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# Microstructural abnormalities in white matter and their effect on depressive symptoms after stroke

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ABSTRACT

The aim of the study was to investigate the existence of microstructural abnormalities in the white matter of the brain in stroke patients, as well as the relationship between these microstructural abnormalities and changes in depressive symptoms over 6 months. Participants were 29 acute ischemic stroke patients and 37 healthy control subjects. Depressive symptoms were assessed in all subjects using the Hamilton Rating Scale for Depression and the Zung Self-rating Depression Scale. Whole brain voxel-based analysis was used to compare diffusion tensor imaging measures of Fractional Anisotropy (FA) between the groups. Six-month follow-up examinations were conducted. Patients showed significantly lower white matter FA values in the left and right anterior limbs of the internal capsule, and 6 months after the stroke they showed significantly increased FA values in these regions. We found a significant negative correlation between the increased ratio of the FA values and the change in depression scale scores at 6-month follow-up. Regional white matter damage may reflect abnormalities in neuroanatomical pathways related to the pathophysiology of depression.



## 1. Introduction

Depression is the most common and serious emotional symptom following a stroke and is associated with excess disability, cognitive impairment and mortality (Whyte and Mulsant, 2002). Although there is no consensus about the relationship between lesion location and post-stroke depressive symptoms, Magnetic Resonance Imaging (MRI) studies have found a high prevalence of depressive symptoms in patients with lesions that affect structures of the prefronto-subcortical circuit (Vataja et al., 2001, 2004). Recent studies have highlighted the specific relevance of the Limbic-Cortical-Striatal-Pallidal-Thalamic (LCSPT) circuit in the pathophysiology of major depressive disorder (Drevets et al., 2008; Hasler et al., 2008) and of depression due to stroke (Terroni et al., 2011; Paradiso et al., 2013).

Diffusion Tensor Imaging (DTI) combines a conventional MRI sequence with additional magnetic field gradients to quantify water diffusion, namely, Fractional Anisotropy (FA), the degree to which diffusion is directionally hindered, which reflects the microstructural integrity of the white matter tracts. Microstructural damage to white matter tracts may confer a biological vulnerability to the onset of depressive symptoms in stroke patients. To our knowledge, however, no studies have investigated the existence of microstructural abnormalities of white matter in stroke patients and examined whether the diminution of microstructural abnormalities decreased the vulnerability to post-stroke depression, as measured by increases in depression scale scores in stroke patients that are noted before the onset of severe depression.

Thus, the primary aim of the present study was to investigate the existence of microstructural abnormalities in white matter tracts in stroke patients, as well as the relationship between the recovery from these microstructure abnormalities and the change in depression scale scores 6 months after a stroke. DTI was performed and whole brain voxel-based analysis was used to compare FA between groups of acute ischemic stroke patients

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and healthy control subjects. Six-month follow-up examinations were conducted. On the day of the MRI scan, depressive symptoms were evaluated with the Hamilton Rating Scale for Depression and the Zung Self-rating Depression Scale.

## 2. Methods

### 2.1. Participants

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the medical ethics committee of the National Cerebral and Cardiovascular Center in Japan. The patients were of Japanese ethnicity and were recruited from the neurology unit of the National Cerebral and Cardiovascular Center hospital. These patients had initially been hospitalized for treatment of acute ischemic stroke.

Stroke was diagnosed by neurologists according to World Health Organization (WHO) criteria. After the assessment, a group of psychiatrists and neurologists reviewed the data and reached a consensus regarding the presence or absence of psychiatric disease, including dementia, according to DSM-IV criteria. Patients were included if they met the following criteria: (1) a focal lesion of either the right or left hemisphere on MRI; (2) absence of other neurological, neurotoxic, or metabolic conditions; (3) modest ischemic insult (modified Rankin scale $\leq 4$) with absence of a significant verbal comprehension deficit; and (4) occurrence of stroke 10–28 days before the examinations. Exclusion criteria were as follows: (1) transient ischemic attack, cerebral hemorrhage, subdural hematoma or subarachnoid hemorrhage; (2) history of a Central Nervous System (CNS) disease such as tumor, trauma, hydrocephalus, and Parkinson's disease; and (3) pre-stroke history of depression. Thirty-eight patients who volunteered to participate in the study were screened for eligibility. We excluded 5 subjects who did not meet the study criteria. In addition, four patients had not completed the MRI scan due to fatigue. A final group of 29 patients met the criteria and participated in this study.

Thirty seven healthy volunteers were recruited from the local area by poster advertisement. Exclusion criteria for the volunteers were a history or present diagnosis of any DSM-IV axis I or any neurological illness. Major characteristics of this cohort are summarized in Table 1. To reliably elucidate differences in white matter integrity between groups, the target total sample size was set at above 52, which was expected to yield power $\geq 0.8$, based on $\alpha \leq 0.05$ and assuming a large effect size ($f=0.4$) with the analysis of covariance (ANCOVA) used in this study (Cohen, 1977), and the sample size of this study met the power requirement.

All patients and volunteers were assessed with a series of standardized, quantitative measurements of depressive symptoms [Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), Zung Self-rating Depression Scale (SDS) (Zung, 1965)] and cognitive function [Mini-Mental State examination (MMSE) (Folstein et al., 1975)] on the day of the MRI scan. A neurological examination [modified Rankin scale: mRS (Brott et al., 1989)] was also carried out in the patients. MRIs were conducted for all of the subjects.

Six-month follow-up MRI examinations were also conducted for 18 of 29 patients and 19 of 37 healthy subjects. The other patients and controls were lost to follow-up because we were unable to contact them at 6 months after the first study or they declined to further participate in this study due to health problems, business, feeling of rejection, and so on. On the day of the follow-up MRI scan, the participants underwent the same battery of depressive, cognitive function and (for the patients) neurological measurements that had been performed at the time of the initial MRI. There were no changes in medication between baseline and follow-up. No patients and healthy subjects were diagnosed as meeting DSM-IV criteria for major depression on the day of the initial MRI. Two patients were diagnosed as meeting criteria for major depression for the first time on the day of the follow-up MRI, and they were prescribed medication after the examinations. No patients were on antidepressant treatment during the examinations.

### 2.2. MRI acquisition

All MRI examinations were performed using a 3-T whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased-array brain coil. DT images were acquired with a locally modified single-shot Echo-Planar Imaging (EPI) sequence by using parallel acquisition at a reduction (ASSET) factor of 2, in the axial plane. Imaging parameters were as follows: repetition time (TR)=17 s; echo time (TE)=72 ms; $b=0$, 1000 s/mm$^2$; acquisition matrix, $128 \times 128$; field of view (FOV), 256 mm; section thickness, 2.0 mm; no intersection gap; 74 sections. The reconstruction matrix was the same as the acquisition matrix, and 2 mm × 2 mm × 2 mm isotropic voxel data were obtained. Motion Probing Gradient (MPG) was applied in 55 directions, the number of images was 4144, and the acquisition time was 15 min, 52 s.

To reduce blurring and signal loss arising from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions (Kim et al., 2002) was used before acquiring DTI scans. To correct for motion and distortion from eddy current and B0 inhomogeneity, FMRIB software (FMRIB Center, Department of Clinical Neurology, University of Oxford, Oxford, England; http://www.fmrib.ox.ac.uk/fsl/) was used. B0 field mapping data were also acquired with the echo time shift (of 2.237 ms) method based on two gradient echo sequences.

High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence (TR=12.8 ms, TE=2.6 ms, flip angle=8°, FOV, 256 mm; 188 sections in the sagittal plane; acquisition matrix, $256 \times 256$; acquired resolution, $1 \times 1 \times 1$ mm). T2-weighted images were obtained using a fast-spin echo (TR=4800 ms; TE=101 ms; echo train length (ETL)=8; FOV=256 mm; 74 slices in the transverse plane; acquisition matrix, $160 \times 160$, acquired resolution, $1 \times 1 \times 2$ mm).

**Table 1**
Demographic characteristics of patients and healthy control subjects.

| Characteristic | Stroke patients ($n=29$) | Healthy controls ($n=37$) | $t_{64}$ or $X^2$ | $P$ |
|---|---|---|---|---|
| Age (years) | 68.7 ± 8.2 | 67.5 ± 5.2 | $t=0.77$ | 0.45 |
| Female sex ($n$, %) | 6 (20.7) | 15 (40.5) | $\chi^2=2.95$ | 0.10 |
| MMSE score | 27.8 ± 3.0 | 29.2 ± 1.0 | $t=2.45$ | 0.02* |
| SDS score | 26.5 ± 5.6 | 24.1 ± 3.6 | $t=2.03$ | 0.05* |
| HAM-D score | 2.6 ± 2.5 | 1.1 ± 1.8 | $t=2.64$ | 0.01* |
| mRS score | 2.2 ± 0.8 | – | | |
| Number of acute infarcts | 1.2 ± 0.6 | – | | |
| Volume of acute infarcts (ml) | 2.0 ± 2.3 | – | | |
| Acute infarcts ($n$, %) in | | | | |
| Frontal cortex | 1 (3.4) | – | | |
| Occipital cortex | 1 (3.4) | – | | |
| Basal ganglia | 13 (44.8) | – | | |
| Thalamus | 4 (13.8) | – | | |
| Subcortical white matter infarcts in | | | | |
| Frontal lobe | 6 (20.7) | – | | |
| Parietal lobe | 1 (3.4) | – | | |
| Temporal lobe | 1 (3.4) | – | | |
| Occipital lobe | 1 (3.4) | – | | |
| Genu of internal capsule | 1 (3.4) | – | | |
| Total | 10 (34.5) | – | | |
| Laterality of acute hemisphere infarcts | | | | |
| Left hemisphere ($n$, %) | 17 (58.6) | – | | |

MMSE=Mini-Mental State Examination. SDS=Zung Self-Rating Depression Scale. HAM-D=Hamilton Rating Scale for Depression. DWMH= deep white matter hyperintensity. PVH=Periventricular hyperintensity. mRS=Modified Rankin Scale. Data are mean ± S.D. * $p < 0.05$.

### 2.3. Image processing

FMRIB software was used to generate FA maps and three eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$) from each individual. First, brain tissue was extracted using the Brain Extraction Tool in FSL software. Brain maps for each of the 55 directions were eddy-corrected, subsequent to which FA values were calculated at each voxel using the FSL FMRIB Diffusion Toolbox.

Image preprocessing and statistical analysis were carried out using SPM8 software (Wellcome Department of Imaging Neuroscience, London, England). Each subject's echo planar image was spatially normalized to the Montreal Neurological Institute echo planar image template using parameters determined from the normalization of the image with a $b$ value of 0 s/mm$^2$ and the echo planar image template in SPM8. Images were resampled with a final voxel size of $2 \times 2 \times 2$ mm$^3$. Normalized maps were spatially smoothed using an isotropic Gaussian filter (8-mm full-width at half-maximum).

### 2.4. Voxel-based analysis

Voxel-based analysis was performed using SPM8 software. FA maps were compared between patients and healthy subjects by ANCOVA with age and gender as covariates of no interest. We included age and gender as covariates because it has been reported that they affect the white matter integrity (Inano et al., 2011). Statistical inference was done with a voxel-level threshold of $p < 0.05$, after family-wise error correction for multiple comparisons, with a minimum cluster size of 50 voxels. The regional FA value was calculated by averaging the FA values for all voxels within the voxel of interest (VOI) corresponding to the cluster composed of