JNS PEDIATRICS

CLINICAL ARTICLE

J Neurosurg Pediatr 35:581–590, 2025

Lower prefrontal blood flow associated with intraindividual weakness in successive processing: a neurocognitive study of pediatric moyamoya disease

Yusuke Kusano, MS,[1,2] Takeshi Funaki, MD, PhD,[3] Keita Ueda, MD, PhD,[4,5] Tsukasa Ueno, MD, PhD,[5,6] Kanade Tanaka, BS,[2] Noyuri Nishida, BS,[2] Ami Tabata, PhD,[1] Yasutaka Fushimi, MD, PhD,[7] Katsuhiko Mitsumoto, MS,[8] Takayuki Kikuchi, MD, PhD,[3] Ryosuke Ikeguchi, MD, PhD,[2] Nan Liang, PhD,[1] Hiroyuki Inadomi, PhD,[1] Susumu Miyamoto, MD, PhD,[9,10] and Yoshiki Arakawa, MD, PhD[3]

[1]Advanced Occupational Therapy, Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto; [2]Rehabilitation Unit, Kyoto University Hospital, Kyoto; [3]Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto; [4]Faculty of Health Sciences, Department of Medical Welfare, Kyoto Koka Women's University, Kyoto; [5]Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto; [6]Integrated Clinical Education Center, Kyoto University Hospital, Kyoto; [7]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto; [8]Department of Clinical Radiology Service, Kyoto University Hospital, Kyoto; [9]Stroke Support Center, Kyoto University Hospital, Kyoto; and [10]Moyamoya Disease Support Center, Kyoto University Hospital, Kyoto, Japan

OBJECTIVE Selective intraindividual weakness in successive processing, which is a unique verbal working memory scale included in the Das-Naglieri Cognitive Assessment System (CAS), is considered one of the intrinsic neurocognitive characteristics in pediatric moyamoya disease (MMD). The aim of the study was to elucidate the association between cerebral blood flow (CBF) and weakness in successive processing, and to identify regions related to the weakness.

METHODS The present cross-sectional study included children who had been diagnosed with MMD and were assessed using neuropsychological tests before surgery between June 2016 and December 2023. According to the CAS manual, intraindividual difference was calculated by subtracting the mean of the 4 standard scores from each standard score. Each patient was classified as either manifesting "intraindividual weakness in successive processing" (intraindividual difference of successive processing < 0) or not (intraindividual difference of successive processing ≥ 0), and CBF acquired with resting-state SPECT was compared between groups. Three-dimensional stereotactic surface projection (3D-SSP) was also used for topographical comparison of CBF.

RESULTS Of 51 children (mean age ± SD at admission 8.0 ± 2.6 years) who underwent preoperative neuropsychological tests, 43 were included in the CBF analysis. Both standard scores and intraindividual difference of the CAS significantly varied across 4 domains ($p = 0.006$ and $p < 0.001$, respectively), and those of successive processing were the lowest. Of the children analyzed, 35 (68.7%) were classified as having intraindividual weakness in successive processing. Multiple logistic regression analysis revealed the severest ischemic grade was significantly associated with intraindividual weakness in successive processing (OR 5.49 [95% CI 1.12–27.06]). Three-dimensional SSP analysis demonstrated a significant CBF decrease in the left dorsolateral and medial prefrontal cortexes in the children showing intraindividual weakness in successive processing compared with those who did not.

CONCLUSIONS Intraindividual weakness in successive processing typical of MMD might be associated with reduced CBF in the dorsolateral and medial prefrontal cortex, predominantly in the left hemisphere. Further studies in this area could contribute to the improvement of long-term social outcomes for patients with MMD.

https://thejns.org/doi/abs/10.3171/2024.11.PEDS24495

KEYWORDS moyamoya disease; pediatrics; successive processing; prefrontal cortex; SPECT; vascular disorders

ABBREVIATIONS ACZ = acetazolamide; CAS = Das-Naglieri Cognitive Assessment System; CBF = cerebral blood flow; DLPFC = dorsolateral prefrontal cortex; ER = extent ratio; MMD = moyamoya disease; mPFC = medial prefrontal cortex; rCBF = regional CBF; ROI = region of interest; SSP = stereotactic surface projection; WISC = Wechsler Intelligence Scale for Children.

SUBMITTED September 27, 2024. **ACCEPTED** November 22, 2024.
INCLUDE WHEN CITING Published online March 28, 2025; DOI: 10.3171/2024.11.PEDS24495.

Moyamoya disease (MMD) is a rare steno-occlusive cerebrovascular disease that commonly occurs in childhood and young adulthood. Ischemic symptoms, such as transient ischemic attack and stroke, are common in pediatric MMD. While the outcomes of pediatric MMD are improving with diagnosis and treatment developments, neurocognitive impairment remains a serious issue and can affect quality of life. Recent studies have revealed a substantial percentage of pediatric patients with MMD (13%–73%) experience neurocognitive impairments.[1,2] Even after bypass surgery, 10%–20% of these patients have difficulty in social adaptation after adolescence.[3–5]

Although neuropsychological tests applicable to children are very limited, pioneering researchers have characterized the neurocognitive profile in pediatric MMD by focusing on the weakness in executive function, including working memory.[1,2,6] Researchers have commonly addressed this issue using the Wechsler Intelligence Scale for Children (WISC), which comprises four domains: verbal comprehension, perceptual reasoning, processing speed, and working memory. We have also addressed this issue in our previous study using a unique neuropsychological test standardized for children, the Das-Naglieri Cognitive Assessment System (CAS), which similarly comprises four domains: planning, attention, simultaneous, and successive processing.[7] In that study, we revealed that "successive processing," a form of verbal working memory function, was selectively impaired in individuals with pediatric MMD.[7] Such a selective neurocognitive weakness might be attributable to reduced cerebral blood flow (CBF) in a specific cortical area. The prefrontal cortex is one of the candidate areas because it is thought to contribute to working memory function[8–10] and is commonly involved in MMD. However, the relationship between neurocognitive function and CBF has not been sufficiently elucidated. Although the correlation between some WISC domains and regional CBF (rCBF) in the left dorsolateral prefrontal cortex (DLPFC) has been reported,[11] that between CAS and rCBF has not yet been identified.

We hypothesized that selective intraindividual weakness in successive processing in the CAS is associated with reduced rCBF in a specific cortical area, especially in the prefrontal cortex. The objective of this study was to identify the hypoperfused area associated with weakness in successive processing. Testing our hypothesis might contribute to understanding the pathophysiology of neurocognitive impairment and lead to appropriate treatment in pediatric MMD.

Methods

This retrospective cross-sectional study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee and was performed in compliance with the Declaration of Helsinki. All patients and families gave either opt-out or written informed assent/consent in accordance with the ethical guidelines for medical and health research involving human subjects in Japan. The STROBE statement was followed.[12]

Patients

This study included children aged 5–16 years who were newly diagnosed with MMD in accordance with the Japanese diagnostic guideline[13,14] and underwent neurocognitive assessment before surgery at Kyoto University Hospital between June 2016 and December 2023. Patients younger than 5 years were excluded because the standardized neuropsychological tests used in this study are not applicable. Patients routinely underwent neurocognitive assessment; however, those who did not undergo sufficient neuropsychological tests for various reasons were excluded. Patients also routinely underwent MRI, angiography, and SPECT at the initial admission.

We also collected clinical data that included sex, initial manifestations of disease, ages at symptom onset and first admission, time interval between onset and first admission, Suzuki angiographic stage,[15] hemodynamic state (or SPECT stage, described in *Analyses of CBF*),[16] use of a sedative agent during SPECT imaging, laterality of disease involvement, presence or absence of posterior cerebral artery involvement, and presence or absence of radiological findings of infarction on MRI.

Neurocognitive Assessment

Both the CAS[17] and WISC, 4th edition (WISC-IV)[18] were performed as preoperative neurocognitive assessments by occupational therapists who were proficient in neuropsychological testing. The standard scores of both the CAS and the WISC-IV are defined as a mean of 100 with a standard deviation of 15. The details of the CAS have been described elsewhere.[7] In brief, the CAS consists of four domains: planning, attention, simultaneous, and successive processing.[17] Successive processing represents a type of verbal working memory (phonological loop proposed by Baddeley[19]), and comprises four kinds of tasks: word series recall, sentence repetition, speech rate, and sentence question (Table 1).[17,20] The CAS defines the calculation of "intraindividual differences"—statistical

TABLE 1. Tasks included in successive processing scale in the Das-Naglieri Cognitive Assessment System

Task	Explanation	Example
Word recall	Recall of a series of words in the exact order	"cat-flower-book"
Sentence repetition	Repetition of sentences comprising color words w/ minimal meaning	"The blue is graying"*
Speech rate (5–7 yrs of age)	Time required to repeat a 3-word series 10 times as fast as possible	"red-yellow-blue"
Sentence question (8–17 yrs of age)	Answering questions comprising color words w/ minimal meaning	"The blue is graying. Who is graying?"; answer: "The blue"*

* Quoted from Das JP, Naglieri JA, Kirby JR. *Assessment of Cognitive Processes: The PASS Theory of Intelligence*. Allyn & Bacon; 1994:52–111.

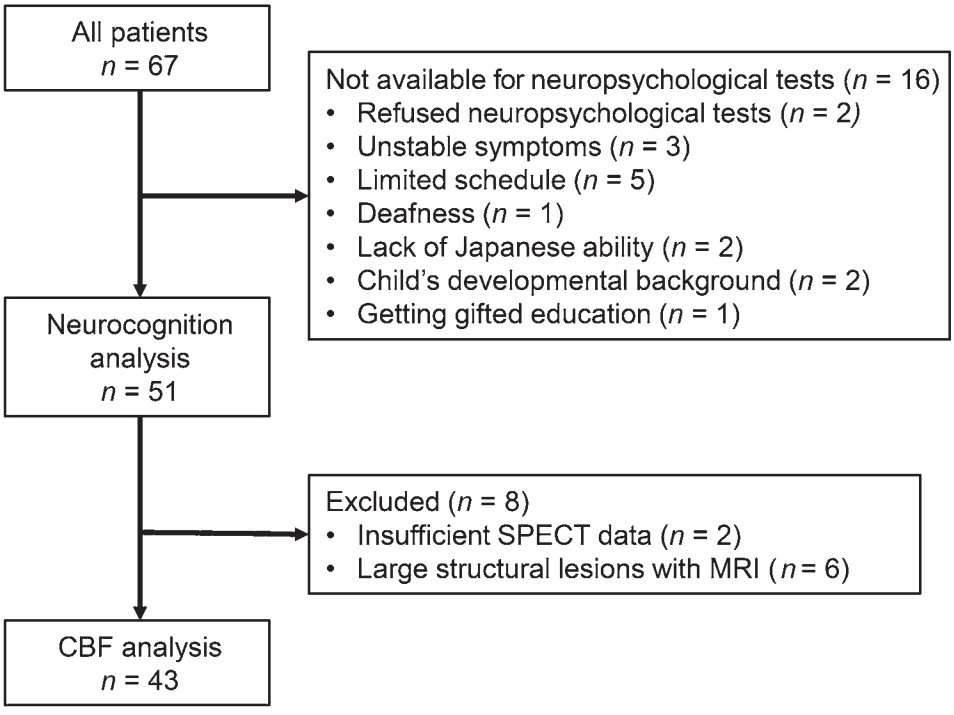

FIG. 1. Flowchart for patient inclusion.

variances, or strengths and weaknesses, across measures within an individual—and might be more sensitive than WISC-IV for detecting the neurocognitive characteristics of MMD.[7] Intraindividual differences are calculated by subtracting the mean of the four standard scores from each standard score,[17,21] and an intraindividual difference less than 0 indicated "intraindividual weakness" in the present study. Each patient was classified as either having intraindividual weakness in successive processing, or not.

Analyses of CBF

CBF was measured by SPECT using a dual-head gamma camera (NM/CT 860, GE HealthCare) with *N*-isopropyl-[^{123}I]-*p*-iodoamphetamine. The hemodynamic state for each hemisphere was classified into a SPECT stage, as follows: stage 0, normal baseline (resting state) rCBF with normal acetazolamide (ACZ)–challenged rCBF; stage 1, normal baseline rCBF with reduced ACZ-challenged rCBF; and stage 2, reduced baseline rCBF with reduced ACZ-challenged rCBF.[16] ACZ-challenged SPECT was not indicated for patients with severely reduced baseline CBF in either hemisphere because of the risk of ischemic complication. Consequently, the hemodynamic status was recorded as stage 2 or non–stage 2 because strict distinction between stage 0 and stage 1 was impossible in some hemispheres.

We also analyzed SPECT using the 3D stereotactic surface projection (3D-SSP) application of NEUROSTAT (University of Utah) software[22,23] to identify the cortical area associated with weakness in successive processing. According to a previous study (COSMO-Japan) by Kikuchi et al., patients with large intracranial structural lesions extending to more than 2 cortical arteries in neuroradiological studies were excluded in the 3D-SSP analysis.[24] Resting-state CBF was compared between those with and without intraindividual weakness in successive processing of CAS using the software; 3D-SSP facilitates comparison of CBF on a pixel-by-pixel basis on the normalized atlas of the brain (automated Talairach atlas) through minimizing anatomical variations across patients. The results were shown as z-score maps using the stereotactic extraction estimation method, which measures the z-score association between the participant's coordinates and the coordinates in the prepared reference from the automated Talairach atlas.[25] Each z-score was normalized by the global brain mean obtained from the corresponding patient because the normal blood flow of the cerebellum, which is often used as a reference, varies according to age and tends to be relatively low at a younger age.[26] Two sample t-statistic values were calculated for each pixel, and then converted to corresponding z values. Resultant images were displayed in 3 dimensions.[25] A z-score exceeding 1.96 was adopted as the threshold for the calculation of the extent ratio (ER), as previously proposed.[24,27] ER is the ratio of the total coordinates with significantly reduced z-value to the total of coordinates in respective segments. An ER of 10% or greater was defined as a region showing significant cerebral hypoperfusion, as previously reported.[27] All regions of interest (ROIs) were automatically set according to the segmentation (level 3, gyrus level) defined in the Talairach atlas.[28] rCBF in each ROI was calculated as the count ratio to the global brain mean (CBF ratio). The reason the global brain was defined as the reference is described above.

TABLE 2. Baseline characteristics

Characteristic	Total	Successive Processing		p Value
		Weakness (IID <0)	No Weakness (IID ≥0)	
No. of pts	51	35	16	NA
Mean age at onset (SD), yrs	6.4 (2.3)	6.3 (2.5)	6.5 (2.0)	0.728
Mean age at admission (SD), yrs	8.0 (2.6)	7.8 (0.4)	8.4 (0.6)	0.440
Mean interval btwn onset & admission (SD), mos	20.5 (29.6)	19.3 (5.0)	23.3 (7.5)	0.657
Female sex, n (%)	32 (62.7)	24 (47.1)	8 (15.7)	0.203
Initial manifestation, n (%)				
TIA	42 (82.4)	29 (82.9)	13 (81.3)	0.889*
Other	9 (17.6)	6 (17.1)	3 (18.8)	
Ischemic stroke	1 (2.0)	1 (2.9)	0 (0.0)	
Hemorrhagic stroke	3 (5.9)	2 (5.7)	1 (6.3)	
Involuntary movement	1 (2.0)	0 (0.0)	1 (6.3)	
Headache	4 (7.8)	3 (8.6)	1 (6.3)	
Median Suzuki stage (IQR)				
Higher stage	3 (3–4)	3 (3–4)	3 (2–3)	0.500
Rt hemisphere	3 (2–3)	3 (2–3)	3 (2–3)	
Lt hemisphere	2 (1–3)	2 (1–4)	2 (1–3)	
SPECT stage 2, n (%)				
Either hemisphere	23 (45.1)	19 (54.3)	4 (25.0)	0.051
Rt hemisphere	18 (35.3)	14 (40.0)	4 (25.0)	0.298
Lt hemisphere	16 (31.4)	14 (40.0)	2 (12.5)	0.0495
Sedation used w/ SPECT, n (%)	21 (41.2)	15 (42.9)	6 (37.5)	0.718
Bilat involvement, n (%)	36 (70.6)	25 (71.4)	11 (68.8)	0.846
Rt unilat	11 (21.6)	6 (17.1)	5 (31.3)	
Lt unilat	4 (7.8)	4 (11.4)	0 (0.0)	
Presence of PCA involvement, n (%)	8 (15.7)	6 (17.1)	2 (12.5)	0.672
Radiological finding of infarction, n (%)	22 (43.1)	15 (42.9)	7 (43.8)	0.952

IID = intraindividual difference; NA = not applicable; PCA = posterior cerebral artery; pt = patient; TIA = transient ischemic attack.
* TIA versus other initial manifestations, 2 × 2 chi-square test.

Statistical Analysis

Comparisons of baseline variables were conducted using the t-test, Wilcoxon rank-sum test, Fisher's exact test, or Pearson's chi-square test, as appropriate. Normality of the data was evaluated using the Shapiro-Wilk test. According to a previous study,[7] one-factor repeated-measures ANOVA was used to compare the standard scores of the CAS with that of the WISC-IV for each individual, and one-way ANOVA was used to compare intraindividual differences of the 4 measures. Post hoc analysis was performed using Tukey's honestly significant difference test. A multiple logistic regression model was used to test whether the SPECT stage (2 vs non-2) was associated with intraindividual weakness in successive processing of CAS (yes/no). According to previous studies,[29–32] age at onset and the radiological finding of infarction were predetermined as potential confounders, and 3 factors (SPECT stage, age at onset, and radiological finding of infarction) were incorporated into the model. Two-sided $p < 0.05$ and 95% confidence intervals not including 1 were considered significant. All statistical analyses were performed using JMP Pro 17.0 (JMP Statistical Discovery).

Results

Patients

A total of 67 patients aged 5–16 years were newly diagnosed with MMD during the study period. Of these, 16 were excluded due to the children and family declining neuropsychological testing (n = 2), unstable symptoms (n = 3), a limited examination schedule (n = 5), deafness (n = 1), lack of Japanese language ability (n = 2), judgment by the psychiatrist that neuropsychological test results were biased because of the child's developmental background (n = 2), and receiving a gifted education (n = 1) (Fig. 1). The remaining 51 patients (mean age ± SD at admission 8.0 ± 2.6 years) were included in the neurocognition analysis. Table 2 summarizes patient demographics.

In the CBF analysis, 8 patients were excluded for insufficient SPECT data (n = 2) and large intracranial structural lesions or bilateral cerebral infarction (n = 6). Thus, the remaining 43 patients were included in the CBF analysis.

Neurocognitive Assessment

As shown in Fig. 2, successive processing in the CAS

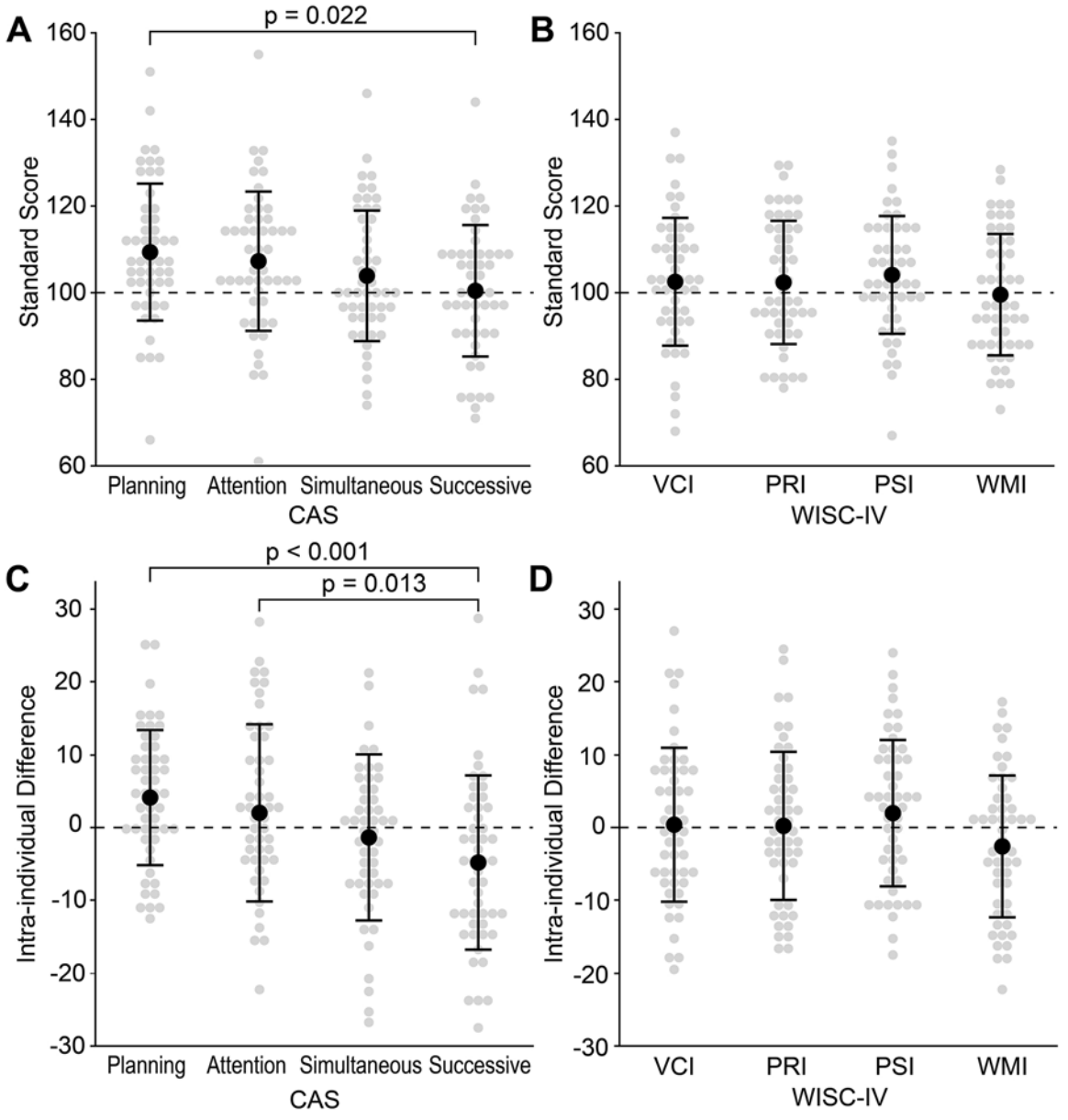

FIG. 2. Graphs showing the results of neurocognitive assessment. **A:** Standard score of the CAS (p = 0.006, one-factor repeated-measures ANOVA). **B:** Standard score of the WISC-IV (p = 0.262, one-factor repeated-measures ANOVA). **C:** Intraindividual difference of the CAS (p < 0.001, one-way ANOVA). **D:** Intraindividual difference of the WISC-IV (p = 0.150, one-way ANOVA). *Black dots* indicate the mean value, and *error bars* indicate the standard deviation. PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; WMI = working memory index.

was the lowest among the 4 measures regarding both the mean standard scores (planning, 109.4 ± 15.8; attention, 107.3 ± 16.1; simultaneous processing, 103.9 ± 15.1; successive processing, 100.4 ± 15.2) and the mean intraindividual differences (planning, 4.1 ± 9.3; attention, 2.0 ± 12.2; simultaneous processing, –1.3 ± 11.4; successive processing, –4.8 ± 12.0). The working memory index in WISC-IV was also the lowest among the 4 measures regarding both the mean standard scores (99.5 ± 14.0) and intraindividual differences (–2.6 ± 9.7). One-factor repeated-measures ANOVA showed the standard scores of the CAS significantly varied across the 4 measures [$F(2.6,130.8) = 4.619$, $p = 0.006$], but those of the WISC-IV did not [$F(3,150) = 1.344$, $p = 0.262$]. One-way ANOVA also revealed that intraindividual differences of the CAS significantly varied across the 4 measures [$F(3,200) = 6.158$, $p < 0.001$], but those of the WISC-IV did not [$F(3,200) = 1.792$, $p = 0.150$]. Tukey's honestly significant difference test revealed the mean standard score of successive processing was significantly lower than that of planning ($p = 0.022$), and the mean intraindividual differences of successive processing were significantly lower than those of planning ($p < 0.001$) and attention ($p = 0.013$).

According to the definition above, 35 of 51 patients

TABLE 3. Multiple-adjusted ORs for intraindividual weakness of successive processing (n = 51)

	Crude		Multivariate Adjustment	
	OR	95% CI	OR	95% CI
SPECT stage 2	3.56	0.96–13.24	5.49	1.12–27.06
Median age at onset*	0.95	0.74–1.23	1.07	0.80–1.43
Infarction	0.96	0.29–3.18	0.52	0.12–2.17

* Every 1-year increase.

(68.6%) were classified as manifesting intraindividual weakness in successive processing.

Association Between Neurocognitive Weakness and CBF

As shown in Table 2, the presence of SPECT stage 2 in the left hemisphere was the only univariate factor associated with intraindividual weakness in successive processing ($p = 0.0495$). Multiple logistic regression analyses, in which 3 predetermined factors (SPECT stage, age at onset, and radiological finding of infarction) were incorporated, revealed that the presence of SPECT stage 2 in either hemisphere was significantly associated with intraindividual weakness in successive processing (OR 5.49 [95% CI 1.12–27.06]) (Table 3).

Figure 3 shows z-score maps of 3D-SSP acquired in 30 patients with intraindividual weakness in successive processing as compared with 13 patients without the weakness. CBF significantly decreased predominantly in the left DLPFC and medial prefrontal cortex (mPFC) in those with intraindividual weakness in successive processing. Stereotactic extraction estimation analyses in the gyrus level also revealed significant CBF decreases in the left superior frontal gyrus (ER 15.6%), left middle frontal gyrus (ER 12.6%), left inferior frontal gyrus (ER 16.9%), left medial frontal gyrus (ER 29.4%), left cingulate gyrus (ER 12.4%), and right medial frontal gyrus (ER 10.9%). In each ROI, the CBF ratio was compared between those with and without intraindividual weakness in successive processing (Fig. 4). Patients with intraindividual weakness in successive processing exhibited a significant decrease of the CBF ratio in the left superior, middle, and inferior frontal gyri ($p = 0.027$); bilateral superior, middle, and inferior frontal gyri ($p = 0.049$); and left medial frontal gyrus ($p = 0.042$). As shown in Fig. 4, the same tendency was observed in the other ROIs: right superior, middle, and inferior frontal gyri and the right and bilateral medial frontal gyri. However, the difference in the CBF ratio was not significant.

Representative Cases

Case 1

A 6-year-old child presented with transient motor weakness in the bilateral extremities while crying (Fig. 5A and B). The patient had difficulty in school because of restlessness and carelessness. Although intelligence was within

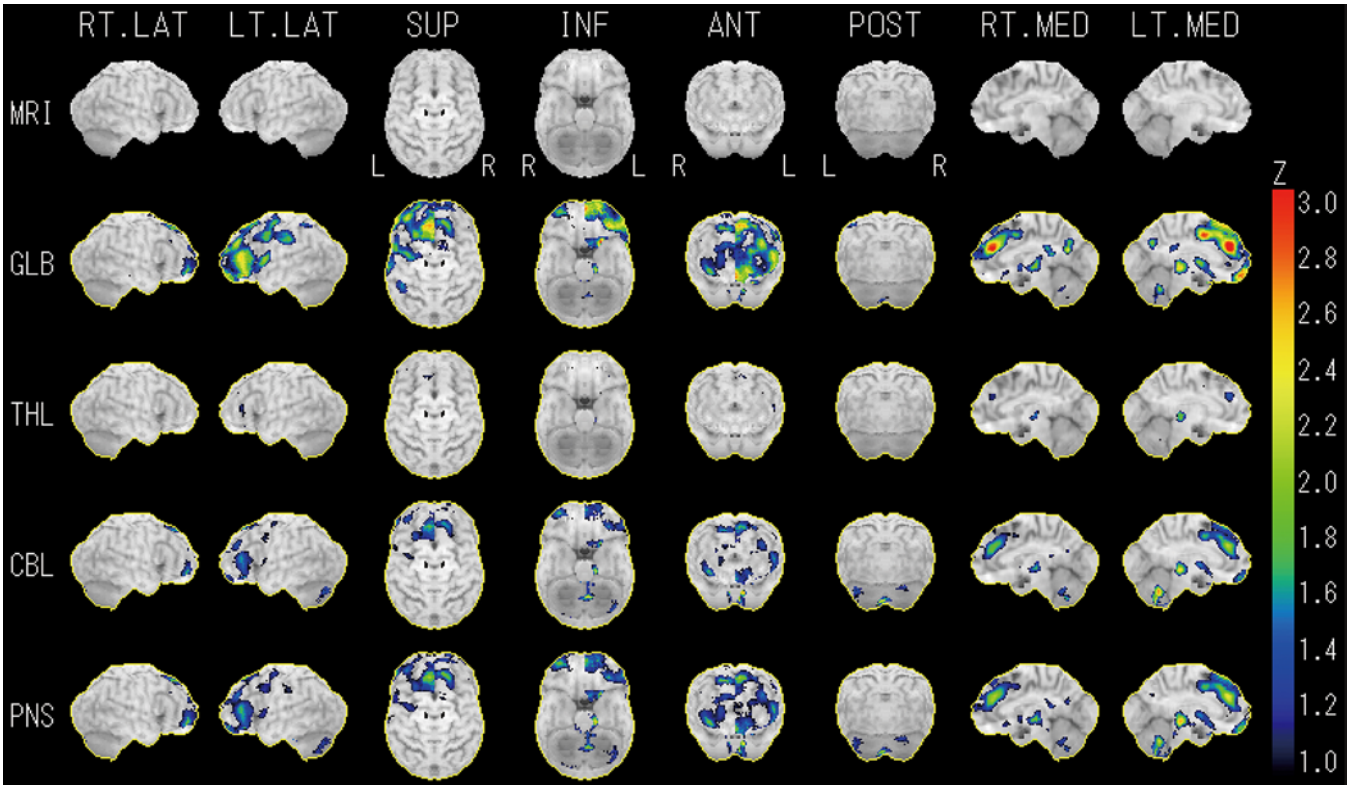

FIG. 3. Z-score maps of the group with intraindividual weakness in successive processing compared with the group without. The global brain (GLB) was selected as the reference in this study. ANT = anterior; CBL = cerebellum; INF = inferior; MED = medial; POST = posterior; PNS = pons; SUP = superior; THL = thalamus. Figure is available in color online only.

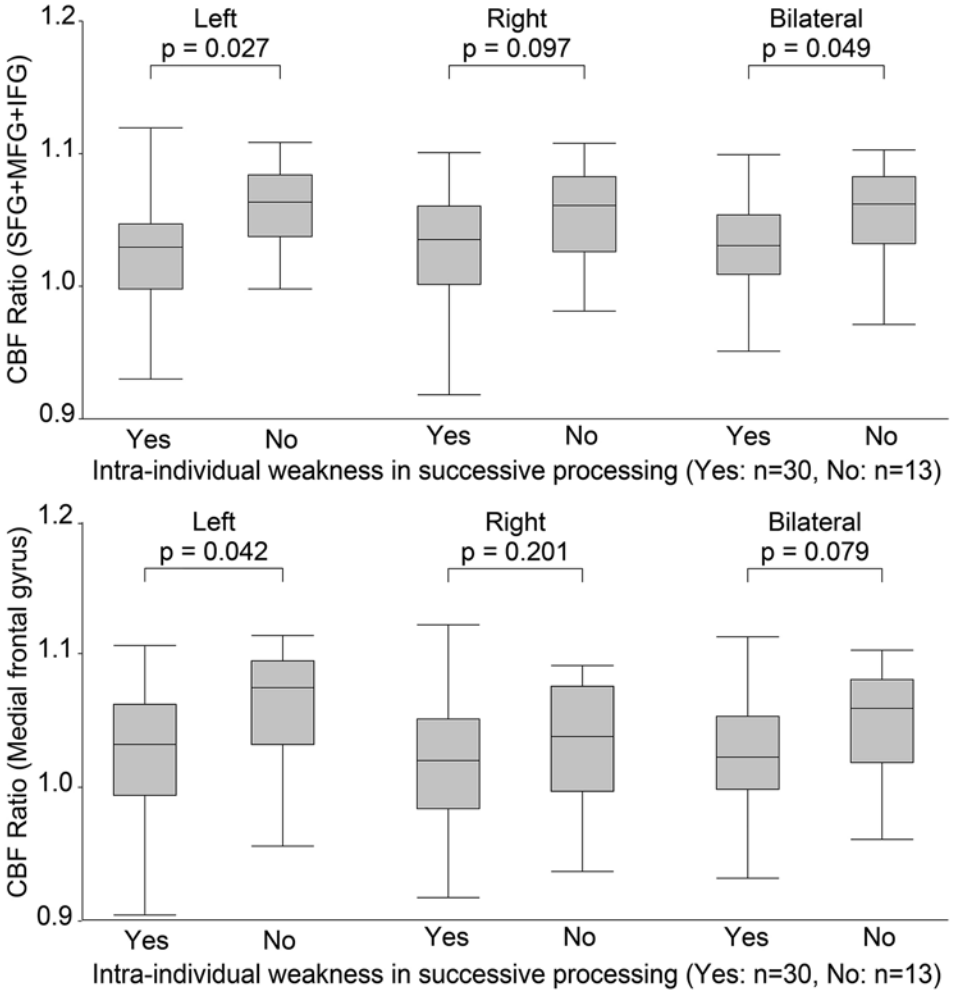

FIG. 4. Box plots showing a comparison of rCBF between the groups with and without intraindividual weakness in successive processing. IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus.

normal range (full-scale IQ in WISC-IV of 95), the CAS revealed selective intraindividual weakness of successive processing. SPECT showed a notable decrease in CBF in the bilateral frontal lobe, including the DLPFC and mPFC.

Case 2

A 5-year-old child presented with transient motor weakness in the left lower limb while crying. The patient had normal intelligence (full-scale IQ in WISC-IV of 100) and no difficulty in preschool (Fig. 5C and D). The CAS revealed no apparent intraindividual weakness among the domains. SPECT showed minimal decrease in resting-state CBF in the right hemisphere, while ACZ-challenged CBF was severely reduced (ACZ-challenged SPECT is not shown in the figure).

Discussion

There are three main findings of our study. First, significant intraindividual weakness of successive processing was observed in the CAS, while no significant variance across domains was observed in the WISC-IV. Second, the presence of severe ischemia, which corresponded to SPECT stage 2, was significantly associated with intraindividual weakness in successive processing. Third, the 3D-SSP analysis demonstrated a significant CBF decrease in the left DLPFC and mPFC in patients with intraindividual weakness in successive processing as compared with patients without. The present study is perhaps the first to reveal the association between successive processing and CBF in pediatric MMD.

Our results are highly consistent with recent studies showing that working memory function is relatively weaker among children with MMD.[1,6,7,11] As shown in our previous study, the task of successive processing in the CAS might be more sensitive than that of working memory in the WISC-IV for detecting neurocognitive weakness in pediatric MMD.[7] This might be attributable to the nature of successive processing tasks, which require not only basic working memory ability but also more complex processing. Our results suggest that standard scores of both the CAS and WISC-IV are the average. However, difficulties in daily living attributable to intraindividual weakness are very common in practice, even if the standard scores

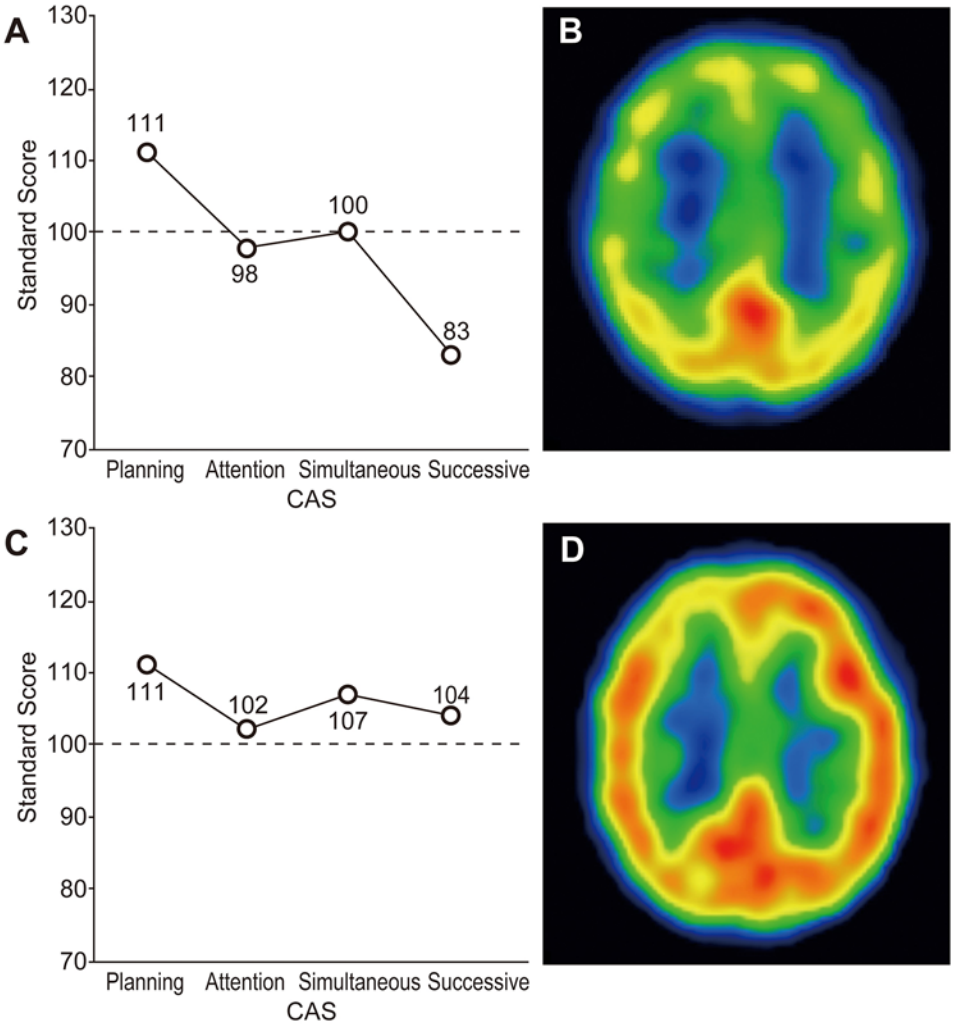

FIG. 5. Representative cases. **A and B:** Case 1. Standard CAS score (A) and resting-state SPECT image (B). The patient had intraindividual weakness in successive processing. **C and D:** Case 2. Standard CAS score (C) and resting-state SPECT image (D). The patient had no significant weakness among the domains. Figure is available in color online only.

are within normal range. Focusing on the standard scores alone can lead to underestimation of such difficulties.

Our results also correspond to previous studies addressing the relationship between neurocognitive function and the prefrontal cortex. Kazumata et al. reported that certain WISC domains were associated with reduced CBF in the left DLPFC.[11] Karashima et al. revealed the working memory index in WISC was the most related to CBF in the anterior area of the right middle cerebral artery territory.[33] Kikuchi et al. found neuronal loss in the bilateral medial frontal lobe in adult patients with MMD who experienced neurocognitive dysfunction.[24] Other studies on diffusion tensor imaging and functional MRI have also suggested the abnormality of structural and functional connectivity in the frontal lobe.[34,35] Our study adds reliable information to these pioneering studies because our methodology avoided creating arbitrary ROIs and minimized the statistical problem of multiple comparisons.

Our results might reasonably be explained by the classic theory that the prefrontal cortex plays an important role in working memory function. Several investigations in neuroimaging have explored the association between working memory function and the bilateral prefrontal cortex, especially the DLPFC.[8,36] While the right DLPFC contributes to visuospatial working memory, the left DLPFC contributes to verbal working memory,[9,37,38] which substantially corresponds to successive processing. On the other hand, the mPFC is considered to contribute to the attention system, such as focal attention and set shifting, both of which are related to executive function.[39,40] Therefore, the mPFC might be involved in more complex tasks included in successive processing, such as sentence questions. In fact, Nakajima et al. reported the medial frontal area was related to the N-back task, which is a more complex working memory task applicable to adults.[41]

Although some researchers have suggested the benefit of bypass surgery for cognitive function,[32,42] it remains controversial whether bypass surgery can improve cognitive function in pediatric MMD. Our findings suggest improvement of CBF in the prefrontal cortex facilitates

the improvement of weakness in working memory function in pediatric MMD. This speculation might partly be supported by a seminal study by Kuroda et al. in which bypass surgery with craniotomy widely covering the frontal lobe was effective at improving intellectual outcome.[43] Further studies focusing on postoperative changes in both neuropsychological test results and CBF might lead to the improvement of social outcomes in pediatric MMD by establishing optimal surgical procedures.

Viewed from a clinical perspective, our study could help determine the optimal timing of surgery and predict the social outcome in pediatric MMD. Ahtam et al. have analyzed diffusion tensor imaging and shown that children with asymptomatic MMD exhibited white matter injury at the watershed regions.[44] Some researchers have also analyzed resting-state functional MRI and found that patients with MMD experiencing cognitive and executive dysfunction exhibited disrupted functional connectivity networks.[45–47] Further research focusing on structural and functional imaging could contribute to a better understanding of the mechanism of neurocognitive impairment in MMD.

The present study had several limitations. First, selection biases were potentially contaminated because this study inevitably excluded younger children for whom neuropsychological testing was not applicable, as well as those requiring emergency surgery due to unstable symptoms. Second, the Talairach atlas included in NEUROSTAT/3D-SSP is based on adult brain anatomy and might not be applicable to children, although the software has commonly been applied to studies targeting both adults and children. Third, CBF might be affected by sedative agents, which were administered in a substantial percentage of SPECT examinations; however, their effects on our results are probably minimal because the proportion used was not substantially different between the comparison and control groups (Table 2).

Conclusions

The results of the present study support our hypothesis that selective intraindividual weakness in successive processing typical of MMD is associated with reduced CBF in the DLPFC and mPFC, predominantly in the left hemisphere. Further studies focusing on CBF in these areas might contribute to the improvement of long-term social outcomes in patients with pediatric MMD.

Acknowledgments

This study was supported by a grant from JSPS KAKENHI (no. JP22K21207).

References

1. Kronenburg A, van den Berg E, van Schooneveld MM, et al. Cognitive functions in children and adults with moyamoya vasculopathy: a systematic review and meta-analysis. *J Stroke*. 2018;20(3):332-341.
2. Kronenburg A, Deckers PT, van den Berg E, et al. The profile of cognitive impairment and hemodynamic compromise in moyamoya: a single-center prospective cohort study. *J Neurosurg*. 2022;138(1):173-184.
3. Funaki T, Takahashi JC, Miyamoto S. Late cerebrovascular events and social outcome after adolescence: long-term outcome of pediatric moyamoya disease. *Neurol Med Chir (Tokyo)*. 2018;58(6):240-246.
4. Miyamoto S, Akiyama Y, Nagata I, et al. Long-term outcome after STA-MCA anastomosis for moyamoya disease. *Neurosurg Focus*. 1998;5(5):E5.
5. Phi JH, Wang KC, Cho BK, et al. Long-term social outcome in children with moyamoya disease who have reached adulthood. *J Neurosurg Pediatr*. 2011;8(3):303-309.
6. Hsu YH, Kuo MF, Hua MS, Yang CC. Selective neuropsychological impairments and related clinical factors in children with moyamoya disease of the transient ischemic attack type. *Childs Nerv Syst*. 2014;30(3):441-447.
7. Kusano Y, Funaki T, Ueda K, et al. Characterizing the neurocognitive profiles of children with moyamoya disease using the Das Naglieri Cognitive Assessment System. *Sci Rep*. 2022;12(1):3638.
8. Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc Lond B Biol Sci*. 1996;351(1346):1445-1453.
9. Barbey AK, Koenigs M, Grafman J. Dorsolateral prefrontal contributions to human working memory. *Cortex*. 2013;49(5):1195-1205.
10. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. *Neuron*. 2012;76(6):1057-1070.
11. Kazumata K, Tokairin K, Sugiyama T, et al. Association of cognitive function with cerebral blood flow in children with moyamoya disease. *J Neurosurg Pediatr*. 2019;25(1):62-68.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349.
13. Kuroda S, Fujimura M, Takahashi J, et al. Diagnostic Criteria for Moyamoya Disease—2021 revised version. *Neurol Med Chir (Tokyo)*. 2022;62(7):307-312.
14. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)*. 2012;52(5):245-266.
15. Suzuki J, Kodama N. Moyamoya disease—a review. *Stroke*. 1983;14(1):104-109.
16. Takahashi JC, Funaki T, Houkin K, et al. Impact of cortical hemodynamic failure on both subsequent hemorrhagic stroke and effect of bypass surgery in hemorrhagic moyamoya disease: a supplementary analysis of the Japan Adult Moyamoya Trial. *J Neurosurg*. 2020;134(3):940-945.
17. Maekawa H, Nakayama K, Okazaki S. *Japanese version of the Das–Naglieri Cognitive Assessment System: Interpretive Handbook*. Nihon Bunka Kagakusha; 2007:33-79.
18. Wechsler D. *Technical and Interpretive Manual for the Wechsler Intelligence Scale for Children*. 4th ed. Ueno K, Fujita K, Maekawa H, Ishikuma T, Dairoku H, Matsuda O, trans. Nihon Bunka Kagakusha; 2010:45-97.
19. Baddeley AD. Developing the concept of working memory: the role of neuropsychology. *Arch Clin Neuropsychol*. 2021;36(6):861-873.
20. Das JP, Naglieri JA, Kirby JR. *Assessment of Cognitive Processes: The PASS Theory of Intelligence*. Allyn & Bacon; 1994:52-111.
21. Naglieri JA. *Essentials of CAS Assessment*. John Wiley & Sons; 1999:69-77.
22. Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer's disease using three-

dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med*. 1995;36(7):1238-1248.
23. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol*. 1997; 42(1):85-94.
24. Kikuchi T, Takagi Y, Nakagawara J, et al. Neuronal loss in the bilateral medial frontal lobe revealed by ^{123}I-iomazenil single-photon emission computed tomography in patients with moyamoya disease: the first report from Cognitive Dysfunction Survey of Japanese Patients with Moyamoya Disease (COSMO-Japan Study). *Neurol Med Chir (Tokyo)*. 2023;63(8):334-342.
25. Mizumura S, Kumita S, Cho K, et al. Development of quantitative analysis method for stereotactic brain image: assessment of reduced accumulation in extent and severity using anatomical segmentation. *Ann Nucl Med*. 2003;17(4):289-295.
26. Chiron C, Raynaud C, Mazière B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med*. 1992;33(5):696-703.
27. Nakagawara J, Osato T, Kamiyama K, et al. Diagnostic imaging of higher brain dysfunction in patients with adult moyamoya disease using statistical imaging analysis for [123I] iomazenil single photon emission computed tomography. *Neurol Med Chir (Tokyo)*. 2012;52(5):318-326.
28. Lancaster JL, Woldorff MG, Parsons LM, et al. Automated Talairach Atlas labels for functional brain mapping. *Hum Brain Mapp*. 2000;10(3):120-131.
29. Imaizumi T, Hayashi K, Saito K, Osawa M, Fukuyama Y. Long-term outcomes of pediatric moyamoya disease monitored to adulthood. *Pediatr Neurol*. 1998;18(4):321-325.
30. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H. Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. *J Neurosurg*. 1992;77(1):84-89.
31. Funaki T, Takahashi JC, Takagi Y, et al. Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease. *J Neurosurg Pediatr*. 2013;12(6):626-632.
32. Kim W, Lee EY, Park SE, et al. Neuropsychological impacts of indirect revascularization for pediatric moyamoya disease. *Childs Nerv Syst*. 2018;34(6):1199-1206.
33. Karashima S, Nakamizo A, Arimura K, Yoshimoto K. Intellectual function and memory in children with moyamoya disease: relationship between Wechsler Intelligence Scale and Benton Visual Retention Test scores and regional cerebral blood flow. *J Neurosurg Pediatr*. 2024;33(4):301-306.
34. Kazumata K, Tokairin K, Ito M, et al. Combined structural and diffusion tensor imaging detection of ischemic injury in moyamoya disease: relation to disease advancement and cerebral hypoperfusion. *J Neurosurg*. 2020;134(3):1155-1164.
35. Hu J, Li Y, Li Z, et al. Abnormal brain functional and structural connectivity between the left supplementary motor area and inferior frontal gyrus in moyamoya disease. *BMC Neurol*. 2022;22(1):179.
36. Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. *Curr Opin Neurol*. 2000; 13(4):415-421.
37. Buckner RL, Wheeler ME. The cognitive neuroscience of remembering. *Nat Rev Neurosci*. 2001;2(9):624-634.
38. Smith EE, Jonides J. Working memory: a view from neuroimaging. *Cognit Psychol*. 1997;33(1):5-42.
39. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. *Annu Rev Neurosci*. 2012;35:73-89.
40. Bissonette GB, Powell EM, Roesch MR. Neural structures underlying set-shifting: roles of medial prefrontal cortex and anterior cingulate cortex. *Behav Brain Res*. 2013;250:91-101.
41. Nakajima R, Okita H, Kinoshita M, et al. Direct evidence for the causal role of the left supplementary motor area in working memory: a preliminary study. *Clin Neurol Neurosurg*. 2014;126:201-204.
42. Lee JY, Phi JH, Wang KC, Cho BK, Shin MS, Kim SK. Neurocognitive profiles of children with moyamoya disease before and after surgical intervention. *Cerebrovasc Dis*. 2011; 31(3):230-237.
43. Kuroda S, Houkin K, Ishikawa T, et al. Determinants of intellectual outcome after surgical revascularization in pediatric moyamoya disease: a multivariate analysis. *Childs Nerv Syst*. 2004;20(5):302-308.
44. Ahtam B, Solti M, Doo JM, et al. Diffusion-weighted magnetic resonance imaging demonstrates white matter alterations in watershed regions in children with moyamoya without stroke or silent infarct. *Pediatr Neurol*. 2023;143:89-94.
45. Sakamoto Y, Okamoto S, Maesawa S, et al. Default mode network changes in moyamoya disease before and after bypass surgery: preliminary report. *World Neurosurg*. 2018;112: e652-e661.
46. Kazumata K, Tha KK, Narita H, et al. Investigating brain network characteristics interrupted by covert white matter injury in patients with moyamoya disease: insights from graph theoretical analysis. *World Neurosurg*. 2016;89:654-665.e2.
47. Christen T, Jahanian H, Ni WW, Qiu D, Moseley ME, Zaharchuk G. Noncontrast mapping of arterial delay and functional connectivity using resting-state functional MRI: a study in Moyamoya patients. *J Magn Reson Imaging*. 2015; 41(2):424-430.

Disclosures

Dr. Fushimi reported grants from Takeda Pharmaceutical Company Limited outside the submitted work. Dr. Arakawa reported grants from Philips, Otsuka, Chugai, Nihon Medi-Physics, Daiichi Sankyo, Stryker, Eisai, Japan Blood Products Organization, Ono Pharmaceutical, Taiho Pharma, Sumitomo Dainippon Pharma, Astellas Pharma, Incyte Biosciences, and Servier; and personal fees from Nippon Kayaku, Novocure, UCB Japan, Ono Pharmaceutical, Brainlab, Merck, Chugai, Eisai, Daiichi Sankyo, Carl Zeiss, Nihon Medi-Physics, and Stryker outside the submitted work.

Author Contributions

Conception and design: Funaki, Kusano. Acquisition of data: Funaki, Kusano, Tanaka, Nishida, Tabata, Mitsumoto. Analysis and interpretation of data: all authors. Drafting the article: Funaki, Kusano. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Funaki. Statistical analysis: Funaki, Kusano. Study supervision: Ueda, Liang, Inadomi, Miyamoto, Arakawa.

Correspondence

Takeshi Funaki: Kyoto University Graduate School of Medicine, Kyoto, Japan. tfunaki@kuhp.kyoto-u.ac.jp.