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Mapping cognitive dysfunction in relapsing multiple sclerosis with mild disability: A cross-sectional study from South India

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Abstract

Background: Cognitive dysfunction in multiple sclerosis (MS) occurs early. Locally adapted neuropsychological data from India in MS is scarce.

Objectives: We aimed to identify the pattern of cognitive impairment in relapsing MS (RMS) with mild disability using a regionally-adapted MS-specific cognitive battery.

Methodology: The study included 59 persons with MS (pwMS) with expanded disability status scale (EDSS)≤ 4 and 62 controls. The battery had 8 neuropsychological tests (Paced Auditory Serial Addition Test [PASAT], Symbol Digit Modalities Test [SDMT], Rey Auditory Verbal Learning Test [RAVLT], Brief Visuospatial Memory Test-Revised [BVMT-R], verbal fluency [VF], Judgement of Line Orientation Test [JOLOT], Wisconsin Card Sorting Test [WCST] and Trail Making Test-B [TMT-B]) with 11 measures. The scores were compared between the groups for pattern and associations of cognitive impairment.

Results: The pwMS cohort had 39 (66.1%) females; mean age of 32.56 (±8.17) years. Scores were significantly worse for pwMS in 10 of 11 tests (except JOLOT). Cohen's-d test showed the largest effect sizes for PASAT, SDMT, VF and TMT-B. Cognitive impairment (defined as ≥2 abnormal tests) were noted in 41 (69.5%) pwMS. Male sex was associated with cognitive impairment ($p = 0.002$).

Conclusions: In pwMS with mild disability, nearly two-thirds had cognitive abnormalities, predominantly involving processing speed, working memory, executive function, and VF.

Keywords: Multiple sclerosis, RRMS, cognition, cognitive dysfunction, MACFIMS

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Introduction

Multiple sclerosis (MS) is a chronic and progressive central nervous system (CNS) disease remarkable for the heterogeneity of clinical presentation and disease course. Cognitive dysfunction is well-recognized as a critical component of MS disease burden with various cross-sectional studies placing the prevalence of abnormal neuropsychological test scores between 30% and 75%.[1] Though the frequency and severity of cognitive dysfunction are more in the progressive forms of MS,[1,2] these abnormalities can be detected early in the disease course and may even precede the overt clinical manifestations.[3]

The last three decades have seen tremendous progress in discerning the profile and patterns of MS-associated cognitive dysfunction. The best validated MS-specific minimal and screening neuropsychological test batteries are the Brief Repeatable Battery of Neuropsychological tests (BRB-N), the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).[4–6] The most commonly compromised domains in persons with MS (pwMS) are speed of information processing and episodic memory, followed by executive function, verbal

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fluency (VF), spatial processing, and multitasking.[4,5,7] Overt dementia is uncommon except in the very late stages of MS.[1]

Studies in the 1970s placed MS prevalence in India between 0.17 and 1.33 per 100,000.[8] Over the last five decades, the reported disease burden in the country has increased manifold with the current estimate being roughly 5 to 10 per 100,000.[8,9] Even with the amplified understanding of the public health burden of MS by health care providers and administrators and better access to disease modifying therapies, cognitive dysfunction in pwMS is a largely neglected problem in clinical care and research in this region.

There is scant published literature from India on MS cognition. A study from central India showed abnormal cognitive profile in 73.3% pwMS compared to healthy controls using a 12-point Montreal cognitive assessment (MoCA) screening test.[10] Another study noted cognitive fatigue in nearly half of pwMS using timed tests.[11] As cognitive deficits in MS are typically subtle, the more commonly employed neuropsychological tests for dementia-screening tend to underestimate the burden. The applicability of the extensively validated MS-specific cognitive batteries has not previously been tested in India. The widely diverse language, cultural and social background in the country is likely to impact the measures. In this study, our objective was to assess the frequency and pattern of cognitive abnormalities in persons with relapsing multiple sclerosis (RMS) with mild disability using a systematic battery of neuropsychological tests covering the MS-specific cognitive domains and adapted appropriately for the local population.

Methodology

The subjects and controls for this study were recruited as part of a single-center cross-sectional study on the neuropsychological profile of RMS and its correlation with multimodality structural and functional magnetic resonance imaging. The current analysis focuses on the neuropsychological scores in the study. The study commenced after approval from the Institutional Ethics Committee. Written informed consent was obtained from all subjects and controls.

Study participants

Adults (aged ≥18 years) fulfilling the 2010 revisions of McDonald's criteria for attack onset MS[12] and Expanded Disability Status Scale (EDSS) ≤ 4 were recruited from the Multiple Sclerosis Clinic in the institute from December 2017 to June 2020. Persons with progressive forms of MS, pediatric onset (before 12 years of age), clinical relapse within 1 month of assessment, active medical conditions or treatment which could compromise cognitive functions (i.e. psychosis, chemotherapy, or corticosteroid treatment within 1 month) and gross visual or motor impairment which could interfere with the neuropsychological tests were excluded. The clinical details, functional scores (FS) and EDSS were recorded at recruitment by a trained neurologist.

The controls were age, sex, and education-matched healthy volunteers without any cognitive symptoms. Persons with any history of a neurological, psychiatric, or other major systemic illness based on history and those on any medications known to alter cognition or alertness within 1 month of testing were excluded.

Neuropsychological evaluation

The neuropsychological tests were administered by a trained neuropsychologist and performed in a standardized manner, during daytime, in a quiet room and in a fixed order. The test administration took approximately 90 to 120 minutes per person. All the participants were residents of Kerala, India with the native language Malayalam as their mother tongue. All the tests were explained and administered orally and in written forms in Malayalam.

We performed a general cognitive assessment with the Malayalam version of Addenbrooke's Cognitive Examination-revised (ACE-R), which is a well-validated neuropsychological test in the population.[13] Neuropsychiatric Inventory (NPI) and Hospital Anxiety and Depression Scale (HADS) were used to analyze anxiety and mood.

The MS-specific cognitive battery comprised of 8 tests which yielded 11 measures. The domains and the neuropsychological measures were (i) Processing speed and working memory: correct responses in Paced Auditory Serial Addition Test-Malayalam version (PASAT) at 2 and 3 seconds and correct responses in Symbol Digit Modalities Test (SDMT); (ii) New learning and episodic memory: sum of 5 learning trials and 20 minutes delayed recall in Rey Auditory Verbal Learning Test (RAVLT) (Malayalam version) and sum of 3 learning trials and 25 minutes delayed recall for Brief Visuospatial Memory Test -Revised (BVMT-R); (iii) Language: sum score of verbal fluency test in Malayalam (VF); (iv) Spatial

processing: standardized score of correct items in Judgment of Line Orientation Test (JOLOT) and (v) Higher executive function: number of correct category sorts in Wisconsin Card Sorting Test—48 cards (WCST) and time to complete the task in trail making test B (TMT-B). The methodology of each test is described in the supplementary table (e-Table 1).

The tests were chosen based on the cognitive domains tested in the MACFIMS battery. We directly applied JOLOT, BVMT-R, PASAT and SDMT whereas we replaced the tests for the remaining domains with comparable neuropsychological tests validated in our population. We used the VF subscale of ACE for language, RAVLT for new learning and episodic memory and a combination of WCST (modified) and TMT-B for executive function.[13–16] Among these, previously validated Malayalam versions were available for all the tests except BVMT-R. The instructions for the latter were validated in Malayalam by translation from English and back-translation using standard techniques.

Statistical analysis

All statistical analysis was performed using IBM SPSS statistics version 25. Descriptive analysis was done using the mean and standard deviation (SD) of each respective variable in both the groups. Comparisons between the RMS and control groups were performed using Student's *t* test. For TMT-B test, where time to complete the task was the score, higher scores indicated worse function. For all the other neuropsychological tests, lower numerical values indicated poorer performance. Accordingly, normative cutoff value for each variable was calculated from the control population using the formula "mean minus 1.5 times SD" for all variables except for TMT-B (where "mean plus 1.5 times SD" was used). These values were used to calculate the frequency of abnormal psychological tests in the RMS group. pwMS with abnormal values in 2 or more of the 11 tests were categorized as cognitively impaired. Cohen's *d* test was performed to assess the effect size of the individual neuropsychological tests by taking the mean and pooled SD of each test in respective RMS and control groups. In general, a Cohen's *d* of >0.5 indicated a larger effect size. Univariate analysis with analysis of variance (ANOVA) and multivariate regression analysis were performed between the cognitively preserved and impaired groups for the clinical and demographic variables. *p*-Values of ≤0.05 were assigned as significant.

Results

Demographic and clinical profile

The study included 59 pwMS (39 females) and 62 healthy controls (HC) (38 females), with a mean age of 32.56 (±8.17) and 31.71 (±7.58) years, respectively. All the subjects were literate and able to read and write Malayalam fluently. The mean years of formal education were comparable between the groups. In pwMS, the duration of illness ranged from less than 1 to 21 years and median EDSS was 1.5 (IQR 1–2.5). At the time of recruitment, 50 (84.7%) pwMS were receiving disease-modifying treatments (DMTs) (Table 1).

Group comparisons and effect sizes of neuropsychological scores

Table 1 shows the comparison of neuropsychological scores between pwMS and HC. The controls performed significantly better than pwMS in all the tests of cognition (PASAT-3, PASAT-2, SDMT, VF, BVMT, RAVLT, WCST, and TMT-B) except JOLOT. In the latter, pwMS significantly outperformed the controls.

Cohen's *d* statistic showed effect size of more than 0.5 for all except JOLOT. The largest effects in discriminating abnormal neuropsychological function were noted for tests of attention, processing speed and literal fluency, namely, PASAT (3 seconds and 2 seconds), SDMT, and VF (Table 2).

Considering the standard cut off in MS cognition of 1.5 SD from the control means, the proportion of pwMS with abnormal values were highest for VF, TMT-B, PASAT and SDMT (Figure 1). The proportion of abnormal values for the tests were 55.9% for VF, 50.9% for PASAT-3, 49.2% for PASAT-2, 47.5% for SDMT, 47.5% for TMT-B, 39.0% for RAVLT-DR, 37.3% for WCST, 33.9% for RAVLT-TL, 30.5% for BVMT-DR, and 27.1% for BVMT-TL (Figure 1). None of the pwMS had impaired JOLOT scores compared to controls.

Association of the cognitive impairment with clinical parameters

Cognitive impairment defined as two or more abnormal neuropsychological tests out of 11, was noted in 41 (69.5%) pwMS. Univariate analysis showed significant association for male sex with cognitive impairment (46.3% males in the impaired group vs 5.6% in the preserved group, $p = 0.002$) while none was noted for current age, years of education, age of onset, number of relapses, disease duration or

Table 1. Comparison of clinico-demographic variables and neuropsychology scores between relapsing remitting multiple sclerosis group and controls.

	People with multiple sclerosis ($N = 59$)	Healthy controls ($N = 62$)	p-Value
Demographic parameters			
Age in years; mean (SD)	32.56 (8.17)	31.71 (7.58)	0.5541
Females; *n* (%)	39 (66.10)	38 (61.29)	0.582
Years of formal education; mean (SD)	15.27 (2.17)	15.81 (1.97)	0.1583
Clinical parameters			
Age of symptom onset (years); mean (SD)	26.27 (8.23)	-	
Duration of illness (years); mean (SD)	5.91 (4.41)	-	
Number of relapses; mean (SD)	3.47 (2.11)	-	
Number on disease modifying therapy; *n* (%)	50 (84.7)	-	
Interferon beta 1a	25 (42.37)		
Glatiramer acetate	1(1.69)		
Dimethyl fumarate	16 (27.12)		
Teriflunamide	3 (5.08)		
Rituximab	5 (8.47)		
None	9 (15.25)		
Duration of therapy (years), ($N = 50$); mean (SD)	2.68 (1.89)	-	
EDSS; median (IQR)	1.5 (1–2.5)	-	
Neuropsychology test scores; mean (SD)			
ACE III-R	90.73 (5.76)	96.00 (3.63)	<0.0001
Verbal fluency score	15.05 (3.86)	18.34 (2.03)	<0.0001
RAVLT total learning trials	48.08 (11.74)	54.81 (8.38)	0.0004
RAVLT delayed recall	9.34 (4.16)	12.13 (2.49)	<0.0001
SDMT correct response	39.71 (12.36)	50.34 (8.22)	<0.0001
BVMT total recall	20.19 (8.11)	24.48 (6.39)	0.0015
BVMT delayed recall	8.34 (3.44)	10.05 (2.05)	0.0014
JOLOT	40.78 (10.03)	23.32 (7.98)	<0.0001
PASAT 3 seconds	29.12 (20.50)	47.58 (10.21)	<0.0001
PASAT 2 seconds	22.22 (16.81)	38.34 (10.03)	<0.0001
WCST correct sorts	4.31 (2.25)	5.64 (1.22)	0.0001
WCST preservatory errors	0.475 (0.704)	0.242 (0.502)	0.0375
Trail making test-A (seconds)	107.66 (47.52)	70.89 (22.69)	<0.0001
Trail making test-B (seconds)	207.88 (72.34)	146.40 (40.40)	<0.0001
HADS anxiety	3.63 (4.80)	0.32 (1.21)	<0.0001
HADS depression	0.63 (1.69)	0	-

Abbreviations: ACE III-R, Addenbrooke's Cognitive Examination III-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; HADS, Hospital Anxiety and Depression Scale; JOLOT, Judgement of Line Orientation Test; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test; *n*, number; SD, standard deviation; SDMT, Symbol Digit Modalities Test; WCST, Wisconsin Card Sorting Test.

EDSS. HADS anxiety scores were insignificantly higher in cognitively impaired pwMS (21.9% abnormal in the impaired group versus 11.1% abnormal in preserved group, $p = 0.476$) whereas HADS depression score was abnormal in a single subject in the impaired group. The significance for sex was retained in multivariate analysis (Table 3).

Discussion

This is one of the few studies to map the cognitive profile of MS in the Indian population using a comprehensive set of MS-specific neuropsychological tests. In this study, more than two-thirds of persons with RMS with mild disability were classified as cognitively impaired based on abnormalities in 2 or more

Table 2. Effect sizes for the 11 neuropsychological scores.

Variables	Control group ($n = 62$)		RMS group ($n = 59$)		Cohen's d and 95% CI
	Mean	SD	Mean	SD	
Verbal fluency score	18.34	2.04	15.05	3.86	1.07 (0.68–1.45)
RAVLT total learning	54.8	8.38	48.08	11.74	0.66 (0.29–1.02)
RAVLT delayed recall	12.13	2.49	9.34	4.16	0.82 (0.44–1.19)
BVMT total learning	24.48	6.39	20.19	8.1	0.59 (0.22–0.95)
BVMT delayed recall	10.04	2.05	8.34	3.45	0.60 (0.23–0.97)
JOLOT	24.32	7.98	40	10.03	−1.74 (−2.15 to −1.31)
PASAT-3 seconds	47.58	10.21	29.12	20.5	1.77 (1.34–2.19)
PASAT-2 seconds	38.34	10.03	22.22	16.8	1.17 (0.78–1.56)
SDMT	50.34	8.21	39.7	12.36	1.02 (0.63–1.40)
WCST correct sorts	5.65	1.21	4.3	2.25	0.75 (0.38–1.12)
TMT-B	146.40	40.39	206.9	70.64	1.05 (0.67–1.43)

Abbreviations: BVMT-R, Brief Visuospatial Memory Test-Revised; CI, confidence interval; JOLOT, Judgment of Line Orientation Test; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test; RMS, relapsing multiple sclerosis; *n*, number; SD, standard deviation; SDMT, Symbol Digit Modalities Test; TMT-B, Trail Making Test-B; WCST, Wisconsin Card Sorting Test.

cognitive tests. Abnormalities were most frequent in information processing and working memory (PASAT and SDMT), language (VF) and executive function (TMT-B) domains which is highly consistent with the seminal studies in MS cognition.[4,5] Of note, clinical variables such as disease duration, disability and number of relapses did not have an impact on the occurrence of cognitive impairment in our MS cohort.

Though the frequency and impact of cognitive dysfunction in MS are well-recognized, many challenges have interfered with their routine evaluation in low- and middle-income countries. The most significant of these is the lack of financial, human, and infrastructure resources for healthcare.[17] Diagnostic neuropsychological tests require normative data and versions of the tests validated in the local language and cultural setting. The neuropsychologist should have expertise in using tests designed specifically for MS, which evaluate domains other than the more prevalent amnestic cognitive impairment. Poor awareness of cognitive problems in MS among the general population and health care providers adds to the burden.[17] The diversity of languages and cultural practices in India has also been a barrier to establishing a uniform protocol for testing cognitive dysfunction for various neurological disorders in the country.[17]

MACFIMS is one of the best validated neuropsychological batteries for detecting cognitive impairment in MS. It has uniquely shown predictive value for employability based on sub-test scores that focus on executive functions and verbal memory.[5] The tests and cognitive domains included in the MACFIMS battery formed the basis for the selection of the MS-specific neuropsychological tests in this study. The MACFIMS battery was designed as a minimal testing for detecting MS-related cognitive dysfunction and not as a comprehensive battery.[5] Additionally, the scores must be interpreted contextually because certain neuropsychological tests, such the BVMT-R and TMT-B, reflect functions across multiple domains.

The frequency and pattern of cognitive abnormalities differ across the wide clinical spectrum of MS. Cognitive abnormalities have been noted even in early or mild MS which has been variably defined based on disease duration or disability. Few studies have specifically focused on RMS with mild disability. The neuropsychological scores and definitions of cognitive impairment along with the setting of the study weigh heavily in the prevalence measures. After the first clinical event, 34.5% of the persons with clinically isolated syndrome have abnormalities in two or more tests.[18] A large multi-centric study from Italy placed the cross-sectional prevalence of impairment in two or more tests (<5th percentile of normative data) in Rao's BRB-N as 34.9% in RMS persons with EDSS ≤4.[19] A population-based study using BRB-N and Stroop test classified one-third of

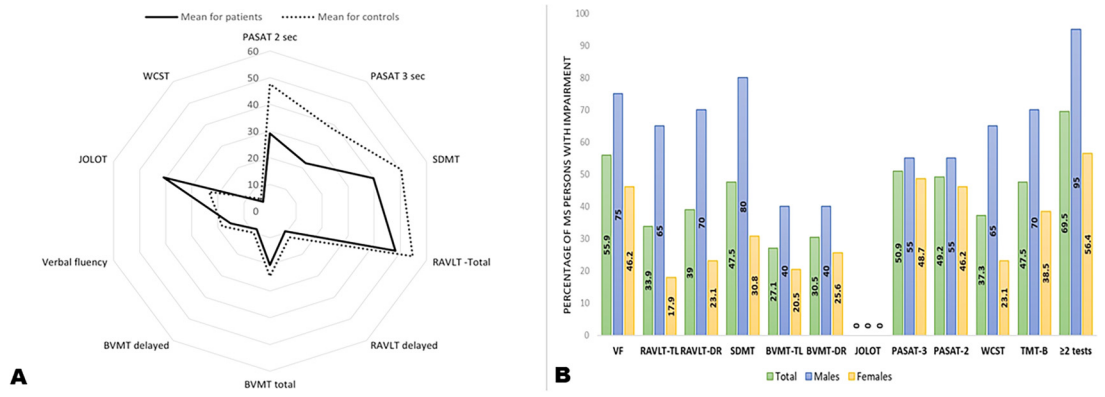

Figure 1. Distribution of abnormal scores in persons with multiple sclerosis ($N = 59$) and healthy control group ($N = 62$). (A) Radar plot for the mean of total scores for the different psychological tests among the two groups (excluding TMT-B where higher scores indicate worse performance) (B) Distribution of persons with multiple sclerosis with abnormal scores in each of the 11 neuropsychological tests compared to the control group classified by sex. Abbreviations: BVMT-R TL, Brief Visuospatial Memory Test-Revised total; BVMT-R DR, Brief Visuospatial Memory Test-Revised delayed recall; JOLOT, Judgment of Line Orientation Test; MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Test; RAVLT-TL, Rey Auditory Verbal Learning Test total; RAVLT-DR, Rey Auditory Verbal Learning Test delayed recall; N, number; SDMT, Symbol Digit Modalities Test; TMT-B, Trail Making Test-B; VF, Verbal Fluency; WCST, Wisconsin Card Sorting Test.

pwMS as cognitively impaired.[20] In another clinic-based Italian study in RMS persons with EDSS ≤2.5 using the Italian version of MACFIMS, 51.5% of the population were classified as cognitively impaired based on impairment (≤1.5 SD) in 2 or more tests.[21] In our group, the referral bias to the tertiary care center could have contributed to a higher frequency of cognitive impairment of 69.5%. A study of MoCA in 30 pwMS in India noted that 73.33% of the cohort performed worse than healthy controls.[10] Although the test may be administered quickly, making it a useful tool for outpatient clinics, it is unable to precisely measure processing speed or new learning deficits—two essential components of MS cognition.

The significantly higher burden of cognitive impairment in males has been previously noted in several studies.[22] While women have a higher prevalence of MS, men more often display progressive and rapidly worsening disease. After controlling the confounders including disease duration and MRI lesion load, men demonstrate higher disease-related cognitive disability and lower brain volumes than women.[22,23] A lower cognitive resilience in men has been hypothesized. Experimental studies in mice models of experimental allergic encephalomyelitis suggest a probable chromosomal link rather than hormonal differences to explain the difference in neuroplasticity.[24]

In our study, the most frequently impaired domains and those with the highest impact were information processing, language, and executive function which is congruent with the global data.[1] A notable difference was the performance of JOLOT as a test for cognitive impairment. For uncertain reasons, pwMS performed better than controls, though the scores in the controls were well within the normal ranges for this age group.[25] Visuospatial orientation is one of the better- preserved domains in MS making assessment of this function a poor screening test in this situation.[26]

Processing speed, which is typically impaired early in MS, was assessed by PASAT and SDMT. Despite its wide usage in clinical research, PASAT has disadvantages related to psychological stress during administration and requirement for arithmetic skills. It is also time-consuming and susceptible to practice effects.[27] SDMT is a briefer test that is self-paced and requires little support from a neuropsychologist. The rapidity of administration and longitudinal validity of the test makes it highly effective in the outpatient clinics and for clinical trials.[1,28] In this study, SDMT and PASAT were equally effective in capturing processing speed abnormalities. However, because of their low calculation skills and incapacity to understand the concept, over 25% of pwMS were assigned a null score on the PASAT. All the subjects could comprehend and complete SDMT.

For the assessment of executive function, we used the modified shortened version of WCST in place of the better validated D-KEFS sorting test as the latter is

Table 3. Multivariate logistic regression analysis for clinical and demographic variables associated with cognitive impairment in persons with multiple sclerosis.

Variable[a]	Odds ratio	95% confidence interval	*p*-Value
Age (<40 y vs ≥40 y)	0.395	0.033–4.725	0.463
Sex (Female vs Male)	16.645	1.630–169.933	**0.018**
Years of formal education (10–15 y vs >15 y)	1.633	0.366–7.280	0.520
Age of onset (≤30 y vs >30 y)	0.568	0.065–4.989	0.610
Duration of illness (≤10 y vs >10 y)	0.672	0.053–8.548	0.760
Number of relapses (1–5 vs >5)	1.776	0.206–15.338	0.602
Duration of therapy (≤5 y vs >5 y)	0.950	0.027–34.024	0.977
EDSS (0–1.5 vs 2–3.5)	0.290	0.063–1.327	0.111
HADS anxiety score (≤7 vs ≥8)	0.137	0.021–0.905	**0.039**

Abbreviations: EDSS, Extended Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; *N*, number; y, years.
Note: Due to the extremely low number of patients with abnormal scores, HADS-Depression score could not be included in the multivariate analysis.
[a]In all the groups, the second category listed was the reference category.

not validated in Indian languages. Previous studies consistently noted high count of perseverative errors in WCST for pwMS.[29] The sorting test with the 128-card version of WCST was shown to have a good correlation with D-KEFS sorting test.[29] The modified WCST did not show a meaningful difference for perseverative errors in this study. The TMT-B test which is well-studied in Indian population[16,17] was additionally performed for working memory and cognitive flexibility. The TMT-B switching task has substantial association with other cognitive tests of MS[30] and demonstrated a good effect size in our population. Abnormalities in phonemic VF in pwMS are closely associated with deficits in executive function.[31]

Memory impairment in MS is related to difficulties with new learning which improves with repetitions. Increasing load on information processing in the form of sustained attention and multitasking (divided attention) referred to as complex attention can be markedly affected in MS as opposed to simple attention which is relatively spared.[32] Moderate effect sizes were noted for verbal and visual learning tasks in this cohort.

Cognitive deficits in MS are typically subtle and may be missed in the screening tests typically geared for detecting degenerative dementias. Nevertheless, the social and functional limitations engendered by this are substantial. People with a higher degree of cognitive dysfunction tend to be more socially isolated and participate in fewer vocational activities. Within 10 years of disease onset, 50% to 80% of pwMS have related loss of employment which in turn contributes to an overall decline in the quality of life.[33] Early identification of the dyscognitive symptoms and implementation of effective interventions have been shown to improve the overall functional connectivity and activation of brain regions associated with different cognitive domains.[26]

The primary strength of this study was the use of the MS-specific neuropsychological test batteries adapted to the ethnic and language requirements. We used a matched control group as normative data on neuropsychological scores are sparse in this age group. The use of a homogeneous population with mild disability was helpful in eliminating the effects related to the disease stage. The study had some notable limitations. Impact of fatigue, sleep disorders, anxiety and

depression on cognitive tests was not studied in this cohort except for a screening administration of HADS. The sample size was inadequate to perform assessments of the impact of therapy in cognitive measures. Majority of the tests leaned heavily on visual and upper limb functions. Though this was of low concern in this population with mild disability, wider use of these tests in all stages of MS may require substantial modifications. Correlations with imaging information are not described in this analysis.

This study has shown that the frequency and patterns of cognitive dysfunction in Indian pwMS generally agree with the pioneering studies and the subsequent data from around the globe. Cognitive dysfunction in MS is not openly discussed and is frequently overlooked in the busy MS clinics. Longitudinal assessment of cognition could help as a predictor for progression[34] and identify relapses[35] making it a crucial component of comprehensive care of MS. The current study provides an insight into the sub-tests which have the highest sensitivity in this population. More population-specific data on the effect of psychological and related co-morbidities and long term follow up is required. Future research using abbreviated protocols in a wider population would help in integration of this critical metric in routine care and as a potential clinical biomarker to assess no evidence of disease activity with the newer MS therapies.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical statement

The study commenced after approval of the Institutional Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthpuram. Written informed consents were obtained from all the participants.

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Supplemental material

Supplemental material for this article is available online.

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