3 months after onset) were assessed using one-way repeated-measures analysis of variance (ANOVA). *Post hoc* paired t-tests were performed for two pairs of time points using Bonferroni correction for multiple comparisons.

For *post hoc* analyses, MTD scores were compared between six pairs of four time points using the Bonferroni-corrected paired t-test with 6 comparisons. One-way repeated measures ANOVA showed significant FA changes in seven white matter tracts and MD changes in four white matter tracts. The FA values of the seven white matter tracts with significant temporal changes were compared between three pairs of three time points using the Bonferroni-corrected paired t-test with 21 comparisons. The MD values of the four white matter tracts with significant temporal changes were compared between three pairs of three time points using the Bonferroni-corrected paired t-test with 12 comparisons.

The neurobehavioral correlations of patients were assessed using robust regression for outlier correction. Independent variables included significant FA or MD changes in the white matter tracts between 1 week and 1 month, and between 1 week and 3 months. The dependent variables included significant changes in the MTD scores in the affected hemifield between 1 week (initial assessment) and 6 months (last assessment). Associations with significant FA changes used Bonferroni-correction with 12 comparisons, and associations with significant MD changes used Bonferroni-correction with 7 comparisons. The relationships between two significant FA changes and one significant MD change that correlated with the MTD changes over 6 months were also investigated, using the Bonferroni correction with 2 comparisons.

Supplementary References

1. Kim YH, Cho AH, Kim D, Kim SM, Lim HT, Kwon SU, et al. Early functional connectivity predicts recovery from visual field defects after Stroke. *J Stroke* 2019;21:207-216.
2. Cui Z, Zhong S, Xu P, He Y, Gong G. PANDA: a pipeline toolbox for analyzing brain diffusion images. *Front Hum Neurosci* 2013;7:42.
3. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273-289.
4. Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage* 2008;39:336-347.

https://doi.org/10.5853/jos.2023.02222