Different aspects of dysexecutive syndrome in patients with moyamoya disease and its clinical subtypes

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OBJECTIVE Dysexecutive syndrome is common in patients with moyamoya disease (MMD), a chronic cerebrovascular disease that is characterized by stenosis of the bilateral internal carotid arteries and progressive collateral revascularization, and MMD can be classified as ischemic or hemorrhagic according to the disease presentation and history. In this study, the authors aimed to determine which aspects of executive function are impaired in patients with MMD, in addition to the specific dysexecutive functions present among its clinical subtypes and the mechanisms underlying dysexecutive function in these patients.

METHODS The authors administered 5 typical executive function tests (the Stroop test, the Hayling Sentence Completion Test [HSCT], the verbal fluency [VF] test, the N-back test, and the Sustained Attention to Response Task [SART]) to 49 patients with MMD and 47 IQ-, age-, education-, and social status–matched healthy controls. The dysexecutive questionnaire (DEX) was also used to assess participants' subjective feelings about their executive function. A total of 39 of the patients were evaluated by CT perfusion (CTP) before the assessments were performed, and the correlations among the performances of the patients on the above tests with the parameters of cerebral blood volume, cerebral blood flow (CBF), mean transit time (MTT), and time-to-peak (TTP) in the frontal lobes of these patients were also analyzed.

RESULTS Many aspects of executive function in the patients with MMD were significantly poorer than those in the healthy controls, and the patients performed particularly poorer on the VF test, HSCT, N-back test, and SART. The patients with hemorrhagic MMD exhibited worse executive inhibition, executive processing, and semantic inhibition compared with those with ischemic MMD, but the latter group presented a worse working memory and poorer sustained attention. There were no significant differences in the DEX scores between the patients with MMD and healthy controls. The other findings were as follows: CBF was significantly positively correlated with the number correct on part B of the HSCT ($r = 0.481$, $p = 0.01$) and accuracy on the 0-back task of the N-back ($r = 0.346$, $p = 0.031$); MTT was significantly positively correlated with accuracy on the 2-back task of the N-back ($r = 0.349$, $p = 0.034$) and factor 5 of the DEX ($r = 0.359$, $p = 0.032$); and TTP was significantly positively correlated with the number correct on part B of the HSCT ($r = 0.402$, $p = 0.034$) and the 1-back reaction time of the N-back ($r = 0.356$, $p = 0.026$).

CONCLUSIONS The patients with MMD exhibited impairments in semantic inhibition, executive processing, working memory, and sustained attention, but they were not aware of these deficits. Moreover, differences in dysexecutive function existed between the different subtypes of MMD. Hypoperfusion of the frontal lobe may be related to working memory and semantic inhibition impairments in patients with MMD.

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KEY WORDS moyamoya disease; dysexecutive function; presentation; vascular disorders

ABBREVIATIONS CBF = cerebral blood flow; CBV = cerebral blood volume; CTP = CT perfusion; DEX = dysexecutive questionnaire; HSCT = Hayling Sentence Completion Test; ICA = internal carotid artery; MMD = moyamoya disease; MTT = mean transit time; ROI = region of interest; RT = reaction time; SART = Sustained Attention to Response Task; TIA = transient ischemic attack; TTP = time-to-peak; VF = verbal fluency.

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MOYAMOYA disease (MMD) is a rare, chronic cerebrovascular disease characterized by bilateral progressive stenosis of the arteries of the circle of Willis, ultimately leading to occlusion of the distal intracranial internal carotid arteries (ICAs) and progressive collateral revascularization.^{2,13,16,21,32} MMD has variable clinical presentations. The disease causes ischemic stroke, intracranial hemorrhage, headache, seizures, and transient ischemic attacks (TIAs).²⁷ MMD presentations can be subdivided into the following 4 categories, which are not mutually exclusive: ischemic, hemorrhagic, epileptic, and “other.”¹⁴ Hemorrhagic and ischemic MMD exhibit some differences. Hemorrhaging in patients with MMD is related to the fragility of the neovessels, and inadequate perfusion leads to ischemic presentations, which are classified as infarction, TIA, and “other.”²¹ Revascularization surgery is effective for improving symptoms and reducing the incidence of subsequent ischemic stroke in patients with ischemic MMD.²³ Whether revascularization surgery is helpful for preventing future intracranial hemorrhaging remains unclear.¹⁷ Some studies have shown that patients who undergo revascularization surgery generally have a lower risk of rebleeding compared with those who undergo conservative treatment, but this difference is not statistically significant.^{11,17,23}

Patients with MMD are known to exhibit impairments in some cognitive functions, especially executive functions.^{13,16,19,29,30,34} For example, Karzmark et al. assessed executive function in 30 patients with MMD by examining the total number of correct responses on the Delis-Kaplan Executive Functioning System Design Fluency Test, Letter and Category Fluency Tests, and part B of the Trail Making Test and found that some of these patients had impaired executive functioning.¹⁹ Notably, executive function is an umbrella term for cognitive processes, including inhibition, working memory, reasoning, task flexibility, problem solving, and planning and execution.^{9,12,25} The aspects of executive function that are impaired in patients with MMD are unknown. Furthermore, whether different clinical subtypes of MMD are associated with different types of dysexecutive function remains unclear. Moreover, the mechanisms underlying the dysexecutive function observed in patients with MMD remain unknown. Although studies have not obtained conclusive results in this regard, most studies have demonstrated that dysexecutive syndrome in patients with MMD is due to hypoperfusion.^{7,26,31} However, some researchers have suggested that there are other relevant risk factors or comorbid conditions that lead to dysexecutive syndrome, such as clinical stroke history, bilateral or unilateral disease, and younger age at onset.^{16,20,33} Therefore, a study of dysexecutive syndrome in different clinical MMD subtypes is warranted. Hence, in the current study, we aimed to determine which aspects of executive function are impaired in patients with MMD compared with healthy controls, and to identify the clinical subtypes and mechanisms underlying dysexecutive function in these patients.

Methods

Study Participants

We enrolled 56 patients in our study who were admitted

to Beijing Tiantan Hospital at Capital Medical University in China from April 1, 2014, to September 15, 2014. All of the patients met the following inclusion criteria: 1) IQ > 70; 2) right-handed; 3) age > 10 years and < 50 years; 4) diagnosis of bilateral MMD based on digital subtraction angiography; 5) no history of revascularization surgery; 6) time interval from symptom onset to assessment of > 1 month; 7) ischemic MMD based on MRI results without intracranial bleeding prior to the assessment, and presentation as infarction, TIA, epilepsy, or other; and 8) hemorrhagic MMD with hemorrhagic presentation and a stable condition upon enrollment. The exclusion criteria were as follows: 1) diagnosis of psychological or mental disease; 2) other brain lesions, such as a brain tumor or brain trauma; 3) serious systemic disease, such as cardiac disease; and 4) severe dyskinesia or a language disorder that would prevent the completion of all of the tests. We also enrolled 4 patients who were diagnosed based on MR angiography, performed at an outpatient department. Additionally, we recruited 65 IQ-, age-, education-, social status- and sex-matched volunteers who had not been diagnosed with MMD or any other cerebral disease as the healthy control cohort. After exclusion of some of the subjects who had low intelligence (IQ < 70) or a high education level and those who did not complete all of the tests, a total of 47 healthy subjects and 49 patients were enrolled. Table 1 shows the patient demographics and clinical information.

Imaging Protocol

A General Electric LightSpeed VCT scanner was used for evaluation of 39 of the patients by CT perfusion (CTP) before cognitive assessments. The mean time interval from CTP scanning to the assessments was 7 ± 3 days. Two neuroradiologists who were blinded to the clinical data jointly analyzed the CTP data using Neuro PCT software (Siemens Medical System) on a Siemens Medical System workstation. Maps of the cerebral blood volume (CBV) and cerebral blood flow (CBF), mean transit time (MTT), and time-to-peak (TTP) were generated as previously described.³⁶ Four parameters were calculated from an average of 8 regions of interest (ROIs) in 2 layers located in frontal white matter with a normal appearance. We modified the ROIs that were selected as previously described.⁷ Each ROI consisted of a circle of 55–60 mm².

Neuropsychological Tests

General Intelligence Test

All participants underwent an IQ evaluation using the Wechsler Adult Intelligence Scale-Third Edition (Chinese version) based on 4 subtests (Information, Digital Span, Similarity, and Arithmetic) or the Wechsler Intelligence Scale for Children-Fourth Edition (Chinese version) for those who were between 6 and 16 years of age.^{15,35}

Executive Function Tests

Comprehensive executive function tests were performed to assess different aspects of executive function, including executive inhibition, semantic inhibition, executive processing, working memory, and sustained attention.

The Stroop test was used to assess executive inhibi-

TABLE 1. Characteristics of participants and clinical information on patients

Variable	MMD Patients	Healthy Controls	t-Test/Chi-Square Test	p Value
No. of cases	49	47		
Mean age $\pm$ SD (yrs)	27.88 $\pm$ 14.063	27.21 $\pm$ 14.709	-0.226	0.821
Sex			0.045	0.831
Male	24	22		
Female	25	25		
Social Status			1.027	0.311
City	21	25		
Noncity (county village)	28	22		
Mean yrs of education $\pm$ SD	7.47 $\pm$ 3.759	8.51 $\pm$ 4.624	1.213	0.228
Mean estimated IQ $\pm$ SD	96.52 $\pm$ 18.064	103.83 $\pm$ 21.464	1.585	0.117
Type of MMD				
Hemorrhagic	13	—		
Ischemic	36	—		
TIA	14	—		
Infarction	19	—		
Epilepsy*	1	—		
Others§†	3	—		
Mean age of onset $\pm$ SD (years)	25.76 $\pm$ 14.952			
Mean duration of disease $\pm$ SD (mos)	19.35 $\pm$ 24.408			

* One patient's presentation was classified as both epilepsy and infarction.

† Presentations for "others" included headache, dizziness, and neck stiffness in our patients. MRI resulted in a diagnosis of ischemia, not infarction.

tion.²⁴ Participants were asked to select colors in the following 3 presentation formats: dots, words, and colors. The total time and number of mistakes were then recorded for each condition.

The Hayling Sentence Completion Test (HSCT) was employed to assess semantic inhibition.³ Participants were asked to complete a sentence with the final word omitted, in either a logical (Part A, initiation section) or illogical manner (Part B, inhibition section). In Part B, any word that is semantically associated with the sentence should be avoided. A shorter latency period and fewer errors on Part A or Part B indicate good initiation or inhibition function. For both Parts A and B, the total time (sum of all terms' reaction times [RTs]), correct number, and mean correct RT (total correct terms' RTs/correct number) were recorded. The numbers of type A and type B errors were also recorded for Part B.

The verbal fluency (VF) test was used to assess executive processing based on the number of words that were verbally produced in response to an animal's name within 1 minute.¹⁸ The total number and repeat number of the animal names were recorded.

The N-back test was used to assess the spatial working memory of each participant.⁴ Using computer software, a square and a plus sign ("+") were presented on the screen, and their relative locations were varied; 0-back, 1-back, and 2-back tasks were used in the current study. The 0-back task required the participants to determine the various relative locations of 2 figures. The 1-back task required the subjects to keep the initial relative locations of the square and "+" in mind and to determine whether the next locations presented were different. The 2-back

task was more difficult. For this task, participants were required to compare the relative locations of the square and "+" between the current trial and the trial before the last. For each trial, the accuracy and mean RT were recorded each time the mouse was pressed.

The Sustained Attention to Response Task (SART) was administered to assess the sustained attention of each subject.^{8,28} The SART is a computer test in which 225 single digits are presented to the test taker over 4.3 minutes. Each digit is presented for 250 msec, followed by a 900-msec mask. The participants were required to press a key in response to the digits except on 25 occasions, when the digit 3 would randomly appear. We recorded the following results: hits (the accuracy with which the participant pressed the mouse when a number other than 3 appeared), the hit RT (the mean RT of the hit), and the correct rejections (the accuracy with which the participant did not press the mouse when the number 3 appeared).

Dysexecutive Questionnaire

The Dysexecutive Questionnaire (DEX) was used to assess all of the participants' subjective feelings about their executive functioning. There were a total of 20 items, and this test was administered to participants aged 18 to 50. For the participants who were younger than 18 years of age, their families were required to complete these items using the DEX-other.¹⁰

Testing Procedure

After signing an informed consent form, each participant was evaluated using the above tests, with a random sequence of test administration, which did not affect the

results of any of the tests. We expressed our appreciation to each participant for his or her involvement in the study. This study was approved by the Institutional Review Board of Beijing Tiantan Hospital in affiliation with Capital Medical University.

Statistical Analysis

A multivariate ANOVA was used to compare cognitive function between the patients with MMD and the healthy controls, patients with hemorrhagic MMD and ischemic MMD, as well as between 3 different ischemic presentations (infarction, TIA, and other). Because there was only 1 patient with epilepsy, which coexisted with infarction, we did not address this presentation. Moreover, age and education were used as covariates in the multivariate ANOVA. We also performed correlation analysis to assess the correlations of CBF, CBV, MTT, TTP, and the time interval from presentation to assessment with all of the test items. The level of statistical significance was set at 0.05.

Results

Differences in Test Performances Between Patients With MMD and Healthy Controls

A summary of the patients' test performances is provided in Table 2. The total number on the VF test was significantly lower for the patients with MMD than that for the healthy controls ($F [1, 94] = 20.150, p < 0.05$), indicating that the patients had poorer executive processing. The total time ($F [1, 94] = 11.222, p < 0.05$, for part A; $F [1, 94] = 10.155, p < 0.05$, for part B), mean correct RTs for both part A and part B ($F [1, 94] = 6.860, p < 0.05$, and $F [1, 94] = 7.952, p < 0.05$, respectively), and the number correct for part B of the HSCT ($F [1, 94] = 38.898, p < 0.05$) were all significantly different between the patients with MMD and healthy controls, suggesting that the semantic inhibition of the patients with MMD was significantly worse compared with that of the healthy controls. The accuracy scores of the patients with MMD did not significantly differ from those of the controls on the 0-back and 1-back tasks of the N-back test ($F [1, 94] = 0.368, p > 0.05$, and $F [1, 94] = 2.537, p > 0.05$, respectively); however, the accuracy of these 2 groups significantly differed on the 2-back task ($F [1, 94] = 8.877, p < 0.05$), indicating that the working memory of the patients with MMD was significantly poorer than that of the healthy controls when the difficulty of the test was increased.

In addition, the RTs for the 0-back task ($F [1, 94] = 4.799, p < 0.05$), as well as hits ($F [1, 94] = 9.774, p < 0.05$) and the hit RT on the SART ($F [1, 94] = 8.641, p < 0.05$) significantly differed between the patients with MMD and healthy controls, suggesting that these patients had poorer sustained attention. However, none of the DEX questionnaire indices were significantly different.

Differences in Dysexecutive Function Among the Different Clinical Subtypes

The performances on all of the executive function tests were compared between the patients with hemorrhagic MMD and ischemic MMD (Table 3). The patients with

hemorrhagic MMD exhibited poorer performances than the patients with ischemic MMD on the Stroop test, VF test, and HSCT, with the exception of the number of type A errors. However, the patients with hemorrhagic MMD performed better than the patients with ischemic MMD on the N-back test and SART, with the exception of the hit RT.

There were no significant differences in test performances among the 3 ischemic subgroups (Table 4); however, the patients with infarction (subgroup 1) performed worse than those with TIA (subgroup 2), who performed worse than those in the "other" subgroup (subgroup 3), according to the results of the Stroop and VF tests. However, on the N-back test and SART, the patients in subgroup 1 performed more poorly than those in subgroup 3, who performed better than those in subgroup 2.

We also found that the patient age at onset was significantly negatively associated with the number of mistakes on the words condition of the Stroop test ($r = -0.326, p = 0.022$), and it was positively associated with the 1-back RT ($r = 0.336, p = 0.018$). The time interval from symptom onset to assessment (mean 19.35 ± 24.408 months) was also significantly negatively associated with the accuracy of the 1-back task ($r = -0.432, p = 0.002$) and the number of type B errors ($r = -0.324, p = 0.03$) and positively associated with the number correct ($r = 0.412, p = 0.005$) on part B of the HSCT.

Correlations Among CTP, the Time Interval From Presentation to Assessment, and Executive Function

CBF was significantly correlated with the number correct on part B of the HSCT ($r = 0.481, p = 0.01$) and accuracy on the 0-back task of the N-back ($r = 0.346, p = 0.031$). MTT was also significantly associated with accuracy on the 2-back task of the N-back ($r = 0.349, p = 0.034$) and factor 5 of the DEX ($r = 0.359, p = 0.032$), and TTP was significantly correlated with the number correct on part B of the HSCT ($r = 0.402, p = 0.034$) and the 1-back RT of the N-back ($r = 0.356, p = 0.026$).

Discussion

The results of the current study indicated that the patients with MMD had poorer executive functioning than the healthy controls, which is consistent with previous studies.^{6,7,13,26,31} We also found that various aspects of executive function, including semantic inhibition, executive processing, working memory, and sustained attention were significantly impaired in the patients. Moreover, the 2-back RTs in the patients with MMD were greater than that of the healthy controls, indicating that the controls spent more time thinking about how to achieve accuracy. Additionally, we found that most of the healthy controls consistently applied a strategy, for example, they used objects that they saw in the room as their answers to part B of the HSCT. However, almost all of the patients with MMD failed to employ a strategy for part B of the HSCT. Thus, patients with MMD may exhibit poorer executive processing and task flexibility.

Unfortunately, the results of the DEX questionnaire did not reflect this impairment in executive functioning

TABLE 2. Performances of patients with MMD and healthy controls on executive function tests

Tests	Patients*	Controls*	F Value	p Value
Stroop			1.603	0.156
Dot condition				
Total time	20.348 ± 9.018	16.05 ± 6.622	7.022	0.010
No. of errors	0.90 ± 1.358	0.56 ± 0.976	1.428	0.235
Word condition				
Total time (sec)	26.262 ± 14.724	20.288 ± 8.506	5.667	0.019
No. of errors	0.84 ± 1.297	0.71 ± 1.342	0.213	0.646
Color condition				
Total time (sec)	41.624 ± 19.309	31.265 ± 14.757	6.812	0.011
No. of errors	3.65 ± 3.461	2.61 ± 3.114	1.446	0.232
VF test			7.768	<0.001
Total no.	13.63 ± 4.978	18.93 ± 6.948	20.150	<0.001
Repeat no.	0.94 ± 1.180	1.71 ± 3.783	1.583	0.212
HSCT			4.306	<0.001
Part A				
Total time (sec)	46.72 ± 25.831	25.02 ± 11.200	11.222	0.001
No. correct	14.47 ± 1.21	14.77 ± 0.679	0.332	0.567
Mean correct RT (sec)	3.40 ± 2.547	1.73 ± 0.925	6.860	0.011
Part B				
Total time (sec)	98.41 ± 49.73	53.79 ± 28.877	10.155	0.002
No. correct	3.21 ± 2.942	6.73 ± 4.177	38.898	0.004
No. Type A errors	5.85 ± 2.819	3.67 ± 3.517	3.531	0.065
No. Type B errors	5.91 ± 2.261	4.63 ± 2.442	3.196	0.079
Mean correct RT (sec)	6.00 ± 4.217	3.29 ± 2.034	7.952	0.006
N-back test			2.980	0.012
0-back				
RT (msec)	554.81 ± 112.175	475.09 ± 83.083	4.799	0.031
Accuracy	0.92 ± 0.121	0.94 ± 0.130	0.368	0.546
1-back				
RT (msec)	772.20 ± 249.823	751.30 ± 223.063	0.017	0.896
Accuracy	0.55 ± 0.215	0.66 ± 0.229	2.537	0.115
2-back				
RT (msec)	749.29 ± 327.278	828.25 ± 312.840	0.961	0.330
Accuracy	0.35 ± 0.159	0.49 ± 0.225	8.877	0.004
SART			7.735	<0.001
Hit	0.868 ± 0.185	0.975 ± 0.032	9.774	0.002
Hit RT (msec)	483.248 ± 123.374	397.784 ± 107.012	8.641	0.004
Correct rejections	0.67 ± 0.215	0.81 ± 0.224	6.832	0.011

* Data given as mean ± SD.

and task flexibility, which suggested that the patients with MMD or their families did not recognize their dysexecutive syndrome, which may have led to a delayed visit to the clinic. A previous study has suggested that patients with MMD exhibit impaired metacognitive executive functioning.³³ Moreover, the impairments in working memory and semantic inhibition that were observed in the patients with MMD in this study were significantly positively associated with the time interval between presentation and assessment, indicating a delayed a visit to the clinic, which

may have led to worsened executive functioning, particularly working memory and semantic inhibition. A previous study has also suggested that a prolonged duration of symptoms and a younger age at onset are associated with cognitive impairment.¹⁶

Patients with MMD with different presentations exhibited differences in executive impairment, according to their results on tests administered in this study. Three highlights in our results should be addressed. First, our results showed that the patients with hemorrhagic MMD

TABLE 3. Performances on executive function tests between patients with hemorrhagic MMD and ischemic MMD

Test	Hemorrhagic Group*	Ischemic Group*	F Value	p Value
No. of patients	13	36		
Stroop			0.239	0.961
Dot condition				
Total time (sec)	20.859 ± 8.990	20.164 ± 9.148	0.143	0.708
No. of errors	1.00 ± 1.472	0.86 ± 1.334	0.720	0.401
Word condition				
Total time (sec)	27.298 ± 13.376	25.889 ± 15.345	0.318	0.576
No. of errors	0.77 ± 0.927	0.86 ± 1.417	0.125	0.725
Color condition			1.654	0.191
Total time (sec)	43.549 ± 19.628	40.930 ± 19.426	0.084	0.773
No. of errors	3.62 ± 3.176	3.67 ± 3.602	0.003	0.959
VF				
Total no.	13.69 ± 3.172	13.61 ± 5.525	0.004	0.950
Repeat no.	1.62 ± 1.502	0.69 ± 0.951	4.929	0.031†
HSCT			1.487	0.216
Part A				
Total time (sec)	52.22 ± 22.234	44.43 ± 27.300	2.436	0.706
No. correct	14.30 ± 1.160	14.54 ± 1.250	0.262	0.903
Mean correct RT (sec)	3.758 ± 1.994	3.251 ± 2.771	1.659	0.564
Part B				
Total time (sec)	97.170 ± 53.230	98.926 ± 49.386	10.234	0.113
No. correct	3.10 ± 1.524	3.25 ± 3.391	1.296	0.907
No. Type A errors	5.30 ± 2.627	6.08 ± 2.918	0.900	0.299
No. Type B errors	6.50 ± 1.900	5.67 ± 2.390	0.113	0.304
Mean correct RT (sec)	6.051 ± 5.219	5.978 ± 3.854	0.013	0.059
N-back			0.724	0.633
0-back				
RT (msec)	551.944 ± 103.249	555.970 ± 117.170	0.410	0.526
Accuracy	0.923 ± 0.109	0.921 ± 0.123	0.477	0.494
1-back				
RT (msec)	759.514 ± 272.308	777.348 ± 244.511	1.598	0.213
Accuracy	0.562 ± 0.243	0.550 ± 0.206	0.025	0.875
2-back				
RT (msec)	631.397 ± 344.694	797.180 ± 312.794	3.777	0.059
Accuracy	0.356 ± 0.166	0.345 ± 0.158	0.065	0.800
SART			1.412	0.235
Hit	0.854 ± 0.162	0.873 ± 0.194	0.009	0.923
Hit RT (msec)	481.411 ± 125.627	483.859 ± 124.412	0.864	0.358
Correct rejections	0.53 ± 0.224	0.72 ± 0.192	6.535	0.014†

* Data given as mean ± SD.

† Statistically significant.

had poorer executive inhibition, executive processing, and semantic inhibition than the patients with ischemic MMD, but the latter group exhibited worse working memory and poorer sustained attention. Hemorrhage related to the fragility of the neovessels is an acute process, leading to much more severe impairment of the normal brain compared with ischemia, which is a chronic process. Chronic processes include compression of neovessels that supply

blood. Moreover, working memory and sustained attention are more vulnerable over time than executive inhibition, executive processing, and semantic inhibition, which are related to stable functioning. Second, in terms of executive inhibition and executive processing, the patients with infarction had poorer results than those with TIA, whose results were poorer than those of the patients in the “other” subgroup. However, the patients in subgroup 1 exhibited

TABLE 4. Executive function performances of the patients with MMD and ischemic presentations of infarction, TIA, and other

Tests	Infarction (n = 19)*	TIA (n = 14)*	Other (n = 3)	F Value	p Value
Stroop				1.025	0.440
Dot condition					
Total time (sec)	21.63 ± 11.331	19.63 ± 5.696	13.36 ± 2.482	1.819	0.179
No. of errors	1.05 ± 1.615	0.79 ± 0.975	0.000 ± 0.000	1.465	0.247
Word condition					
Total time (sec)	29.444 ± 18.549	23.687 ± 9.942	13.643 ± 1.625	3.526	0.042†
No. of errors	1.00 ± 1.732	0.86 ± 1.732	0.00 ± .00±1	1.258	0.298
Color condition					
Total time (sec)	48.43 ± 21.93	34.89 ± 11.941	21.66 ± 1.439	5.894	0.007†
No. of errors	4.05 ± 4.116	3.71 ± 4.116	1.00 ± 4.116	0.782	0.466
VF				0.996	0.437
Total no.	12.58 ± 5.368	14.36 ± 5.368	16.67 ± 5.368	2.170	0.131
Repeat no.	0.74 ± 0.991	0.71 ± 0.991	0.33 ± 0.991	0.195	0.824
HSCT				0.852	0.613
Part A					
Total time (sec)	42.557 ± 28.359	40.589 ± 23.392	63.417 ± 36.475	0.895	0.424
No. correct	14.33 ± 1.723	14.78 ± 0.441	14.67 ± 0.577	0.361	0.702
Mean correct RT (sec)	3.340 ± 3.509	2.751 ± 1.586	4.394 ± 2.717	0.447	0.646
Part B					
Total time (sec)	102.37 ± 53.196	85.415 ± 47.632	125.65 ± 38.008	1.289	0.297
No. correct	2.83 ± 3.070	4.00 ± 4.301	2.67 ± 1.528	0.455	0.641
No. Type A errors	6.33 ± 2.964	5.22 ± 3.073	7.67 ± 2.082	0.995	0.387
No. Type B errors	5.83 ± 2.290	5.78 ± 2.949	4.67 ± 0.577	0.272	0.765
Mean correct RT (sec)	6.229 ± 4.311	4.421 ± 2.869	9.649 ± 2.045	2.294	0.127
N-back				0.884	0.568
0-back					
RT (msec)	613.436 ± 133.88	507.809 ± 114.328	571.810 ± 76.672	2.701	0.083
Accuracy	0.870 ± 0.183	0.920 ± 0.090	0.990 ± 0.017	1.247	0.301
1-back					
RT (msec)	830.872 ± 236.056	684.761 ± 226.322	944.177 ± 39.005	0.683	0.513
Accuracy	0.50 ± 0.182	0.58 ± 0.210	0.71 ± 0.140	2.742	0.078
2-back					
RT (msec)	808.361 ± 338.161	754.470 ± 274.577	922.630 ± 412.377	0.305	0.740
Accuracy	0.335 ± 0.153	0.377 ± 0.177	0.267 ± 0.085	1.039	0.367
SART				0.732	0.715
Hit	0.827 ± 0.254	0.935 ± 0.067	0.887 ± 0.068	1.226	0.307
Hit RT (msec)	513.482 ± 102.683	437.808 ± 144.507	511.150 ± 126.271	1.984	0.155
Correct rejections	0.703 ± 0.212	0.732 ± 0.181	0.803 ± 0.110	1.034	0.368

* Data given as mean ± SD.

† Statistically significant.

worse results than those in subgroup 3, whose results were better than those of the patients in subgroup 2 in terms of working memory and sustained attention. Third, we found that the time interval from presentation onset to assessment was negatively associated with working memory but positively associated with semantic inhibition, which may indicate that the natural progression of MMD may be associated with not only improvements in some aspects of

executive function, but also worsening in other aspects. Further study is needed to clarify the effects of disease progression on executive function. Previous studies have indicated that revascularization surgery could improve the cognitive functioning of patients with MMD.^{5,22} However, determining when surgery should be performed and which aspect of executive function is altered in patients with different subtypes of MMD require additional research. Fur-

ther postoperative testing of these patients should be performed to clarify these issues.

Hypoperfusion of the frontal lobe may lead to some aspects of executive impairment in patients with MMD, especially regarding semantic inhibition and working memory. The results concerning the correlation between CTP and test performance in the current study indicated that perfusion of the frontal lobe was negatively correlated with semantic inhibition and working memory. The patients with infarction (located in the frontal lobes of all of the patients in subgroup 1) exhibited the worst performances on all of the tests in the 3 ischemic subgroups. This finding suggested that more severe ischemia led to poorer executive functioning, which is partially consistent with the results of previous studies, indicating that dysexecutive function results from hypoperfusion.^{7,26} Many neuroimaging and lesion studies have identified the functions that are most often associated with particular regions of the prefrontal cortex, including the dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex.¹ Moreover, both hemorrhagic and ischemic MMD always lead to occlusive bilateral ICAs, which are the most common arteries that supply blood to the frontal lobe.^{7,26} Other researchers have also suggested that cognitive impairment in patients with MMD may be attributed to stroke history or comorbid conditions. Su et al. have determined that smoking and Suzuki angiographic classification are clinical risk factors for cognitive impairment in patients with hemorrhagic MMD.³¹ Williams et al. have also suggested that stroke history and bilateral disease are risk factors.³³

The current study has some limitations. First, our sample size was small, particularly the patients with presentations classified as “other.” Second, all of our patients came from a single center, so the sample representation may not be optimal. Third, additional neuroimaging to detect frontal lobe function should have been performed to explore the potential mechanisms of dysexecutive function. Fourth, we did not include patients with ischemic or hemorrhagic disease due to an etiology other than MMD in the control group, which was matched to the patient group in terms of age, education level, and social status.

In summary, the current study provided evidence of the specific dysexecutive syndrome present in patients with MMD and its potential relationships with hemorrhage and ischemic presentation. Furthermore, our findings shed light on the consequences of cognitive dysfunction in MMD and its clinical subtypes and the potential mechanisms of the underlying dysexecutive impairments. In the future, we will seek to determine whether surgical revascularization improves dysexecutive syndrome in patients with hemorrhagic and ischemic MMD, as well as the aspects of executive function that may be altered.

Conclusions

The patients with MMD exhibited poorer executive functioning, especially with regard to semantic inhibition, executive processing, working memory, and sustained attention. However, they did not report subjective feelings related to their dysexecutive syndrome. The patients with hemorrhagic MMD showed poorer executive inhibition,

executive processing, and semantic inhibition than the patients with ischemic MMD, and the latter group showed worse working memory and poorer sustained attention. The patients with infarction exhibited the worst executive inhibition among the 3 subgroups of patients with ischemic MMD, and CTP of the frontal lobe was significantly correlated with perfusion of the frontal lobe, suggesting that chronic cerebral hypoperfusion results in impairments in the working memory and semantic inhibition aspects of dysexecutive function; however, this correlation may not fully explain other aspects of dysexecutive function.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Wan, Fang, Huang, Chan, Wang. Acquisition of data: Fang, Zhang, Chan. Analysis and interpretation of data: all authors. Drafting the article: Fang. Critically revising the article: Wan, Huang, Chan. Reviewed submitted version of manuscript: Wan, Huang, Wang. Statistical analysis: Zhang, Wang. Administrative/technical/material support: Wang. Study supervision: Wang.

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