Long-term study of the cognitive profile of Moyamoya Disease in adults

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Moyamoya Disease (MMD) is a rare cerebrovascular disorder which can have significant cognitive consequences. The aim of the current study was to describe comprehensively the domain-specific cognitive profile of adult patients with MMD and to assess whether this changes in the absence of recurrent stroke over long-term follow-up. Comprehensive neuropsychological assessment covering seven cognitive domains was conducted on 61 adult patients with MMD at baseline and then at up to 3 further time points during follow up (median=2.31, 4.87 and 7.12 years). Although 27 patients had had prior surgical revascularisation, none had surgery between neuropsychological assessments. Cognitive impairment was common. At baseline, impairment in executive functions was most frequent (57%), followed by performance IQ (36%), speed of information processing (31%) and visual memory (30%). We found that the neuropsychological profile remains broadly stable over long-term follow-up with no clear indication of improvement or significant decline. The pattern of impairment also did not differ depending on age of onset or whether there was a history of either prior stroke at presentation or revascularisation surgery at presentation.

Key Words: Moyamoya—Stroke—Vascular—Neuropsychology—Cognition

Introduction

Moyamoya Disease (MMD) is a rare cerebrovascular disorder characterised by progressive stenosis and occlusion of one or both intracranial carotid arteries and their main branches associated with the development of a basal collateral network.[1] Ischaemic stroke presentations are most common, with a bimodal peak for diagnosis in the first and fourth decades of life.[2] Whilst the rate of stroke across the lifespan is low, the persistent threat of a stroke event is ever present, affecting quality of life and mood.[3]

Investigation into the cognitive consequences of MMD has been limited, particularly in adults. Early studies have suggested that a third of patients experience cognitive impairment.[4] Executive functions and speed of information processing appear to be the most frequently affected cognitive domains.[5–10] A meta-analysis of 153 adult patients with MMD found that 31% of patients experience cognitive impairment.[11] Executive functions and memory were the most frequently impaired perhaps in keeping with the early anterior circulation involvement of the disease, while visuospatial functions was the least commonly affected. Although cognitive changes can often be a direct conseqeunce of ischaemic infarcts and/or haemorrhage secondary to MMD,

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changes are also noted even in the absence of a history of stroke.[6] One explanation is that MMD causes long-term cerebral hypoperfusion, likely to preferentially affect white matter microstructure and connectivity, which may lead to cognitive decline without focal stroke.[7,12,13] Another is that MMD commonly results in ischaemia in the arterial border zones. To date, whether the described impact of MMD on cognition remains stable or progressively declines over the long-term remains unclear.

Most previous studies have focused on comparing cognition pre- and post-surgical EC-IC bypass revascularisation within a relatively short time interval, and findings have generally been equivocal e.g.,[14–16] for a review see.[17] Only three studies have examined cognitive changes in MMD over a time period greater than two years. Imaizumi et. al., examined general intellectual functioning (IQ) in thirty-eight patients with paediatric-onset MMD, without surgical revascularisation, over an average period of eight years.[18] An initial decline in IQ was reported in the five to ten years following symptom onset, with no additional decline after ten years. No other cognitive domains were examined. Miyoshi et. al., examined IQ and memory abilites in a group of sixty-six adult MMD patients without cerebral infarction and did not observe change in any cognitive domain after two years.[19] A follow-up study of the same patient group after five years, again showed no change.[20] Critically however, executive functions and processing speed, two domains commonly affected in MMD and expected to be influenced by reduced perfusion, were not considered. A more detailed investigation into the cognitive status of adult MMD patients across time, covering the spectrum of cognitive domains, has thus far not been reported.

The aim of the current study was therefore to describe comprehensively the domain-specific cognitive profile in a cohort of adult patients with MMD and to assess whether this changes in the absence of recurrent stroke over long-term follow-up.

Methods

Participants

Patient data were selected from a prospectively collected database of individuals who attended a specialist multidisciplinary Moyamoya clinic at the National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, London (a tertiary neurology centre) between April 2016 and December 2018. Patients were included if they fulfilled all the following criteria: (1) neuro-radiologically confirmed Moyamoya Disease, (2) 18 years or older at time of first neuropsychological assessment, (3) were seen for neuropsychological assessment on at least two occasions. For patients assessed at multiple time points, only the first four neuropsychological assessments following initial diagnosis were considered. Only assessments conducted within the neuropsychology department at the NHNN were considered for consistency and ease of comparison. Patients were excluded if they had: Moyamoya syndrome (n=11), no established Moyamoya diagnosis (n=10), neurological comorbidities or other factors affecting neuropsychological test performance such as learning difficulty (n=3), global aphasia (n=2), psychiatric history (n=1), or had a stroke between assessment timepoints (n=3). The demographic and clinical information collected included age of symptom onset, sex, presenting symptoms, ethnic background, surgical revascularisation, date of neuropsychological assessments and years of education.

Neuropsychological assessment

All patients underwent comprehensive neuropsychological assessment conducted by a Clinical Neuropsychologist, assessing the following domains: general intelligence, visual memory, verbal memory, language, perception, executive functions, and speed of information processing (see appendix 1). As patients received a tailored collection of tests that was considered appropriate by the clinical neuropsychologist at the time, not all patients received the exact same set of tests. The clinical neuropsychologist was blind to the purpose of the study at the time of the assessment. Performance on tests was scored according to published standardised normative data. For all other tests, raw scores were used. Impairment in each cognitive domain was classed as scoring at or below the fifth percentile on any one test within the domain. For general intellectual functioning, impaired performance was considered as a difference of 15 or more points between estimated premorbid scores (NART[21] or Schonell Graded Word Test[22]) and WAIS IQ[23] scores, or an IQ less than 70 in the absence of premorbid scores. For the memory domain, where both recall and recognition measures were administered, impairment was defined as scoring at or below the fifth percentile in the delayed recall condition.

Statistical analyses

All data were analysed using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). Neuropsychological data were analysed for skewness and kurtosis, and tested for normality using the Kolmogorov-Smirnoff test.

Chi-square analysis was used to evaluate the difference in proportion of patients impaired and not impaired across the different cognitive domains between MMD patients (1) with paediatric and adult symptom onset, (2) with and without surgical revascularisation, (3) with and without prior stroke, (4) assessment time point 1 (T1) and time point 2 (T2), (5) assessment time point 2 (T2) and time point 3 (T3), and (6) assessment time point 3 (T3) and time point 4 (T4). Given the attrition of the sample size across time points, to maximise statistical power we also conducted an analysis comparing the first and last time point of assessment for each patient irrespective of how many assessments they completed.

Based on previous literature, we wanted to investigate in further detail performance in the domains of general intellectual functioning,[18] executive functioning,[6,7] and speed of information processing[5,6]; as these domains are thought to be most commonly affected in MMD. Thus, in addition to proportion of impaired patients, we also examined changes in raw scores on tests within these domains to look for absolute change across time. Given the variability in the tests administered within each domain, tests selected for further review were those most widely administered (i.e. with the largest sample size), these were: the Wechsler Adult Intelligence Scale (third edition)[23] – Verbal Intellectual Quotient (WAIS-III VIQ) and Performance Intellectual Quotient (WAIS-III PIQ) for intelligence; Recognition Memory Test for Words (RMT-W),[24] Recognition Memory Test for Faces (RMT-F),[24] Adult Memory and Information Processing Battery (AMIPB) the Story and Figure subtests for memory[25]; Stroop Colour-Word (Stroop C-W),[26]Phonemic Fluency 'S' for executive functions[27]; and Symbol Digit Modalities Test (SDMT)[28] for speed of information processing. To compare performance across time points, paired *t*-tests were used where data were normally distributed and the Wilcoxon-signed tests when not normally distributed. A significance level of $p < .05$ was adopted and Bonferroni corrections were made for multiple comparisons. Statistical analysis was conducted only where more than five patients had completed the test at a given time point.[29]

Results

Demographics

A total of 61 patients met the inclusion criteria. Demographic information for the sample is presented in Table 1. Nearly half the sample was Caucasian (49%), followed by Asian (30%), Mixed (7%), Black Afro Caribbean (5%), with 10% unknown. All patients were seen for at least two assessments with a median time interval of 2.31 years (range= 0.34-5.65) between the baseline assessment (T1) and second assessment (T2). A subset was seen for a third assessment (n=35) with a median time interval of 4.87 years (range=1.62-11.64) between T1 and T3, and a fourth assessment (n=16) with a median time interval of 7.12 years (range=4.61-13.68) between T1 and T4.

Of the sample, the majority of patients had adult symptom onset of symptoms (61%). Ischaemic stroke (39%) was the most common presenting symptom. Slightly under half the group (44%) received neurosurgical revascularisation prior to inclusion in the study, but no patients had surgical revascularisation between the assessment time-points. All patients were managed using standard optimised medical therapy to control vascular risks.

Overall performance

At initial assessment (T1), 79% of patients exhibited cognitive impairment in one or more domains. 21% were impaired in two domains, 21% in three domains and 16% were impaired in four or more domains. Executive functions were most frequently impaired (57%), followed by performance IQ (36%), speed of information processing (31%), visual memory (30%), language (26%), verbal IQ (23%), perception (12%) and verbal memory (7%). Raw scores for each neuropsychological test across the domains for the four time points is presented in Appendix 2.

The proportion of patients cognitively impaired did not differ significantly between those with paediatric symptom onset and those with adult symptom onset either regarding the number of domains impaired (p>0.1) or in

Table 1. *Summary of demographic variables (*n = *61).*

	N (%)	Mean (Range)	SD
Age at symptom onset*			
Paediatric	23 (38)	9 (4-16)	3.99
Adult	37 (61)	34 (18-63)	11.24
Age at each time point			
T1	61	32 (16-63)	12.32
T2	61	34 (19-67)	12,64
T3	35	36 (20-69)	11.49
T4	16	37 (25-53)	10.21
Premorbid Intellectual Functioning (NART/Schonell)	54	94.41	12.57
Education (Years)	41	12.78	2.98
Sex (Males/Females)	12 (20) /49 (80)		
Intervention (Surgery/No Surgery)	27 (44) /34 (56)		
Presenting symptoms of MMD			
Ischaemic Stroke	24 (39)		
Transient Ischaemic Attack	20 (33)		
Intracerebral Haemorrhage	7 (11)		
Other	10 (17)		

*One patient was asymptomatic and referred to the clinic due to a strong familial history

terms of the proportion impaired in each of the separate cognitive domains (p>0.1 for all comparisons). Similarly, no significant difference was found in the proportion of patients impaired between those who had received prior surgical revascularisation and those who had not, or those who had experienced a stroke prior to the first assessment or not (p>0.1 for all comparisons). Therefore, these groups were collapsed into a single group for subsequent analyses.

Comparing overall domain performance between T1 and T2

The number of overall domains impaired did not differ between T1 and T2 (p>0.1). Examining the individual domains, the proportion of patients impaired was most reduced for visual memory (T1: 30% vs T2:13%) and language (T1:26% vs T2:13%), whereas there was a slight increase in the proportion of impaired patients for executive functions (T1:57% vs T2:64%) and speed (T1:31% vs T2:42%). Fig. 1 shows the proportion of patients impaired for each domain across the four time points.

Comparing test-specific performance between T1 and T2

Performance on measures of IQ, memory and speed of information processing are reported in Table 2. Performance on one timed measure of executive function was better at T2 compared with T1 ('S' Fluency). Otherwise, there was no significant difference in performance between time points for the other tests.

Comparing overall domain performance between T2 and T3

The number of overall domains impaired did not differ between T2 and T3 (p>0.1). Examining the individual domains, the proportion of patients impaired was most reduced for executive functions (T2: 64% vs T3:40%) and visuo-perception (T2:12% vs T3:0%), while verbal memory was the only domain that had a slight increase in impaired patients (T2: 2% vs T3: 3%).

Comparing test-specific performance between T2 and T3

Between T2 and T3, there was no significant difference in performance on any of the tests (p>0.1).

Comparing overall domain performance between T3 and T4

The number of overall domains impaired did not differ between T3 and T4 (p>0.1). The proportion of patients impaired was most reduced for performance IQ (T3: 21% vs T4:7%) and verbal IQ (T3:13% vs T4:0%), whereas there was a slight increase in impaired patients for visual memory (T3:9% vs T4:19%).

Comparing test-specific performance between T3 and T4

Between T3 and T4, there was no significant difference in performance on any of the tests (p>0.1).

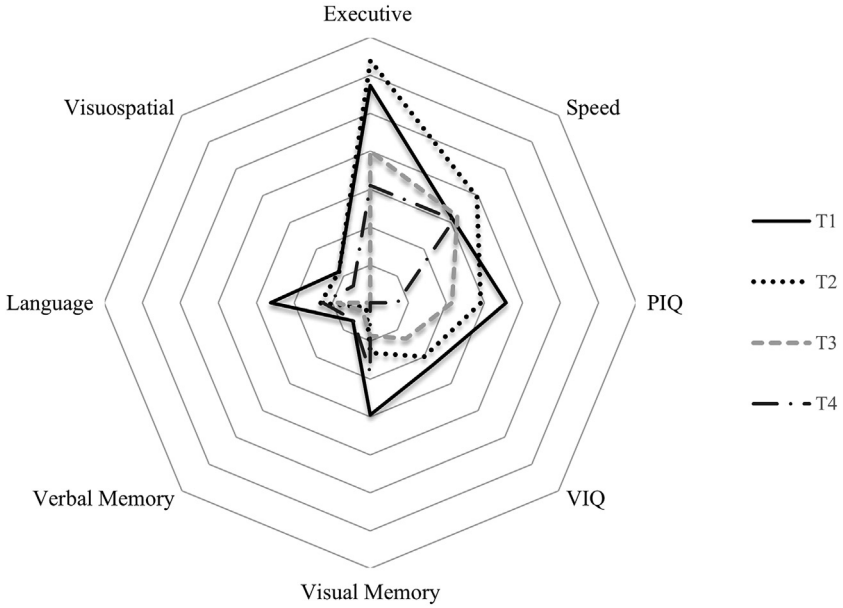

Fig. 1. *Radial plot demonstrating percentage of patients impaired in each cognitive domain across the four assessment time points. Each line represents a 10% increment (range: 0–70%) with the inner circumference representing 10% and the outer circumference representing 70%*

Table 2. *Raw scores on specific neuropsychological measures across the four time points.*

Cognitive Domain and Tests	T1			T2			T3				T4			
	n	Mean	SD	Mean	SD	*p-value*	N	Mean	SD	*p-value*	n	Mean	SD	p-value
General Intellectual Functioning														
WAIS-III VIQ	53	87.71	13.83	88.38	13.73	*.729^*	29	86.70	11.63	*.789^*	12	89.00	12.73	*.339^^*
WAIS-III PIQ	54	85.14	15.62	86.78	14.79	*.158^^*	27	87.32	13.80	*.834^*	12	92.46	16.46	*.200^*
Verbal memory														
RMT W	42	46.31	4.38	47.29	2.39	*.961^^*	21	47.46	1.98	*.579^^*	11	47.46	1.98	*.370^*
AMIPB % Ret - Story	14	92.69	12.92	96.24	14.11	*.476^*	7	89.88	22.40	*.069^*	2	97.37	4.55	-
Visual memory														
RMT F	25	39.10	4.98	40.85	4.95	*.251^*	9	43.55	5.50	*.617^*	4	41.60	4.21	-
AMIPB % Ret - Figure	10	102.56	25.28	105.07	27.43	*.813^^*	8	92.25	29.54	*.906^^*	2	93.68	9.45	-
Executive functions														
Stroop C-W	40	89.22	20.77	92.70	18.21	*.057^^*	25	93.39	18.97	*.182^^*	13	96.15	20.71	*.438^^*
'S' Fluency (no. of words)	39	11.86	5.59	13.71	6.53	***.001^^****	23	14.15	4.47	*.705^*	12	12.33	4.49	*.387^*
Information processing speed														
SDMT	35	44.78	10.76	44.08	13.24	*.902^*	18	43.81	10.74	*.960^*	8	43.45	20.54	*.155^*

Comparisons for each test were completed with a ^paired sample t-test, or ^^Wilcoxon signed rank test where data was not normally distributed. * $p<0.05$, ** $p<0.01$. Analysis was not conducted when there were fewer than five patients who had completed the test at a given time point (-). Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ), Recognition Memory Test – Words (RMT W), Recognition Memory Test – Faces (RMT F), Adult Memory and Information Processing Battery – Story percentage retained (AMIPB % Ret – Story) and Figure (AMIPB % Ret – Figure), Stroop Colour Word test (Stroop C-W), Verbal fluency – S item only ('S' Fluency), Trail Making Test- Part A (TMT-A), and Symbol Digit Modalities Test (SDMT).

Comparing overall domain performance between T1 and the last assessment

To maximise statistical power we also conducted an analysis comparing the first (T1) and last time point of assessment for each patient irrespective of how many assessments they completed. The number of overall domains impaired was significantly reduced between T1 and the last assessment (p=0.006). The proportion of patients impaired was most reduced for visual memory (T1: 30% vs Last: 13%) and language (T1: 26% vs Last:13%).

Comparing test-specific performance between T1 and the last assessment

Performance on both timed measures of executive function was improved ('S' Fluency: p=0.002 and Stroop Colour Word Test: p=0.05). Otherwise, there was no significant difference in performance between time points for the other domains.

Discussion

The aim of the current study was to comprehensively characterise the cognitive profile of MMD in a large cohort of adult patients and to examine whether this changes over long-term follow-up. To our knowledge, we present the most complete examination of cognitive functions in adult MMD so far, assessing seven separate cognitive domains. Our findings showed that cognitive impairment was common, with executive functions, Performance IQ and processing speed most impaired. Impairments generally persisted over time with no clear indication of improvement or significant decline over a maximum of 13 years follow-up.

In our sample, 79% of patients were found to have cognitive impairment in one or more cognitive domains and 58% in two or more domains. This is far higher than the median proportion of 31% reported in the recent meta-analyses of six adult studies, with a range of 0% to 69%.[11] One potential reason for this may be that our comprehensive battery allowed us to detect impairment in a wider range of cognitive functions. Most previous studies have either focused on a single domain e.g.,[7,8]or had neuropsychological batteries that were incomplete (e.g. Festa et. al., did not assess visual memory or visuo-perceptual processing[5]; Kazumata et al., only assessed IQ, Executive Functions and Attention[30]). With our comprehensive battery, we found that executive functions, performance IQ, speed of processing and visual memory were the most commonly affected domains. In addition, although less common, memory, visuo-perceptual processing and language impairments were also found. Our findings highlight the importance of a thorough neuropsychological investigation when assessing patients with MMD so that impairments are not missed.

Our finding that executive functions and processing speed were commonly impaired in our sample is broadly consistent with previous findings, highlighting the vulnerability of these domains in MMD.[5–10] In addition, we found that a high proportion of patients also had compromised performance IQ. This is consistent with paediatric

studies that have found reduced IQ associated with MMD, irrespective of a stroke history.[31,32] Notably, children who had compromised performance IQ and subsequently underwent revascularization surgery were found to show significant improvement.[32] The impact of MMD on a global cognitive measure such as performance IQ points to how large vessel hypoperfusion can have a generalised impact on cognition. The finding that visual memory, but not verbal memory, was also commonly affected is somewhat unexpected. Though memory impairment in MMD patients is commonly reported, with a meta-analysis showing a median proportion of 37% affected,[11] the dissociation between the visual and verbal domain seems rarer as they are often collapsed into one domain. One possibility for this difference may be that visual memory performance is more vulnerable to being affected by executive difficulties.[33,34] Given the prevalence of executive difficulties in MMD it may be that visual memory difficulties are a secondary consequence. Notably, visual memory was also the domain for which there was the greatest improvement of all the domain between T1 and T2 as well as T1 and the last assessment, further suggesting that performance in this domain may not be reflecting a genuine chronic cognitive change in this sample. Further investigation is warranted into how domains of impairment in MMD might interact with each other.

In group comparisons, we did not find any significant differences in the frequency of cognitive impairment or the likelihood of impairment across cognitive domains when we compared patients who (1) had paediatric symptom onset versus those with adult symptom onset, (2) had or not had revascularisation surgery, and (3) had or not had a stroke prior to the first neuropsychological assessment. It is important to note that we excluded the small proportion of patients attending our clinic who had a stroke during follow up. Each of the three above factors is thought to be relevant in considering cognitive outcomes in MMD. However, many studies either do not report on these variables and treat all the patients as one group e.g.,[4] or they only have patients from one of the categories thereby preventing any possibility of direct comparison. Of the studies that do examine these factors, our findings appear broadly consistent. Studies that directly compare the cognitive performance of MMD patients who have had or not had a stroke have not found significant differences.[5,35] Similarly, comparisons of performance in patients pre- and post-revascularisation surgery tend to show overall no difference in cognitive performance in adults,[13,15] while one study showed significant improvement in tests of speed and attention post-operatively.[16] A recent study by Yanagihara and colleagues suggests that cognitive changes post-revascularisation surgery might be more nuanced and depend on variables such as the magnitude of cerebral blood flow change pre- and post-surgery and whether there is acute post-surgical cerebral hyper-perfusion.[36] At a group level, our study findings suggest that consideration of symptom onset, history of stroke or revascularisation surgery alone is not sufficient in determining the likelihood or pattern of cognitive impairment in MMD.

Most importantly, our study showed for the first time that the neuropsychological profile of adult patients with MMD, in those without intercurrent vascular events, remains relatively stable over a median period of 7.12 years. Our findings extend upon the two other studies that have investigated cognitive change over time[19,20] by covering a far more comprehensive spectrum of cognitive domains and a longer time frame. Across time points, executive functions was the domain most frequently impaired. Over three follow-ups, there was no evidence of worsening performance either in terms of the proportion of patients with impairment across domains or when comparing performance of patients individually on measures of IQ, memory, executive functions and speed of information processing. In fact, the proportion of patients classified as impaired significantly diminished over time. Frequency of impairment in visual memory and language decreased at the second time point, and in executive functions at the third time point. Examining selected tests, performance on one timed measure of executive function, phonemic fluency, improved only between the first two assessment but not later time points. Improvement in performance may reflect a recovery of once-compromised cognitive functions though given the chronicity of the disease process in the majority of our cohort, this seems unlikely. Alternatively, the improved performance might reflect a practice effect that is inherent in the assessment process and the psychometric properties of some individual tests e.g.[37,38] though the relatively long duration between assessment time points in our study should have mitigated the effect. A meta-analysis study by Calamia and colleagues[38] showed that while practice effects were present across all neuropsychological tests, there was large variability in the effect size not only between cognitive domains but also between tests within a domain. Furthermore, practice effect for specific tests was also impacted differently by factors such as age of participants, length of test-retest interval and use of alternate forms. Perhaps it may also be that the absence of improvement in some domains and tests might be equally meaningful. It has been shown for example that the lack of practice effect in patients with mild cognitive impairment can be predictive of worse outcomes at one year.[39] Thus, the absence of significant change in scores across time points in some domains/tests need to be interpreted cautiously. The lack of a neurologically-intact control group in our study unfortunately limits our ability to draw any firm conclusions at present.

Our findings have important clinical implications. We demonstrate that in the absence of acute stroke or surgery, cognitive function in adult MMD is at least stable over a relatively long period of time. Our results suggest that

although many patients had evidence of cognitive impairment at baseline likely to reflect loss of neurones from infarction or hypoperfusion secondary to the moyamoya arteriopathy, the arteriopathy does not progress in the majority of patients during adult life. This is broadly in keeping with the early findings of Imaizumi and colleagues which showed that intellectual functioning in paediatric MMD declines during the first years of the disease but then stabilizes after 10 years.[18] Although chronic hypoperfusion may cause changes to brain microstructure[7,12,13] and correlate with the severity of cognitive impairment,[13] its impact on cortical and subcortical functions appears relatively stable in adulthood.

Some limitations of our study should be considered. Sufficiently powered studies in this area are understandably difficult given the rarity and heterogeneity of MMD. We opted to include all patients with available neuropsychological data as a group in the current study and broadly categorised performance as impaired or not impaired using a stringent cut-off, at the expense of considering some other factors such as phenotypic presentations, disease duration or neuroimaging features. Although more detailed studies at an individual level are useful, group studies such as ours allow for an understanding of more general patterns of disease phenomonology which can have important clinical utility. Another limitation of our study was that there was an attrition rate of approximately a half between assessment time points two and three, and three and four. Information regarding non-attendance at the clinic were not routinely collected and thus not possible to formally evaluate. It is possible therefore that some of the missing data might represent patients who have deteriorated across time points, though this seems unlikely as one might expect that patients who experience cognitive or neurological changes might be more motivated to attend clinic. Given the relatively reduced sample size in some assessed domains, the statistical certainty of some of the findings need to be interpreted cautiously.

In conclusion, cognitive impairment amongst MMD patients is common, with executive functions most commonly affected. The neuropsychological profile remains broadly stable up to 13 years after first assessment in an adult clinic, and is not adversley affected by stroke or revascularisation surgery at the outset. This is useful and reassuring information for patients and their families/carers.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. This study included anonymised data collected as part of standard care, and approved in accordance with a Service Evaluation Agreement approved by the local Research Ethics Committee (National Hospital for Neurology and Neurosurgery).

Declaration of Competing Interest

none

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Appendix 1 – List of Neuropsychological Tests Administered

Premorbid Intellectual functioning
National Adult Reading Test (NART) [1]
Schonell Graded Word Reading Test [2]
General intellectual functioning
Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) [3]
Raven Advanced Progressive Matrices – Set 1 [4]
Memory
Recognition Memory Tests (RMT), Words and Faces [5]
Adult Memory and Information Processing Battery (AMIPB), Story and Figure recall [6]
The Camden Memory Test: Topographical Recognition Memory Test [7]
The Camden Memory Test: Paired Associate Learning Test [7]
The Doors and People Test [8]
Naming
Graded Naming Test [9]
Oldfield Naming Test [10]
Visuo-perception
Visual Object and Space Perception Battery (VOSP) [11]
Executive functions
Stroop Colour Word Test [12]
Hayling Sentence Completion Test [13]
Modified Card Sorting Test [14]
Cognitive Estimation Test [15]
Phonemic fluency [16]
Speed of Processing
Symbol Digit Modalities Test (SDMT) [17]
Trail-Making Test Part A [18]
'A' Cancellation [19]

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Appendix 2. Raw scores on all neuropsychological measures across the four time points (n>5 at T1).

Cognitive Domain and Tests		T1			T2		T3			T4	
	n	Mean	SD	Mean	SD	n	Mean	SD	n	Mean	SD
General Intellectual Functioning											
WAIS-III VIQ	53	87.71	13.83	88.38	13.73	29	86.70	11.63	12	89.00	12.73
WAIS-III PIQ	54	85.14	15.62	86.78	14.79	27	87.32	13.80	12	92.46	16.46
Raven APM	7	6	2.5	6.86	2.41	4	6.5	3.1	1	7	
Verbal memory											
RMT W	42	46.31	4.38	47.29	2.39	21	47.46	1.98	11	47.46	1.98
AMIPB % Ret - Story	14	92.69	12.92	96.24	14.11	7	89.88	22.40	2	97.37	4.55
Visual memory											
RMT F	25	39.10	4.98	40.85	4.95	9	43.55	5.50	4	41.60	4.21
AMIPB % Ret - Figure	10	102.56	25.28	105.07	27.43	8	92.25	29.54	2	93.68	9.45
RMT Topographical	24	23.96	4.84	25.40	2.82	15	25.40	2.82	6	25.83	2.56
Executive functions											
Stroop C-W	40	89.22	20.77	92.70	18.21	25	93.39	18.97	13	96.15	20.71
'S' Fluency (no. of words)	39	11.86	5.59	13.71	6.53	23	14.15	4.47	12	12.33	4.49
Modified Card Sorting	20	5.27	1.38	5.70	.80	14	6	0	5	6	0
Hayling	7	6	1	5.75	1.2	4	6	.81	2	7	0
Information processing speed											
TMT-A (time in secs)	8	43.45	20.54	49.47	32.24	3	30.50	7.72	3	31.00	9.62
SDMT	35	44.78	10.76	44.08	13.24	18	43.81	10.74	8	43.45	20.54
Language											
Graded Naming	38	17.32	4.98	18.74	3.96	23	17.65	4.14	12	17.66	5.19
Oldfield Naming	24	23.33	2.67	23.45	2.24	13	24.54	1.85	6	24.33	2.33
Visuo-perception											
VOSP Object Decision	24	17.62	1.52	17.75	1.52	14	18.71	1.32	6	18.67	1.21
VOSP Incomplete Letters	30	19.36	.85	19.34	.66	14	19.86	.36	2	19	1.41
VOSP Position Discrimination	9	17.66	1.93	18.8	1.47	2	20	0	0	-	-
VOSP Silhouettes	6	18.17	5.49	18.86	4.59	3	22	2	2	23	4.24
VOSP Cube Analysis	13	8.61	1.44	8.53	1.72	7	8.86	.9	3	9	1.72

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