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ORIGINAL ARTICLE

Postoperative change of neuropsychological function after indirect revascularization in childhood moyamoya disease: a correlation with cerebral perfusion study

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Abstract

Purpose The relationships between postoperative functional improvement in various cognitive domains and regional hemodynamic change have not been sufficiently studied in childhood moyamoya disease (MMD). The present study aimed to examine the cognitive benefit of indirect revascularization, the underlying biological mechanism, and factors affecting surgical outcome in childhood MMD.

Methods Twenty-three patients with MMD aged under 20 years received neuropsychological examinations before and after indirect revascularization surgery, evaluating intellectual function, verbal and visual memory, and executive function. Among them, 13 patients had magnetic resonance perfusion (MRP) studies, in which regional cerebral perfusion was rated.

Results Postoperative improvement was observed in verbal memory performances ($p = 0.02$–0.03) and in cerebral perfusion at all 26 cerebral hemispheres ($p = 0.003$–0.005), especially in the middle cerebral artery (MCA) territories ($p = 0.001$–0.003). Hemodynamic improvement in the left MCA territories was significantly correlated with improvement of both verbal new learning ($p = 0.01$) and intellectual function ($p = 0.004$). Postoperative cognitive improvement of immediate recall and verbal intellectual function was associated with female sex ($r = -0.42$) and symptom duration ($p = -0.03$), respectively. Hemodynamic improvement in the MCA territories was related to longer follow-up intervals ($p = 0.02$).

Conclusion The findings revealed that the selective postoperative cognitive improvement was associated with increased regional perfusion in the MCA territories, and indicate the importance of early intervention and the potential of indirect revascularization regarding long-term outcome.

Keywords Cerebral revascularization · Stroke · Hemodynamics · Treatment outcome · Moyamoya disease

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Introduction

Moyamoya disease (MMD) is a rare cerebrovascular condition with progressive stenosis and occlusions of the circle of Willis, which commonly affects the distal parts of the intracranial cerebral arteries (ICAs) [8]. This pathological change induces collateral vessels to grow at the basal portion of the brain, which initially compensates for reduced blood flow and eventually disappears as the disease progresses [8]. The etiology of MMD has not been clear, while genetic, angiogenic, infectious, and radiological factors have been proposed [19]. MMD has a bimodal age of onset, with the highest peak at 5 to 14 years and the second peak at ages 40 to 44 years [3]. Common clinical symptoms in childhood MMD include transient ischemic attacks (TIAs), cerebral infarction, and epilepsy, among others [3, 13]. Cognitive impairments also have been reported, including deficits of intellectual function, executive function, memory, and verbal fluency [9, 14, 18, 23].

The main treatment option for childhood MMD is indirect revascularization that establishes collateral circulation by inducing spontaneous angiogenesis between the brain surface and the vascularized donor tissues [13]. Although the surgical effect takes time to develop, the bypass procedure eventually provides extensive surgical collaterals that improve cerebral hemodynamics [7, 22, 24]. Thus, revascularization has been expected to restore cognitive impairment induced by MMD [1, 14, 15].

However, without the empirical evidence showing a linkage between postoperative cognitive and hemodynamic change, the observed behavioral improvement may be merely a result of practice effect due to repeated testing [25]. As far as we are aware, only one study of 14 adult moyamoya patients [15] and two case reports [1, 10] have examined this issue with correlational study of cognitive and hemodynamic change in a single cohort. The underlying mechanism responsible for the reported postoperative cognitive improvement remained unclear, especially in the younger population.

Therefore, the present study aimed to examine the relationship between postoperative change of cognitive function and cerebral perfusion, with a supplementary goal to explore factors related to treatment outcomes in patients with childhood MMD.

Materials and methods

Participants

Eligible participants were patients diagnosed with MMD aged between 3 to 20 years at a neurosurgery clinic from June 2009 to July 2018. MMD was confirmed with cerebral angiography. Exclusion criteria included moyamoya syndrome and the ones who did not received both pre- and postoperative neurocognitive tests. Overall, 23 patients were included in the neuropsychological analysis (Fig. 1). The average age of participants (13 females) were 11.81 years ($SD = 4.62$) when receiving the first neuropsychological examination. Age of onset was 9.32 years on average ($SD = 3.92$). Symptom duration was 29.63 months on average ($SD = 43.85$). The most common initial symptom was TIAs (65.2%), followed by epilepsy (17.4%), and/or headache (8.7%) as well as syncope (8.7%). On cerebral angiographic studies, most patients were Suzuki stages III to IV. The average staging is 3.5 of the 46 cerebral hemispheres. Nine patients were found to have old infarction and none had recent infarction in the neuroimaging examination.

All participants received both neuropsychological and neuroimaging examinations within 1 week before surgery, and at least 6 months after surgery. Although all 23 patients received cerebral perfusion evaluation, 10 of them received computed tomographic perfusion and 13 had magnetic resonance perfusion (MRP) examinations due to protocol change throughout the years. The current study only included MR perfusion data of the 13 patients for correlation study with the cognitive change.

Surgical treatment [7]

All patients received bilateral encephalo-duro-arterio-synangiosis (EDAS) and 6 of them received additional frontal encephalo-pericranio-synangiosis (EPS) for hypoperfusion area shown on perfusion study. EDAS was performed by laying the posterior branch of the superficial temporal artery (STA) flap on the surface of the brain, mostly in the middle cerebral artery (MCA) territory. EPS surgery was performed by infolding of the pericranial flap to touch the cortical arteries. In every craniotomy procedure, we routinely infolded the dural flaps to facilitate the effect of synangiosis.

Angiographic evaluation

Regarding the development of collaterals after indirect revascularization, postoperative cerebral angiographic studies on 44 cerebral hemispheres showed that 90.9% of the revascularized hemispheres developed adequate collateral formation with Matsushima grade A (29 hemispheres) or B (11 hemispheres) [17]. Two patients did not receive postoperative angiography after the final operation (2 hemispheres). Postoperative complication was observed in one patient where a small new infarct was found in the ipsilateral posterior cerebral artery (PCA) territory.

Neuropsychological examinations

All participants received intellectual tests, while only those above 6 years old ($N = 20$) received memory and executive

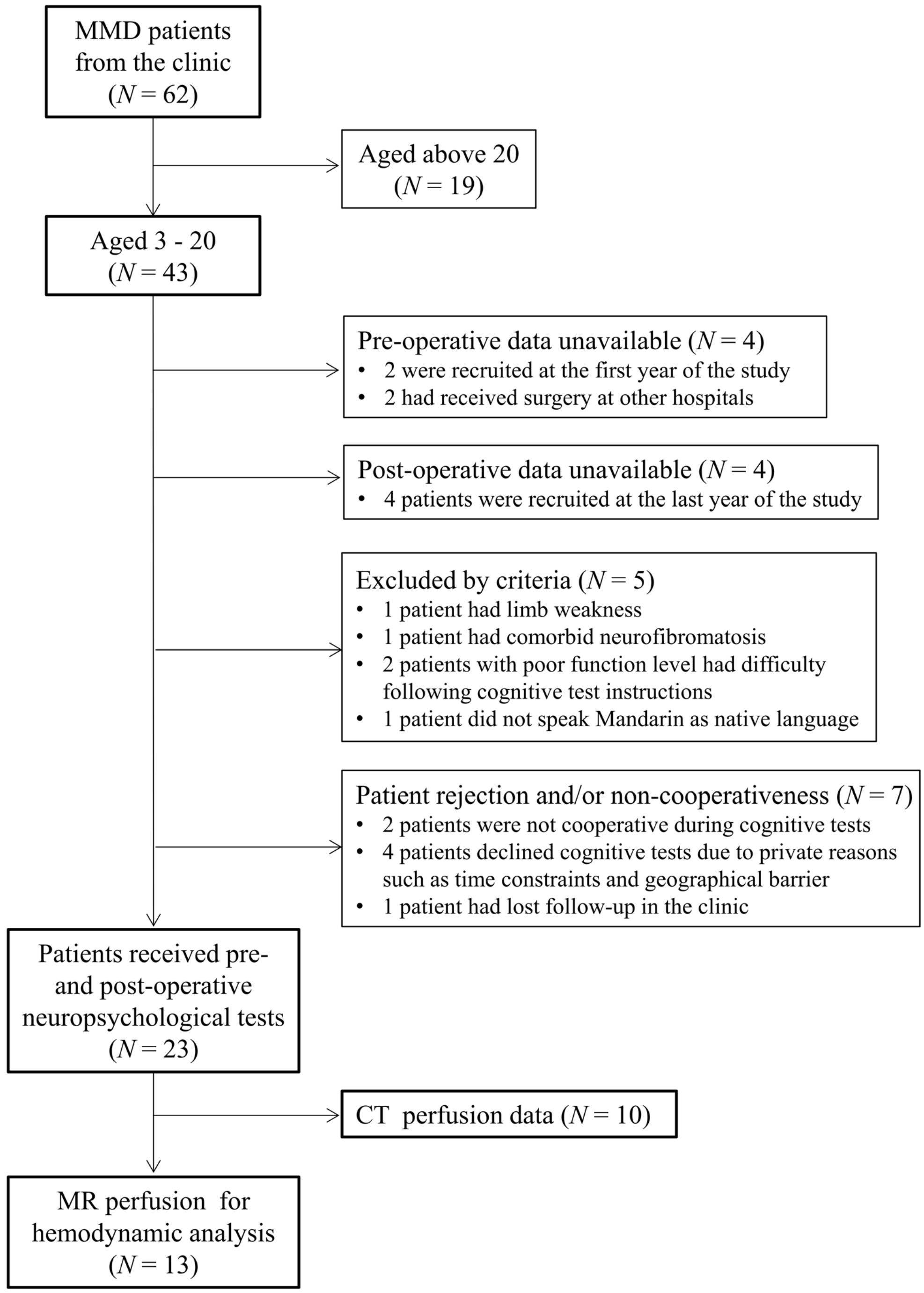

Fig. 1 Flow chart of subject recruitment

function tests considering the test complexity for the patient's age.

Intellectual function was assessed by the Wechsler intelligence tests [4–6]. Full Scale Intelligence Quotient (FSIQ) was derived to indicate general intellectual function, with 4 participants' FSIQs estimated by a tetrad of subtests [2] due to time constraints and fatigue. Four additional factorial indices are available for participants aged above 6 years, including the Verbal Comprehension, the Perceptual Reasoning (or the Perceptual Organization), the Working Memory, and the Processing Speed indices. For participants younger than 6 years, the Verbal and the Performance IQs were compiled into the Verbal Comprehension and the Perceptual Reasoning indices, respectively.

Verbal learning and memory were examined by a Word List test [20], in which four supra-span trials of 12 words were to be learned. A total immediate recall score indicating new learning ability and an intentional 30-min delayed recall score were obtained for each participants. Visual memory was assessed by the administration A of the form C of the Benton Visual Retention Test (BVRT) [21]. The participants were asked to reproduce 10 geographic line-drawings each after a 10-s exposure. The scores included the number of correct and the number of erroneous responses (e.g., omission, misplacement, rotations, and distortions).

Executive function was evaluated by the verbal fluency task. We only adopt the semantic verbal fluency task (to generate as many examples of fruit as possible within 1 min) because there is no proper equivalent form of phonemic fluency task in the Mandarin. This task requires updating, switching, and strategic retrieval of semantic knowledge, which is considered a facet of executive function.

MRP study and post-processing [16]

Dynamic susceptibility contrast MRP was used. The imaging parameters were TR/TE = 1000/40 ms, flip angle = 90°, thickness = 5 mm, gap = 3–5 mm depending on the head size, and 12 slices covering from the middle of the cerebellum up to the top of the cerebrum. A total of 0.1 mmol/kg contrast medium (Gadovist®, Bayer) was injected 5 s after the DSC imaging commenced, with injection rate of 3 cc/s, followed by a 20 cc saline flush. The time-to-peak (TTP) maps were post-processed; the window level was adjusted according to the value of the cerebellum TTP. The window width was fixed to 15 s. The cerebellum and the cerebrum with normal TTPs would appear blue, and the areas of prolonged TTP would appear green to red on the color maps. We used a standardized MRP scoring system [16] for semi-quantification of the TTP map (Fig. 2). Fourteen cerebral cortical regions from three levels (the ganglionic, the ventricular roof, and the high convexity) were selected for evaluation. The levels were about 2 cm apart. An area of blue color larger than 1/2 of one region is counted as 1 point, otherwise, it is counted as 0 points. The total TTP score of one hemisphere ranges from 0 to 14 points: 4, 8, and 2 for the anterior cerebral artery (ACA), MCA, and PCA territories, respectively.

Statistical analysis

Descriptive statistics were used to summarize basic information of the participants, where missing data were managed by mean imputation. The distribution of the values was examined and box plots were used to inspect potential statistical outliers. Nonparametric statistics were adopted due to violation of the assumption of normality and small sample size. Thus, Wilcoxon signed-rank tests were used to compare pre- and post-operative neuropsychological and neuroimaging results. Point-biserial correlation analyses were used to examine the potential effect of additional EPS.

In order to compare the relationship between cognitive and hemodynamic changes, difference scores were calculated by subtracting preoperative scores from postoperative scores. Spearman rank correlation coefficients were then used to examine the relationships between cognitive and hemodynamic change scores. Subsequently, partial correlation coefficients were computed to control for confounding factors, such as age. The relationships of postoperative change with demographic (i.e., age) and clinical variables (i.e., age of onset, symptom, and follow-up interval) were also explored with Spearman or point-biserial correlation coefficients, where appropriate. Type one error, alpha value, was set at 0.05.

Results

After indirect revascularization, all patients ($N = 23$) had clinical improvement with a mean follow-up period of 1–2 years.

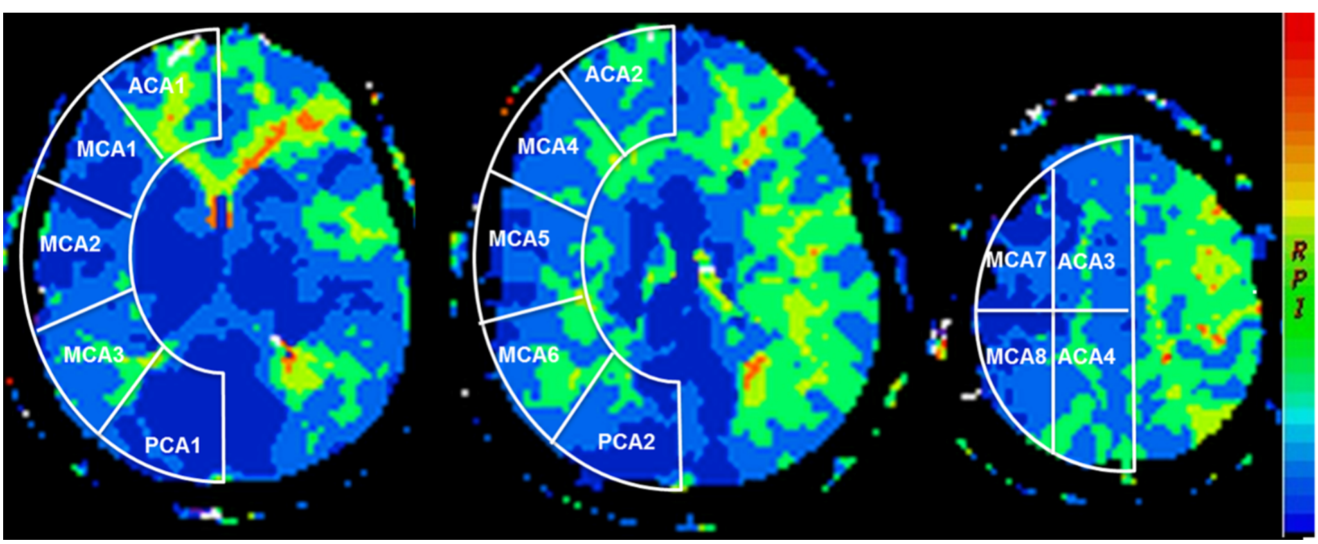

Fig. 2 Illustration of the time-to-peak (TTP) scoring system. From left to right, the basal ganglia, ventricular roof, and high convexity levels. There are total 14 cortical regions in a hemisphere. An area of blue color larger than 1/2 of one region is counted as 1 point, otherwise, it is counted as 0 points

The test interval of neurocognitive examinations was 22.02 months on average ($SD = 15.26$) and the interval of MRP studies was 16.36 months on average ($SD = 6.88$). Missing data were found in 3, 1, 6, and 4 participants on the FSIQ, the Word List, the BVRT, and the semantic verbal fluency tasks, respectively, and managed by mean imputation.

Postoperative cognitive changes

There was significant overall improvement of verbal memory function following surgical treatments (Table 1), as evidenced by performances on immediate recall ($p = 0.03$) and delayed recall ($p = 0.02$) of the Word List tests. The improvement was observed in 69.6% and 52.2% of the patients during immediate and delayed recall, respectively. There was no other significant difference when comparing pre- and postoperative cognitive performances. Point-biserial correlation coefficients showed no significant relationship between additional EPS and change scores of any neuropsychological test ($p = 0.09$–0.58).

Postoperative perfusion change

Postoperative MRP of the 26 cerebral hemispheres showed increased TTP scores in 84.6% of the right hemispheres and 92.3% of the left hemispheres (Table 2). Regional improvement was the most prominent in the MCA territories, as evidenced in 84.6% and 100% of the right and the left hemispheres, respectively. Wilcoxon sign-rank tests further proved that the postoperative perfusion change was significant at the group level both in the right ($p = 0.005$) and the left ($p = 0.003$) hemispheres, especially over the right ($p = 0.003$) and the left ($p = 0.001$) MCA territories.

Among the 13 patients received pre- and postoperative MRP studies, 4 of them underwent additional EPS. Point-biserial correlation coefficients showed significant relationships between additional EPS and perfusion change in bilateral ACA territories (the right side: $r = 0.69$, $p = 0.01$; the left side: $r = 0.58$, $p = 0.04$), yielding a large effect size.

The relationship between postoperative cognitive and hemodynamic changes

The postoperative cognitive changes including change scores of all cognitive indices were studied and correlated with the regional cerebral hemodynamic changes.

Spearman correlational analyses conducted with the 13 patients who received both pre- and postoperative neuropsychological and MRP examinations showed that the postoperative change of immediate recall was significantly correlated with change scores of the left MCA territories ($\rho = 0.66$, $p = 0.01$) with a large effect size (Fig. 3a). The correlation remained significant after controlling for age ($r = 0.68$, $p = 0.02$). However, a negative correlation was also observed between change scores of immediate recall and cerebral perfusion in the left PCA territories ($\rho = -0.69$, $p = 0.009$). There was no significant correlation

Table 1 Pre- and postoperative neuropsychological examination results

	N	Preoperative			Postoperative			Z	p	Effect size r	Improvement (%)	Deterioration (%)	Stable (%)
		Median	$Q1$	$Q3$	Median	$Q1$	$Q3$						
Intellectual function													
Full scale IQ	20	99	90	112	101.5	96	105	−0.40	0.69	0.08	12 (52.2%)	11 (47.8%)	0 (0.0%)
Verbal Comprehension		98	89	115	101.8	95	109	−0.63	0.53	0.13	13 (56.5%)	9 (39.1%)	1 (5.3%)
Perceptual Reasoning/Organization		100	90	116	99.7	94	108	−0.52	0.60	0.11	10 (43.5%)	12 (52.2%)	1 (5.3%)
Working Memory		100	97	106	101.5	97	111	−0.33	0.75	0.07	12 (52.2%)	10 (43.5%)	1 (5.3%)
Processing Speed		100.8	86	111	101.1	94	113	−0.21	0.83	0.04	13 (56.5%)	10 (43.5%)	0 (0.0%)
Memory Function													
Word List	22												
Immediate recall		32	21	36	33	27	37	-2.24^{*}	0.03	0.47	16 (69.6%)	4 (17.4%)	3 (13.0%)
Delayed recall		9	5	10	9	8	11	-2.30^{*}	0.02	0.48	12 (52.2%)	6 (26.1%)	5 (21.7%)
Benton Visual Retention Test	17												
Number Correct		6.9	6	8	7.1	7	9	−0.55	0.59	0.11	12 (52.2%)	7 (30.4%)	4 (17.4%)
Number Error		4.1	2	5	3	2	4	−1.42	0.16	0.30	15 (65.2%)	7 (30.4%)	1 (5.3%)
Executive function													
Verbal fluency	19	13.3	11	15	13	10	16	0.000	1.000	0.00	12 (52.2%)	10 (43.5%)	1 (5.3%)

$^{*}p < 0.05$

Table 2 Pre- and postoperative time-to-peak ratings ($N = 13$)

	Preoperative			Postoperative			Z	p	Effect size	Improvement		Deterioration		Stable	
	Median	$Q1$	$Q3$	Median	$Q1$	$Q3$			r	(%)		(%)		(%)	
Right hemisphere	7	4	11.5	12	11	12.5	− 2.84**	0.005	0.79	11	(84.6%)	2	(15.4%)	0	(0%)
ACA†	2	0.5	4	2	1	4	− 0.36	0.72	0.10	4	(30.8%)	4	(30.8%)	5	(38.5%)
MCA	4	1	6.5	8	8	8	− 2.96**	0.003	0.82	11	(84.6%)	0	(0%)	2	(15.4%)
PCA	2	2	2	2	2	2	− 1.00	0.32	0.28	1	(7.7%)	0	(0%)	12	(92.3%)
Left hemisphere	7	4	9	11	9	12.5	− 2.97**	0.003	0.82	12	(92.3%)	1	(7.7%)	0	(0%)
ACA†	1	0	3.5	2	1	3.5	− 0.46	0.64	0.13	6	(46.2%)	4	(30.8%)	3	(23.1%)
MCA	4	1	5	8	7	8	− 3.19**	0.001	0.89	13	(100%)	0	(0%)	0	(0%)
PCA	2	2	2	2	0.5	2	− 1.86	0.06	0.52	0	(0%)	4	(30.8%)	9	(69.2%)

** $p < 0.01$

† Note that additional frontal EPS was significantly correlated with perfusion change in bilateral ACA territories (the right side: $r = 0.69$, $p = 0.01$; the left side: $r = 0.58$, $p = 0.04$)

between change scores of delayed recall performance and cerebral perfusion in the left MCA territory ($\rho = -0.39$, $p = 0.18$). A similar negative correlation was present between change scores of delayed recall and that of the left PCA perfusion ($\rho = -0.60$, $p = 0.03$).

Although there was no significant postoperative intellectual change at the group level, the change scores of the FSIQ was significantly correlated with the change scores of cerebral perfusion over the left hemispheres ($\rho = 0.65$, $p = 0.02$), especially that in the left MCA territories ($\rho = 0.74$, $p = 0.004$) with a large effect size (Fig. 3b). Even after controlling for age, the correlation between change scores of the FSIQ and change scores of cerebral perfusion remained significant over the left hemispheres ($r = 0.67$, $p = 0.02$) and over the left MCA territories ($r = 0.08$, $p = 0.002$). Furthermore, postoperative change of the Verbal Comprehension index was significantly correlated with perfusion change in the left MCA territory ($\rho = 0.61$, $p = 0.03$), showing another large effect size. A similar pattern of negative correlation was observed between change scores of the Verbal Comprehension index and change scores of the left PCA perfusion state ($\rho = -0.72$, $p = 0.006$). There was no other significant correlation observed between change scores of cognitive performances and that of cerebral perfusion.

Factors associated with postoperative improvement

Regarding postoperative cognitive change, correlational analyses showed that the change scores of the immediate recall was significantly correlated with sex ($r = -0.42$, $p = 0.05$), favoring females. The change of the Verbal Comprehension

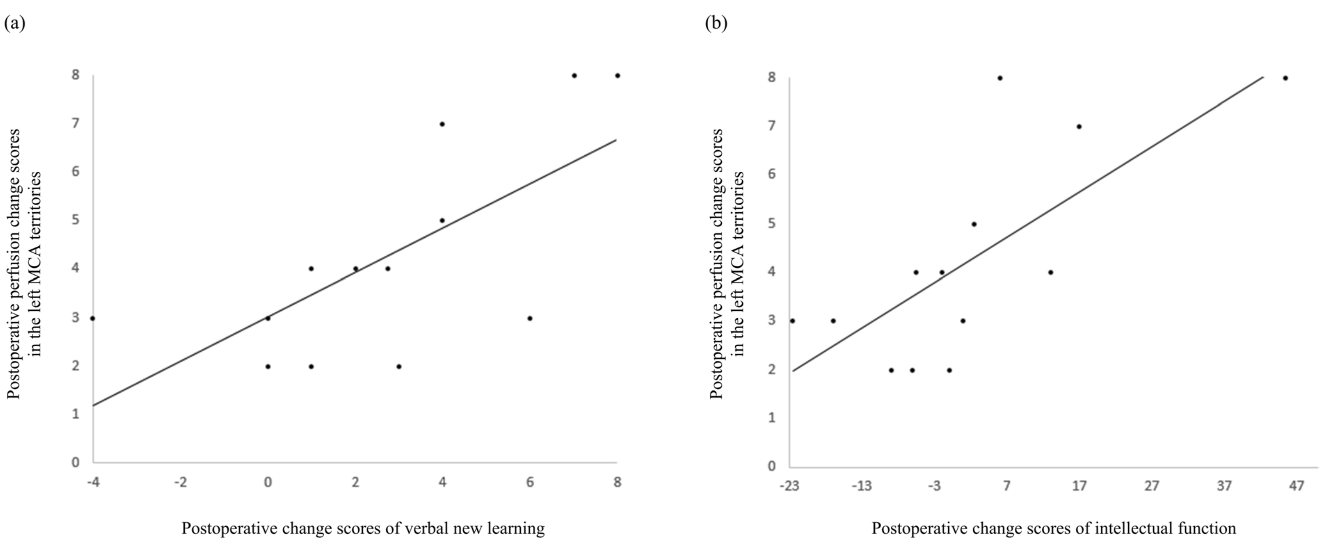

Fig. 3 Correlation between postoperative cognitive and hemodynamic changes. The plot shows **a** significant relationship between postoperative change scores of cerebral perfusion in the left MCA territories and the change scores of verbal new learning as measured by immediate recall of the Word List test, and **b** significant relationship between postoperative change scores of cerebral perfusion in the left MCA territories and the change scores of intellectual function

index was otherwise inversely correlated with symptom duration ($\rho = -0.46$, $p = -0.03$), indicating greater postoperative improvement in patients with shorter symptom duration. There was no other significant correlation between change scores of cognitive performances and other pre-determined variables.

As for cerebral hemodynamics, postoperative perfusion change scores in the left MCA territories was significantly correlated with follow-up intervals ($\rho = 0.64$, $p = 0.02$), showing better postoperative hemodynamic improvement as the follow-up interval increased. Inspection of data showed that in the first year following indirect revascularization, the average change scores in the left MCA territories was 2.25, while it became 5 and 5.33 for those who have received MRP follow-up in the second and the third year, respectively. There was no other significant correlation between postoperative perfusion change and pre-determined variables.

Discussion

This study aims to examine the relationships between cognitive and hemodynamic changes following indirect revascularization in childhood MMD. The results shows that the selective, remarkable improvement of verbal new learning is significantly correlated with hemodynamic improvement in the left cerebral hemispheres, especially in the left MCA territories. This perfusion improvement in the left MCA territories was also significantly correlated with intellectual improvement that was observed in a subset of the patients. The finding confirmed that the potential surgical benefit on cognitive outcome was associated with biological alteration and does not merely result from practice effect at the behavioral level.

Limited studies investigated the neural mechanisms underlying postoperative cognitive change in patients with MMD. Case reports of adult patients showed correlations between cognitive improvement and increased perfusion after direct bypass [10] and burr hole surgery [1]. Recently, Lei and coworkers found that significant improvement of executive function was correlated with postoperative radiological change over the right frontal lobe, especially the dorsolateral regions, after unilateral combined STA-MCA bypass and encephalo-duro-myo-synangiosis in 14 adult moyamoya patients [15]. As far as we are aware, the current study is the first to investigate this issue in childhood MMD.

The present results implied that the cognitive benefit of surgical treatment was selective. The finding was in line with the surgical mechanism of EDAS plus dural infolding that targets on the MCA territories which partially support memory function. Although significant group-wise improvement was only reported in verbal memory, a small to medium effect size was also observed in visual memory ($r = 0.30$, Table 1). Similarly, the correlation between visual memory and the right MCA regional perfusion improvement achieved small effect size both for correct scores ($\rho = 0.30$) and error scores ($\rho = -0.20$) of the BVRT. Future studies with larger sample size may render a clearer picture. Meanwhile, this finding is in line with previous reports of postoperative memory improvement after EDAS and/or EPS [12, 14], although we did not find significant improvement of Performance IQ as in these studies. In Kim and coworkers' larger scale study [12], they found significant improvement of overall memory performance and executive function following parietal cover surgery. Lee and coworkers [14] also found improvement of visual memory in addition to more efficient visuo-motor coordination after EDAS/ EPS procedures.

When examining factors that may have an influence on postoperative surgical outcome, it is noted that more improvement of regional perfusion in the left MCA territory was associated with longer follow-up intervals. This observation implicates a promising potential of indirect revascularization regarding long-term hemodynamic outcome once the collateral is established by indirect revascularization. However, we need to stress that in this study, the change scores of the postoperative hemodynamic study were collected at the time of postoperative cognitive follow-up in each patient. The interval ranged from 6 months to 6 years. During the follow-up period, the frequency of MRP studies was more than the cognitive studies. Though we found that postoperative perfusion change scores in the left MCA territories was significantly correlated with follow-up intervals, the interpretation of this findings as "the longer follow-up interval correlated with better postoperative hemodynamic improvement" should be cautious. In our previous study using the same TTP maps and scoring system to quantify the sequential perfusion changes in patients with moyamoya disease, we found that the score improvement shows a trend up as the follow-up interval increases, the score improvements are most robust at 0–3 months than at 3–6 months of follow-up. The changes stabilized after 6 months. The difference between the 6- and 12-month scores was minor [16]. On the other hand, it is noticed that more improvement of verbal comprehension was associated with shorter symptom duration at the time of intervention, indicating the importance of early surgical treatment that may render a better cognitive outcome.

Interestingly, a sex effect was revealed in terms of postoperative cognitive improvement, where female patients showed more improvement on verbal new learning after surgery. The same correlation was not observed between sex and other variables such as age, age of onset, symptom duration, follow-up interval, baseline cognitive or perfusion scores. This finding is partially contradictory to a previous report [11] where female patients were more prone to preoperative TIAs and postoperative complications than males. However, the same report still found favorable postoperative outcome in females patients. The possible sex difference in terms of surgical outcome awaits further corroboration.

The observation of inverse correlations between change scores of memory recall and that of cerebral perfusion in the left PCA territories may be due to two possible mechanisms. First, this inverse correlation pattern may not relate to the revascularization. The underlying moyamoya pathology may involve the PCA territories in a subset of the participants. Second, the postoperative improvement in the MCA territory may reduce the compensatory flow from the PCA. The change scores of immediate and delayed recall may thus inversely correlated with the perfusion in the PCA territory.

There are several limitations of the current study. The sample size was relatively small, and the representativeness was restricted by the exclusion of patients whose clinical condition hampered test administration. Missing values also made the overall results less integral, and the findings may partly be influenced by attrition bias. Another limitation is the variability of cognitive testing time, which results in a potential confounding factor of long-term restoration effect. Lastly, our patients received bilateral EDAS plus dural infolding as the primary surgical treatment. Thus, the surgical benefit was prominent in the MCAs but rather limited in the ACA and the PCA territories, although some improvement was observed in the ACA-MCA and MCA-PCA watershed areas. We found patients undergone additional frontal EPS with more perfusion improvement in the ACA territories; however, the sample size was too small for statistical comparisons. It awaits future study to investigate the cognitive benefit of different combination of surgeries.

In conclusion, the present study examined the biomechanism underlying cognitive improvement following indirect revascularization, and factors related to postoperative outcomes in childhood MMD. The results showed remarkable memory improvement that was associated with increased regional perfusion in the MCA territories. Better postoperative cognitive and hemodynamic improvements were associated with female sex, shorter symptom duration at time of intervention and longer follow-up intervals. The results implied the importance of early intervention and the promising potential of indirect revascularization regarding long-term hemodynamic outcome.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yen-Hsuan Hsu, Ya-Fang Chen, Chie-Cheng Yang, and Meng-Fai Kuo. The first draft of the manuscript was written by Yen-Hsuan Hsu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards This study was approved by the Research Ethics Committee of National Taiwan University Hospital (200910036R). All participants and/or their proxies signed written informed consent before entering the study.

Conflict of interest The authors declare that they have no conflicts of interest.

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