Memory, Executive, and Intellectual Functions in Adults with Moyamoya Disease

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Memory, Executive, and Intellectual Functions in Adults with Moyamoya Disease

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■ OBJECTIVE: **Cognitive function can decline in adults with moyamoya disease (MMD). Memory, which is an essential but complex and multifaceted function, underpins executive and intellectual functions. However, the relationship between memory and executive or intellectual functions in adults with MMD has not been well studied. The relationship between memory and cerebral blood flow has also not been elucidated. This study investigated correlations between memory, executive function, and intellectual function, and associations between cerebral blood flow and memory in adults with MMD.**

■ METHODS: **Memory, executive function, and intellectual function were assessed using the Wechsler Memory Scale-Revised (WMS-R), Frontal Assessment Battery (FAB), and Wechsler Adult Intelligence Scale (WAIS) third or fourth edition, respectively, in 31 adults with MMD. Cerebral blood flow was measured with iodine ^{123}I-iodoamphetamine single-photon emission computed tomography.**

■ RESULTS: **WMS-R scores correlated significantly with total FAB and WAIS scores before and after revascularization. Cerebral blood flow in the left posterior cerebral artery territory correlated positively with WMS-R and WAIS scores pre- and postoperatively. Postoperative cerebrovascular reserves of the right cerebellum, pons, and vermis were positively associated with visual memory, and postoperative cerebrovascular reserve of the pons was also associated with general memory.**

■ CONCLUSIONS: **Memory function correlates with executive and intellectual functions in adults with MMD. The FAB, which requires about 10 min to administer, might be useful to screen for memory dysfunction. Memory might be vulnerable to hypoperfusion in the posterior cerebral artery territory among adults with MMD. Postoperative cerebrovascular reserve might help predict memory dysfunction in adults with MMD.**

INTRODUCTION

Moyamoya disease (MMD) is a chronic cerebrovascular condition characterized by progressive stenosis of arteries in the circle of Willis.[1] MMD has a high prevalence in Asia, including Japan and South Korea, compared to European countries and North America.[2-4] The incidence of MMD in Denmark was 0.07 per 100,000 person-years from 2008 onwards in a population-based study,[3] and the incidence in the United States was 0.086 per 100,000 person-years,[4] representing low rates compared to the incidence in Japan of 0.94 per

Key words
- Cerebral blood flow
- Executive function
- Intellectual function
- Memory
- Moyamoya disease

Abbreviations and Acronyms
ACA: Anterior cerebral artery
ACZ: Acetazolamide
CI: Confidence interval
CVR: Cerebrovascular reserve
FAB: Frontal assessment battery
FSIQ: Full-scale intelligence quotient
IQR: Interquartile range
MCA: Middle cerebral artery
MMD: Moyamoya disease
MRI: Magnetic resonance imaging
OR: Odds ratio
PCA: Posterior cerebral artery
POI: Perceptual organization index
PRI: Perceptual reasoning index
PSI: Processing speed index
rCBF: Regional cerebral blood flow
VCI: Verbal comprehension index
VIQ: Verbal intelligence quotient
WAIS: Wechsler Adult Intelligence Scale
WMI: Working memory index
WMS-R: Wechsler Memory Scale-Revised

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100,000 person-years.[2] However, the incidence of MMD has been increasing worldwide in recent years,[5] including in Denmark,[3,6] mainly due to increased detection rates with growing awareness of the pathology and the widespread use of magnetic resonance imaging (MRI) and other diagnostic modalities.[3]

Cognitive function, predominantly executive function, can be impaired in adults with MMD.[7,8] Cognition is hierarchically structured with executive function and cognitive control at the top, and primary perceptual processes at the bottom, and the cognitive domains are not independent of each other.[9] Among cognition, memory function, which involves information encoding, storage, and retrieval, is the essential but most complex and multifaceted function.[9] While memory function can underpin executive and intellectual functioning, the relationships between these in adults with MMD has not been well studied.

Whether memory function is impaired in adults with MMD remains somewhat controversial,[7,10,11] but memory appears to be impaired in approximately 30% of patients.[8,12] The Wechsler Memory Scale-Revised (WMS-R) is the test most widely used worldwide as a comprehensive standardized memory test for individuals of ages 16 to 74, comprising 13 subtests scored on 5 indices of verbal memory, visual memory, general memory, attention/concentration, and delayed memory. However, the WMS-R requires 45–60 min to complete.[13] The most widely used intelligence test, the Wechsler Adult Intelligence Scale (WAIS),[14,15] takes even longer, needing approximately 120 min to be administered. The Frontal Assessment Battery (FAB), on the other hand, is widely used as a screening test for executive function and takes only 5–10 min.[16] Moreover, specific subitems on the FAB have been shown to be associated with cerebral blood flow in the brain regions responsible for the various cognitive domains in adults with MMD.[17]

The aim of this study was to elucidate the correlation between memory, executive function, and intellectual function, as assessed by the WMS-R, FAB, and WAIS, respectively, in adults with MMD. We also aimed to assess the association between cerebral blood flow and memory function to identify brain regions in which hypoperfusion is associated with memory dysfunction.

MATERIALS AND METHODS

Patients

Consecutive adults with MMD admitted to our institution for revascularization surgery between February 2017 and April 2023 were enrolled in this study. The inclusion criteria were as follows: 1) patients >15 years old; 2) administration of the WMS-R, FAB, and WAIS before revascularization surgery; and 3) no hemianopsia or aphasia. MMD was diagnosed based on findings from digital subtraction angiography in all cases. This study was approved by the Kyushu University Ethics Review Board and was performed in accordance with the relevant guidelines and regulations. All patients provided written informed consent prior to enrollment.

Neurocognitive Assessment

The WMS-R[13] and FAB[16] were adopted to assess memory and executive functions, respectively. The third edition of the WAIS (WAIS-III)[14] and fourth edition (WAIS-IV)[15] provided index scores for overall intellectual ability (full-scale intelligence quotient [FSIQ]), verbal ability (Verbal Comprehension Index [VCI] on WAIS-IV and verbal intelligence quotient [VIQ] on WAIS-III), visuospatial ability (Perceptual Reasoning Index [PRI] on WAIS-IV and Perceptual Organization Index [POI] on WAIS-III), auditory attention and mental manipulation (Working Memory Index [WMI]), and visual-motor speed (Processing Speed Index [PSI]), with mean scores of 100 and standard deviation (SD) of 15. A trained evaluator who was blinded to the study objectives administered all neurocognitive tests.

Single-Photon Emission Computed Tomography

Regional cerebral blood flow (rCBF) was evaluated preoperatively in all cases using iodine ^{123}I-iodoamphetamine dual-table autoradiography with an automatic region of interest definition tool (NEURO FLEXER; Nihon Medi-Physics, Tokyo, Japan). The rCBF values were also measured after the acetazolamide (ACZ) challenge test. Cerebrovascular reserve (CVR) was expressed using the following equation: CVR = (post-ACZ rCBF - resting rCBF)/resting rCBF.

Statistical Analysis

Age, rCBF, and CVR are provided as mean ± standard deviation. Unless otherwise indicated, other data are provided as the median and interquartile range (IQR). Statistical analysis was performed using the Wilcoxon rank-sum test for nonparametric data. Differences in binary variables were assessed using Fisher's exact test. Correlations between scores on WMS-R and FAB or WAIS scores were assessed using Spearman's correlation coefficient. Linear regression analysis was performed for paired neurocognitive test scores and rCBF or CVR. Differences were considered significant for values of $P < 0.05$. All statistical analyses were performed using JMP Pro version 17.0 software (SAS Institute, Cary, NC).

RESULTS

Patients

Thirty-four adults with MMD underwent revascularization during the study period. Two patients were excluded due to the presence of hemianopsia or aphasia. One patient was excluded because she did not complete the preoperative neurocognitive tests. That patient underwent urgent ventricular drainage followed by revascularization. Finally, 31 adults with MMD who met the criteria were enrolled in this study. All patients underwent the WAIS (WAIS-III in 27 patients; WAIS-IV in 4 patients), and 26 underwent FAB before revascularization. All patients underwent superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis in at least 1 hemisphere, and 14 patients underwent bilateral anastomosis. After revascularization (median, 6 months), 23 patients underwent the WMS-R and WAIS and 20 underwent the FAB (one of whom had not undergone the preoperative FAB).

The preoperative demographic characteristics of the included patients are summarized in Table 1. Median WMS-R standard scores, total FAB score, and WAIS standard scores are summarized in Table 2. Median WMS-R scores were within the normal range, but scores were less than 85 in 9 patients for verbal memory, in 6 for visual memory, in 8 for general memory, in 5 for attention/concentration, and in 7 for delayed memory. No significant associations were seen between WMS-R scores and age, sex, initial presentation, hypertension, diabetes mellitus, smoking, antiplatelet therapy, disease laterality, cerebral infarction, or ivy sign on MRI. Scores for visual memory were significantly lower in patients with dyslipidemia (77.5 ± 15.2) than in those without (100.0 ± 14.4; $P = 0.0101$). Modified Rankin scale scores were negatively associated with scores on verbal memory, visual memory, general memory, attention/concentration, and delayed memory ($r^2 = 0.296$, $P = 0.0016$; $r^2 = 0.187$, $P = 0.0150$; $r^2 = 0.332$, $P = 0.0007$; $r^2 = 0.363$, $P = 0.0003$; and $r^2 = 0.355$, $P = 0.0004$, respectively). The right Suzuki stage was negatively associated with scores on attention/concentration ($r^2 = 0.159$, $P = 0.0262$). Scores on attention/concentration were lower in patients with posterior cerebral artery (PCA) involvement (86.7 ± 21.8) than in those without PCA involvement (102.8 ± 9.6, $P = 0.0157$).

Correlation Between WMS-R and FAB or WAIS

Preoperative scores on WMS-R correlated significantly with total FAB scores (n = 26) and WAIS scores (n = 31), except for the correlations between VCI/VIQ and verbal memory, visual memory, general memory, or delayed memory (Table 3). Total FAB score was most significantly correlated with visual memory ($P < 0.0001$), while FSIQ, VCI/VIQ, PRI/POI, WMI, and PSI correlated most significantly with attention/concentration ($P < 0.0001$, $P = 0.0009$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively).

Postoperative WMS-R scores were also highly correlated with total FAB scores (n = 19) and WAIS scores (n = 23), except for the correlation between total FAB score and visual memory or attention/concentration, and the correlation between visual memory and VCI/VIQ or PRI/POI (Table 4). Total FAB score and PSI correlated most significantly with verbal memory and general memory, respectively ($P = 0.0041$ or $P < 0.0001$, respectively), while FSIQ, VCI/VIQ, PRI/POI, and WMI correlated most significantly with attention/concentration ($P < 0.0001$, $P = 0.0014$, $P = 0.0015$, and $P < 0.0001$, respectively). PSI also correlated with significantly attention/concentration ($P < 0.0001$).

Association Between WMS-R and rCBF

Resting rCBF and CVR were measured before revascularization in all cases and at a median of 6 months after revascularization in all but 6 cases. Preoperative associations between WMS-R and resting rCBF are summarized in Table 5 (n = 31). Resting rCBF in the left PCA territory was associated with verbal memory, general memory, attention/concentration, and delayed memory ($P = 0.0466$, 0.0292, 0.0075, and 0.0247, respectively). Resting rCBFs of the left hemisphere, left MCA territory, left MCA posterior territory, right thalamus, left cerebellum, and vermis were associated with attention/concentration ($P = 0.0366$, 0.0441, 0.0261, 0.0387, 0.0465, and 0.0409, respectively). Postoperative associations between WMS-R and resting rCBF are summarized

Table 1. Baseline Demographic Characteristics

Age at Examination (years)	43.6 ± 12.5
Female (%)	28 (90.3)
Initial symptom (%)	
Transient ischemic attack	14 (45.2)
Infarction	7 (22.6)
Intracranial hemorrhage	6 (19.4)
Seizure	2 (6.5)
Headache	1 (3.2)
Asymptomatic	1 (3.2)
Medical history (%)	
Hypertension	3 (9.7)
Diabetes mellitus	2 (6.5)
Dyslipidemia	4 (12.9)
Smoking	5 (16.1)
Use of anticoagulant	24 (77.4)
Modified Rankin scale	0 [0, 1]
Disease laterality (%)	
Bilateral	22 (71.0)
Right	3 (9.7)
Left	6 (19.3)
Suzuki stage	
Right	3 [3, 3]
Left	3 [3, 4]
Posterior cerebral artery involvement (%)	12 (38.7)
Infarction on magnetic resonance imaging (%)	21 (67.7)
Ivy sign on magnetic resonance imaging (%)	18 (58.1)

Table 2. Median Score for WMS-R, FAB, and WAIS

WMS-R (n = 31)	
Verbal memory	97 [74, 106]
Visual memory	100 [93, 108]
General memory	99 [78, 105]
Attention/Concentration	98 [90, 108]
Delayed memory	100 [85, 110]
FAB (n = 26)	16.5 [15, 18]
WAIS (n = 31)	
FSIQ	91 [79, 98]
VCI/VIQ	90 [84, 95]
PRI/POI	95 [85, 103]
WMI	90 [74, 96]
PSI	89 [75, 105]

WMS-R, Wechsler Memory Scale-Revised; FAB, frontal assessment battery; WAIS, Wechsler Adult Intelligence Scale; FSIQ, full-scale intelligence quotient; VCI, verbal comprehension index (WAIS-IV); VIQ, verbal intelligence quotient (WAIS-III); PRI, perceptual reasoning index (WAIS-IV); POI, perceptual organization index (WAIS-III); WMI, working memory index; PSI, processing speed index.

Table 3. Spearman's Correlation Coefficient (r_s) for Preoperative WMS-R and FAB or WAIS

		WAIS (n = 31)				
WMS-R	**FAB (n = 26)**	**FSIQ**	**VCI/VIQ**	**PRI/POI**	**WMI**	**PSI**
Verbal memory	0.5443†	0.3840*	0.2297	0.4946†	0.5765‡	0.4302*
Visual memory	0.7084§	0.4671†	0.3549	0.5788‡	0.5584†	0.4688†
General memory	0.6205‡	0.4569†	0.2964	0.5711‡	0.6389‡	0.4879†
Attention/Concentration	0.6176‡	0.6972§	0.5652‡	0.7139§	0.8083§	0.8110§
Delayed memory	0.5061†	0.5037†	0.2764	0.6342‡	0.5718‡	0.5151†

WMS-R, Wechsler Memory Scale-Revised; FAB, frontal assessment battery; WAIS, Wechsler Adult Intelligence Scale; FSIQ, full-scale intelligence quotient; VCI, verbal comprehension index (WAIS-IV); VIQ, verbal intelligence quotient (WAIS-III); PRI, perceptual reasoning index (WAIS-IV); POI, perceptual organization index (WAIS-III); WMI, working memory index; PSI, processing speed index.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.
§$P < 0.0001$.

in **Table 6** (n = 25). Resting rCBF in the left PCA territory was associated only with attention/concentration ($P = 0.0277$). Preoperative CVR was not associated positively with WMS-R. In contrast, postoperative CVR in the right cerebellum, pons, and vermis was positively associated with visual memory ($r^2 = 0.418$, $P = 0.0015$; $r^2 = 0.372$, $P = 0.0033$; $r^2 = 0.329$, $P = 0.0066$, respectively), and postoperative CVR in the pons was associated with general memory ($r^2 = 0.192$, $P = 0.0464$).

Associations between WAIS and rCBF were also analyzed. Preoperatively, resting rCBF in the left PCA territory was associated with FSIQ, WMI, and PSI ($r^2 = 0.150$, $P = 0.0316$; $r^2 = 0.153$, $P = 0.0294$; and $r^2 = 0.221$, $P = 0.0077$, respectively). The rCBF in the left MCA posterior territory and vermis was associated with WMI ($r^2 = 0.147$, $P = 0.0331$; $r^2 = 0.132$, $P = 0.0442$, respectively). Postoperatively, resting rCBF in the left PCA territory and left thalamus was associated only with PSI ($r^2 = 0.267$, $P = 0.0115$; and $r^2 = 0.198$, $P = 0.0334$, respectively). Preoperative CVR was not positively associated with WAIS, while postoperative CVR in the right cerebellum, pons, or vermis was associated with FSIQ ($r^2 = 0.341$, $P = 0.0055$; $r^2 = 0.339$, $P = 0.0056$; and $r^2 = 0.321$, $P = 0.0074$, respectively) and PRI/POI ($r^2 = 0.305$, $P = 0.0094$; $r^2 = 0.302$, $P = 0.0099$; and $r^2 = 0.314$, $P = 0.0083$, respectively). Postoperative CVR of the right cerebellum or pons was also associated with PSI ($r^2 = 0.216$, $P = 0.0338$; $r^2 = 0.190$, $P = 0.0484$, respectively).

Postoperative changes in rCBF and WMS-R, FAB, and WAIS

Twenty-six patients underwent postoperative evaluation of rCBF. Wilcoxon signed-rank tests revealed that resting rCBFs in the right and left MCA territories and MCA posterior territory were

Table 4. Spearman's Correlation Coefficient (r_s) for Postoperative WMS-R and FAB or WAIS

		WAIS (n = 23)				
WMS-R	**FAB (n = 19)**	**FSIQ**	**VCI/VIQ**	**PRI/POI**	**WMI**	**PSI**
Verbal memory	0.6267†	0.5038*	0.5460†	0.4297*	0.6080†	0.6517‡
Visual memory	0.2146	0.5565†	0.3579	0.4090	0.3687	0.5449†
General memory	0.5595*	0.5918†	0.5554†	0.5179*	0.6367†	0.7484§
Attention/Concentration	0.3521	0.7273§	0.6247†	0.6219†	0.7494§	0.7264§
Delayed memory	0.4628*	0.5046*	0.4196*	0.5135*	0.5958†	0.6855‡

WMS-R, Wechsler Memory Scale-Revised; FAB, frontal assessment battery; WAIS, Wechsler Adult Intelligence Scale; FSIQ, full-scale intelligence quotient; VCI, verbal comprehension index (WAIS-IV); VIQ, verbal intelligence quotient (WAIS-III); PRI, perceptual reasoning index (WAIS-IV); POI, perceptual organization index (WAIS-III); WMI, working memory index; PSI, processing speed index.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.
§$P < 0.0001$.

Table 5. Coefficient of Determination (r^2) for Preoperative Regional Cerebral Blood Flow and Wechsler Memory Scale-Revised

	Wechsler Memory Scale-Revised (n = 31)				
	Verbal Memory	Visual Memory	General Memory	Attention/Concentration	Delayed Memory
Hemisphere					
Right	0.008	0.008	0.011	0.097	0.011
Left	0.072	0.042	0.078	0.142*	0.092
ACA					
Right	0.035	0.0246	0.041	0.065	0.037
Left	0.050	0.023	0.053	0.065	0.063
MCA					
Right	0.009	0.003	0.010	0.092	0.005
Left	0.069	0.028	0.070	0.133*	0.077
MCA anterior					
Right	0.034	0.024	0.038	0.112	0.020
Left	0.053	0.021	0.052	0.091	0.050
MCA posterior					
Right	0.001	0.001	0.001	0.072	<0.0001
Left	0.083	0.034	0.085	0.159*	0.100
PCA					
Right	0.001	0.008	<0.001	0.102	0.001
Left	0.130*	0.126	0.154*	0.222†	0.162*
Basal ganglia					
Right	0.001	0.008	0.003	0.071	0.006
Left	0.012	0.007	0.014	0.057	0.025
Thalamus					
Right	0.009	0.044	0.021	0.139*	0.043
Left	0.025	0.043	0.037	0.113	0.075
Cerebellum					
Right	0.092	0.048	0.094	0.112	0.060
Left	0.070	0.059	0.084	0.130*	0.072
Pons	0.073	0.006	0.057	0.070	0.039
Vermis	0.050	0.017	0.050	0.136*	0.032

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
*$P < 0.05$.
†$P < 0.01$.

significantly increased after revascularization ($P < 0.001$ each) (Table 7), followed by the right and left MCA anterior territory, right and left hemisphere, left ACA territory, right and left PCA territory, right and left basal ganglia, right and left thalamus, and pons.

Changes in WMS-R, FAB, and WAIS are summarized in Table 8. On WMS-R, verbal memory, general memory, and delayed memory increased after revascularization ($P < 0.0001$, $P = 0.0002$, and $P = 0.0006$, respectively), while visual memory and attention/concentration were unchanged ($P = 0.0549$ and 0.7790, respectively). In contrast, total FAB and WAIS scores were unchanged after surgery. As described above, resting rCBF in the left PCA territory was associated with WMS-R and WAIS scores, but no associations between postoperative changes to rCBF in the left PCA territory and postoperative changes in WMS-R or WAIS scores were evident.

Table 6. Coefficient of Determination (r^2) for Postoperative Regional Cerebral Blood Flow and Wechsler Memory Scale-Revised

	Wechsler Memory Scale-Revised (n = 23)				
	Verbal Memory	Visual Memory	General Memory	Attention/Concentration	Delayed Memory
Hemisphere					
Right	0.003	0.069	0.002	0.067	0.009
Left	0.011	0.082	0.033	0.091	0.045
ACA					
Right	<0.001	0.110	0.016	0.070	0.036
Left	0.003	0.073	0.020	0.039	0.033
MCA					
Right	0.009	0.055	<0.001	0.073	0.006
Left	0.009	0.054	0.023	0.074	0.026
MCA anterior					
Right	0.012	0.090	<0.001	0.082	0.014
Left	0.007	0.057	0.021	0.041	0.021
MCA posterior					
Right	0.005	0.030	<0.001	0.064	0.002
Left	0.013	0.050	0.028	0.105	0.033
PCA					
Right	0.001	0.095	0.015	0.076	0.021
Left	0.041	0.170	0.086	0.210*	0.145
Basal ganglia					
Right	0.033	0.052	0.003	0.047	<0.001
Left	0.001	0.020	0.006	0.054	0.008
Thalamus					
Right	0.005	0.120	0.034	0.095	0.040
Left	0.024	0.107	0.057	0.120	0.066
Cerebellum					
Right	0.006	0.044	<0.001	0.049	0.002
Left	0.003	0.108	0.006	0.069	0.016
Pons	0.003	0.035	0.001	0.070	0.006
Vermis	<0.001	0.045	0.004	0.096	0.008

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
*$P < 0.05$.

To assess the effect of revascularization on memory function, changes in WMS-R scores that had been less than 85 preoperatively were evaluated. Eleven patients showed one or more WMS-R standard scores below 85 preoperatively, of whom 8 were re-evaluated postoperatively. WMS-R standard scores that were less than 85 preoperatively improved postoperatively in 5 of 7 verbal memory scores, 3 of 4 visual memory scores, 5 of 6 general memory scores, 2 of 4 attention/concentration scores, and 3 of 5 delayed memory scores.

DISCUSSION

We showed that WMS-R correlated well with FAB and WAIS scores even though the FAB does not assess memory, and the WAIS evaluates only working memory by digit span test, suggesting that memory function is fundamental to executive and intellectual functions in adults with MMD. Since the WMS-R and WAIS require a long time to administer, screening with the FAB first then performing comprehensive tests limited to cases

Table 7. Regional Cerebral Blood Flow Before and After Revascularization (ml/100 g) (n = 26)

	Preop	Postop	Changes	*P* Value
Hemisphere				
Right	32.1 ± 4.3	35.4 ± 8.1	3.3 ± 7.0	0.0132*
Left	31.8 ± 4.5	35.3 ± 8.0	3.5 ± 7.0	0.0156*
ACA				
Right	32.2 ± 4.9	34.7 ± 8.5	2.5 ± 7.4	0.0769
Left	32.2 ± 4.5	35.3 ± 8.1	3.1 ± 7.0	0.0249*
MCA				
Right	31.9 ± 5.0	35.5 ± 8.7	3.6 ± 7.3	0.0086†
Left	31.7 ± 4.7	35.4 ± 8.0	3.7 ± 7.1	0.0094†
MCA anterior				
Right	32.3 ± 5.7	35.0 ± 9.6	2.8 ± 8.2	0.0102*
Left	32.4 ± 4.7	36.1 ± 8.0	3.7 ± 7.1	0.0132*
MCA posterior				
Right	32.4 ± 4.9	36.7 ± 8.5	4.3 ± 7.3	0.0040†
Left	31.8 ± 5.2	35.6 ± 8.5	3.8 ± 7.3	0.0094†
PCA				
Right	36.7 ± 5.1	40.6 ± 9.1	3.9 ± 8.1	0.0288*
Left	35.1 ± 7.8	38.7 ± 11.3	3.6 ± 8.2	0.0231*
Basal ganglia				
Right	34.0 ± 4.1	37.2 ± 8.7	3.2 ± 8.2	0.0356*
Left	34.0 ± 4.0	37.6 ± 8.0	3.6 ± 8.0	0.0231*
Thalamus				
Right	32.8 ± 4.3	35.6 ± 8.0	2.8 ± 6.9	0.0382*
Left	32.8 ± 4.0	35.5 ± 8.2	2.7 ± 7.4	0.0409*
Cerebellum				
Right	35.2 ± 5.8	37.7 ± 9.1	2.5 ± 7.6	0.1333
Left	36.1 ± 5.9	38.6 ± 10.1	2.5 ± 8.0	0.1202
Pons	26.1 ± 4.4	28.3 ± 6.1	2.3 ± 6.1	0.0467*
Vermis	35.5 ± 5.3	38.1 ± 7.7	2.5 ± 7.1	0.1140

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
*$P < 0.05$.
†$P < 0.01$ for two-tailed Wilcoxon signed-rank test.

showing abnormalities on FAB might be practical, particularly in outpatient settings.

Memory dysfunction in adults with MMD remains controversial because of the lack of high-level evidence due to the rarity of this entity.[7] In a study of 29 adults with MMD, verbal memory on the Delayed List Recall was impaired at 31% and working memory on the Trail Making Part B at 25%.[10] Conversely, a study of 36 adult patients demonstrated memory as having the lowest impairment rate.[11] A meta-analysis of 101 adult patients revealed the median proportion of patients with impaired memory to be 37% (range, 7%–54%) as well as impaired processing speed in 28% (range, 21%–39%), impaired attention and executive functions in 37% (range, 19%–54%), impaired visual perception and construction in 23% (range, 22%–29%), and impaired language in 35% (range, 20%–40%), with median z-scores of −0.4 (range, −1.1 to −0.2), −0.9 (range, −1.7 to −0.8), −0.9 (range, −0.95 to −0.4), −0.4 (range, −0.5 to −0.2), and −0.6 (range, −0.8 to −0.15), respectively.[8] A recent study of 61 adult MMD patients using comprehensive neuropsychological assessments showed declines in executive function in 57%, PIQ in 36%, PSI in 31%,

Table 8. WMS-R, FAB, and WAIS Before and Six Months After Revascularization

	Preop	Postop	Changes
WMS-R (n = 23)			
Verbal memory	97 [74, 107]	102 [88, 120]	11 [1, 17]†
Visual memory	101 [93, 108]	108 [100, 114]	6 [−4, 10]
General memory	99 [76, 107]	102 [90, 116]	8 [2, 16]*
Attention/Concentration	98 [87, 108]	97 [87, 107]	−2 [−8, 7]
Delayed memory	100 [90, 110]	109 [98, 115]	4 [0, 10]*
FAB (n = 19)	17 [15, 18]	18 [17, 18]	1 [0, 2]
WAIS (n = 23)			
FSIQ	92 [83, 98]	97 [84, 103]	3.5 [−1.5, 8.5]
VCI/VIQ	91 [86, 97]	95 [84, 101]	1 [−2, 8.25]
PRI/POI	95 [87, 108]	101 [83, 103]	6 [−7,11]
WMI	92 [85, 98]	96 [88, 102]	1 [−2, 4.5]
PSI	92 [81, 105]	94 [75, 107]	1 [−3.5, 10]

WMS-R, Wechsler Memory Scale-Revised; FAB, frontal assessment battery; WAIS, Wechsler Adult Intelligence Scale; FSIQ, full-scale intelligence quotient; VCI, verbal comprehension index (WAIS-IV); VIQ, verbal intelligence quotient (WAIS-III); PRI, perceptual reasoning index (WAIS-IV); POI, perceptual organization index (WAIS-III); WMI, working memory index; PSI, processing speed index.
*$P < 0.001$.
†$P < 0.0001$ for two-tailed Wilcoxon signed-rank test.

visual memory in 30%, language in 26%, VIQ in 23%, perception in 12%, and verbal memory in 7%, and these declines persisted for up to 13 years.[12] Hypoperfusion has been hypothesized as a principal cause of cognitive decline in adults with MMD.[10,18] Frontal lobe CVR was significantly lower in adult MMD patients with executive dysfunction (−13.5%) than in those without (20.3%, P = 0.019).[18] Improved cerebral perfusion after revascularization was suggested to be associated with improved cognitive functioning, albeit in a small number of patients.[19,20] A study of 31 adults with MMD demonstrated that WMS scores decreased at least one point at 5 years after revascularization in 7 patients, with significant worsening in 2 and significant improvement in 4.[21] Memory thus appears to be impaired in about 30% of adults with MMD and can worsen even after revascularization surgery, suggesting the importance of periodic memory assessments.

Our study showed that rCBF in the left PCA territory was associated with memory functions in adults with MMD. The significance of PCA involvement in MMD has been highlighted in recent years. The degree of PCA steno-occlusion correlated positively with ipsilateral internal carotid artery stenosis in children and adults with MMD and ipsilateral cerebral infarction in adults with MMD.[22] PCA involvement is supposed to be associated with further reductions in rCBF because the PCA is a crucial collateral blood channel into the affected anterior circulation via leptomeningeal anastomosis in MMD.[23] PCA involvement has been associated with unfavorable social outcomes in children and poor cognitive functions in adults with MMD. Funaki et al. reported that 17.9% of children with MMD continued to suffer from social adaptation problems after reaching adulthood, even after revascularization, and identified PCA involvement as a risk factor for unfavorable social outcomes (odds ratio [OR] 7.44, 95% confidence interval [CI] 1.22−67.79), independent of the presence of infarction in the anterior circulation (OR 9.96, 95% CI 1.08−355.82).[23] In adults with MMD, stenosis scores of the left and right PCA at baseline were significantly associated with 5-year changes in executive function and right PCA scores at baseline were associated with 5-year changes in neurocognitive function.[24] The association between PCA involvement and cognitive dysfunction is possibly due to reduced PCA-mediated collateral blood flow to the anterior circulation or impaired networks connecting the occipital lobe and frontal and parietal lobes. The networks between the parieto-occipital and frontal lobes mediated by the occipito-frontal fasciculus may provide a basis for the involvement of the PCA in frontal and parietal lobe function.[25,26]

In our study, the associations between memory and rCBF in the left cerebral hemisphere, left MCA posterior territory, right thalamus, left cerebellum, and vermis, which were evident preoperatively, were postoperatively attenuated. A similar trend was observed for intellectual functions. Revascularization markedly improved the rCBF of the MCA territory, predominantly of the posterior MCA territory. This might be the underlying mechanism by which postoperative memory and intellectual functions were no longer affected by rCBF in the MCA territory.

We also found that postoperative CVR of the right cerebellum, pons, or vermis was associated with visual memory and general memory on the WMS-R as well as FSIQ, PRI/POI, or PSI on the

WAIS. Growing evidence suggests that the cerebellum contributes significantly not only to motor function, but also to nonmotor mental activity, including higher-order cognitive functions.[27-31] Inconsistent with our results, continuous theta burst stimulation to the right cerebellar hemisphere reduced accuracy on the verbal version of the Sternburg task but not on the visual version of the Sternburg task compared to the left cerebellar hemisphere, indicating that the right cerebellum was selectively involved in verbal working memory and did not affect visual working memory.[30] In contrast, transcranial magnetic stimulation to the right cerebellar hemisphere reduced the ability to correctly recognize the order of appearance of geometrical stimuli, indicating that the right cerebellum plays a role in short-term memory for the incoming order of visual stimuli.[27] A functional magnetic resonance imaging(fMRI) study showed that cerebellar lobes VIIb and VIIIa, which are connected to the frontoparietal-dorsal attention network, were selectively activated during the identification of remembered visual stimuli, suggesting that the network responsible for the persistent storage of visual information involves the cerebellum.[28] An experiment using positron emission tomography demonstrated that conscious recall of episodic memory without motor or sensory inputs or outputs (pure thought experiment) activated the right cerebellum as well as the left medial dorsal thalamus, medial and left orbitofrontal cortex, anterior cingulate, and left parietal regions, supporting involvement of the right cerebellum in the conscious retrieval of episodic memory as part of a memory network of frontal lobe-cerebellar-thalamocortical interactions.[29] In terms of verbal working memory, another fMRI study revealed that the right superior cerebellum as well as the left inferior operculum and premotor cortex was most robustly activated during the initial encoding phase of the task, while the right inferior cerebellum as well as the left inferior parietal lobule were most robustly activated during the maintenance phase of the task.[31]

Limitations

Due to the rarity of this pathological entity, the number of patients enrolled in this study was small. It should be noted that the correlation between FAB and memory function might not be as strong or comprehensive as the correlation between WMS-R and memory function. Furthermore, the fact that memory function as assessed by the WMS-R showed improvement after revascularization surgery, whereas neither FAB nor WAIS scores changed, suggests that FAB and WAIS might be less sensitive to detecting changes in memory function after surgery. In addition, since the FAB does not comprehensively assess the various dimensions of memory, including information encoding, storage, and retrieval, use of a dedicated memory assessment tool such as the WMS-R is preferable if the primary goal is to specifically assess memory function in adults with MMD. In addition, results from post-revascularization studies might limit the applicability of the results to other populations and disease stages. Observations in this study might not be directly applicable to patients worldwide because the features of MMD vary by race.[32] Further accumulation and analysis of data worldwide are desirable.

CONCLUSIONS

Despite these limitations, the present study showed that memory function correlated with executive and intellectual functions in adults with MMD. Furthermore, WMS-R scores correlated well with FAB scores, suggesting that the FAB, which requires about 10 min to administer, might be useful in screening for memory dysfunction. WMS-R was associated with rCBF in the left PCA territory, suggesting that memory might be vulnerable to hypoperfusion in the PCA territory in adults with MMD. Furthermore, postoperative CVR might help predict memory dysfunction in adults with MMD.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Naoki Maehara: Writing – review & editing. **Akira Nakamizo:** Conceptualization, Writing – original draft. **Koichi Arimura:** Data curation, Validation. **Koji Yoshimoto:** Project administration.

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