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ORIGINAL ARTICLE

The computer-based Symbol Digit Modalities Test: establishing age-expected performance in healthy controls and evaluation of pediatric MS patients

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Abstract Decreased information processing speed (IPS) is frequently reported in pediatric multiple sclerosis (MS) patients. The computerized version of the Symbol Digit Modalities Test (c-SDMT) measures IPS over eight consecutive trials per session and additionally captures changes in performance within the session. Here, we establish normative c-SDMT performance and test–retest reliability in healthy children (HC) and explore differences in the overall c-SDMT-performance between HC and MS patients. This cross-sectional study included 478 HC (237 female, 49.5%) divided into five age groups (2 years each), and 27 MS patients (22 female, 81.5%) aged 8–18 years. The average time to complete the c-SDMT increased with age ($|r|$ 0.70, 95% CI −0.74, −0.64). Test–retest reliability was high (ICC = 0.91) in HC. The total time to complete the c-SDMT did not differ between children with MS and sex- and age- matched HC ($p = 0.23$). However, MS patients were less likely to show faster performance across all the successive eight trials compared to HC ($p = 0.0001$). Healthy children demonstrate faster IPS with increasing age, as well as during successive trials of the c-SDMT. The inability of pediatric MS patients to maintain the increase in processing speed over successive trials suggests a reduced capacity for procedural learning, possibly resulting from cognitive fatigue.

Keywords Pediatric MS · Processing speed · Symbol Digit Modalities Test · Neurocognition

Introduction

Multiple sclerosis (MS) is an acquired demyelinating disease of the central nervous system (CNS). Approximately 3–5% of MS patients experience their first attack during childhood [1]. Cognitive impairment occurs in 30–50% of children with MS and negatively affects daily life, school performance, and vocational achievement [2, 3]. Decreased information processing speed (IPS) is one of the most frequently observed cognitive deficits in children and adolescents with MS.

IPS is a cognitive function closely linked to the state of myelination of the brain, with increasing IPS normally developing in adolescence. Given the focal insult of MS lesions on myelinated pathways, and given that pediatric MS onset occurs during the period of myelin maturation, IPS may be particularly impacted in pediatric MS [2]. Evaluation of IPS in a clinical setting may, therefore, serve as a useful screening method to identify pediatric MS

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patients in need of more comprehensive cognitive evaluation.

Due to its sensitivity, the traditional Symbol Digit Modalities Test (SDMT) has been included in the Brief Repeatable Neuropsychological Battery (BRNB) for MS and is widely used to assess IPS in clinical and research MS settings [3–8]. In neuroimaging studies, performance on the SDMT was repeatedly associated with MRI evidence of MS pathology [9, 10]. The SDMT has recently been considered as an outcome measure to assess cognitive outcome in clinical trials [4].

The SDMT has also been proposed as a valuable cognitive assessment tool for pediatric MS. Performance on the SDMT discriminates between healthy controls and pediatric MS patients. Reduced performance in the SDMT correlated with decreased thalamic volume, with greater white matter abnormalities as measured by diffusion tensor imaging, and with reduced corpus callosal area in pediatric MS patients [5]. Furthermore, the SDMT is sensitive to change in cognitive function over time in pediatric-onset MS [7].

A computerized version of the Symbol Digit Modalities Test (c-SDMT) was recently validated in an adult MS cohort [8]. The c-SDMT shows comparable sensitivity and specificity to the traditional paper-SDMT in detecting overall cognitive impairment on a neuropsychological test battery in adult MS patients [8], but has not been used in healthy children and adolescents or in children with MS. The c-SDMT consists of eight consecutive trials, with nine symbol–digit pairings made per trial. The time per individual trial, the total time for all trials, and the mean time per trial are recorded by the program, permitting determination of change in IPS over repeated trials. Therefore, the c-SDMT yields insight into both IPS and procedural learning.

The current study evaluated performance and participant tolerability of the c-SDMT in a large cohort of healthy children and adolescents and then compared the age-specific performance of the healthy children to the performance of pediatric MS patients. As IPS increases with myelin maturation [11], we anticipated increases in IPS and procedural learning on the c-SDMT over the course of childhood to adolescence. We hypothesized that pediatric MS patients would show slower IPS and less benefit from sequential practice on the c-SDMT as compared with healthy youth.

Methods

Study design and participants

We performed a cross-sectional study of 478 healthy children and adolescents, and 27 pediatric MS patients. Participants and their parents or guardians provided written informed consent. Assent was also obtained from children younger than 12 years. Healthy participants were recruited at the Ontario Science Centre from July to August 2013. MS patients were recruited consecutively from the MS Clinic at the Hospital for Sick Children, Toronto, Canada. The diagnosis of MS was conferred according to the 2005 or 2010 McDonald diagnostic criteria, as appropriate, depending on the date of first attack [12, 13]. All participants were between 8 and 17 years 11 months of age at testing. Participants were excluded if they had a history of traumatic brain injury associated with loss of consciousness, had visual impairment such that the test could not be completed, were receiving medications with known psychotropic effects, or if they endorsed use of recreational drugs. Participants with attention deficit disorder, anxiety, or depression requiring medication were excluded. MS patients were evaluated for more than 30 days from a clinical relapse or exposure to corticosteroid therapy. Clinical disability for MS patients was evaluated using the Expanded Disability Status Scale (EDSS).

Data collection

Participant's medical history was reviewed. Current placement (grade level), identification of having an exceptionality within the school system (i.e. giftedness, learning disorders), or requirement for educational support was recorded.

For the MS patients, age at first attack, disease duration, medications at the time of testing and the Expanded Disability Status Scale (EDSS) score on the day of testing were recorded. Disease duration was defined as the time difference between age at testing and age at first attack.

Testing procedure

Standardized instructions were provided and participants performed one practice run before formal administration of the c-SDMT. As illustrated in Fig. 1, the c-SDMT presents an array of nine symbol–digit pairings at the top of the screen and another nine randomly arranged symbols below. The participant views the array and is required to verbally associate the digit for each corresponding symbol below. The examiner presses a button at the completion of each trial to start the next trial. A session consists of eight consecutive trials, with the nine symbols being presented in different order during each trial. The total time to complete the session (seconds) and the time for each trial (Trial 1–Trial 8) are recorded, and the average time per trial is calculated for each participant. The computer program had no time limitation; on average, the task takes approximately 5 min to complete. All examiners underwent the same structured training regarding how to give the

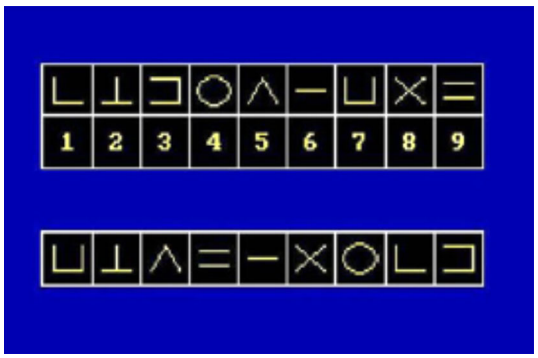

Fig. 1 Screen capture of the c-SDMT

standardized instructions and the test itself (training supervised by SB). Every examiner performed a total of three supervised practice runs to ensure equality of application before applying the test to the participants.

To assess test–retest reliability, a randomly selected subset of healthy children ($n = 272$) completed the c-SDMT across two sessions performed within the time frame of 2 h. The short inter-test interval was a practical consideration, based on the typical duration of time that the families spent at the Science Centre.

After completion of the session, participants' acceptance of the test was assessed using an orally administered questionnaire which queried whether or not the participant liked performing the test and whether they felt that the computer presentation was satisfactory. Participants also rated their level of tiredness (How tired did you feel when you were doing the test? "not at all", "a little bit", "very tired").

Statistical analysis

The primary outcome was the average time per trial (i.e. total time taken to complete the c-SDMT divided by eight trials). Secondary outcomes included test–retest reliability (evaluated in healthy participants), and the proportion of participants that gave positive satisfaction ratings for the test.

The sample size of healthy participants was based on normative studies of psychological functioning in children, requiring approximately 50–75 children per age group to provide precise findings (=confidence intervals) [14]. The group of 27 MS patients represents a convenience sample.

Categorical variables were summarized as frequencies and percent. Continuous variables were tested for normality and then summarized as median (IQR). Independent proportions were compared using Chi-squared or Fisher's exact test. Two independent sample medians were compared using Wilcoxon's rank-sum test. The comparison of more than two sample medians was analyzed using the Kruskal–Wallis test. The correlation between continuous variables was assessed using Spearman rank correlation coefficient, where $|r| > 0.7$ was considered a high, 0.5–0.7 a moderate and <0.5 a low correlation.

For each healthy participant, the time to complete each of the eight trials was recorded and the final time was calculated as the average across all eight trials. We then grouped the healthy participants into 2-year age groups. For each age group, the median time per age group was calculated. Multiple linear regression models analyzed the relationship of participant and clinical variables on c-SDMT performance. Participant factors included in the linear regression model were selected a priori based on their known (age at testing, comorbid attention disorders, giftedness, tiredness) or potential association (parental education, sex) with IPS [15–21]. Model assumptions, including normality of the residuals, verification of influential outliers, linearity, homoscedasticity and multicollinearity were assessed [22]. Test–retest reliability was assessed using an intraclass correlation coefficient (2.1). In a post hoc sensitivity analysis, we repeated the analysis excluding the self-identified gifted children.

To compare performance on the c-SDMT between HC and MS patients, a 1:4 matching was performed with a subset of HC, i.e. each MS patient was matched with four randomly selected healthy participants of the same sex and age (age range within 3 months). The average time per trial and the time difference between Trial 1 and Trial 8 of each MS patient were compared with the mean performance of the four matched HCs, using Wilcoxon rank-sum test and sign test, respectively.

Two-tailed p values <0.05 were considered statistically significant (unless specified differently). Analyses were performed using SAS V 9.4 (SAS Institute Inc., Cary, NC).

Results

Out of the 500 healthy participants who consented, data from 22 were excluded due to computer-related problems (data were inadvertently not saved). Age, gender and participant characteristics present in more than 5% of the participants were assessed in univariate analyses for their association with IPS (Table 1a). As expected, IPS increased with age ($|r|$ 0.70, 95% CI −0.74, −0.64). In the linear regression model, increasing age and academic giftedness were associated with faster IPS after adjusting for potential confounders (Table 2). Furthermore, adolescents in the control group demonstrated faster performance at the end of eight consecutive trials, which was not observed in participants below 12 years of age (Table 3). This finding was not altered when self-reported gifted participants were excluded from the analysis (Table 3).

Table 1 Association of information processing speed with potential predictors in (a) healthy participants, and (b) MS patients

	Median (IQR) time per trial in seconds	*p* value
(a) Healthy participants		
Age[a]		**<0.001**
8–9 years ($n = 89$)	20.0 (17.8–22.6)	
10–11 years ($n = 116$)	16.1 (14.0–18.0)	
12–13 years ($n = 105$)	13.6 (12.3–15.4)	
14–15 years ($n = 93$)	12.8 (11.7–13.6)	
16–17 years ($n = 75$)	12.0 (10.8–13.0)	
Gender		0.078
Female ($n = 237$)	13.8 (12.2–17.3)	
Male ($n = 241$)	14.7 (12.8–17.4)	
ADHD		0.835
Yes ($n = 28$)	14.3 (12.7–16.6)	
No ($n = 450$)	14.2 (12.5–17.4)	
Gifted		**0.022**
Yes ($n = 77$)	13.3 (12.1–15.8)	
No ($n = 401$)	14.3 (12.6–17.7)	
Tiredness		**0.037**
No ($n = 316$)	14.0 (12.4–17.1)	
A little bit ($n = 153$)	14.7 (12.5–18.2)	
Very tired ($n = 4$)	15.0 (13.2–20.4)	
Unknown ($n = 5$)	13.9 (13.0–18.2)	
First language spoken		0.380
English ($n = 393$)	14.5 (12.5–17.9)	
French ($n = 23$)	13.9 (12.3–15.7)	
Other ($n = 62$)	13.5 (12.4–15.4)	
Highest level of education of mother		0.830
High school ($n = 54$)	13.6 (12.4–16.4)	
College ($n = 112$)	14.2 (12.8–16.8)	
University ($n = 269$)	14.2 (12.5–17.7)	
Unknown ($n = 30$)	13.6 (12.0–17.3)	
Highest level of education of father		0.172
High school ($n = 67$)	13.3 (12.4–15.7)	
College ($n = 112$)	14.7 (12.5–17.7)	
University ($n = 269$)	14.4 (12.5–17.7)	
Unknown ($n = 30$)	13.5 (12.0–17.3)	
(b) MS patients		
Age at testing[a]		0.822
10–11 years ($n = 2$)	15.2 (12.8–17.6)	
12–13 years ($n = 7$)	13.2 (11.7–17.2)	
14–15 years ($n = 8$)	12.5 (11.4–13.1)	
16–17 years ($n = 10$)	13.2 (12.4–21.1)	
Age at first attack	$\|r\|$ 0.08	0.700
Gender		
Female ($n = 22$)	12.9 (11.5–15.9)	0.374
Male ($n = 5$)	13.1 (12.7–17.9)	
Tiredness		
No ($n = 20$)	12.7 (11.4–15.8)	0.308
A little bit ($n = 6$)	13.2 (12.9–13.2)	
Very tired ($n = 1$)	21.2	
Unknown ($n = 0$)	–	
DMT		
Yes ($n = 16$)	13.3 (12.2–17.6)	**0.037**
No ($n = 11$)	12.6 (11.2–13.2)	
Disease duration[a]		
>1 year ($n = 17$)	13.0 (12.0–16.7)	0.772
<1 year ($n = 10$)	12.7 (11.5–14.4)	
>2 years ($n = 8$)	13.3 (12.6–17.4)	0.370
<2 years ($n = 19$)	12.8 (11.5–15.9)	
EDSS	$\|r\|$ 0.07	0.738

Statistically significant results are highlighted in bold

[a] These variables were categorized for the purpose of descriptive statistics

Test–retest reliability of the c-SDMT was excellent (ICC = 0.91, $p < 0.001$).

Of the 27 MS patients, 22 (81.5%) were female. Median (IQR) age at testing was 15.7 (13.3–16.7) years and median (IQR) age at first attack was 13.6 (11.2–15.1) years. Median (IQR) time from first attack to test date was 1.6 years (0.7–2.4 years). At the time of testing, 16 were receiving disease-modifying therapy (DMT, interferon-beta (7), glatiramer acetate (4), natalizumab (4), rituximab (1) and dimethyl fumarate (1). Median (IQR) EDSS was 1.5 (1.0–2.0).

In univariate analyses, sex, age at testing, age at first attack, reported level of tiredness, EDSS and disease duration were not associated with median IPS (Table 1b). MS patients receiving DMT had slower IPS than untreated MS patients (median time per trial 13.3 versus 12.6 s, $p = 0.037$). Receiving DMT was associated with longer disease duration ($p = 0.054$) but not with number of relapses ($p = 0.440$). Prompt initiation of DMT is the standard recommended care plan for all patients in the pediatric MS program. For the present study, however, participants were not interviewed to determine the individual rationale for use of or avoidance of DMT.

Sample size permitted two variables to enter linear regression modeling. We selected DMT based on univariate analyses, and age at testing based on findings in the healthy control cohort. We found that only DMT, but not age, remained a statistically significant predictor of slower

Table 2 Linear regression model on rank-transformed data assessing potential predictors of c-SDMT performance in healthy participants

Predictor	Adjusted beta coefficient (95% CI)	Test statistic	*p* value
Omnibus *F* test [*F*(ndf, ddf), *p* value]		31.15 (16, 461)	<0.001
Age group			
8–9 years	0 (ref)	–	–
10–11 years	−91.76 (−119.12, −64.41)	−6.59	<0.001
12–13 years	−182.76 (−210.75, −154.77)	−12.83	<0.001
14–15 years	−243.98 (−272.79, −215.18)	−16.64	<0.001
16–17 years	−280.95 (−311.68, −250.22)	−17.97	<0.001
Gifted (self-reported)	−41.99 (−66.10, −17.88)	−3.42	<0.001
Sex	15.97 (−1.91, 33.84)	1.76	0.078
ADHD	−13.561 (−51.49, 24.37)	−0.70	0.472
Feeling tired			
Not at all	0 (ref)	–	–
A little bit	−1.16 (−20.30, 17.97)	−0.12	0.905
Very tired	−1.71 (−99.99, 96.58)	−0.03	0.973
Unknown	−34.46 (−121.60, 53.15)	−0.77	0.442
Highest level of education completed by mother			
High school	16.29 (−15.76, 48.33)	1.00	0.318
College	2.99 (−22.26, 28.23)	0.23	0.816
University	0 (ref)	–	–
Unknown	−6.89 (−62.20, 48.42)	−0.24	0.807
Highest level of education completed by father			
High school	1.76 (−28.27, 31.79)	0.12	0.908
College	11.68 (−14.73, 37.43)	0.88	0.378
University	0 (ref)	–	–
Unknown	1.71 (−52.82, 56.24)	0.06	0.951

Table 3 Difference in IPS increase between Trial 1 (T1) and Trial 8 (T8) in healthy participants categorized per 2-years age group

Age group in years	T1 median (IQR) in seconds	T8 median (IQR) in seconds	Diff median (IQR) in seconds	*p* value
8–9	20.1 (17.0–23.3)	19.6 (16.9–22.8)	0.2 (–2.9–2.4)	0.45
10–11	16.6 (14.5–18.8)	16.3 (13.9–18.8)	0.4 (−2.4 to 1.7)	0.28
12–13	14.9 (12.8–16.9)	13.8 (11.5–15.9)	0.9 (−3.3 to 0.9)	**0.0037**
14–15	13.8 (12.4–14.7)	12.6 (11.4–13.8)	0.8 (−2.5 to 0.4)	**<0.0001**
16–17	12.6 (11.4–14.4)	11.5 (10.4–13.6)	1.1 (−2.1 to 0.1)	**<0.0001**
Exclusion of the self-identified gifted participants				
8–9[a]	20.2 (17.3–23.3)	19.9 (17.3–22.8)	0.2 (−3.4 to 2.4)	0.50
10–11[a]	16.6 (14.6–19.3)	16.4 (13.9–19.2)	0.4 (−2.4 to 1.7)	0.39
12–13[a]	15.3 (13.1–17.1)	13.9 (12.3–16.6)	0.8 (−3.6 to 0.9)	**0.018**
14–15[a]	13.8 (12.3–14.8)	12.8 (11.4–13.8)	0.8 (−2.5 to 0.2)	**<0.0001**
16–17[a]	12.9 (11.5–14.6)	11.5 (10.5–13.8)	1.2 (−2.1 to 0.1)	**<0.0001**

Statistically significant results are highlighted in bold

[a] Separate analyses at the lower end of the table with exclusion of gifted ($n = 77$) participants

performance (adjusted β-coefficient 2.8; 95% CI 0.11–5.6; $p = 0.042$).

We then compared the performance between MS patients and age- and sex-matched healthy youth. The median (IQR) score was 12.1 s (11.8–12.8) in healthy children and 12.8 s (11.7–15.9) in MS patients ($p = 0.23$). Over eight consecutive trials, MS patients were less likely to show sustained faster performance across successive trials compared to age-matched controls (Fig. 2). The median (IQR) reduction in time over eight consecutive trials was −0.7 (−2.1 to 1.5) s in MS patients and −2.0 (−3.0 to −1.5) in healthy participants ($p < 0.001$).

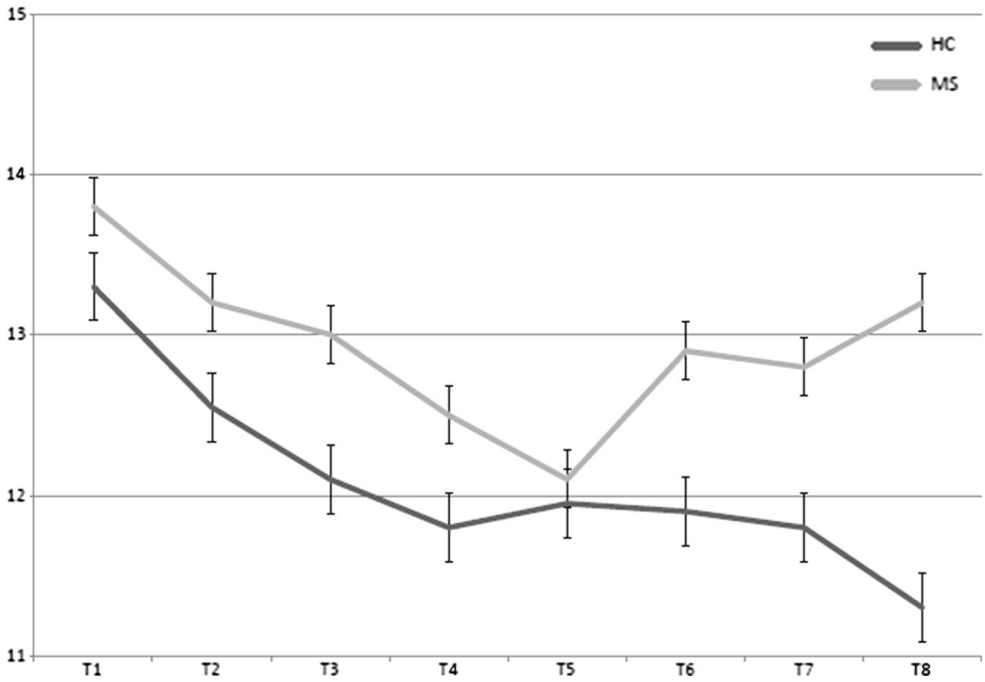

Fig. 2 The time per individual trial (in seconds) is illustrated for the MS patients (MS) and healthy controls (HC) evaluated on eight consecutive trials (T1–T8)

In 16 MS patients, the c-SDMT was performed twice, after a median (IQR) interval of 6 months (2.5–10.0). The median (IQR) time per trial changed from 13.1 (12.0–17.3) s to 13.3 (10.8–16.1) s, which was not statistically significant ($p = 0.33$).

In the assessment of the child's satisfaction of the c-SDMT, over 85% of the participants (healthy controls and MS patients) indicated that they liked the test. The results of the questionnaire are shown in more detail in Supplementary Table 1.

Discussion

We evaluated performance and participant acceptance of the c-SDMT in healthy children and adolescents. We then compared performance between healthy participants and pediatric MS patients. Patients with MS did not differ from age- and sex-matched healthy participants in their overall performance on the c-SDMT; however, the MS patients failed to show a sustained increase in speed over the eight consecutive trials, highlighting a possible deficit in procedural learning or increasing cognitive fatigue over sequential practice of the task.

The c-SDMT reliably captures increases in IPS with increasing age and myelin maturation in healthy children and adolescents [23–25]. After the age of 12 years, healthy participants demonstrated the capacity to increase speed over the eight consecutive trials, a skill that does not seem to be yet developed in younger children.

Interestingly, age did not emerge as a predictor for IPS in patients with MS. This is most likely due to the skewed age representation in the MS population with most patients already having reached adolescence. Inclusion of younger MS patients in future studies is required to evaluate this further. In healthy participants, the age-related IPS increase is notable between eight and 13 years, with only a modest further increase in speed between 14 and 18 years of age (Table 3).

As shown in Fig. 2, healthy controls perform more quickly on serial trials, while the MS patients initially appeared to increase speed but did not maintain this increase across all the eight trials. Failure to maintain speed across trials might be due to cognitive fatigue or decreased attention. The subjective level of tiredness reported by MS patients did not differ from that reported by age-matched healthy participants, although it is possible that subjective tiredness may not adequately capture cognitive fatigue. Interestingly, an fMRI study using the c-SDMT in adult MS patients showed that while MS patients did not differ in their overall performance from healthy adults, they did demonstrate increased overall brain activation, which may conceptually be a surrogate for increased brain "effort" and, thus, increased likelihood of cognitive fatigue for a given task [26].

Patients with MS treated with DMT demonstrated slower IPS values relative to untreated patients. It is noteworthy that although all patients with MS were offered treatment, a significant proportion (41%) still declined treatment. While there was no statistically significant association between being on DMT and number of relapses, there was a trend towards longer disease duration being associated with using a DMT.

The SDMT is a valid tool to assess the impairment of information processing speed in adult MS patients [27].

Furthermore, it is sensitive to cognitive decline over time [28]. Similar findings have been shown in the pediatric MS population. Previous studies assessing IPS with the oral version of the SDMT (which provides only an overall score as there are no serial trials in this version) showed pediatric MS patients to be impaired in their SDMT performance compared to controls [2, 6, 29, 30]. Several factors may account for why the overall c-SDMT scores did not reveal deficits in our pediatric MS cohort. First, the pediatric MS patients in the present study may be less cognitively impaired than those in the published cohorts, although a full cognitive evaluation would be required to determine this. The pediatric MS patients in the present study had a mean disease duration of only 1.6 years, which is shorter than the average disease duration of previously reported pediatric MS cohorts (2.3–4.4 years) [2, 6, 29, 30].

The primary goal of our work was to explore both the feasibility and tolerability of a computerized version of the SDMT, as such a tool would permit data entry immediately into computerized databases, is applicable for use in patients with motor impairment as it does not require use of a pen, and permits evaluation of within-test procedural learning which is not assessed by the paper version of the SDMT. We also hypothesized that today's youth would enjoy a computerized test more than they would a pen-and-paper assessment. We, thus, evaluated participant perceptions of the test. Our data demonstrating the overall positive experience of participants with the c-SDMT provide the impetus to test this tool in a larger MS cohort.

Our study has several limitations. First, this study represents the first step in testing the feasibility of the c-SDMT and assessment of acceptance and tolerability in the pediatric population. More validation of the c-SDMT is needed. Second, while test–retest reliability of the c-SDMT was excellent, evaluation of test–retest reliability was performed during the same day in the healthy participants. This was due to practical reasons given the testing venue. The proximity of the two tests might raise the concern of practice effect. However, the c-SDMT controls to a certain extent for practice effects by providing a new symbol/digit key every time a test is performed. Thus, while participants gained familiarity with test procedures, they could not have memorized symbol–digit pairings. Third, we evaluated the c-SDMT only in English-speaking healthy participants. While the test itself is language-agnostic, the c-SDMT instructions require translation for use in a broader population.

In summary, we demonstrated that the c-SDMT is an age-sensitive test instrument for IPS. The c-SDMT provides some unique advantages over the paper version of the conventional SDMT. The 8-trial aspect of the c-SDMT permits insight into processing speed over consecutive trials, which is not a component of the conventional SDMT. Furthermore, the c-SDMT taps sustained attention, in addition to processing speed, working memory, and visual attention which are evaluated by the traditional SDMT. Given that it was the failure to improve in IPS across trials that distinguished the MS group, the c-SDMT may be a superior tool for pediatric MS evaluation. As pediatric therapeutic trials emerge, the SDMT is likely to be included as a secondary outcome measure, as it is in adult MS trials. We suggest that direct comparison of the conventional SDMT to the c-SDMT be a priority, so as to best identify a sensitive metric for pediatric MS outcomes.

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Compliance with ethical standards

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