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SUBMISSION OF FINAL REPORT

1. **Title of the Research Scheme:** Validation of the Malayalam version of the Montreal Cognitive Assessment (MoCA) scale and a prospective evaluation of mild cognitive impairment in Parkinson's disease using the Malayalam version ("MoCA-M"). (Ref No: 5/4-5/106/Neuro/2013-NCD-1)

2. **Name, Degree and Designation of the Officer-in Charge and Co-investigators:** **Principal Investigator:** Dr. Syam K., MD, DM. Professor of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala. Phone: 0471-2524268, 9847310745 E-mail: drsyam@sctimst.ac.in
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3. **Name of the Institution:** Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala. PIN 695011

4. **Year in which the scheme was started:** 2017

5. **Date from which the scheme was sanctioned:** 1st March 2017

6. ICMR grant sanctioned and the actual expenditure from the year of inception till the date of termination

Year	Grant sanctioned	Actual Expenditure Incurred
Year 1	Rs. 3,81,100/-	Rs. 3,40,100/-
Year 2	Rs. 3,47,500/-	Rs. 3,88,500/-
Year 3	Rs. 5,46,940/-	Rs.5,46,940/-

7. Aims and Objectives with which the scheme was started:

The study was done in 2 phases.

The aim of the first Phase: Cross-cultural adaptation of Montreal Cognitive assessment (MoCA) scale into the regional language (Malayalam) and study of its validity for cognitive assessment in Parkinson's disease (PD).

The aims of Phase 2: (1) Cognitive evaluation of a cross-sectional sample of patients with PD using the screening tool (Malayalam version of MoCA- the "MoCA-M") as well as using a detailed and comprehensive battery of neuropsychological tests as per standard recommendations for cognitive testing in PD. (2) Determining the prevalence of PD-MCI in the study population (3) Longitudinal neuropsychological follow-up of the cohort for a period of 2 years aiming at exploring the decline of cognitive functions I any, over time.

8. Details of the report of work done:

<u>Materials and Methods used:</u>

Phase 1 (Cross Cultural Adaptation of MoCA and Validation of MoCA-M): The study was conceived in 2013, and the proposal was submitted to ICMR for funding. Part of the study (first phase) was completed by 2015, during the waiting period for sanction of funds. The Phase 1 involved translation / cross-cultural adaptation of MoCA to Malayalam and its validation. Translation and cross-cultural adaptation were done after getting the permission from copyright holders of the original version of MoCA and following the standard guidelines for validation / cross-cultural adaptation of Neuropsychological tests. For validation, the test (MoCA-M) was administered to patients with Parkinson's disease, and matched healthy

controls. Other standard neuropsychological tests (Addenbrooke's Cognitive Examination - ACE/ Mini Mental Status Examination -MMSE) were also applied for comparison. A subgroup of subjects was re-examined using the MoCA-M after an interval of 2 weeks to determine the test-retest reliability.

Phase 2: Estimation of the prevalence of PD-MCI and a longitudinal follow-up of PD-MCI using MoCA-M and other Neuropsychological test batteries: During the second phase, 170 patients were recruited and underwent comprehensive clinical and neuropsychological evaluation required to make a level II diagnosis of PD-MCI, as per the published Movement Disorder Society Criteria (2012) for the same. 60 healthy control subjects were also recruited for normative data for the neuropsychological test battery, to define the cut-off scores for MCI. The patients underwent follow-up clinical and neuropsychological evaluation, to determine the decline in neuropsychological test performance over time and the ability of MoCA -M to detect the same.

Results:

Phase 1: Translation and cross-cultural adaptation of MoCA to Malayalam and its validation has been done and the results published (Cited below). We translated MoCA into Malayalam and cross-culturally adapted the relevant items, following standard guidelines. The Malayalam version (MoCA-M) was applied to 70 patients with Parkinson's disease and 60 age and education matched healthy controls. Metric properties were assessed and the scores were compared with performance in validated Malayalam versions of Mini Mental Status Examination (MMSE) and Addenbrooke's Cognitive Examination (ACE). MoCA-M showed good internal consistency and test-retest reliability and its scores correlated with MMSE (patients: $R=0.70$; $p<0.001$; healthy controls: $R= 0.26$; $p=0.04$) and ACE (patients: $R=0.8$; $p <0.001$; healthy controls: $R=0.52$; $p<0.001$) scores. The reliability and validity of MoCA-M for assessing cognition in Malayalam speaking PD patients was thus established.

Table 1 shows the test-retest reliability of MoCA M and table 2 shows a comparison of MoCA-M, MMSE and ACE scores between patients and healthy controls, in the first part of the study.

Table 1. Test-retest reliability of MoCA-M

	Pearson's correlation coefficient	P value
Visuospatial / Executive	0.87	<0.0001
Naming	0.63	<0.0001
Attention	0.96	<0.0001
Language	0.95	<0.0001
Abstraction	0.96	<0.0001
Delayed Recall	0.96	<0.0001
Orientation	0.58	0.001
Total	0.97	<0.0001

MoCA-M – Montreal Cognitive Assessment- Malayalam

Table 2. The MoCA-M, MMSE and ACE Scores of patients and healthy controls

	Patients	Healthy Controls	P value
MoCA-M	24.7 ± 4.1	27.7 ± 1.8	<0.0001
MMSE	28.7 ± 1.9	29.3 ± 0.8	0.021
ACE	85.5 ± 9.4	91.6 ± 4.8	<0.0001

MoCA-M - Montreal Cognitive Assessment- Malayalam; MMSE- Mini Mental Status Examination; ACE- Addenbrooke's Cognitive Examination

Phase 2: For the second phase, a comprehensive Neuropsychological battery consisting of MoCA-M, MMSE, ACE, and two tests in each of the five cognitive domains (Attention, Executive Functions, Memory, Language and Visuospatial Functions) was compiled. (Ref: *Litvan I et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012 Mar;27(3):349-56.*) The tests used include the following: (1) Attention – Digit Span Test and the Attention/ concentration sub-section of ACE (2) Executive Functions- Trail Making Test and Wisconsin Card Sorting Test (3)

Memory: Visual Reproduction and Logical Memory Test of Weschler Memory Scale (4) Language: Frenchay's Aphasia Battery and the Language section of ACE (5) Visuospatial Functions – Position Discrimination and Cube Analysis of the Visual Object and Space Perception Battery. In addition, Beck's Depression Inventory for Screening for Depression, Neuropsychiatric Inventory (NPI) for Neuropsychiatric symptoms and Clinical Dementia Rating Scale are also being used.

The normative data from the 60 healthy volunteers who participated in the second part of the study was used to define the cut-off scores for PD-MCI as per the standard guidelines, and the patients were classified into PD-MCI – Single-domain, PD-MCI Multidomain and PD-Normal cognition.

Tables 3 shows the comparison of baseline demographic and neuropsychological data of patients compared to healthy volunteers. As it can be seen in table 3, patients with PD performed worse in almost all the tests of global and domain-specific neuropsychological tests. Table 4 shows the cut-off scores determined to define PD-MCI, using the tests decided a-priori, with two tests each for each of the five cognitive domains.

Table 3: The comparison of baseline demographic and neuropsychological characteristics of patients, compared to healthy volunteers

Characteristic	Patients (N=170)	Healthy Volunteers (N=60)	P value
Age at assessment (Years)	54.8±8.6	53.2±7.7	0.19
Number of years of education	13.1±2.6	13.8±2.8	0.10
Percentage of male subjects	66.5	36.7	<0.001
Duration of Parkinson's disease (Years)	6.1±4.0	NA	NA
MoCA-M Total Score	25.6±2.9	27.2±2.1	<0.001
MMSE	28.9±1.2	27.5±2.0	<0.001
ACE- Total Score	86.3±8.7	91.8±6.9	<0.001
ACE-Orientation	9.7±0.6	10.0±0.2	0.002
ACE-Concentration	7.7±0.1	7.3±0.1	0.01
ACE- Memory	25.5±5.6	28.7±5.4	<0.001
ACE-Fluency	12.1±1.5	12.9±1.3	<0.001
ACE-Language	27.2±1.2	27.6±0.7	0.02
ACE-Visuospatial	4.9±3.5	4.8±0.4	0.80
BDI	9.9±8.4	4.5±6.3	<0.001
NPI	4.7±5.1	1.8±3.6	<0.001
TMT-A- Errors	0.2±0.8	0.1±0.2	0.2
TMT-A – Time	153.3±55.1	106.1±39.7	<0.001
TMT-B- Errors	2.3±4.7	0.6±0.9	0.004
TMT-B - Time	325.8±138.2	228.2±92.1	<0.001
Digit Span Test	11.8±3.4	10.5±2.7	0.002
WCST- Perseverations	0.5±0.7	0.2±0.5	0.003

WCST- Errors	3.6±3.5	2.2±3.0	0.005
WCST- Categories passed	4.6±1.8	5.0±1.7	0.1
WMS-Visual Memory	26.1±7.7	31.5±6.3	<0.001
WMS- Visual Memory-Delayed	18.3±10.1	26.7±10.4	<0.001
WMS- Logical Memory-Immediate	17.3±6.6	21.8±6.4	<0.001
WMS-Logical Memory-Delayed	12.8±7.0	17.9±7.4	<0.001
VOSP- Position discrimination	19.7±0.7	19.9±0.3	0.01
VOSP-Cube analysis	8.0±2.8	8.8±2.4	0.06
Frenchay's aphasia screening test	28.6±1.1	29.1±1.0	0.003

Table 4: Tests selected *a priori*, in each of the five cognitive domains for making a diagnosis of PD-MCI and the cut-off scores determined for each of the tests (mean +/- 1.5 standard deviations) using data from healthy volunteers

DOMAINS	TESTS	MEAN	SD	1.5 SD	CUTOFF SCORES
Attention-Working Memory	1. Trail B-errors	0.57	0.91	1.36	>1.93
	2. Digit span overall	11.82	3.36	5.04	<6.77
Executive Functions	1. Verbal Fluency	12.90	1.27	1.91	<10.99
	2. WCST errors	2.18	3.02	4.53	>6.71
Language	1. ACE	27.63	0.66	0.99	<26.64
	2. Aphasia test	29.11	0.97	1.45	<27.66
Memory	1. VR-D	26.73	10.35	15.53	<11.20
	2. LM-D	17.92	7.37	11.06	<6.85

Visuo-spatial functioning	1. Cube analysis	8.80	2.38	3.57	<5.24
	2. Position Discrimination	19.93	0.32	0.48	<19.45

Based on cut-off scores defined from normative data, 72 of the 170 patients had MCI at baseline, indicating a prevalence of 42.4%. The MCI was multi-domain in 70 (2 domains in 30 patients, 3 domains in 25 patients, 4 domains in 11 patients and all 5 domains in 4 patients); single domain MCI was seen in only 2 patients. Among the domains involved in PD- MCI patients, memory was the most common (N=55; 76.4%) followed by attention (N=45; 62.5%), executive functions (N=39; 54.2%) Language (N=38; 52.8%) and visuospatial functions (N=23;31.9%). Patients with MCI tended to be older (56.3 ± 8.5 years Vs 53.8 ± 8.7 years; p= 0.06) and had longer duration of motor symptoms (6.8 ± 3.9 years Vs 5.6± 4.0 years; p =0.05) and lower MoCA scores (24.1 ± 3.2 Vs 26.6 ± 2.1; p <0.01) compared to those without

The patients with PD were followed up for two years. 124 patients were available for 1-year follow-up and 70 patients, for 2-year follow up. Tables 5 and 6 show the comparison of baseline neuropsychology data with one-year and two-year data in patients with PD.

Table 5: Comparison of base-line vs 1-year follow up neuropsychology tests (N=124)

Characteristic	Baseline	One-year follow- up	P Value (Baseline Vs 1-year)
MoCA-M Total Score	25.8±2.6	25.8±2.8	0.90
MMSE	27.5 ± 1.9	27.5 ± 1.8	0.80
ACE- Total Score	87.4±7.7	86.3±8.9	0.02
ACE- Orientation	9.8±0.4	9.7±0.6	0.12
ACE- Concentration	7.3 ±1.0	7.4±0.9	0.41
ACE- Memory	26.1±5.4	25.7±5.6	0.20
ACE-Fluency	12.2±1.6	12.0±1.4	0.16
ACE- Language	27.4±1.1	27.2±1.3	0.003
ACE-	4.6±0.6	5.0±0.4	0.24

Visuospatial			
BDI	8.2±7.0	9.5±8.3	0.05
NPI	2.1±2.0	4.9±5.1	<0.001
TMT-A- Errors	0.1±0.2	0.1±0.3	0.18
TMT-A – Time	137.5±51.7	157.5±54.2	<0.001
TMT-B- Errors	2.1±3.7	2.0±3.6	0.93
TMT-B - Time	317.6±138.8	328.3±137.8	0.30
Digit Span Test	10.4±2.6	10.4±2.5	0.96
WCST-Perseverations	0.5±0.7	0.4±0.7	0.40
WCST- Errors	3.8±3.6	3.3±3.4	0.14
WCST-Categories passed	4.6±1.7	4.7±1.7	0.30
WMS-Visual Memory	27.9±7.1	26.5±7.7	0.004
WMS- Visual Memory-Delayed	20.8±9.6	18.3±10.4	<0.001
WMS- Logical Memory-Immediate	18.0±6.4	17.7±6.7	0.39
WMS-Logical Memory-Delayed	13.8±6.9	13.1±7.1	0.15
VOSP-Position discrimination	19.8±1.0	19.7±0.7	0.12
VOSP-Cube analysis	7.8±3.0	7.9±2.9	0.58
Frenchay's aphasia	28.6±0.9	28.6±1.2	0.96

screening test			

Table 6: Comparison of base-line vs 2-year follow up neuropsychology tests (N= 70)

Characteristic	Baseline	One-year follow- up	P Value (Baseline Vs 1-year)
MoCA-M Total Score	25.4±2.9	25.8±2.6	0.19
MMSE	27.2±1.8	27.7±1.7	0.16
ACE- Total Score	87.6±7.0	86.7±8.2	0.22
ACE- Orientation	9.8±0.4	9.7±0.4	0.37
ACE- Concentration	7.5±0.8	7.2±1.1	0.02
ACE- Memory	26.5±5.0	26.0±5.2	0.32
ACE-Fluency	12.0±1.6	11.9±1.5	0.75
ACE- Language	27.9±0.8	27.1±1.3	<0.001
ACE- Visuospatial	4.9±0.8	5.3±0.5	0.19
BDI	7.8±6.7	8.9±8.4	0.22
NPI	1.5±1.7	5.2±5.3	<0.001
TMT-A- Errors	0.03±0.17	0.11±0.32	0.03
TMT-A – Time	129.9±46.2	166.9±53.7	<0.001
TMT-B- Errors	1.8±3.8	2.1±3.8	0.42
TMT-B - Time	315.0±147.2	335.4±130.8	0.17
Digit Span Test	10.0±2.7	10.4±2.6	0.18

WCST-Perseverations	0.56±0.75	0.5±0.74	0.59
WCST- Errors	4.0±3.8	3.6±3.4	0.39
WCST-Categories passed	4.6±1.7	4.9±1.7	0.17
WMS-Visual Memory	28.9±6.1	26.0±7.1	<0.001
WMS- Visual Memory-Delayed	21.8±9.1	16.8±9.0	<0.001
WMS- Logical Memory-Immediate	17.0±6.2	17.4±6.5	0.43
WMS-Logical Memory-Delayed	12.9±7.2	12.7±6.7	0.85
VOSP-Position discrimination	19.7±0.9	19.5±0.9	0.16
VOSP-Cube analysis	8.5±2.0	7.9±2.7	0.03
Frenchay's aphasia screening test	28.5±0.7	28.7±1.1	0.48

It is seen that the executive functions (Performance in Trail making test -A), language (Language domain of ACE) and visual recall tended to worsen with time, in the patient population (Tables 5 and 6). In addition, the neuropsychiatric status (as indicated by the Beck's Depression Inventory and Neuropsychiatric Inventory scores) also worsened during follow up. These are compatible with the natural history of a neuro-degenerative disease like PD. No patient developed new-onset dementia during the follow up period.

9. An abstract, highlighting the results achieved by the research project for inclusion in the Council's research information bulletin:

Objective: We aimed to design a neuropsychological test battery, including the Malayalam Version of Montreal Cognitive Assessment (MoCA), to diagnose Mild

Cognitive Impairment (MCI) and to estimate the prevalence of MCI in Malayalam-speaking patients with Parkinson's disease (PD) from South India. We also did a longitudinal follow up of cognitive functions in patients with PD to examine how the neuropsychological functions decline over time **Background**: MCI is common in PD and a risk factor for PD-Dementia. Guidelines for diagnosis of PD-MCI have been published. However, a comprehensive test battery as per published guidelines is currently unavailable for use in South Indian population speaking Malayalam, numbering around 40 million. There is also little data on the prevalence of MCI among Indian PD patients. **Methods**: The first phase of the project aimed at creation and validation of the Malayalam version of MoCA. This was done as per standard guidelines for translation and cross-cultural adaptation of neuropsychological tests, assessing its metric properties like test-retest reliability and comparing with other standardized Neuropsychological tests. The Malayalam version (MoCA-M) was found to be a valid and reliable tool for cognitive assessment and the results of the first phase have been published. For detailed Neuropsychological assessment for Phase 2 of the project, we compiled a test battery comprising of two neuropsychological tests in Malayalam in each of the five cognitive domains, namely attention and working memory, executive functions, language, memory and visuospatial functions. Normative data from 60 healthy volunteers was used to decide cut-off scores for defining PD-MCI. The test battery was applied to 170 consecutive non-demented patients with PD to estimate the prevalence and characteristics of PD-MCI. The patients were also followed up longitudinally with annual Neuropsychological assessments. **Results**: Healthy volunteers and patients did not differ significantly with regard to age or level of education. 72 (42.4%) of the patients were found to have PD-MCI at baseline. Among the patients with PD-MCI, multi-domain involvement was seen in all except two patients. Memory, followed by attention were the most common domains affected. Patients with PD-MCI tended to be older, had longer duration of PD and lower MoCA scores at baseline, compared to patients without PD-MCI. A decline in executive functions and memory was noted during longitudinal follow-up, in PD patients. No patient developed dementia during follow up. **Conclusions**: We designed a neuropsychological test battery to diagnose PD-MCI in Malayalam speaking South Indian population. The prevalence of PD-MCI (42.4%) estimated with the battery is comparable to that reported from other populations. Multi-domain involvement was seen in the majority with MCI. Patients with PD-MCI performed poorer on the Malayalam version of MoCA, one among the most widely used cognitive screening tests for PD. Longitudinal cognitive assessments over a span of two years showed decline in memory and executive functions in the PD group.

10. **Publications: (1)** Krishnan S, Justus S, Meluveettil R, Menon RN, Sarma SP, Kishore A. Validity of Montreal Cognitive Assessment in Non-English-speaking patients with Parkinson's disease. Neurol India. 2015 Jan-Feb;63(1):63-7.

    Two other publications in pipeline.

    Presentation in International Conference:

    Syam Krishnan, Remya Ramesh, Gangadhara Sarma S, Ramshekhar N Menon, Asha Kishore. Mild Cognitive Impairment in Parkinson's disease in South Indian population – Development of a test battery and assessment of prevalence and characteristics. Presented in

the International Congress of Parkinson's disease and Movement disorders, Nice, France, September 22- 26, 2019.

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