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Early neuropsychological markers of cognitive involvement in multiple sclerosis

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ABSTRACT

Background: Cognitive impairment due to multiple sclerosis (MS) is common and often limits occupational functioning, contributes to disability, and reduces quality of life. Early detection of cognitive involvement in MS is critical for treatment planning and intervention, and frequent, regular cognitive monitoring may provide insight into subtle changes in disease progression.
Objective: To compare the sensitivity and specificity of clinical, computer-based and experimental measures to early cognitive involvement in MS.
Methods: Cognitive functioning was compared in MS participants early in the disease course to matched healthy controls using conventional, computer-based and functional assessments: the Brief International Cognitive Assessment in MS (BICAMS); the computer-based Cogstate Brief Battery (CBB); the Attention Network Test-Interaction (ANT-I), including intra-individual variability; and the Test of Everyday Cognitive Ability (TECA), a functional measure of instrumental activities of daily living.
Results: MS participants (n = 25, mean disease duration= 5.82 ± 3.65 years) and demographically matched healthy controls (n = 29) completed the cognitive assessments. The Cogstate measure of choice reaction time (AUC = 0.73, p = .004), intra-individual variability on the ANT-I (AUC = 0.79, p = .001), and TECA (AUC = 0.78, p = .001) scores were the most sensitive and specific markers of cognitive involvement in MS.
Conclusions: Brief, repeatable, computer-based measures of reaction time and variability detect early MS associated cognitive involvement.

1. Introduction

Multiple sclerosis (MS) is a chronic and progressive autoimmune disease of the central nervous system, which commonly affects cognitive functioning [1–5]. Early detection of cognitive involvement in MS can have major implications for treatment planning, intervention and prevention of further decline [6]. Moreover, monitoring cognitive involvement repeatedly over time starting early in the disease course may provide critical insight into disease progression, even in the absence of any new physical symptoms.

Among the most common cognitive changes associated with MS are reduced processing speed, attention difficulties, decreased working memory capacity, and poorer new learning ability (in both verbal and visual modalities) [7,8]. In particular, slowed information processing speed is a cognitive hallmark of the disease, and is thought to underlie impairments in other cognitive domains in MS [9–11]. With the continued characterization of the cognitive sequelae of MS, there is a critical need for brief, sensitive and specific screening measures [12].

In 2012, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was proposed as a standard for a brief cognitive screen in MS [13]. The BICAMS includes the oral condition of the Symbol Digit Modalities Test (SDMT [14]), considered the most sensitive brief measure of cognitive impairment in MS [15–19], as well as auditory and visual learning measured across trials on the California Verbal Learning Test – Second Edition (CVLT-II [20]) or Rey Auditory Verbal Learning Test (RAVLT [21]) and the Brief Visuospatial Memory Test – Revised (BVMT-R [22,23]), respectively. Importantly, the BICAMS subtests include alternate forms, allowing for repeated testing while minimizing practice effects.

Computerized neuropsychological assessment is also emerging as a tool for measuring subtle cognitive changes in MS [24]. In particular, the simple and choice reaction time tests on the Cogstate Brief Battery (CBB;

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Cogstate Ltd.), measuring sustained visual attention and processing speed, were found to reliably discriminate between individuals with MS and matched healthy controls [25–27]. In addition to increased sensitivity and reliability [25–27], advantages in using computer-based assessments include efficient and standardized administration, precision of measurements, extensive normative data, and instant normed-based output. Moreover, the CBB includes numerous stimuli that are randomly sampled in each administration, and it has been demonstrated to have little practice effect with repeat administrations [28,29].

In the experimental setting, the Attention Network Test (ANT [30];) and its variant, the Attention Network Test – Interaction (ANT-I [31];), measuring efficiency of specific networks of the attention process, and specifically the executive network (measured by response when confronted with competing stimuli), have also been used to characterize cognitive involvement in early MS [32–34]. Further, intra-individual variability (IIV) in reaction time across the repeated trials on the ANT-I and other tasks of attention and processing speed may be particularly useful in characterizing cognitive and neurologic status in MS, providing a measure of response consistency that is independent from speed or accuracy [33,35–38]. Higher variability in cognitive performance (i.e., less consistency) has been demonstrated in individuals with MS [39], suggesting a unifying neuronal substrate that may be inherent to the disease [35,37,38]. Moreover, this variability may hinder the ability of neuropsychological measures to capture a coherent cognitive profile in MS patients [35]. Thus, IIV may allow for a more sensitive and accurate measure of cognitive status in MS, relative to mean-level performance [35].

There is also a need to include ecologically valid measures of cognitive ability to capture the influence of impairment across daily living. Standard instrumental activities of daily living measures were developed for use in aging and dementia populations [40,41], which are not appropriate for younger adults nor sensitive to the milder and more subtle impairments that occur in MS [42,43]. To meet this need, we included the validated and repeatable measure, the Test of Everyday Cognitive Ability (TECA [43]), that has a series of real-world tasks (e.g., counting money, following a shopping list) designed specifically for use in MS and with minimum motor requirements.

While the BICAMS battery, and the SDMT in particular, are considered the gold standard for cognitive screening in individuals with MS, technology has enabled precise measurement of response time through computer-based administration. Measurement of the consistency of response across timed trials (e.g., IIV computation) may provide more specific, accurate and sensitive screening measures, particularly at early stages of the disease, when cognitive changes are often subtle.

In this study, we compared younger adults with early stages of relapsing-remitting MS (with no to minimal physical disability) to matched healthy controls (HC) using these measurement approaches. We hypothesized that tests measuring information processing speed will be the most sensitive to early cognitive involvement in MS. We further hypothesized that response variability versus averaged performance on tasks of processing speed, will provide the best estimator of cognitive involvement early in the disease.

2. Methods

2.1. Participants

Twenty-five individuals with early-stage MS and 29 demographically-matched HC were recruited from the MS Comprehensive Care Center at Stony Brook Medicine, Stony Brook, NY (see Table 1 for demographic data). All MS participants had a diagnosis of relapsing-remitting MS (RRMS) according to established criteria [44]. Potential MS participants were excluded if they had any clinical relapse and/or high-dose steroid use within the past month. Any concurrent medications that participants were taking had to be kept constant in the three months prior to data collection visits. Exclusion criteria for both MS and HC participants included having learned English language after the age of 12 years [45], any history of primary psychiatric and/or neurological disorder (other than MS), and an estimated verbal IQ of less than 85 on a reading test (The Wide Range Achievement Test, 3rd edition; WRAT-3 [46]). In addition, due to the adverse effects depression may have on cognitive functioning, independent of MS-related neurological effects, individuals with elevated depression symptoms were excluded as well (in MS: Beck Depression Inventory Fast Screen score > 4; in HC: positive endorsement of the one-item depression screen [47]).

Table 1
Demographic and clinical features of the samples.

Characteristics	MS (n = 25)	HC (n = 29)	p
Age in years (mean ± SD/range)	26.15 ± 5.18 (18–36)	23.78 ± 7.73 (18–59)	0.20
Gender (% female)	56%	55%	0.41
WRAT-3 Word Recognition Standard Score (mean ± SD)	109.92 ± 7.18	110.93 ± 5.59	0.56
Education in years (mean ± SD/range)	14.8 ± 1.8 (12−20)	15.5 ± 1.9 (13−20)	0.18
BDI-FS	1.95 ± 2.22	1.25 ± 1.48	0.25
EDSS (median, range)	2.0 (0–6)		
Disease duration (mean ± SD/range)	5.82 ± 3.65 (0−11)		
Age of onset (mean ± SD/range)	20.56 ± 6.81 (11–36)		
Disease modifying medication (data available for n = 18; n (%))	Rebif = 2 (11) Tysabri = 4 (22) Rituxan = 4 (22) Tecfidera = 2 (11) Gilenya = 4 (22) Copaxone = 1 (6) None = 1 (6)		

All participants provided written informed consent to study procedures that were approved by the Institutional Review Board and the Committee on Research Involving Human Subjects at Stony Brook Medicine, Stony Brook, New York. All participants completed cognitive testing in one research study visit.

2.2. Cognitive measures

Below is a brief description of each of the tasks utilized in the study (see Table 2 for summary).

2.2.1. Brief International cognitive assessment for multiple sclerosis (BICAMS)

The battery is comprised of three measures; (1) SDMT [14,48] oral administration; a task primarily assessing information processing speed, and involves timed visual number-symbol decoding. (2) BVMT-R [22,23] learning trials; a visual learning task which involves three trials of drawing reproductions from memory following short exposures (10 s each). The total raw score is summed over the three learning trials. (3) RAVLT [21] learning trials; a verbal/auditory learning task, involving immediate recall of a list of 15 unrelated words over 5 exposures. The total raw score is summed over the five learning trials.

2.2.1.1. Scoring. Total raw score was recorded for each of the three measures and converted to age (BVMT-R [22]; RAVLT [21]) or age, gender, and education (SDMT [49]) normative z scores. The z scores were then averaged across the three tests for one representative BICAMS z score for each participant [50–52]. Group median score was inserted for 5 missing values on the BVMT-R (one MS participant and 4 HC participants), and a missing value for one HC participant on the SDMT.

Table 2
Summary of cognitive measures.

Battery	Test	Main Cognitive Domain	Main Outcome Measure	Administration Time	Practice Effects	Normative Data
BICAMS				**12 min**	Minimal with alternate forms	
	SDMT oral	Visual processing speed	Total correct	90 s		$N = 663$
	BVMT-R learning	Visual learning	Total correct	4 min		$N = 588$
	RAVLT learning	Verbal/auditory learning	Total correct	6 min		$N = 132$
CBB				**12 min**	minimal	$N > 2500$
	DET	Psychomotor speed	Reaction time	3 min		
	IDN	Visual attention Processing speed	Reaction time	3 min		
	ONB	Working memory Processing speed	Reaction time	4 min		
ANT-I				**23 min**	minimal	–
	Alerting	Attention	Reaction time	–		
	Orienting	Attention	Reaction time	–		
	Executive control	Attention	Reaction time	–		
IIV				–		–
	ANT-I	Response consistency	Individual SD	–		
	CBB (DET/IDN)	Response consistency	Individual SD	–		
TECA				**15 min**	Minimal with alternate forms	$N = 49$
	TECA proportion score	Instrumental activities of daily living	Total proportion (reaction time + accuracy)	–		

In bold are total administration times for each battery.

2.2.2. Cogstate brief battery (CBB)

This battery includes three computerized tests: (1) Detection (DET); a test of psychomotor speed, involving visual signal detection (card turning over on the screen) and rapid motor response (pressing a "yes" key on keyboard). (2) Identification (IDN); a test of visual attention and processing speed, involving making visual judgments (whether a card is red) and pressing the corresponding key (either "yes" or "no" keys on a keyboard). (3) One Back Test (ONB); measuring working memory and processing speed, where participants are presented with different cards and required to make a rapid judgment on whether a new card is the same as the last card presented on the screen and pressing the corresponding "yes" or "no" keys on the keyboard.

2.2.2.1. Scoring. Reaction time scores on each of the three CBB subtests were converted to age-normative z score [53]. The z scores were then averaged across the three tests for one representative CBB z score for each participant [25,26]. Group median reaction time was inserted for a missing value on the DET task for one MS participant.

2.2.3. Attention network test – interactions (ANT-I)

The ANT [30] was designed to evaluate the alerting, orienting, and executive control networks of attention [30,54]. The ANT-I is a modified version of this task, designed to examine not only the three attention networks, but also the interactions between them [31]. To that end, the task utilizes visual cues for the orienting system, and auditory cues for the alerting system. The ANT-I requires participants to judge whether a central arrow, which is flanked by two additional arrows on each side, is pointing left or right. The alerting component is manipulated by the presence or absence of an auditory cue (50 ms) before the presentation of the target arrow. The orienting component is manipulated by the presence or absence of a visual spatial cue that can be either valid (same location as target arrow) or invalid (opposite location from target arrow). The executive control attention component is manipulated by the direction of the flanking arrows, which can be either congruent (same direction as the central arrow) or incongruent (opposite direction from the central arrow).

2.2.3.1. Scoring. For the ANT-I, the alerting network score was calculated for each participant as mean reaction time in the No Tone condition minus mean reaction time in the Tone condition. The orienting network score was calculated as mean reaction time in the Invalid condition minus mean reaction time in the Valid condition, and the executive control network score was calculated as mean reaction time in the Incongruent condition minus mean reaction time in the Congruent condition. Of note, the ANT-I does not have a composite score, and each of the attention networks is examined separately.

2.2.4. Intra-individual variability (IIV)

2.2.4.1. Scoring. For each participant, IIV was calculated across the reaction time values over the ANT-I and the CBB, following several steps. First, response time outliers were removed from each dataset (3 SDs below or above the group mean). Next, a linear regression was created using response time as the dependent variable and predictor variables depending on the specific properties of each computerized measure (see below). The resultant scaled residuals were converted to t-scores and the standard deviation of these t-scores constituted the IIV index score.

Predictor variables for the linear regression created for the ANT-I IIV score included group membership (MS or HC), trial number (1–40), and block number (1–6). Predictor variables for the linear regression created for the CBB measures included group membership and trial number (1–35) and IIV scores were created individually for the ANT-I (across conditions), DET and IDN tasks. Group median IIV was inserted for a missing value for one MS participant in the DET task.

Lower IIV scores correspond to less variability (a score of 1 means an individual's performance is perfectly consistent) while higher scores correspond to higher levels of variability in an individual's performance. Higher variability is considered worse performance and has been linked to cognitive and medical vulnerability [33,35,36].

2.2.5. Test of everyday cognitive ability (TECA)

This test measures timed instrumental activities of daily living in MS [43]. The TECA contains 10 items encompassing different domains of daily living activities (e.g., communication, finance, nutrition, shopping, medications) and involving cognitive demands that are sufficiently complex, but with minimal motor involvement, making the task particularly suitable to MS. Thus, the TECA allows for a more ecologically valid assessment of everyday cognitive functioning within the laboratory or clinical settings. Duration of administration is

approximately 15 min.

2.2.5.1. Scoring. The items are scored according to completion time and accuracy [43]. For each task, a total proportion score (reaction time/total time allotted for the task) is calculated for each participant, resulting in a score ranging from 0.0 to 1.0. Then, the proportion scores across the 10 tasks are averaged for each participant for a total TECA score; higher scores indicate worse performance on this task. Group median total score was inserted for a missing value for one HC participant.

2.3. Statistical analysis

To compare the discriminability of the measures between the groups, a multivariate analysis of variance (MANOVA) was utilized, with Group (MS vs. HC) as the independent variable, and the composite scores on the BICAMS, CBB, and IIV measures as the dependent variables. A separate MANOVA was used to compare scores on each of the subtests (i.e., BICAMS and CBB individual subtests, IIV scores on CBB and ANT-I separately, attention network scores on the ANT-I, and TECA) between the groups. To test sensitivity and specificity of each of the measures in differentiating between the groups, receiver operating characteristic (ROC) curves were created and the area under the curve (AUC) was calculated for each of the main measures, as well as for each of the subtests and the TECA. Percent impairment on each of the measures and subtests was also compared between the groups. Clinical impairment was defined as $z < -1.5$ and < -2.0 for the BICAMS and CBB respectively, based on published guidelines [26,55,56]. Finally, to evaluate the relationship between performance on cognitive measures and daily cognitive functioning, an exploratory linear stepwise regression model tested the predictive power of the different cognitive tests in relation to TECA performance.

All analyses were performed using SPSS version 25.0 (IBM Corp, 2017).

3. Results

3.1. Participants

The groups did not significantly differ in age ($p = .20$), gender ($p = .41$), or WRAT-3 reading recognition standard scores, as an estimate of premorbid IQ ($p = .56$) (Table 1).

3.2. Group comparisons across measures

There was a strong correlation between IIV on the ANT-I and the CBB tasks, ($r = 0.75$, $p = .000$). For the purposes of group comparisons, these measures were combined for analyses as Total IIV. A MANOVA comparing groups according to composite scores (BICAMS, CBB, Total IIV) demonstrated a significant group effect at the multivariate level ($F(3,50) = 4.78$, $p = .005$, $\eta_p^2 = 0.22$). As expected, tests of between subject effects revealed that all three measures, BICAMS ($F(1,52) = 8.81$, $p = .005$, $\eta_p^2 = 0.15$), CBB ($F(1,52) = 10.36$, $p = .002$, $\eta_p^2 = 0.17$) and Total IIV ($F(1,52) = 8.79$, $p = .005$, $\eta_p^2 = 0.15$), significantly differentiated between the groups, with decreased performance in the MS relative to the HC group.

A separate MANOVA comparing groups according to performance on each of the subtests (BICAMS and CBB individual subtests, IIV scores on CBB and ANT-I separately, attention network scores on the ANT-I, and TECA) indicated a significant group effect on the multivariate level ($F(12,41) = 2.38$, $p = .02$, $\eta_p^2 = 0.41$). Tests of between subject effects revealed that the IDN ($F(1,52) = 13.35$, $p = .001$, $\eta_p^2 = 0.20$), ANT-I IIV ($F(1,52) = 9.05$, $p = .004$, $\eta_p^2 = 0.15$), and TECA ($F(1,52) = 17.96$, $p = .000$, $\eta_p^2 = 0.26$) were the most sensitive measures to differentiate between the groups. The SDMT ($F(1,52) = 7.21$, $p = .01$, $\eta_p^2 = 0.12$), BVMT-R ($F(1,52) = 4.95$, $p = .03$, $\eta_p^2 = 0.09$), DET ($F(1,52) = 6.24$, $p = .02$, $\eta_p^2 = 0.11$), ONB ($F(1,52) = 4.10$, $p = .048$, $\eta_p^2 = 0.07$), ANT-I Executive Control ($F(1,52) = 4.96$, $p = .03$, $\eta_p^2 = 0.09$), and CBB-IIV ($F(1,52) = 5.68$, $p = .02$, $\eta_p^2 = 0.10$) discriminated between the groups as well.

3.3. Sensitivity and specificity

Among the main measures, Total IIV (AUC = 0.73, SE = 0.07, $p = .004$) was the most sensitive and specific, followed by composite CBB (AUC = 0.69, SE = 0.07, $p = .02$) and BICAMS (AUC = 0.67, SE = 0.08, $p = .04$) (Table 3, Fig. 1).

Among the different subtests (including TECA), the tests with the greatest sensitivity and specificity, as measured by AUCs, were ANT-I IIV (AUC = 0.79, SE = 0.07, $p = .000$) and TECA (AUC = 0.78, SE = 0.06, $p = .000$), followed by the IDN task (AUC = 0.73, SE = 0.07, $p = .004$) (Table 3, Fig. 1).

3.4. Clinical impairment

Across measures, the SDMT had the highest rate of impairment in the MS group relative to HC (MS = 44%, HC = 3%, $p = .001$), followed by the IDN (MS = 24%, HC = 0%, $p = .005$), the BVMT-R (MS = 28%, HC = 7%, $p = .038$), overall BICAMS (MS = 20%, HC = 0%, $p = .011$) and CBB (MS = 20%, HC = 0%, $p = .011$) (Table 4).

3.5. Prediction of daily functioning

An exploratory linear stepwise regression model identified the IDN task as the best predictor of TECA scores, explaining 29% of the variance ($R^2 = 0.29$, $\beta = -0.53$, $p = .000$). A second model included both IDN ($\beta = -0.4$, $p = .001$) and BICAMS composite score ($\beta = -0.27$, $p = .04$), accounting for 35% of the variance ($R^2 = 0.35$). All other variables were excluded from the models.

4. Discussion

Using computer-based reaction time measures, we detected differences in MS vs. control participants even among younger adults and those early in the disease course. Measures most sensitive and specific to differentiating between the groups (AUC > 0.7) were IDN, Total and ANTI-IIV, and TECA, showing that, as hypothesized, slowed and variable processing speed is the hallmark of the earliest changes in cognitive performance in MS.

Table 3
Mean scores on neuropsychological measures for each group, as well as sensitivity and specificity of the tests and subtests as measured by their AUCs.

	MS Mean (SD)	HC Mean (SD)	AUC (*p*-value)
BICAMS (total)	−0.62 (1.2)	0.15 (0.68)	0.67 (0.04)*
SDMT	−1.05 (1.91)	−0.11 (1.24)	0.67 (0.03)*
RAVLT	−0.30 (1.38)	0.16 (0.99)	0.59 (0.28)
BVMT-R	−0.51 (1.22)	0.19 (1.10)	0.67 (0.04)*
CBB (total)	−1.13 (1.13)	−0.35 (0.60)	0.69 (0.02)*
DET	−1.38 (1.32)	−0.66 (0.73)	0.67 (0.03)*
IDN	−1.15 (1.44)	−0.08 (0.61)	**0.73 (0.004)****
ONB	−0.85 (1.13)	−0.31 (0.84)	0.64 (0.08)
IIV (total)	6.71 (3.65)	4.52 (1.47)	**0.73 (0.004)****
ANT-I IIV	7.09 (4.38)	4.37 (1.99)	**0.79 (0.000)*****
CBB IIV	6.30 (3.35)	4.67 (1.44)	0.63 (0.10)
TECA (total)	0.33 (0.11)	0.22 (0.07)	**0.78 (0.000)*****
ANT-I Alerting	46.54 (55.45)	29.20 (23.72)	0.54 (0.62)
ANT-I Orienting	48.09 (31.11)	51.09 (13.59)	0.42 (0.32)
ANT-I EC	105.27 (40.08)	86.74 (18.68)	0.66 (0.049)*

AUC = area under the curve.
In bold are total administration times for each battery.
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

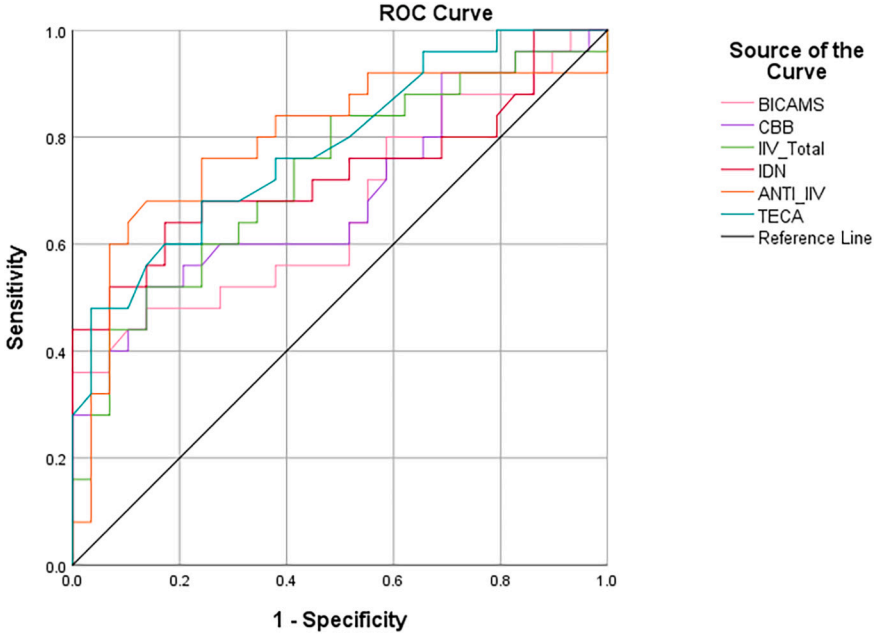

Fig. 1. Receiver operating characteristic (ROC) curves for the three main measures (BICAMS, CBB, and IIV), as well as the subtests identified as having the largest area under the curve (AUC; IDN, ANT-I IIV, and TECA).

Table 4
Proportion of participants in each group with impairment on the BICAMS and CBB tests and subtests, as well as the sensitivity and specificity of each of the measures for detecting impairment (dichotomous classification).

	MS	HC	Sensitivity	Specificity	*p*-value (χ^2)
BICAMS (total)	5/25	0/29	20%	100%	0.01*
SDMT	11/25	1/29	44%	97%	**0.000****
RAVLT	6/25	2/29	24%	93%	0.08
BVMT-R	7/25	2/29	28%	93%	0.04*
CBB (total)	5/25	0/29	20%	100%	0.01*
DET	5/25	1/29	20%	97%	0.05
IDN	6/25	0/29	24%	100%	**0.005****
ONB	5/25	1/29	20%	97%	0.05

MS = multiple sclerosis; HC = healthy controls.
In bold are values that are statistically significant at alpha level of 0.01.
* $p < 0.05$
** $p < 0.01$

While the SDMT in particular, and the BICAMS more generally, are widely used in both clinical and research settings [57], they were less sensitive and specific in differentiating between the study groups compared to the computer-based measures. Specifically, while as expected [12,13,15–19], the SDMT was the most sensitive in detecting impairment among the MS participants, it was overall less sensitive and specific in differentiating between participants with and without MS (as determined by its AUC value) compared to a computerized task of processing speed, as well as individual variability in reaction time on this task. The increased precision and accuracy provided by computerized tasks over multiple timed trials may offer an advantage of sensitivity compared to paper and pencil tasks, especially when measuring subtle changes in processing speed. It has been shown, for example, that the Processing Speed Test (PST), a tablet-based version of the SDMT where responses are pressed on the screen vs. spoken aloud, can similarly discriminate between individuals with and without MS, and is better correlated with cerebral lesion load [58]. That the HC group also showed some impairment on the cognitive measures (albeit in a very small percent of the group) may speak to the inherent variability in test performance [59–61]. It seems, however, that this variability was less prominent on the computerized tests, relative to paper and pencil tests, which may support the advantage of computerized measures. An additional advantage of the CBB is its extensive and globally-based normative database in comparison to the SDMT [62].

To our knowledge, no information processing speed task studied in MS samples to date has been free from motor responses, and therefore, the contribution of motor slowing in performance should be considered. The SDMT requires both oculomotor function for rapid visual scanning, as well as motoric speech output. The CBB tasks require a minimal motor response for the button press. However, comparing the DET (simple RT) to IDN (choice RT) allows for some separation of cognitive vs. motor slowing as the IDN task includes a more advanced cognitive component. Cognitive slowing is suggested by the greater sensitivity of the IDN task in discriminating between the groups. Future studies are needed to more precisely separate cognitive vs. motor slowing in cognitive processing speed performance tasks.

Another consideration for interpretation of our findings is the role of cognitive fatigue. The symptom of fatigue is common in MS, even in its earliest stages. However, MS fatigue is defined by self-report, with poor correspondence to either cognitive or functional performance-based measures [63]. The functional measurement of fatigue or fatigability is less clearly defined across studies, with varying paradigms used to demonstrate its presence, including measures across sustained effortful tasks of attention [64] and processing speed [65]. Of particular relevance is the suggestion that cognitive fatigue can be defined by increased response variability [38]. This may be particularly relevant for longer tasks, such as the ANT-I, as studies have shown that cognitive fatigability can affect cognitive performance even after relatively short periods of time (<20 min) [66,67].

Together, these findings provide preliminary support for the benefit in utilizing computerized testing and novel computational approaches (e.g., IIV) in identifying early stages of cognitive involvement in MS, which may be used in conjunction with the SDMT to optimize detection of cognitive involvement at early stages of the disease. It should be additionally noted that face-to-face administration of cognitive tasks may provide important behavioral observations that are lacking in computerized approaches. Longitudinal studies with larger sample sizes would be critical in correlating the sensitivity of the different measures in detection of early cognitive involvement with the development of more substantial cognitive impairment later in the course of the disease.

The CBB IDN task showed sensitivity and specificity to cognitive involvement in MS and high levels of impairment relative to controls, even at early stage of the disease. Moreover, the IDN task was the single best predictor of estimated daily functioning, as measured by the TECA, on our exploratory analysis. These findings are in accordance with our previous study, showing that the IDN task is particularly sensitive to cognitive involvement in pediatric-onset MS [26], as well as other studies in the adult MS population [24,68]. This task of choice reaction time requires rapid information processing, decision making and response, and may be more sensitive than a simple reaction time task (DET), as well as than a working memory task (ONB) (consistent with [9]) on the CBB. The IDN task is administered on a computer, with a total duration of only 3 min, and does not require direct supervision [68]. The sensitivity and specificity of the IDN task, together with the ease and short duration of administration, make this an ideal screening measure to consider implementing in the clinical setting.

In what may be a first comparison of IIV across separate tasks in MS, IIV was significantly and strongly correlated between the ANT-I and CBB trials. Total IIV, and particularly, ANT-I-IIV, were also sensitive and specific to cognitive functioning in MS vs. HC, consistent with previous studies [33,35,36]. Together, these findings support the hypothesis that variability in performance is a core cognitive feature of MS early in the disease course. The greater sensitivity of IIV across the ANT-I vs. CBB tasks (IDN and DET combined) is likely due to the task length, with 20 min vs. 6 min of reaction time trials.

A unique strength of the current study is our inclusion of the TECA as a real-world measure of daily functioning. The TECA was highly sensitive and specific to early detection of cognitive involvement in MS. This finding demonstrates both the importance of measures that can characterize the impact of cognitive involvement on activities of daily living, and the need for these measures that are appropriate for use in the younger age groups and more subtle types of cognitive involvement in MS.

For at least some MS participants, the information processing changes will progress to the impairment level, and to involve other aspects of cognitive functioning such as learning and memory [69,70]. For these at-risk patients, early detection is especially critical, as it can lead to prevention strategies and interventions, which may be more achievable than restoration of function once impaired. Indeed, accumulating research over the past two decades have consistently showed that cognitive remediation, administered by a therapist at the clinic, or at home through guided telerehabilitation and adaptive computer training programs, can be an effective approach for improving cognitive functioning in MS and/or delaying decline [8,71–75]. In general, individuals earlier in disease course and better baseline performance may benefit to a greater extent from cognitive remediation techniques [76]. That said, more research is needed to better characterize individual factors that may affect cognitive training outcomes and to tailor individual treatment that would optimize outcomes in patients with MS.

A main weakness of the study is the relatively small sample sizes in both groups. As such, our findings should be considered preliminary, and conclusions should be interpreted with caution. Nonetheless, the validity of our findings is supported by the well-established and validated cognitive measures used in this study, and the comparison of performance of both groups to the large normative databases available for each of the tests. Future studies with larger samples would be necessary to further support the validity and generalizability of the current findings. In addition, this study did not include other mood measures that may contribute to cognitive functioning in MS; however, participants were screened for depression prior to participation, to limit the potential confounding effects of mood on cognitive performance, especially in these early stages of disease when cognitive changes may be subtle. The exclusion of participants with depressive symptoms, on the other hand, may have resulted in an unrepresentative sample, considering the relatively high prevalence of depression in individuals with MS [77], thus restricting the generalizability of our findings. In a similar vein, as our goal was to examine cognitive markers that will be sensitive to early stages of the disease, our sample only included individuals with MS who are in their initial phase of disease course and with minimal disability levels (while EDSS range was 0–6, median EDSS in the MS sample is 2.0, with only three participants having EDSS score of 4.0, and one participant having an EDSS score of 6.0). Future studies should include participants with a wider range of disease duration and severity, as well as mood symptoms.

Finally, the effects of drug modifying therapies (DMTs) on cognitive functioning in MS is an important area of study, particularly as they are being prescribed earlier in the disease course and for long term use following evidence-based clinical practice recommendations, and are considered the standard of care in pediatric MS. Future longitudinal studies assessing the deferential effects of the different DMTs on cognition in MS, including the differential effects between higher and lower efficacy treatments and timing (e.g., earlier treatment), would be invaluable in expanding our knowledge in this relatively understudied topic.

In sum, these findings support the growing body of evidence that MS in even its earliest stages may involve aspects of cognitive functioning. Brief, computer-based measures of timed responses may be the most sensitive approach in detecting the initial cognitive involvement and identifying those most at risk for future impairment. Including real-world task-based measures suitable for use in MS may be helpful in characterizing the true impact of these initial subtle changes.

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Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

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