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The Symbol Digit Modalities Test is an effective cognitive screen in pediatric onset multiple sclerosis (MS)

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ABSTRACT

Objective: To evaluate the Symbol Digit Modalities Test (SDMT) as a tool for identifying pediatric-onset MS patients at risk for cognitive impairment.
Background: The SDMT is a brief measure of cognitive processing speed that is often used in adult MS patients. Approximately one-third of pediatric-onset MS patients have cognitive impairment and there is a need for an effective screening instrument.
Design/methods: Seventy (70) consecutive outpatients with pediatric-onset MS underwent clinical evaluations including the SDMT and were compared to those with other pediatric neurological diagnoses (OND, $n = 40$) and healthy controls (HC, $n = 32$). A subset of the MS group and all healthy controls completed neuropsychological evaluation within one year of SDMT administration.
Results: The MS group performed worse on the SDMT compared to the HC group ($p = 0.02$). Thirty-seven percent (37%) of the MS, 20% of the OND, and 9% of HC groups scored in the impaired range. For MS participants who underwent neuropsychological testing ($n = 31$), the SDMT showed 77% sensitivity and 81% specificity for detecting neuropsychological impairment when administered within one year and reached 100% sensitivity when the interval was under two months ($n = 17$). Overall, older age and increased disability predicted poorer SDMT performance (age $r = -0.26$, $p = 0.03$) and the Expanded Disability Status Scale score or EDSS ($r = -0.47$, $p < 0.001$), while a history of optic neuritis predicted better performance ($p = 0.04$). Optical coherence tomography measures were not related to SDMT performance.
Conclusion: In this preliminary study, the SDMT was an effective brief screen for detecting cognitive impairment in pediatric-onset MS.

1. Introduction

The Symbol Digit Modalities Test (SDMT) is a brief test of information processing speed that has become the most commonly used cognitive measure in adults with multiple sclerosis (MS) [1–3]. Approximately one-half of the adult MS population is estimated to have some degree of cognitive impairment [4] and the SDMT has been demonstrated to be a sensitive and reliable indicator of those at risk [4–6].

In a sample of 100 adults with MS compared to 50 demographically-matched healthy controls, Parmenter and colleagues [7] found that the SDMT was an effective brief screen correctly categorizing 72% of those with cognitive impairment on a more extensive battery of test (the Minimal Assessment of Cognitive Function in MS or MACFIMS). The SDMT is one of the three measures recommended by for the Brief International Cognitive Assessment for MS (BICAMS) [4]. Performance on the SDMT is a strong predictor of employment status in MS patients, and those who are unemployed perform worse on SDMT testing [8].

The SDMT has been linked to MS-related brain MRI pathology [2,9,10] including brain MRI total lesion load [11], cortical lesion number, cortical lesion volume, and overall white matter lesion volume [12]. In one MS sample, the SDMT score was also positively correlated with concentration of CSF amyloid-beta, with reductions shown to be a marker of cognitive impairment [13]. Worsening SDMT has been used to detect change within an individual MS patient. For instance, MS patients experiencing an acute relapse worsened on the SDMT when compared to in MS patients who were neurologically stable [14].

While typically affecting adults, up to 5% of MS cases are reported in children and adolescents. One-third of pediatric-onset MS patients have some degree of cognitive impairment on neuropsychological testing [15,3]. Cognitive deficits in pediatric-onset MS patients overlap with those found in adults [3] and commonly include information processing speed, working memory, verbal learning, and visuospatial abilities. However, as in adults, deficits may be mild and therefore difficult to identify during routine monitoring visits.

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It is especially critical to detect cognitive involvement in pediatric-onset MS patients because of both the long-term effects of early cognitive impairment and the potential mitigating effects of early intervention. Children and adolescents with MS may be at even greater risk for cognitive impairment over time as a consequence of ongoing demyelination, which prevents normal maturation of neural connections [16]. A brief and sensitive screen for cognitive impairment is needed for pediatric-onset MS patients [4].

Despite the wide use of the SDMT in adult MS, few studies have reported SDMT performance in pediatric-onset MS. In an Italian sample, 63 pediatric MS participants, aged 8 to 18 years, were found to score lower than 57 healthy controls on the SDMT, but the mean difference did not reach statistical significance [16]. In a U.S. sample, 43 pediatric MS participants, ages 6 to 17 years, scored significantly lower than 45 healthy controls on the SDMT [8]. A Canadian study of 35 pediatric MS patients compared to 33 controls found that a greater proportion of MS patients had SDMT scores falling below 1.5 SD from the mean (12% vs. 0%) [17]. Little is known concerning the relationship between SDMT performance and other clinical characteristics of pediatric-onset MS, and whether it is an effective screening tool to identify those at risk for cognitive impairment.

To better understand the utility of the SDMT for the pediatric-onset MS patient population, we evaluated the SDMT as a screen for cognitive impairment in pediatric-onset MS patients compared to pediatric neurologic outpatients seen at our outpatient center diagnosed with a neurologic diagnosis other than MS (other neurological diagnosis or OND) and to healthy pediatric controls (HCs). SDMT performance was examined in relation to MS clinical descriptors and, for a subset of patients, performance on a battery of neuropsychological tests.

2. Method

This study was approved by the Stony Brook Institutional Review Board. In the case of minors, a parent provided consent, and participants signed assent forms.

MS and OND participant SDMTs were collected from consecutive patients presenting for neurological evaluation at the Lourie Center for Pediatric MS between May 2009 and October 2013. MS participants met criteria for pediatric-onset MS (disease onset prior to age 18 years) [18]. OND participants were pediatric patients who came to the Lourie Center for diagnostic evaluation and did not meet criteria for MS, and included diagnoses such as neuromyelitis optica (NMO), acute disseminating myelitis (ADEM), or migraine. The specific diagnoses for this sample are reported in the Results section below. Patients who met diagnostic criteria for either radiologically isolated syndrome (RIS) or clinically isolated syndrome (CIS), and therefore at high risk for MS [18], were excluded from the study. MS and OND participants with an acute relapse or requiring steroids in the preceding 30 days were excluded. Additional eligibility criteria for participants were fluency in English (having learned before the age of 6 years and not currently enrolled in an English Language Learners or ELL program at their school) and without intellectual disability classification. Participants must have also been without any other primary neurological or medical disorder in addition to their MS or OND. Participants judged to have primary psychiatric impairment in addition to their MS by the treating neurologist (LBK) were also excluded.

Healthy control (HC) participants were recruited through community-based advertisements and were evaluated between May and August of 2013. Control participants were required to be in good health without any current medical or psychiatric diagnosis, with no history of head injury, seizures, or other neurologic illness; to be fluent in English; and not receiving any special education services.

2.1. Measures

At the time of the outpatient visit, all MS participants and OND participants were neurologically evaluated with a structured clinical assessment, which included determination of their Expanded Disability Status Scale [19] (EDSS; administered by LBK). Disease duration based on symptom onset and annual relapse rate prior to the time of the evaluation were calculated. For MS participants, the presence or absence of optic neuritis in each patient's history was determined and, for those evaluated after June 2010, optical coherence testing (OCT) was performed.

The SDMT was administered at the time of clinical evaluation for all patients presenting to the Lourie Center and at the time of study participation for the healthy controls. The SDMT has a key at the top of the page with numbers and symbols; participants are required to refer to the key to correctly decode several lines of symbols. After completing sample items correctly, participants are timed for 90 s and the total number correct is their raw score. Following the Rao adaptation from the Brief Repeatable Battery for MS [6], the oral condition (answers provided verbally) was used to limit the influence of motor slowing.

Two equivalent SDMT forms were used for this study, the original form and one of the three alternates with demonstrated equivalency.[1][1] The forms were randomly administered across the MS and OND participants in the clinic, and the healthy control participants all received the original form. For group comparisons, raw SDMTs were converted to z scores based on published age- and gender-based normative data [20]. Impaired SDMT performance was defined as falling one standard deviation or more below the normative mean.

2.2. Neuropsychological battery

Neuropsychological testing completed within one year or less of an SDMT administration was available for 31 (44%) of the MS participants and 32 (100%) of the HC participants. Table 1 shows the tests and measures included for the current analyses. The MS participants were administered a standard battery, previously described elsewhere [3]. HC participants were administered a similar and abbreviated battery, with different verbal learning and executive functioning tests.

For group comparisons, performance on each neuropsychological measure was converted to an age-normative z score using published normative data. The z scores for each measure were then averaged for a composite neuropsychological performance index z score (NP z score). Additionally, for each participant, the total percent impairment was calculated according to the number of completed test measures that fell one standard deviation or more below published norms. Those participants with greater than one-third impaired scores across their neuropsychological evaluation were categorized as having neuropsychological impairment [3].

3. Results

3.1. Demographics

Participants were seventy (70) pediatric-onset MS patients, forty (40) OND patients, and thirty-two (32) HCs. The OND group had a range of diagnoses including: migraine (20%), non-specific sensory symptoms with normal brain magnetic resonance imaging results (17.5%), optic neuritis (12.5%), NMO (12.5%), ADEM (7.5%), leukodystrophy (5%), transverse myelitis (5%), autoimmune lymphoproliferative disease (2.5%), developmental delay (2.5%), Lyme disease (2.5%), meningoencephalitis (2.5%), neuropathy (2.5%), possible mitochondrial disorder (2.5%), trigeminal neuralgia (2.5%), and motor tic (2.5%).

[1] The alternate SDMT form was kindly provided by Dr. Ralph Benedict and is available for research use by request through the publisher WPS.

Table 1
Summary of neuropsychological battery measures by group (representative measure of total score, unless otherwise specified)[a].

	MS	Healthy controls
General intellect	WASI [31] or WASI-II [32], 2 or 4 subtest IQ	WASI-II [21] 2 Subtest IQ
Attention	WISC-IV [35] or WAIS-IV [36] Digit Span[a]	WISC-IV [35] or WAIS-IV [36] Digit Span[a]
Verbal learning and memory	CVLT-C [28] or II [29][a], total trial learning and delayed free recall	CVLT-C [28] or II [29] or SRT[a], total trial learning and delayed free recall
Visual learning and memory	BVMT-R [4], total trial learning and delayed free recall	BVMT-R [4], total trial learning and delayed free recall
Visuomotor	Beery VMI [34], WISC-IV or WAIS-IV Coding	Beery VMI, WISC-IV[b] or WAIS-IV Coding
Executive function	DKEFS Trail Making Test (scores for each of five conditions)	DKEFS Color–Word Interference Test (scores for each of four conditions)
Language	Expressive One-Word Vocabulary Test, DKEFS Verbal Fluency Test	DKEFS Verbal Fluency Test
Achievement	WIAT-III Pseudoword Decoding	

[a] WASI = Wechsler Abbreviated Scale of Intelligence [31,32] – first or second edition, two- or four-subtest IQ estimate [30]; WAIS-IV = Wechsler Adult Intelligence Scale—fourth edition [36]; WISC-IV = Wechsler Intelligence Scale for Children, fourth edition [35]; CVLT-C [28] or -II = California Verbal Learning Test, child version (for under age 16 years) or second edition [29]; SRT = Selective Reminding Test; BVMT-R = Brief Visuospatial Memory Test, revised [4]; EOWVT = Expressive One Word Vocabulary Test [32]; VMI = Beery–Buktenica Visuomotor Integration Test [34]; DKEFS = Delis–Kaplan Executive Function System [22]; WIAT = Wechsler Individual Achievement Test, 2nd edition [33].
[b] WISC-IV version for those 16 and under.

Demographic characteristics for the study groups are depicted in Table 2. Participants' ages ranged from eight (8) to twenty-three (23) years, and the OND group was significantly younger than either the MS group ($p < 0.001$) or the HC group ($p = 0.01$). The groups also significantly differed according to race, c^2 (6, $N = 139$) = 29.68, $p < 0.001$, with the MS group having a greater percentage of African-Americans (33%) than either the OND (6%) or HC (0%) groups.

3.2. Clinical features of the MS group

The clinical features of the MS group are also shown in Table 2. The majority of MS patients had no disability and only minimal signs in 1+ functional groups, with a median baseline EDSS of 1.0 and a range of 0 to 4. In the MS group, average disease duration was 2.55 (±1.52) years, with a range of 0.16 to 6.34 years. In the MS group, the average number of relapses prior to testing was 2.87 (±2), with a range of one to nine relapses; the average annual relapse rate was 1.93 (±1.18). Half of the MS participants (n = 35) were on a disease modifying therapy.

3.3. SDMT performance

As summarized in Table 3, the MS group's SDMT z scores were significantly lower than the HC group, t (100) = −2.38, $p = 0.02$, $d = -.5$ and was also lower than the OND group approaching significance, t (108) = −1.78, $p = 0.08$, $d = -.3$. The OND had a lower mean performance than the HC group but this difference was not significant ($p = 0.48$).

Each group's mean SDMT z score fell within the average range. However, 37% of the MS group had scores in the impaired range compared to 20% of the OND and 9% of the controls, c^2 (2, $N = 142$) = 9.85, $p = 0.007$.

Among the MS participants, 56% received the original form and the remaining participants received the alternate form, with no significant difference in performance between forms ($p = 0.67$). The same pattern of significant results were found when analyses were repeated using raw instead of z scores, both with and without controlling for age. Therefore, for group comparisons and descriptions below, z scores were used where applicable.

Table 2
Demographic and clinical characteristics of groups.

Characteristic	MS mean (±sd) or n (%)	OND mean (±sd) or n (%)	Control mean (±sd) or n (%)
Age	16.4 (2.5)	13.9 (3.3)*	16.3 (3.02)
	n = 70	n = 40	n = 32
% female	44 (63)	21 (52.5)	24 (73)
	n = 70	n = 40	n = 32
Race	n = 65	n = 34	n = 30
Caucasian	37 (55)	26 (76)	26 (81)
African American	22 (33)**	2 (6)	0 (0)
Asian	0 (0)	4 (12)	2 (6)
Mixed/other	8 (12)	2 (6)	4 (13)
% Hispanic	19 (29)	6 (18)	9 (29)
	n = 67	n = 34	n = 32
Characteristics of MS group	Mean (±sd)	Median	Range
EDSS at testing	1.20 (±1.26)	1.0	0.0–4.0
Disease duration (years) (n = 55)	2.34 (±2.25)	1.56	0.01–9.49
Relapses n = 70			
Median; range	2.87 (±2)	2.0	1.0–9.0

* Significantly lower than MS ($p < 0.001$) and HC groups ($p = 0.01$).
** Significantly higher proportion than OND or HC group ($p < 0.001$).

3.4. SDMT compared with neuropsychological testing

The MS participants with neuropsychological testing within one year of an SDMT administration (n = 31) did not differ from the larger MS group in SDMT performance (z score $p = 0.88$), EDSS ($p = 0.95$), age ($p = 0.11$), or gender distribution ($p = 0.83$). The duration between the SDMT administration and neuropsychological evaluation ranged from 0 to 11.9 months, with an average of 2.76 ± 3.84 months. As with the larger MS group, this subset also performed significantly worse on the SDMT compared to the controls (z score M −0.48 ± 1.32 vs. 0.24 ± 1.14, $p = 0.02$).

The MS group performed significantly lower than the HC group on neuropsychological testing (NP z score M = −0.26 ± 0.74 vs. 0.39 ± 0.55, $p < 0.001$) (see Table 4). For the HC and MS participants combined, SDMT z score was significantly correlated with both NP z score ($r = 0.62$, $p < 0.001$; shown in Fig. 1) and percent impairment ($r = -0.47$, $p < .001$).

Ten (32%) of the MS participants were categorized as having neuropsychological impairment versus one (3%) of the HC participants. For the MS group, the SDMT sensitivity was 77% and specificity was 81% for detecting neuropsychological impairment. Fig. 2 shows this as an ROC curve, where the area under the curve (AUC) was 0.83. Consistency increased when the SDMT and neuropsychological testing were closer in time, with 100% of those with neuropsychological impairment also having SDMT impairment when administered within 1.8 months or less of the other (n = 17).

The effect sizes for the neuropsychological composite scores ($d = -1.0$) and percent impairment ($d = -1.1$) were greater than for the SDMT ($d = -0.6$). The groups were also compared according to performances on the specific measures of estimated IQ (Wechsler Abbreviated Scale of Intelligence or WASI, first or second edition, two- or four subtest estimate [31,32]), and two measures sensitive to impairment in adult MS, verbal learning (total trials for California Verbal Learning Test—child version or second edition, CVLT-C or -II [28,29] or the Selective Reminding Test or SRT) [22] and visual learning (total trials for the Brief Visuomotor Retention Test—Revised or

Table 3
SDMT Scores by Group.

	MS (n = 70)	OND (n = 40)	HC (n = 32)
SDMT z score (mean ± SD)	−0.41 ± 1.55*	0.05 ± 1.14	0.24 ± 1.14
SDMT impaired (n, %)	27 (39%)	9 (22%)	3 (9%)
Raw SDMT score (mean ± SD)	51.21 ± 13.51*	47.52 ± 12.2	59.00 ± 13.68
Raw SDMT	41	31.5 ± 13.4	
Age 6–7.9	(n = 1)	(n = 2)	
Raw SDMT	30 ± 9.9	31.75 ± 8.3	31.33 ± 8.62
Age 8–9.9	(n = 2)	(n = 4)	(n = 3)
Raw SDMT		39.13 ± 7.1	49
Age 10–11.9		(n = 8)	(n = 1)
Raw SDMT	47.4 ± 8.71	52.5 ± 9.8	
Age 12–13.9	(n = 5)	(n = 4)	
Raw SDMT	54.23 ± 15.43 (n = 13)	56.6 ± 8.2	61.33 ± 11.61
Age 14–15.9		(n = 8)	(n = 9)
Raw SDMT	52.15 ± 13.1 (n = 39)	53.6 ± 9.9	58.25 ± 11.83
Age 16–17.9		(n = 11)	(n = 8)
Raw SDMT	49.2 ± 15.3 (n = 6)	45 ± 2.8	66.09 ± 8.81
Age 18–19.9		(n = 2)	(n = 11)
Raw SDMT	59 ± 3	55	
Age 20–21.9	(n = 3)	(n = 1)	
Raw SDMT	36		
Age 22–23.9	(n = 1)		

* For MS and OND participants, clinical features and SDMT score closest to the time of neuropsychological evaluation.
* SDMT impairment defined as falling 1 SD or more below published norms. Neuropsychological impairment determined as falling one standard deviation or below published norm; overall impairment defined as one-third or more completed measures falling into the impaired range.
* MS group lower than the HC group (p = 0.02) and OND group (p = 0.08).

BVMT-R) [4]. The groups did not significantly differ on any of these three measures: estimated IQ, t (55) = −0.64, p = 0.53, d = −.2, verbal learning t (57) = −.72, p = 0.47, d = −.2, and visual learning t (44) = −1.15, p = 0.27, d = −.3. While not as discriminating as a score derived from multiple neuropsychological tests, the SDMT had the largest effect size among the individual measures examined here.

Within the MS participants, SDMT performance was most strongly correlated with the Delis–Kaplan Executive Function System (DKEFS) [23] Trail Making measures (score averaged across the five trials, n = 24, r = 0.69, p < 0.001), Expressive One-Word Vocabulary Test (EOWVT [24,32]; n = 22, r = 0.62, p = 0.002), BVMT-R learning (total trials, r = 0.51, p = 0.01), and both verbal learning and delayed recall (CVLT-C or -II [25], n = 27, total trials r = 0.43, p = .03 and delayed recall r = 0.40, p = 0.04).

3.5. Clinical predictors of SDMT performance in MS

Linear multiple regression was used to test whether clinical features of age, EDSS, duration of illness, and number of relapses were predictive of SDMT performance. This model explained 30% of the variance in SDMT scores, with uniquely significant predictors being both EDSS, beta = −0.43, p < 0.001 and age, beta = −0.30, p = 0.02. For the MS participants, worse (lower) SDMT performances were moderately correlated with a higher EDSS score (r = −0.47, p < 0.001) and older age (r = −0.26, p = 0.03), but not disease duration or total relapses.

OCT measures were not significantly correlated to SDMT performance (r = −0.10, p = 0.59 and r = −0.18, p = 0.35 for right and left-eye, respectively). Further, those with a history of optic neuritis were less likely to be impaired on the SDMT (24% versus 49%, Fisher's exact p = 0.03).

4. Discussion

We found that the SDMT is an effective screen for cognitive impairment in pediatric-onset MS. The MS participants had worse performance than both pediatric patients with other neurological diagnoses and pediatric healthy controls. Overall, 37% of the MS participants were impaired on the SDMT. This can be compared to an impairment rate of 32% in the subset of MS participants who received neuropsychological evaluation. It is notable that an impairment rate of approximately one-third of pediatric MS patients has been consistently found across varying batteries, definitions of impairment, and country of origin [3,6,26].

The SDMT was positive for impairment in more cases than when defined by an aggregate measure of neuropsychological evaluation. This may be interpreted as the SDMT having greater sensitivity for detecting

Table 4
Impairment in the subset with SDMT and neuropsychological testing.

	MS (n = 31)	HC (n = 32)	P value	Cohen's d
Age in years (mean ± SD)	16.06 ± 3.66	16.19 ± 2.97	0.87	
Estimated IQ* MS n = 26, HC n = 31	106.69 ± 12.06	108.87 ± 13.35	0.52	
Neuropsychological testing composite z score (mean ± SD)	−0.27 ± 0.74	0.39 ± 0.55	<0.001*	−1.0
Percent impaired scores (mean ± SD)	30 ± 32%	5 ± 8%	<0.001*	1.1
SDMT z score within one year or less of neuropsychological testing	−0.48 ± 1.32	0.24 ± 1.14	0.02*	−0.6
SDMT impairment**	11 (35%)	3 (9%)		
NP percent impairment**	10 (32%)	1 (3%)		

*IQ estimate based on WASI [31] or WASI-II [32], depending on time of administration; MS participants received four subtest estimate; control participants received two subtest estimate.
**SDMT impairment defined as falling below one standard deviation from published norms, NP overall impairment defined as having one-third or more scores falling below one standard deviation from published norms.

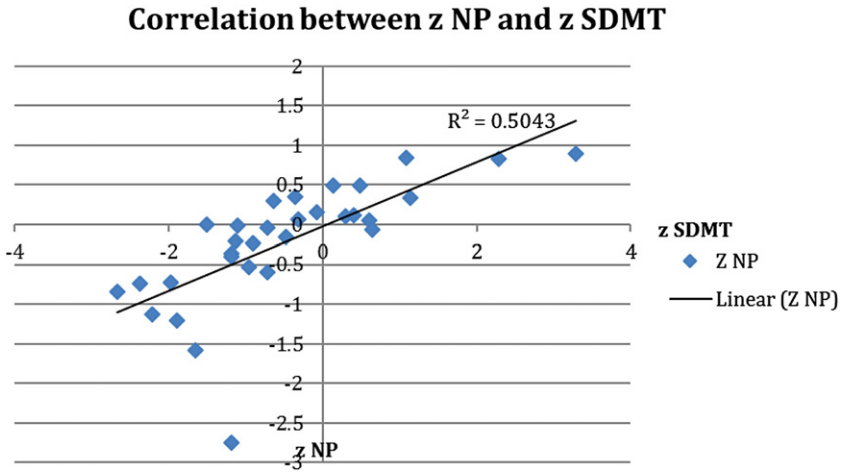

Fig. 1. SDMT z score is predictive of neuropsychological evaluation aggregate z-score in the pediatric MS group (n = 31).

cognitive impairment than a representative score from a diverse battery of tests. However, the SDMT administered within one year of neuropsychological testing had good sensitivity and specificity for predicting neuropsychological impairment and became even more accurate as a predictor when administered more closely in time. These findings are generally consistent with those reported in adult MS populations, with similar sensitivity (77% in this study vs. 82% reported in an adult MS sample) and higher specificity (81% in this study vs. 60% reported in an adult MS sample) found in the original study in adult MS by Parmenter and colleagues [7]. Interestingly, when an ROC curve is plotted, both studies have a very similar AUC (0.83 in this study compared to 0.84 reported in the adult study). These data suggest that if the SDMT were used as a screen for cognitive impairment, very few patients would be missed.

The moderate effect size of 0.5 for the SDMT in our sample was somewhat lower than what has been found in the literature. Strober et al. [20] reported an effect size of 1.3 in an adult MS population. Benedict et al. [37] references several early studies with effect sizes ranging from 1.0 to 1.2

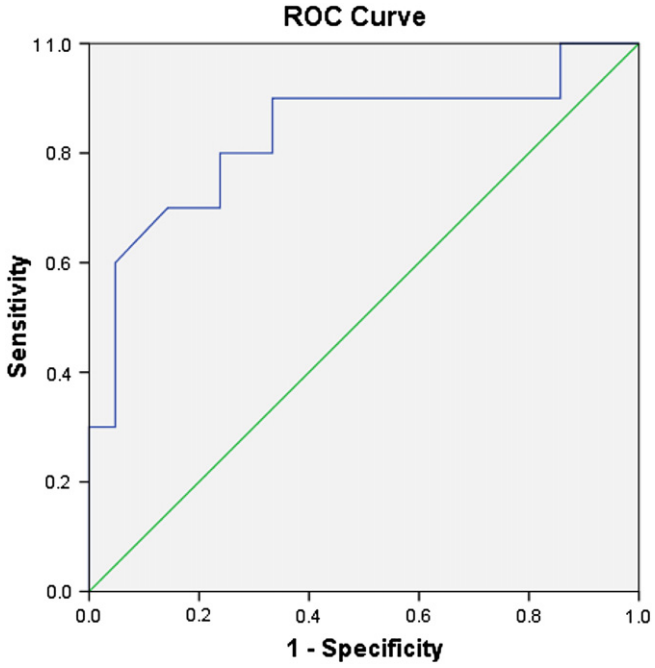

Fig. 2. ROC curve for detecting neuropsychological impairment in the MS group (n = 31), as shown with most participants with and neuropsychological impairment also having an impaired SDMT score. Area under the curve (AUC) = 0.83.

and in his population of 291 adult MS patients the SDMT effect size was 1.31. It may be expected that with continued disease into adulthood, the SDMT strengthens in its ability to discriminate between MS and healthy participants. Nonetheless, for the subset with neuropsychological testing, while percent of impaired scores across multiple measures had the strongest effect size (1.1), the SDMT had the largest effect size (0.6) when compared to other individual measures of IQ (0.2), verbal learning (0.2), and visual learning (0.3). Within the MS participants, SDMT was strongly related to multiple measures including speeded visuomotor processing, verbal and visual learning, and expressive vocabulary.

4.1. SDMT and clinical features of pediatric MS

Overall, consistent with prior studies, the MS participants had a low disease burden, indicated by a median EDSS score of 1.0. Age and EDSS negatively correlated with SDMT scores, indicating that both older age and increased disability predicted poorer SDMT performance.

Visual system impairment has been raised as a confounding variable in SDMT performance for MS patients [6,9]. We found no correlation between optical coherence tomography measures and SDMT performance. Further, in our sample, there was a significantly lower proportion of SDMT impairment in those with a history of optic neuritis, which is consistent with the observation that optic neuritis is associated with an overall milder disease course in both adults and pediatric patients [27].

4.2. Study limitations

To adjust for age and gender, we first converted raw scores to z-scores based on age- and gender-normative means reported in the original SDMT manual that is in current use [1]. These represent the largest normative pediatric sample sizes collected for the SDMT to date (n = 1579 participants ages 8 through 17), provide data for each year of age by gender, and would be the norms that are readily available for use by clinicians.

The appropriateness of these norms has been questioned due to their being collected in the 1970s [9]. While more current norms are needed, it is not clear what changes would be expected in a pediatric sample over time on this specific task. A smaller and more recent study (n = 83) [9] provides norms for administration of the oral version only. These reported norms have higher mean scores for each two-year age band, resulting in higher rates of impairment when applied in our sample (37 to 56% for MS participants and 9 to 30% for control participants). These elevated impairment ratings are inconsistent with the results of the broader neuropsychological battery. In this study, the manual norms yielded scores more consistent with published rates of

impairment in pediatric MS, the findings of the neuropsychological battery, and what would be ordinarily expected in a healthy control sample. In addition, analyses of the raw SDMT scores in our study repeated without the use of norms (i.e., raw scores, with and without controlling for age) resulted in the same pattern significant of group differences. Collecting parental education data in our study would have allowed for the calculation of the more sensitive regression-based norms [9]. Ultimately, a larger and closely matched healthy control group is necessary.

There are several additional limitations to the current study. The OND group was not as closely matched on age to the other two groups, and there were significant differences in racial distribution between the MS and HC participants. At our pediatric center, African-American patients represent a larger proportion than would be expected for the general population. This finding is consistent with other reports suggesting that African-Americans may be over-represented among the pediatric MS population [38,39]. An ongoing goal for investigators is to characterize demographic features and differences between the pediatric and adult MS population, as well as identifying any features that may be associated with pediatric onset.

Other limitations concerned the available data for comparison to the SDMT. The neuropsychological testing batteries differed slightly between the MS and HC participants. Further, some of the MS participants' batteries were incompletely administered due to limited clinic time. In future studies, a consistent battery of tests should be administered to all groups. In addition, we did not measure mood in patients, and therefore cannot comment on whether symptoms of depression or anxiety influenced performance. Nonetheless, the measures included in this study provided an adequate general estimate of neuropsychological functioning for comparison to the SDMT.

5. Conclusion

In summary, as in adults with MS, these preliminary data support the use of the SDMT as a screen for cognitive function in pediatric-onset MS. Patients found to have a SDMT in the impaired range or those with a marked decline on a repeated visit would be the best candidates for neuropsychological evaluation to confirm and classify degree of cognitive impairment.

Conflict of interest

The authors declare that there is no conflict of interest.

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