Chronic Ischemia Alters Brain Microstructural Integrity and Cognitive Performance in Adult Moyamoya Disease

Ken Kazumata, MD; Khin Khin Tha, MD; Hisashi Narita, MD; Ichiro Kusumi, MD; Hideo Shichinohe, MD; Masaki Ito, MD; Naoki Nakayama, MD; Kiyohiro Houkin, MD

Background and Purpose—The mechanisms underlying frontal lobe dysfunction in moyamoya disease (MMD) are unknown. We aimed to determine whether chronic ischemia induces subtle microstructural brain changes in adult MMD and evaluated the association of changes with neuropsychological performance.

Methods—MRI, including 3-dimensional T1-weighted imaging and diffusion tensor imaging, was performed in 23 adult patients with MMD and 23 age-matched controls and gray matter density and major diffusion tensor imaging indices were compared between them; any alterations in the patients were tested for associations with age, ischemic symptoms, hemodynamic compromise, and neuropsychological performance.

Results—Decrease in gray matter density, associated with hemodynamic compromise (P<0.05), was observed in the posterior cingulate cortex of patients with MMD. Widespread reduction in fractional anisotropy and increases in radial diffusivity and mean diffusivity in some areas were also observed in bilateral cerebral white matter. The fractional anisotropy (r=0.54; P<0.0001) and radial diffusivity (r=−0.41; P<0.01) of white matter significantly associated with gray matter density of the cingulate cortex. The mean fractional anisotropy of the white matter tracts of the lateral prefrontal, cingulate, and inferior parietal regions were significantly associated with processing speed, executive function/attention, and working memory.

Conclusions—In adult MMD, there were more white matter abnormalities than gray matter changes. Disruption of white matter may play a pivotal role in the development of cognitive dysfunction. (Stroke. 2015;46:354-360. DOI: 10.1161/STROKEAHA.114.007407.)

Key Words: diffusion ischemia magnetic resonance imaging moyamoya disease white matter disease

Moyamoya disease (MMD) is characterized by the presence of net-like collateral vessels at the brain base that are caused by progressive major cerebral artery occlusion.1 Executive function/attention and working memory, primarily mediated by the lateral prefrontal region, are impaired, suggesting that lateral prefrontal ischemia is responsible for neurocognitive dysfunction.2,3 A recent investigation revealed the association of neurocognitive dysfunction with reduced cerebral blood flow.3 Nevertheless, not all patients with neurocognitive dysfunction had cerebral infarction on conventional MRI. Thus, ischemia-induced subtle microstructural alterations, which are beyond the detectability of conventional MRI, underlie neurocognitive dysfunction in MMD.

Subtle gray matter changes, not shown on conventional MRI, are successfully detected in many diseases, such as mild cognitive impairment and schizophrenia, through voxel-by-voxel comparison of gray matter density on 3-dimensional (3D) MRI.4,5 Diffusion tensor imaging (DTI) is reportedly highly sensitive to microstructural alterations in diffusion characteristics of white matter.6-9 To the best of our knowledge, no reports have evaluated gray matter changes in MMD using 3D MRI. There are only few reports on DTI assessments of MMD white matter integrity.5-8 Nevertheless, these reports used a specified region-of-interest approach and evaluated only 2 major DTI indices, such as fractional anisotropy (FA) and mean diffusivity (MD). Voxel-based analysis of white matter can provide detailed topographical characteristics of white matter integrity, and tractography can show the integrity of the major white matter tracts that run in anatomic regions. Furthermore, additional information for characterizing chronic ischemia-induced white matter damage can be extracted by incorporating other major DTI indices, such as axial diffusivity (AD) and radial diffusivity (RD).

Here, we investigated the brain’s microstructure across different regions in adult MMD by a voxel-based analysis of gray and white matter and tractography, and evaluated the relationship of these microstructural alterations with hemodynamic compromise and neurocognitive dysfunction.
Materials and Methods

Participants
This prospective study was approved by the Research Ethics Committee of Hokkaido University Hospital. Written informed consent was obtained from all participants.

The inclusion criteria were clinical diagnosis of idiopathic MMD according to the consensus criteria and guideline for MMD proposed by the Research Committee on Spontaneous Occlusion of the Circle of Willis and age of >20. The exclusion criteria were moyamoya syndrome with conditions such as Down syndrome and neurofibromatosis, cortical infarction or subcortical lesion of >8 mm in the largest dimension on conventional MRI, intracranial hemorrhage, revascularization surgery before the study, apparent neurological deficit because of stroke, and comorbid illnesses that could affect cognition. After exclusions, 23 patients (6 men, 17 women; 21–58 years; mean age, 40.9±9.5 years) were enrolled. The selection period was 25 months (from April 2012 to April 2014).

The inclusion criteria for controls were no clinical evidence of psychiatric or neurological disorders, normal intelligence quotient as assessed by the Japanese version of the Nelson Adult Reading Test, no brain lesions on conventional MRI, and no medication that could affect cognitive function. The control group also comprised 23 subjects (10 men, 13 women; 25–56 years; mean age, 39.0±8.1 years). The mean estimated intelligence quotient was 108.3±6.6.

Hemodynamic Status Assessment
Cerebrovascular reactivity assessed by single positron emission computed tomography was used to determine the hemodynamic status in patients with MMD. A cerebrovascular reactivity of <15% in the left or right middle cerebral artery territory was considered as a hemodynamic compromise. Single positron emission computed tomography was performed within 7 days from MRI in 18 patients (Appendix I in the online-only Data Supplement).

Neuropsychological Assessment
The neuropsychological assessment was performed in all patients with MMD. A neuropsychological battery sensitive to cognitive dysfunction because of frontal lobe injury was used and comprised the Wechsler Adult Intelligent scale-III, Wisconsin Card Sorting test, Trail Making Test (TMT; parts A and B), continuous performance task, Stroop test, and reading span test. Details are provided elsewhere (Appendix II in the online-only Data Supplement). Neuropsychologists blinded to the clinical data performed the tests. The interval between the neuropsychological tests and MRI was <1 month.

MRI Analysis
MRI was performed on a 3.0-T imager (Achieva TX; Philips Medical Solutions, Best, The Netherlands). Three-dimensional magnetization–prepared rapid gradient-echo T1-weighted imaging and axial single-shot spin-echo echo-planar DTI were performed to evaluate subtle gray and white matter alterations. The scan parameters are detailed elsewhere (Appendix III in the online-only Data Supplement). In addition, axial fast spin-echo T2-weighted imaging and fluid-attenuated inversion recovery imaging were also performed in patients with MMD to rule out cortical and subcortical infarctions and evaluate white matter hyperintensities.

Image Processing and Evaluation

Identification of Gray Matter Alterations
Three-dimensional magnetization–prepared rapid gradient-echo images were used to compare gray matter density voxel-by-voxel between patients with MMD and controls. The steps for voxel-based morphometry of FSL (FSL-VBM, version 4.1, http://www.fmrib.ox.ac.uk/fsl) using default parameters were followed (Appendix IV in the online-only Data Supplement). Age was considered as a covariate. A P<0.05 after correction for family-wise error was considered statistically significant.

Identification of White Matter Alterations
To identify subtle white matter alterations, the 4 major DTI indices (FA, MD, AD, and RD) were first extracted from the DTI using the Diffusion Toolbox of FSL and the default parameters. Correction for eddy current distortions and motion was performed before extracting the indices. Differences in the major DTI indices between patients with MMD and controls were then tested using tract-based spatial statistics, which is a part of FSL. The default parameters and steps recommended by the software developers were used (Appendix V in the online-only Data Supplement). Age was a covariate, and results were corrected for multiple comparisons across space using threshold-free cluster enhancement. For each major DTI index, the mean value and number of voxels reaching statistical significance (threshold-free cluster enhancement-corrected; P<0.05) were calculated.

Probabilistic tractography was performed using FLIRT and BEDPOSTX (Appendix VI in the online-only Data Supplement). Sixteen cortical regions and bilateral thalami, which mediate intelligence, working memory, executive function/attention were selected as the seed regions. The entire brain was selected as the target region. For each probabilistic tract, the number of voxels and mean FA value were calculated.

Correlation of Microstructural Alterations With Hemodynamic Compromise and Neurocognitive Function
Voxels with abnormal gray matter density in patients with MMD were tested for correlation with the major DTI white matter indices. Any gray or white matter alterations were tested for correlation with age, presence of ischemic symptoms, hemodynamic compromise, and neuropsychological performance. Pearson product-moment correlation analysis (correlation with age, Wechsler Adult Intelligent scale-III, TMT A and B) or permutation tests performed >10,000 times (presence of ischemic symptoms, hemodynamic compromise, Wisconsin Card Sorting Test, Stroop test, continuous performance task, and reading span test; a cutoff value was applied for the latter 4 tests) were used for these purposes. For all correlations or comparisons, a P<0.05 was considered statistically significant.

Results

Patient Characteristics
Patient characteristics are summarized in Table. There were no significant differences in age (P=0.47) and sex (P=0.35) between patients and controls. Cerebral blood flow at rest, cerebrovascular reactivity, and prevalence of comorbid risk factors did not vary significantly between the symptomatic (ie, transient ischemic attack, n=10 and asymptomatic, n=13) patients. White matter hyperintensities were observed in 10 (43.5%) patients with MMD on T2-weighted or fluid-attenuated inversion recovery images. Hyperintensities were also more frequent in the symptomatic patients (7/10; P<0.05). The mean full-scale intelligence quotient of patients with MMD was 94±13. The neuropsychological assessment results of the patients are summarized in Table 1 in the online-only Data Supplement. There were no significant differences in the full-scale intelligence quotient or scores of other Wechsler Adult Intelligent scale indices or other components of the neuropsychological battery between symptomatic and asymptomatic patients.

Gray Matter Alterations
FSL-VBM revealed a significant reduction in the density of the bilateral posterior cingulate cortex (PCC; Figure 1).
White Matter Alterations
Tract-based spatial statistics showed a significant widespread FA decrease and RD increase in patients with MMD, (55.2% and 42.5%, respectively, of the entire skeleton; Figure 2). Some voxels with FA and RD alterations also revealed significant MD increases. Voxels showing MD increases occupied 20.9% of the mean FA skeleton. Regarding AD, no voxels survived after correction for multiple comparisons, although AD decreases were observed mainly at the superior longitudinal fasciculus and cingulate bundle when correction was not performed (uncorrected $P<0.05$).

Probabilistic tractography also revealed decreases in the mean FA of several white matter tracts in patients with MMD. The number of voxels of each tract of patients with MMD did not vary significantly from that of controls.

Correlation of Microstructural Alterations With Hemodynamic Compromise and Neurocognitive Function
The density of the cingulate cortex of the patients significantly correlated with the mean FA ($r=0.54; P<0.0001$) or RD ($r=-0.41; P<0.01$) of the white matter skeleton (Figure 3).

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Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age, y</th>
<th>Clinical Presentation</th>
<th>Location of WMH</th>
<th>Suzuki Grade</th>
<th>Hemodynamic Compromise</th>
<th>Comorbid Illness</th>
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<tr>
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<td>3</td>
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<td>Moderate</td>
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<tr>
<td>M</td>
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<td>TIA</td>
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</tr>
<tr>
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<td>Left frontal deep white matter</td>
<td>3</td>
<td>3</td>
<td>Moderate</td>
</tr>
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</table>

Asymptomatic: Patients with neurological episodes such as syncope and transient ischemic attack (TIA) in childhood but remained asymptomatic after adolescence. Hemodynamic compromise was rated as severe when cerebrovascular reactivity (CVR) was <5% from the baseline, moderate when 5 ≤ CVR<10%, and normal when 10% ≤ CVR. 10% (Appendix I in the online-only Data Supplement). WMH indicates white matter hyperintensities.
superior frontal, right middle frontal, and left middle cingulate cortex of patients with higher Stroop test performance were significantly higher than those of their counterparts. Similarly, these values of the tracts originating from the bilateral middle frontal, right anterior cingulate cortex, and left middle cingulate cortex were significantly higher in patients with higher reading span test performance than their counterparts.

Discussion
Adult patients with MMD suffer long disease duration. Thus, adult MMD is useful for studying the subtle effects of chronic hypoperfusion on the brain microstructure. This study revealed a decrease in the bilateral PCC density and widespread white matter areas with an FA decrease and RD increase in patients with MMD, alterations that were associated with age. In addition, the bilateral PCC density was significantly associated with hemodynamic compromise, and the mean FA values of the white matter tracts of the dorsolateral prefrontal, cingulate, and inferior parietal regions were significantly associated with neuropsychological performance.

PCC is associated with arousal, attention, internally directed thoughts, and environmental change detection.15 Focal lesion confined to PCC has rarely been reported, therefore, neurocognitive consequences have remained unclear. In stroke, memory disturbances rather than a perceptual error has been reported, however, concomitant involvement in the fornix and the corpus callosum might have been responsible for the cognitive dysfunctions in a large part.16 Connectivity of PCC is reduced in aging, trauma, Alzheimer disease, autism, schizophrenia, depression, and attention deficit hyperactivity disorder.15,17,18 PCC comprises part of the default mode network and its failure to deactivate during the task is considered responsible for the attention lapses.19 In this study, we speculate that the volume reduction in the cingulate may be because of the reduced white matter connectivity. Vulnerability of the posterior part of the cingulum may be explained by its high energetic demand, where PCC consumes 40% greater cerebral blood flow and glucose compared with other brain lesions.20
We speculate that PCC is one of the key neural substrates of attention deficit frequently observed in adult MMD.

White matter is vulnerable to chronic ischemia.\textsuperscript{21} The reported white matter changes in chronic ischemia include demyelination, axonal loss, and gliosis.\textsuperscript{22–24} The observed altered DTI indices of white matter also reflect these changes. The major DTI indices are sensitive to changes in the brain’s microstructure associated with myelination, axonal membrane integrity, axon and glial density, and coherence of axonal orientation.\textsuperscript{25} Generally, neuronal or axonal loss and myelin degeneration are associated with MD increase, which is because of the loss of cell structures that restrict water molecular diffusion, and with FA decrease, which is because of a decline in the alignment degree of highly organized cellular structures (axons and myelin). The observation of a wider area of FA alterations than MD alterations suggests that FA is more sensitive to white

Figure 3. The scatterplots show the relationship between the mean values of each major diffusion tensor imaging index of the entire white matter skeleton and the gray matter density of the cingulate cortex. Significant positive and inverse correlations were observed between the mean fractional anisotropy (FA; $r=0.54; P<0.0001$) and radial diffusivity (RD; $r=-0.41; P<0.01$) and the gray matter density, respectively. AD indicates axial diffusivity; and MD, mean diffusivity.

Figure 4. The spatial distribution of areas revealing significant correlations between the mean fractional anisotropy (FA) of white matter tracts derived by probabilistic tractography and neuropsychological performance (uncorrected $P<0.05$). Results of probabilistic tractography of a patient are shown. Processing speed significantly correlated with the mean FA of the tracts originating from the left superior frontal (SF) gyrus; Trail Making Test (TMT) A with the left middle frontal (MF) and bilateral supramarginal gyrus; TMT B and A with the left posterior cingulate cortex; the Stroop test with the right SF, MF, and the left middle cingulate cortex (MCC); and the reading span test (RST) with the right SF, bilateral MF, right anterior cingulate cortex, and left MCC. The color scale represents the $P$ values.
matter alterations. More specific information about myelin and axonal damage can be obtained by incorporating the directional DTI metrics, such as RD and AD. The former reportedly reflects the degree of myelin breakdown, whereas the latter reflects axonal damage and Wallerian degeneration.26,27 The preferential increase in RD observed in this study may reflect that the major pathological change in white matter in MMD is from demyelination/myelin breakdown. In this study, the exploratory analysis revealed a trend toward AD decrease in the long white matter tracts that run posteroanteriorly, although none of these voxels survived after correction for multiple comparisons. The tendency toward AD decreases in these tracts may reflect axonal swelling associated with Wallerian degeneration. We hypothesize that these white matter tracts are more vulnerable to ischemia compared other tracts.

In this study, the altered white matter integrity did not significantly associate with hemodynamic compromise. Taken together, the observed correlations between the mean FA of the white matter skeleton and age suggest that the disease duration may have a higher effect on white matter integrity than the severity of ischemia.7,8 Alternatively, chronic ischemia in MMD may lower the threshold for age-related decline in white matter integrity.21 Our results also showed an age-related decline in the PCC density, which suggests regional variation in vulnerability to chronic ischemia. The present results may provide some insight into the potential role of the revascularization surgery. It is conceivable that the already damaged gray and white matter may be less likely to normalize even after hemodynamic improvements. Given that the duration of chronic ischemia rather than severity may have more effect on the white matter integrity, early surgical intervention might be effective for preventing microstructural damage and cognitive dysfunctions in adults. Similarly, early surgical intervention may facilitate normal white matter development and intellectual outcome in children.

Consistent with previous reports, impaired executive function/attention and working memory were observed in >30% of patients with MMD.2,3,28 In this study, we investigated the role of the dorsolateral prefrontal cortex, inferior parietal lobe, and cingulate cortex because these areas are reportedly associated consistently with executive function and working memory/attention.29–31 The mean FA values of the dorsolateral prefrontal area (middle and superior frontal gyri) significantly correlated with neuropsychological performance, suggesting that the area serves as a domain for working memory, executive function, and attention. This observation is consistent with that of previous studies demonstrating the association between cognitive function and the integrity of white matter fiber tracts integrating the frontoparietal cortical areas.29 The frontoparietal control network constitutes the dorsolateral prefrontal cortex, anterior cingulate cortex, presupplementary motor area, anterior insula, and PCC.15 It should be emphasized that the mean FA values of the fibers originating from the left PCC were associated with TMT B and A in this study. TMT B and A is not associated with visuospatial and working memory and serves as a relatively pure indicator of executive control abilities.32 This observation indicates that the white matter connection from PCC is associated with executive function.

This study had some limitations. First, the study population was small. The lack of neuropsychological data for assessing the frontal lobe functions in the controls may have resulted in a lack of statistical significance across comparisons. Second, the seed regions putatively associated with frontal lobe-mediated cognitive functions were used for probabilistic tractography. However, previous functional MRI studies demonstrated that the temporal lobe is also associated with working memory.33 Third, white matter integrity is associated with age and sex.34 Sex was not completely matched in the study population and may have influenced the results of the comparison between patients and controls. Further investigation in a large population, preferably a multicenter study, is warranted to help identify the prevalence of cognitive dysfunction and the relationship with other neuroimaging markers,35 which will ultimately lead to determine optimal indication for the revascularization surgery.

Conclusions

Steno-occlusive changes in the major cerebral arteries in MMD cause microstructural brain damage, primarily in the cerebral white matter and impair executive function, working memory, and attention. The clinical significance of this study findings is that early detection of microstructural changes can enable early therapeutic intervention to improve patient cognitive outcome.

Sources of Funding

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Disclosures

None.

References


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phenomenon is associated with increased diffusion in white matter of patients with Moyamoya disease. Stroke. 2010;41:1610–1616. doi: 10.1161/STROKEAHA.110.579540.


ONLINE SUPPLEMENT

Appendix-I: Hemodynamic status assessment

Cerebrovascular reactivity (CVR) was expressed as the percent changes of the regional cerebral blood flow (rCBF) from the baseline after intravenous acetazolamide injection. CVR less than 15% in the left or right middle cerebral artery territory was considered as hemodynamic compromise. In 5 of 13 asymptomatic MMD patients, the hemodynamic status had already been evaluated by using positron emission computed tomography (PET) in 2004-2009. All of them had normal resting state rCBF, cerebral blood volume and oxygen extraction fraction. As none of them had ischemic episode, no further hemodynamic assessment was carried out. These patients were rated as free of hemodynamic compromise based on the results of PET study.

Appendix-II: Neuropsychological assessment

The WAIS-III provides the index scores for overall intellectual ability (Full-scale IQ), language, verbal ability (Perception Reasoning/ Organization Index), auditory attention and mental manipulation (Working Memory/ Freedom from Distractibility Index), and visual-motor speed (Processing Speed Index) — with the mean score of 100 and standard deviation of 20.

The WCST measures the ability for strategic planning, organized search, utilization of environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding. It is known as a measure of executive function.

The Trail-Making Test - Part A and B assess the speed of information processing and executive functioning, respectively.

The CPT measures a person’s sustained and selective attention and impulsivity. It is composed of repetitive, "boring" task that requires concentration over a period of time.

The Stroop test measures sustained attention. A reaction time delay was examined in naming the color of the word printed in an unmatched color.

The RST is a complex verbal test which evaluates both storage and processing (i.e., reading) elements of working memory. The scores are expressed as the total number and proportion of words correctly recalled.

Appendix-III: The MR imaging scan parameters
The scan parameters for DTI were as follows: repetition time (TR)/echo time (TE)/flip angle = 5051 ms/85 ms/90°, field of view = 224 x 224 mm², matrix size = 128 x 128, b-value = 1000 s mm⁻², the number of diffusion gradient directions = 32, slice thickness = 3 mm, the number of slices = 43, and the number of excitation = 1. The 3D-MPRAGE was performed with TR/TE/flip angle = 6.8 ms/3.1 ms/8° and inversion time (TI) = 1100 ms. The scan parameters for T2-weighted imaging were TR/TE = 4137 ms/90 ms and effective echo train length = 15. Those for FLAIR imaging were TR/TE = 10000 ms/100 ms and TI = 2700 ms.

Appendix-IV: Comparison of grey matter density

The 3D-MPRAGE images were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration. The resulting images were then averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Next, all native grey matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with sigma of 3 mm. Finally, voxelwise general linear model was applied using a permutation-based non-parametric testing.

Appendix-V: TBSS

TBSS was used to align all subjects’ FA images to FMRIB58_FA standard-space image and affine the aligned images into 1x1x1 mm³ MNI152 standard space. An average FA image was created for each section. Then, the average FA images were used to create a mean FA skeleton by applying a threshold of 0.2. Cross-subject statistics were performed for the voxels that form the skeleton. The nonlinear warps and skeleton projection were then applied to the other DTI indices, i.e., radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AD). TBSS of RD, MD, and AD was subsequently performed.

Appendix-VI: Probabilistic tractography

The seed regions were generated by using automated anatomical atlas (AAL), and were transformed into the native T1-weighted images using FLIRT algorithm. For fiber tracking, the probability distribution of diffusion directions in each voxel was estimated by using Bayesian sampling techniques.
The voxels which had fewer streamlines than 15% of the maximum number of streamlines across all voxels in each reconstructed tract were excluded. The reconstructed probability maps in each region were transformed to the binary images. Seed mask images were subtracted from the binarized probability maps for creating white matter masks to measure the mean FA values of subcortical tissue.

**Supplemental Table I. The neuropsychological performance of the MMD patients**

<table>
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<tr>
<th>Study</th>
<th>cut-off</th>
<th>The range (mean ± SD) of scores achieved by all patients</th>
<th>Percent of patients with the scores lower than the cut-off value</th>
<th>The mean (SD) score achieved by the asymptomatic patients</th>
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<tr>
<td>Working memory</td>
<td>58-123</td>
<td>(93±14)</td>
<td>34.8%</td>
<td>95.3 (12.1)</td>
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<tr>
<td>Processing speed</td>
<td>63-133</td>
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<td>30.4%</td>
<td>95.7 (10.7)</td>
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<td>TMT-A</td>
<td>87</td>
<td>(72.2 ± 20.1)</td>
<td>13.0%</td>
<td>73.3 (18.7)</td>
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<tr>
<td>TMT-B</td>
<td>100</td>
<td>(93.5± 34.8)</td>
<td>26.0%</td>
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<td>B-A</td>
<td>60</td>
<td>(21.2±33.2)</td>
<td>8.7%</td>
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<td>WSCT CA</td>
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<td>CPT error</td>
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<tr>
<td>RT</td>
<td>480 ms</td>
<td>312.7 - 1533 (494 ± 250.6)</td>
<td>34.8%</td>
<td>428.7 (95.2)</td>
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<td>RST</td>
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Supplemental Table II. The p-values (correlation coefficient) achieved in testing the correlation/association between the mean FA values of each cortical and subcortical-seed based probabilistic tract and Neuropsychological performance

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<th>WM</th>
<th>PS</th>
<th>TMT -A</th>
<th>TMT -B</th>
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<td>0.94 (0.03)</td>
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**Abbreviations:** IQ; Intelligent quotient score, VIQ; Verbal IQ, PIQ; Performance IQ, fIQ; full scale IQ, VC; verbal comprehension, PR; Perceptual reasoning, WM; working memory, PS; Processing speed, TMT; Trail-making test, WSCT; Wisconsin card sorting test, Stroop; Stroop test, CPT; Conceptual performance task, RST; Reading span test.

**Note:** Uncorrected \( p<0.05 \) is bolded. The \( p \)-values which approach 0.05 are bolded and shown in italic.
Figure legends

Appendix-Figure I.
The scatterplots show correlation between the mean FA of the white matter skeleton and age. A significant inverse correlation was observed in the MMD patients ($r=-0.57$, $p<0.005$), but not in the control subjects ($r=-0.19$, $p=0.38$).
References

成人もやもや病において脳微細構造の健全性および認知機能レベルは慢性虚血により変化する

Chronic Ischemia Alters Brain Microstructural Integrity and Cognitive Performance in Adult Moyamoya Disease

Ken Kazumata, MD; Khin Kin Tha, MD; Hisashi Narita, MD; Ichiro Kusumi, MD; Hideo Shichinohe, MD; Masaki Ito, MD; Naoki Nakayama, MD; Kiyohiro Houkin, MD

1 Departments of Neurosurgery; 2 Radiobiology and Medical Engineering; and 3 Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, Japan

背景および目的：もやもや病（MMD）における前頭葉機能障害の根拠にある評価は明らかでない。本研究では、成人MMD患者を対象に慢性虚血による微かな脳微細構造の変化の有無を検討し、その変化と神経心理学的検査データとの関連を評価した。

方法：成人MMD 23例および年齢の一致する対照23例で3D TI強調画像および拡散テンソル画像を含むMRIを施行し、白質病変と主な拡散テンソル画像指標を各群で比較した。年齢、虚血症状、脳血行動態、神経心理学的検査データと患者に認められた変化の関連を検討した。

結果：MMD患者の後帯状皮質、脳血行動態不全（p < 0.05）に伴う灰白質差密度の低下が認められた。また、異方性比の拡張好な低下と、一部領域の拡散伝播数および平均拡散伝播数の上昇が両側の白質に認められた。白質の異方性比（r = 0.54, p < 0.0001）および拡散伝播数（r = -0.41, p < 0.01）は、皮質病変の白質病変と有意に関連した。外側前頭前野、帯状回、下頸小葉領域の白質神経の平均異方性比は、処理速度、実行機能／注意力、作業（業）記憶と有意に関連した。

結論：MMD患者では白質の変化より白質の異常が多くみられた。白質の損傷は認知機能障害の発症において中心的役割を果たしていると思われる。


KEYWORDS 拡散、虚血、磁気共鳴画像法、もやもや病、白質疾患

もやもや病（MMD）は、脳主幹動脈の進行性閉塞を原因として脳基底部に発生した脳の拡散異常を特徴とする。主に外側前頭前野を介する実行機能／注意力および作業（業）記憶に影響が及ぼす領域を含む病態に引き起こす。近年、MMDの神経機能障害と脳血行動態不全の関連が明らかにされた。しかし神経機能障害の有無については従来のMRIでの検出の限界がある。従来のMRIでは検出されない微かな白質変化は、3次元（3D）MRIで白質病変を検出すことに比較することにより、容易に検出可能である。従来のMRIでの検出に成功している。報告によれば、拡散テンソル画像（DTI）は白質の拡散異常の特微を微細構造の変化に対する敏感度が高い。著者らは、3D MRIでMMDの手術前変化を検出した報告がある。MMDの白質変形性をDTIで検出した報告はわずかながら存在する。しかし、これらの報告では詳細の関連領域が使用され、評価した主なDTI指標は異方性比（FA）および平均拡散係数（MD）の2つのみであった。白質のボックス解析は、白質の変化に伴う累積的な局所的特徴を明らかにすることが可能であり、トラクトグラフィーは解剖学的領域を主な白質神経系の健全性を視覚化することができる。さらに、轴方向拡散係数（AD）や放射拡散係数（RD）といった主なDTI指標を加えることによって、慢性虚血による白質損傷を特徴付けるために追加の情報を抽出することもできる。

本研究では、白質および白質のボックス解析とトラクトグラフィーで成人MMDのさまざまな脳領域の微細構造を調査し、このような微細構造変化と脳血行動態不全および神経機能障害の関係を評価した。

対象および方法

研究参加者

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選択基準は、Willis動脈輪閉塞症調査研究班の提唱する
るMMDの合意基準およびガイドラインに基づいて特発性MMDと臨床診断された21歳以上の患者、とした。除外基準は、グレン症候群や神経線維腫症などを合併した疑似もやもや症候群（quasimoyamoya syndrome）、従来のMRIで最大径8mmを超える皮質梗塞または皮質下病変、頭蓋内出血、本研究参加前の血行再建術、脳卒中による明らかな神経脱落症状、認知機能に影響を及ぼす患者、とした。これらを除外後、23例（男性6例、女性17例、21～58歳。平均40.9±9.5歳）が登録に至った。選択期間は25カ月（2012年4月～2014年4月）であった。

対照の選択基準は、精神または神経学的疾患の臨床的エビデンスがないこと、日本語版Nelson Adult Reading Testによる評価で認知機能が正常範囲であること、従来のMRIで病変が確認されないこと、認知機能に影響を及ぼす薬剤を使用していないこと、とした。対照群の構成は23例（男性10例、女性13例、25～56歳。平均39.0±8.1歳）であった。認知指数の推定平均値は108.3±6.6であった。

血行動態の評価
MMD患者の血行動態は、SPECT（単一光子撮影学的脳血流解析法）による脳血管反応性の評価で判断した。左または右中大脳動脈領域の脳血管反応性が15％未満のものを血行動態不全とみなした。18例ではMRAから7日以内にSPECTを施行した（データ補遺資料I）。

神経心理学的評価
MMD患者すべてに神経心理学的評価を実施した。前頭葉損傷による認知機能障害に感度が高い神経心理学的検査を使用し、ウェクスター成人知能検査（WAIS）III、ウィスコンシンカードソーティング検査、トレーリングメイキング検査（TMT、AおよびB）、持続処理課題、ストループ検査、リーディングスパン検査を組み込んだ。詳細は別途記載した（データ補遺資料II）。臨床データについて盲検化された神経心理士がこれらのテストを実施した。神経心理学的検査とMRIの間隔は1カ月未満であった。

MRI解析
MRIは3.0teslaの断層撮影装置（Achieva TX、Philips Medical Solutions, Best, The Netherlands）で実施した。
3D MPRAGE（magnetization-prepared rapid gradient-echo法）によるT1強調画像と軸位断シンギュレット・スピンエコー・エコーブラー法によるT2強調画像の撮影により、微小な灰白質および白質の変化を評価した。画像パラメータの詳細は別途記載した（データ補遺資料III）。さらに皮質および皮質下梗塞を除外して白質高信号域を評価するため、MMD患者で軸位断高スピンエコーT2強調画像およびFLAIR（fluid-attenuated inversion recovery）画像を撮影した。

画像処理および評価
灰質白質変化の識別
3D MPRAGE画像でMMD患者および対照の灰白質密度を共にことに比較した。FSLのポターエ定位計測ステップ（FSL-VBM、バージョン4.1、http://www.fmrrib.
ox.ac.uk/fsl）はデフォルトのパラメータを使用した（データ補遺資料IV）。年齢は共変量とした。Family-wise error補正後、p<0.05を統計学的有意と判定した。

白質変化の識別
微小な白質の変化を見分けるため、FSLのDiffusion Toolboxおよびデフォルトパラメータを使用したDTIから、4つの主要なDTI指標（FA、MD、AD、RD）を最初に抽出した。これからの指標を抽出する前に、滴電流の歪みおよび動きを補正した。次に、MMD患者と対照の主要なDTI指標の差をFSLの一部である白質神経路の空間統計により検討した。ソフトウェア開発者の推奨するデフォルトのパラメータおよびステップを使用した（データ補遺資料V）。年齢を共変量とし、関値のないクラスタ強化（threshold-free cluster enhancement）法で結果に多重比較の空間補正を行った。主要なDTI指標それぞれについて、統計学的有意であったポケルルの平均値と数（関値のないクラスタ強化法で補正、p<0.05）を計算した。

FLIRTおよびBEDPOSTX（データ補遺資料VI）で確率的トラクトグラフィーを実施した。短編、作動記憶、実行機能/注意力に介在する16の皮質領域と両側の視床をシード領域として選択した。ターゲット領域には脳全体を選択した。各々の確率の神経路について、ポケルル数と平均FA値を計算した。

微細構造変化と脳血管行動態評価および神経認知機能の相関
MMD患者で異常な灰白質密度を示すポケルルは、主要なDTI白質指標の相関分析を行った。灰白質でも白質であるかを示すパラメータおよび、脳血管行動態不全、神経心理学的検査データとの相関について

注：FSLはMRI/DTI画像解析ソフトウェアライブラリー。
注：ファミリーワイズ・エラー：多重検定で第一種エラーを起こす確率。
いて分析した。上記の目的のため，Pearson の相関係数 (年齢，WAIS-III，TMT A より B との相関）または 10,000 回を超える順列並べ替え検定（仮説検定の有無，脳血行動態不全，ウィスコンシンカードシートング検査，ストループ検査，持続処理課題，リーニングスパン検査。後者 4 つの課題にはカットオフ値を適用）を使用した。相関および比較はすべて p < 0.05 で統計的に有意と判定した。

結 果

患者の特徴

患者の特徴を表に要約する。患者と対照の年齢 (p = 0.47) および性別 (p = 0.35) に有意差はなかった。症候性患者（過去性脳虚血発作 n = 10）と無症候性患者 (n = 13) で，安静時脳血流量，脳血管反射性，一時的障害因子の保有率に大きな差はなかった。T2 強調画像および FLAIR 画像で，MMD 患者 10 例（43.5％）に白質高信号域が認められた。高信号域は症候性患者でも多くかった (7/10, p < 0.05)。MMD 患者の脳血管形成指数は平均 94 ± 13 であった。患者の神経心理学的評価の結果を表1に要約する。症候性患者と無症候性患者において，総合知能指数，WAIS 検査のスコア，その他の神経心理学的検査の項目に大きな差はなかった。

灰白質変化

FSL-VBM で両側後帯状皮質 (PCC) の密度に有意な低下が認められた（図1）。

白質の変化

白質神経路の空間的統計では，MMD 患者で広範囲にわたる有意な FA の低下と RD の上昇が認められた [それぞれ全構造の 55.2％および 42.5％，図2]。FA および RD に変化があったボクセルも，有意な MD の上昇を示した。MD の上昇を示したボクセルは平均 FA 構造の 20.9％を占めた。AD に関しては，多重比較の補正をしなかった場合，主に上腕動静脈および帯状動静脈で低下が認められた (未補正 p < 0.05)。補正した場合そのようなボクセルは認められなかった。

確率的トラックグラフィーでも，MMD 患者の白質神経路の一部で平均 FA の低下が認められた。MMD 患者の各神経路のボクセル数は対照群と大きく変わらなかった。

微細構造変化と脳血行動態不全および神経認知機能の相関

患者の帯状皮質の密度は，白質構造の平均 FA (r = 0.54, p < 0.0001) または RD (r = -0.41, p < 0.01) と有意な相関を示した（図 3）。MMD 患者の両側後帯状皮質の密度（http://fmri. wfubmc.edu/software/PickAtlas）および白質構造の平均 FA は，年齢と逆相関関係にあった（それぞれ r = -0.43, p < 0.01 および r = -0.57, p < 0.005）。データ補遺図1。症候性患者と無症候性患者の間で所見白質密度および主要 DTI 指標に差はなかった。脳血行動態不全の患者は，対照に比べて後帯状皮質密度が有意に低下したが，白質構造の主要 DTI 指標それぞれの平均値は 2 群で差がなかった。

後帯状皮質密度も白質構造の主要 DTI 指標の平均値も，神経心理学的検査データと有意な関連はなかった。しかし，次に白質神経路の平均 FA 値は神経心理学的検査データと有意に関連した（データ補遺図2，図 4）：左上側前頭回由来の神経線維と処理速度 (r = 0.45)：左中前頭回，左前頭回，右前頭回，左上側前頭回の神経線維と TMT A（それぞれ r = 0.43，0.43, 0.48）：左後帯状皮質由来の神経線維と TMT B および A（r = 0.43）。ストループ検査の成績が高かった患者の右上側前頭回，右中前頭回，左中側状皮質に由来する神経路の平均 FA 値は，対照群より有意に高値であった。同様に，両側中前頭回，右後帯状皮質および左中帯状皮質に由来する神経路の平均 FA 値も，対照よりリーニングスパン検査の成績が高い患者で有意に高値であった。

考察

成人 MMD 患者の罹患期間は長く，そのため脳の微細構造に対する慢性低灌流の微妙な影響を研究するには，成人 MMD は有効である。本研究は MMD 患者の両側後帯状皮質密度の低下と，広範で白質構造における FA の低下および RD の上昇を明らかにしたが，これらの変化は年齢と関連していた。さらに，両側後帯状皮質密度は脳血行動態不全および有意に関連し，背側前頭静脈，帯状動脈，下頭頂小葉領域の白質神経路の平均 FA 値は神経心理学的検査データと有意に関連した。

後帯状皮質は覚醒，注意力，内向的思考，環境変化の発見に関連する 15。後帯状皮質に限った局所的病変はほとんど報告されていないため，神経認知機能への影響はいまだ不明である。脳卒中では知覚的誤りよりも記憶障害が報告されているが，脳卒中および脳梗塞に伴う病変が認知機能障害の大きな原因と考えられる 16。後帯状皮質の結合性は加齢，外傷，アルツハイマー病，自閉症，統合失調症，うつ病，注意力欠乏多動障害で低下する 15,17,18。後帯状皮質はデフォルトモードのネットワークの一部を構成するため，作業中にその活動を停止で
表 患者の特徴

| 性別 | 年齢（歳） | 臨床症状 | WMHの場所 | W | 産 | 右 | 左 | 左 | 産 | 右 | 左 | 存在症
|------|----------|---------|-----------|---|---|---|---|---|---|---|---|---|---
| 女   | 58       | 無染性   | 右深部白質 | 3 | 4 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 36       | TIA     | 右側深部白質 | 3 | 3 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 49       | TIA     | 左側深部白質 | 3 | 3 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 33       | TIA     | なし | 3 | 4 | なし | なし | なし | なし | 高血圧
| 女   | 51       | 無染性   | なし | 3 | 4 | なし | なし | なし | なし | なし | なし | なし | なし
| 男   | 49       | 無染性   | なし | 3 | 3 | なし | なし | なし | なし | なし | なし | なし | なし
| 男   | 42       | 無染性   | なし | 1 | 4 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 53       | 無染性   | なし | 4 | 2 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 34       | 無染性   | なし | 3 | 3 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 40       | TIA     | 右前頭白質 | 3 | 2 | 中等度 | 中等度 | 高血圧
| 女   | 40       | TIA     | 右前頭白質 | 2 | 2 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 25       | TIA     | 両側深部白質 | 3 | 3 | 中等度 | 中等度 | 高脂血症
| 女   | 46       | TIA     | ン | 4 | 4 | なし | なし | なし | なし | なし | なし | なし | なし
| 女   | 47       | TIA     | 両側深部白質 | 4 | 4 | なし | なし | なし | なし | なし | なし | なし | なし
| 男   | 43       | 無染性   | なし | 3 | 3 | 中等度 | 中等度 | 糖尿病
| 女   | 21       | 無染性   | 右側頭部白質 | 3 | 1 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度
| 女   | 49       | TIA     | なし | 3 | 5 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度
| 女   | 39       | TIA     | なし | 3 | 2 | 中等度 | なし | なし | なし | なし | なし | なし | なし
| 女   | 36       | TIA     | なし | 3 | 3 | 中等度 | なし | なし | なし | なし | なし | なし | なし
| 男   | 44       | TIA     | なし | 3 | 3 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度
| 男   | 39       | TIA     | なし | 3 | 2 | 中等度 | 中等度 | 中等度 | 中等度 | 中等度 | 中等度 | 中等度 | 中等度
| 男   | 36       | TIA     | 両側深部白質 | 3 | 3 | 中等度 | 中等度 | 高血圧
| 男   | 23       | TIA     | なし | 3 | 3 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度 | 重度

無染性：小児期に失神や一過性脳虚血发作（TIA）などの神経学的異常があったが、青年期以後は無染性のまま推移した患者。脳虚血行動態不全は脳血管性（CVT）が検査から5%未満の場合は重篤、5%以上10%未満の場合は中等度、10%以上の場合は正常と判断した。10%（データ補修資料1）。WMH：白質高信号領域。
過去の報告と一致して、実行機能／注意力および作動記憶の障害は MMD 患者の約 30%で認められた。本研究では背外側前頭野皮質、下頭頂小葉、帯状皮質の役割を調査したが、これらの領域は常に実行機能／作動記憶／注意力と関与する報告されている。背外側前頭野（中頭回および上頭回）の平均 FA 値と神経心理学的検査データの有意な相関は、ここが作動記憶、実行機能、注意力を担当する領域であることを示唆する。この観察結果は、認知機能と前頭頭頂皮質領域を統合する白質神経路の健全性の関連を明らかにした過去の研究と一致する。前頭頭頂領域の制御ネットワークは背外側前頭野皮質、前帯状皮質、前頭葉運動野、前頭皮質、後帯状皮質から構成される。本研究において、左後帯状皮質に由来する神経線維の平均 FA 値が TMT B および A と関連していたことは注目すべき結果である。TMT B および A は視覚記憶および作動記憶には関係なく、比較的純粋な実行御制能力の指標として役立つ。今回観察結果は後帯状皮質からの白質結合が実行機能に関与していることを示す。

本研究案の一部は、日本学術振興会の研究助成を受けて行われたものです。
的MRIの研究で側頭葉の作動記憶と関連することが明らかになっている。第三に、白質の健全性は年齢および性別に関連する。対象者の性別が完全に一致していないため、患者群と照合群の比較結果に影響したかもしれない。認知機能障害の有無率および他の神経画像マーカージとの関係を特定するには、大規模集団での、できれば多施設共同研究による調査研究がさらに必要である。

**結論**

MMDにおいて、脳主幹動脈の狭薬閉塞性変化は主に脳白質の微細構造に損傷を与え、実行機能、作動記憶、
研究内容の変化を早期発見すれば早期の治療介入により認知機能の転帰を改善させ得る可能性である。

研究費着
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情報開示
なし。

References

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