Cognitive Impairment in Pediatric Onset Multiple Sclerosis (MS) is Detected by the Brief International Cognitive Assessment of Multiple Sclerosis (BICAMS) and

Computerized Cognitive Testing

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**ABSTRACT**

Background: Cognitive impairment is a common and troubling feature of pediatric-onset multiple sclerosis (POMS). Brief cognitive assessment in the outpatient setting can identify and longitudinally monitor cognitive involvement so that early intervention is possible

Objectives: The goal of this study was to measure the sensitivity of two cognitive assessment approaches that are brief, repeatable, and suitable for clinical practice and for multicenter investigation.

Methods: Participants with pediatric-onset MS (POMS, n=69) were consecutively-evaluated as part of outpatient neurologic visits and compared to healthy control participants (HC, n=66) using the Brief International Cognitive Assessment in MS (BICAMS) approach and timed information processing measures from Cogstate, a computer-based assessment.

Results: There was strong agreement in the detecton rate of impairment between both assessments, with 26% for the BICAMS and 27% for Cogstate. Two of the Cogstate tasks were the most sensitive individual measures.

Conclusions: Both the BICAMS and Cogstate timed processing measures offer practical, sensitive, and standardized approaches for cognitive screening assessment in POMS.

1. **INTRODUCTION:**

Cognitive impairment is a common and troubling feature of multiple sclerosis (MS) across the lifespan. For younger patients experiencing the onset of MS in the context of ongoing neurodevelopment, it is particularly critical to identify cognitive impairment at its earliest point with the goal of ensuring full cognitive development and preventing academic decline.

At least one-third of pediatric MS patients have some degree of cognitive impairment, compared to at least one-half or more of those with adult MS[1](#_ENREF_1). Pediatric-onset of MS is relatively rare and therefore requires specialized centers and multicenter collaboration to advance research[2](#_ENREF_2). Self-report of cognitive impairment in POMS does not distinguish between those with and those without objective cognitive impairment[3](#_ENREF_3). There is a need for an objective standardized assessment that can be easily and uniformly administered across centers.[4](#_ENREF_4)

The Brief International Cognition Assessment in MS (BICAMS) was developed by an international committee as an assessment tool for adult MS to detect cognitive deficits in both clinical and research settings[5](#_ENREF_5), [6](#_ENREF_6). It is validated in a variety of languages and consists of three tests: the oral trial condition of the Symbol Digit Modalities Test (SDMT) [7](#_ENREF_7), the learning trials from the California Verbal Learning Test-second edition (CVLT-II [8](#_ENREF_8)) or Rey Auditory Verbal Learning Test (RAVLT [9](#_ENREF_9)) and the Brief Visual Memory Test-Revised (BVMT-R) [10](#_ENREF_10). For verbal learning, the RAVLT has an additional advantage as it offers the ability for continuous administration using one form for ages 8 years and older. While the SDMT has been found to be as sensitive as a screening measure in pediatric-onset MS[11](#_ENREF_11), the BICAMS has not yet been validated in this population.

 Computerized-based cognitive assessment offers advantages of precise, easily-and uniformly-administered assessment. Cogstate is a widely-used platform designed for cognitive evaluation in multi-center clinical trials[12](#_ENREF_12) that may be suitable for use in pediatric-onset MS. For instance, Cogstate measures have been used to report cognitive outcomes related to medication toxicity and the effects of varying diseases[13-16](#_ENREF_13). Regulatory authorities (the Food and Drug Administration, European Medicines Agency) have approved the use of Cogstate tests for monitoring the safety of central nervous system penetrant drugs in multiple pediatric indications. Cogstate may also be applicable in clinical practice settings. As part of its assessment package, Cogstate has an extensive normative database for cross-sectional and longitudinal comparison across the lifespan (ages 10 to 99 years), with a total of over 50,000 globally-representative participants for normative comparison[17](#_ENREF_17).

Extensive cognitive assessment in POMS requires resources and tools that are unavailable outside of few specialist centers. Could a brief cognitive screen identify children and young people at risk of significant cognitive impairment and identify those who require more extensive cognitive assessment and management? The purpose of this study was to test two brief cognitive assessment approaches in a consecutively-recruited outpatient sample of pediatric-onset MS participants (POMS). We compared sensitivity of the measures to pediatric participants with a comparison group of locally-recruited healthy controls (HC).

1. **MATERIALS AND METHODS:**

2.1 Participants

This study was approved by the Stony Brook Institutional Review Board. Patient participants were consecutively recruited during their routine outpatient visits to the Lourie Center for Pediatric MS in Stony Brook, New York between December 2013 and April 2015. Healthy Controls (HC) were recruited between May 2014 and April 2015 through community-based advertisements.

Eligibility for patients included the diagnosis of POMS defined as MS onset prior to age 18 years, following current established criteria[18](#_ENREF_18), and without any other primary neurologic or psychiatric condition. Due to diagnostic uncertainty, potential participants with radiologically isolated syndrome (RIS) and clinically isolated syndromes were excluded. Any potential participant was excluded if they had a history of a condition that may separately contribute to cognitive impairment (e.g. head trauma) or primary neurodevelopmental disorders (e.g., autism spectrum disorder, fetal alcohol syndrome). All participants were also required to score above 85 on the reading subtest of the Wide Range Achievement Test, 3rd Edition (WRAT-3) [19](#_ENREF_19) reading test, be fluent in English (learned before the age of 6 years and not currently enrolled in a school English Language Learner program).

2.2 Study Procedures

We collected demographic information, clinical history forms, and, for the POMS participants, performed a neurological examination including the Expanded Disability Status Scale (EDSS) [20](#_ENREF_20).

2.3 Cognitive Testing:

All cognitive testing was administered by the center neuropsychologist or a psychometrician on the same day as the outpatient neurology visit. **The total administration time for both full assessments was approximately 30 minutes and required a minimal level of training requirements using a bachelor’s degree level psychometrician.
 The BICAMS administration requires 15 minutes or less.** Participants were first administered the oral version of the SDMT, followed by five learning trials from the RAVLT and three learning trials from the BVMT-R. To account for exposure to the tests in previous administrations, alternate forms with up to four equivalent SDMT forms[21](#_ENREF_21), six RAVLT forms, and six BVMT-R forms were used during follow-up visits.

 The Cogstate Brief Battery consists of three speeded processing tasks: Detection (DET, measuring processing speed), Identification (IDN, measuring continuous visual attention), and One-Back (ONB, measuring speeded working memory).  **Each individual task requires approximately three to four minutes to administer, for a total administration time of 15 minutes or less.**

Cogstate measures were administered on a 17” laptop computer on a table. Tasks were presented with standardized instructions read aloud by a test administrator, followed by practice trials. Each task has stimuli consisting of playing cards centered on a green screen; responses are answered “yes” or “no”, using keys “D” and “K” on the keyboard respectively. Figure 1 shows an example of the DET and IDN task presentation. Validity checks for expected item accuracy and outlier detection ensure that only valid assessments are included[17](#_ENREF_17). Completion and performance checks were applied to the speeded Cogstate measures using pre-specified criteria based on expected minimal accuracy for validity [22](#_ENREF_22).

Insert Figure 1 about here

2.4 Statistical Methods

All data was recorded with the Research Electronic Data Capture (REDCap) system [23](#_ENREF_23). Representative measures were as follows: BICAMS: total correct for SDMT, total learning score for BVMT-R, total learning score for RAVLT; Cogstate: response times for Detections (DET), Identification (IDN), One-Back (ONB). To obtain a standard metric for comparison, raw scores were converted to z-scores based on published normative data from for each of the respective BICAMS test [9](#_ENREF_9), [10](#_ENREF_10), [24](#_ENREF_24) and from Cogstate’s global normative database [17](#_ENREF_17). Following prior studies and guidelines for clinical interpretation for each battery [17](#_ENREF_17), a z-score of equal to or less than -1.5 for the BICAMS and -2.0 for Cogstate measures was used to define clinical impairment[12](#_ENREF_12), [13](#_ENREF_13). Participants were categorized as “cognitively impaired” if they scored in the impaired range on at least one measure.

**RESULTS**

A total of 69 POMS and 66 HC participants completed the BICAMS assessment. Table 1 shows the demographic and clinical features of the groups. Participants’ ages ranged from seven to twenty-one years. The groups also significantly differed according to race (p<0.001), with the MS group having the greater percentage of African-Americans (26%) to HC (0%).

Clinical features of the POMS group are also shown in Table 1. The median EDSS was 1.0 with a range of 0 to 3.5. In the POMS group the disease duration ranged from less than one year to 15 years, with a mean of was 2.55 (±2.90) years.

Insert Table 1 about here

*BICAMS and Cogstate performance*

**All but two of POMS participants, who completed the BICAMS, also completed the Cogstate battery. Of the healthy controls, 48 of 66 also completed the Cogstate battery. The primary reasons for not completing the Cogstate were time limitations at the clinical or healthy control research visit, followed by absence of computer availability.** As shown in Table 2, among the BICAMS measures, the BVMT-R significantly differed between the two groups while the SDMT and RAVLT trended towards significant differences. Two of the three Cogstate measures (DET, IDN but not ONB) significantly discriminated between the POMS and HC groups.

Insert Table 2 about here

**Sensitivity of Measures**

**On all measures, POMS demonstrated greater impairment in comparison to the HC group. Figure 2 illustrates the percent impairment for individual measures between the two groups (POMS and HC).**

Insert Figure 2 about here

**Limiting the MS participants to those 18 years and under (n=57) did not change the pattern of results. When comparing those over and under 18 years of age, there were no significant difference in proportion of impairment found with either the BICAMS (p=0.41) or Cogstate (p=0.29) batteries.**

**3.2 Consistency of Measures**

**Overall, BICAMS and Cogstate agreed in the classification of impairment in 74% of the full sample, with 69% agreement of the POMS cases and 85% agreement of the HCs whose scores were classified as impaired.**

**Table 3 shows the consistency of the BICAMS and Cogstate measures across participants. The SDMT and RAVLT performances significantly correlated with all three Cogstate measures: DET (r’s=0.40 and 0.33, p’s<0.001), IDN (r’s=0.49 and 0.42, p’s<0.001,), and ONB (r’s=-.48 and 0.29, p’s≤0.001). In contrast, the BVMT-R did not show any significant correlation across any of the Cogstate measures, (r’s <0.19, p’s>0.03).**

Insert Table 3 about here

**3.3 Specificity of Measures**

**Overall, BICAMS and Cogstate had had 91% and 92% specificity, respectively, for identifying impairment in POMS vs. HC participants. Each assessment approach is effective in identifying those POMS participants with cognitive impairment, and when positive, both approaches are strongly specific.**

3.4 Relation to Disease Factors

 Among the POMS group, a binary logistic regression found neither BICAMS nor Cogstate impairment was predicted by age of onset or disease duration. There was no single clinical factor that significantly predicted impairment for either the BICAMS (*X*2[2, 66]=0.40, p=0.82, R2=0.008) or Cogstate (*X*2[2, 69]= 1.41, p=0.48, R2=0.03) assessments. For the n=61 POMS participants with identified age of onset, there was no difference in those with onset before or after 14 years of age (n=22 vs. 39, respectively) for frequency of impairment on either the BICAMS or Cogstate assessments (*X*2[1, 61]= 0.64, p=0.4) or Cogstate (*X*2[1, 61]= 0.76, p=0.54.

**Discussion**

 In this consecutively-recruited sample of participants with exclusively pediatric-onset MS, we found that the routine administration of a brief cognitive assessment for POMS patients is feasible in an outpatient setting. We have previously shown that the SDMT is a useful cognitive screen[11](#_ENREF_11) and have subsequently shown here that there is a clear utility for the BICAMS in initial screening for cognitive impairment. Administration time for both the BICAMS and Cogstate measures was approximately 15 minutes each. All measures demonstrate ease of administration in a standardized format with multiple forms available to minimize practice effects.

Both the BICAMS and Cogstate are sensitive to cognitive impairment in POMS, clearly differentiate MS participants from HCs, and may be used to detect cognitive deficit in the clinical setting. **Relative to normative data, rates of impairment were found to be 26% for the BICAMS and 27% for the Cogstate measures.** Both approaches appear to be useful with consistent rates of impairment and overall strong agreement. The BICAMS assessment may reflect the broader range of areas of functioning that are tested, while Cogstate may be relatively more sensitive to subtle impairments in cognitive processing.

Overall rates of cognitive impairment found in this study are consistent with the rates reported by other studies using more extensive neuropsychological testing batteries [1](#_ENREF_1), [25-28](#_ENREF_25). As expected, estimated impairment in this pediatric-onset sample is relatively lower than what has been reported in adult MS samples using these assessment approaches, with up to 58% impairment reported in adult MS using the BICAMS[29](#_ENREF_29).

Among the BICAMS measures, as would be expected, the SDMT was the measure with the most impairment among the POMS sample and consistent with the pattern reported for adults[30](#_ENREF_30). However, the most sensitive individual measures were both from Cogstate (DET and IDN). Together with the SDMT, these findings indicate that information processing speed is the most sensitive area of MS-related cognitive involvement in POMS as well as adults with MS. The higher impairment rate found using either of the two Cogstate tasks indicates that these computer-based speeded information processing measures may be most sensitive to the detection of MS-related impairment overall.

There was high agreement between both assessment approaches. Additionally, Cogstate was found to be significantly correlated to the SDMT and RAVLT, but not the BVMT-R. This finding is likely due to the contribution of information processing speed to performance on the SDMT and RAVLT, while is not a core component for the BVMT-R performance. It is not clear why the third Cogstate measure, ONB, was not sensitive in this study. In addition to speeded cognitive response, this task also includes a working memory component. Therefore, its relative insensitivity in this study suggests that it is information processing speed that is specifically affected by early disease process. Further, continued use of Cogstate should include only the DET and IDN measures.

**While pediatric onset refers to initial diagnoses under the age of 18 years, we included participants with pediatric onset who at the time of testing were up to the age of 21 years. Patients up to this age are frequently included in pediatric neurology practices and this age range is consistent with other POMS studies**[**31**](#_ENREF_31)**. The wider age range also facilitates analyses of cognitive functioning with disease features for example by providing a broader range of disease durations. Cognitive performance on both BICAMS and Cogstate was generally unrelated to disease features, including overall neurologic disability, disease duration, and age of onset. It has been suggested that younger age of onset may be associated with a poorer clinical course, possibly including cognition**[**32**](#_ENREF_32)**,** [**33**](#_ENREF_33) **. However, this was not supported by our findings here, and may be better addressed through longitudinal study.**

One of the limitations to this study is the absence of more specific markers of disease activity such as neuroimaging, as well as a direct measure of real-world function. For future studies, it would be important to include both sets of assessments in a larger sample over time (to investigate test-retest reliability and sensitivity to change) along with neuroimaging measures and a functional scale in order to determine the measures that are most closely linked to disease status and relevant to everyday functioning. Expanding the use of BICAMS to a pediatric age range would also benefit the development of more sensitive regression-based normative data that are available for adults [24](#_ENREF_24). **Cogstate has the advantage of an extensive and globally-based normative database, and is also relatively language free with the option for instructions to be administered in several languages.** Both BICAMS and Cogstate offer a preliminary step towards a feasible, validated international cognitive assessment for multicenter treatment trials in POMS, which need to address outcomes tailored to POMS[34](#_ENREF_34).

**Conclusions:**

In sum, BICAMS is a feasible approach for cognitive screening in pediatric onset MS as well as in adults, and this study supports its use in characterizing cognitive functioning across the lifespan in MS. Incorporating the information processing measures in Cogstate may contribute to greater sensitivity of a single measure and is an approach that is very feasible both in the clinical setting and for multi-center research. Overall, both batteries are largely in agreement of impairment ratings with the BICAMS detecting higher impairment, likely due to its broader range of areas tested. A strength of the Cogstate measures is the near-absence of practice effects [35](#_ENREF_35), and therefore may be particularly useful for detecting change over time.

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**Conflict of interest statement**

No conflicts of interest.

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**Table 1. Demographic and Clinical Features of the Samples**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **POMS (n=69)** | **HC (n=66)** |  **t-test p value** |
| Age in years (mean±SD/range) | 16.6±2.9 (7 to 21) | 16.2±4.1 (8 to 21) | 0.47 |
| Gender (% Female) | 62% | 59% |  |
| Ethnicity (% Hispanic) | 33% | 11% |  |
| Race (%) |  |  | <0.001 |
|  White | 62% | 59% |  |
|  African American | 26% | - |  |
|  Asian | 3% | 21% |  |
|  Mixed/Other | 6% | 7% |  |
| WRAT-3 Word RecognitionStandard Score (mean±SD) | 105.0±9.8 (n=56) | 107.4± 8.4 (n=57) | 0.16 |
| EDSS (median, range) | 1.0 (0 to 3.5) |  |  |
| Disease Duration  | 2.45±2.84 (0.04 to 15.05) |  |  |
| Age of Onset | 14.3±2.5 (3 to 17 years) |  |  |

**Table 2. Mean Age-normative z-scores by Group**

|  |  |  |  |
| --- | --- | --- | --- |
| *BICAMS*  | *POMS (n=69)* | *HC (n=66)* |  *p value* |
| SDMT Total z-score (mean±SD) |  -0.50 ±1.11 |  -0.18 ± 0.81  |  0.06 |
| BVMT-R Total z-score (mean±SD) |  0.18± 1.28  |  0.48 ± 1.05 |  0.05\* |
| RAVLT z-score (mean±SD) |  -0.2±1.1 |  0.2±1.0 |  0.06 |
| *Cogstate POMS (n=67) HC (n=48)* |
| DET z-score (mean±SD) |  -0.8± 1.5 |  0.1 ± 1.0 |  <0.001\* |
| IDN z-score (mean±SD) |  -0.7 ±1.3 |  0.1 ±0.94 |  <0.001\* |
| ONB z-score (mean±SD) |  -0.5 ±1.2 | -0.3±0.9 |  0.23 |

|  |
| --- |
| **Table 3. Correlations between performance on Cogstate and BICAMS measures (z scores)** |
| *Neuropsychological Measure* | *SDMT* | *BVMT-R* | *RAVLT* |
| Detection | r=0.40, p<0.001 | r=0.16, p=0.08 | r=0.33, p<0.001 |
| Identification | r=0.49, p<0.001 | r=0.19, p=0.03 | r=0.42, p<0.001 |
| One Back(ONB) | r=0.48, p<0.001 | r=0.11, p=0.20 | r=0.29, p=0.001 |
|  |