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Binocular Low-Contrast Letter Acuity and the Symbol Digit Modalities Test Improve the Ability of the Multiple Sclerosis Functional Composite to Predict Disease in Pediatric Multiple Sclerosis

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Abstract

Background—Outcome measures to capture disability, such as the Multiple Sclerosis Functional Composite (MSFC), were developed to enhance outcome measurements for clinical trials in adults with multiple sclerosis (MS). The MSFC initially included three components: a timed 25-foot walk [T25FW], 9-hole peg test [9HPT], and the Paced Auditory Serial Addition Task [PASAT]. Modifications to the original MSFC, such as adding binocular low-contrast letter acuity (LCLA) or substituting the symbol digit modalities test (SDMT) for the PASAT, improved the capacity to capture neurologic impairment in adults. Similar outcome scales for pediatric MS have not yet been established.

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Objective—To determine whether the three-component MSFC or a modified MSFC with LCLA and the SDMT better identifies neurological deficits in pediatric MS.

Methods—We evaluated 5 measures (T25FW, 9HPT, Children's PASAT [ChiPASAT], SDMT, and binocular LCLA [Sloan charts, 1.25% contrast]) in children with MS (disease onset <18 years) and healthy controls. To be able to compare measures whose scores have different scales, Z-scores were also created for each test based on the numbers of standard deviations from a control group mean, and these individual scale scores were combined to create composite scores. Logistic regression models, accounting for age, were used to determine whether the standard 3-component MSFC or modified versions (including 4 or 5 metrics) best distinguished children with MS from controls.

Results—Twenty pediatric-onset MS subjects, aged 6–21 years, and thirteen healthy controls, aged 6–19 years, were enrolled. MS subjects demonstrated worse scores on the 9HPT ($p=0.004$) and SDMT ($p=0.001$), but not the 25FTW (adjusted for height, $p=0.63$) or the ChiPASAT ($p=0.10$): all comparisons adjusted for age. Decreased (worse) binocular LCLA scores were associated with MS (vs. control status, $p=0.03$, logistic regression; $p=0.08$, accounting for age). The MSFC composite score for the traditional 3 components did not differ between the groups ($p=0.28$). Replacing the ChiPASAT with the SDMT (OR 0.72, $p=0.05$) better distinguished MS from controls. A modified MSFC-4 with the SDMT replacing the ChiPASAT and including binocular 1.25% LCLA had the greatest capacity to distinguish pediatric MS from controls (OR 0.89, $p=0.04$, logistic regression). Including all 5 metrics as a composite MSFC-5 did not improve the model ($p=0.18$).

Conclusions—A modified MSFC (25FTW, 9HPT, SMDT, and binocular 1.25% LCLA) is more sensitive than the traditional MSFC or its components to capture the subtle impairments that characterize pediatric MS and should be validated in order to be considered for future pediatric MS trials.

Keywords

multiple sclerosis; pediatrics; outcome measures

1. Introduction

Standardized tools that reliably quantify neurologic impairment in pediatric multiple sclerosis (MS) have not been established. MS clinical trials in adult patients have used the Expanded Disability Status Scale (EDSS)(Kurtzke 1983). Although the EDSS incorporates eight Functional Systems scores (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral, and ambulation), the EDSS summary score itself is heavily influenced by ambulation status. Gait impairment and sustained disability in children with MS are less common than in adults; thus the EDSS may not be a sensitive metric for pediatric MS. In one observational study of 76 pediatric MS patients, baseline mean EDSS scores were 1.4 ± 0.8 and did not change (mean of 1.2 ± 0.9) after a mean follow-up of 30 months (standard deviation 15 months) irrespective of treatment(Ghezzi et al. 2005). Another study of 84 pediatric MS and 258 adult MS patients demonstrated a >2 fold higher relapse rate in the

pediatric MS group but median EDSS scores did not differ between the groups, and remained low (median 1.5, range 0–8) over a 6-year period (Benson et al. 2014).

The Multiple Sclerosis Functional Composite (MSFC), consisting originally of a timed 25-foot walk (T25FW), a 9-hole peg test (9HPT), and Paced Auditory Serial Addition Task (PASAT), was developed as an outcome tool for adults to capture the most relevant dimensions of function and disability, including ambulation, arm function, and cognition (Rudick et al. 1997; Cutter et al. 1999; Rudick et al. 2002). The MSFC is brief and can be administered by a non-clinician. Compared to the EDSS, MSFC and its component scores are more reliable and correlate better with disease stage than does the EDSS (Polman & Rudick 2010). The Children's PASAT (ChiPASAT) has been adapted for children ages 8–15 years (Johnson et al. 1988; Dyche & Johnson 1991) and replaces the PASAT when using the MSFC for younger MS patients.

Developers of the MSFC and MS outcomes committees have incorporated low-contrast letter acuity as a visual outcome component for inclusion in the MSFC. The original MSFC did not include a test of vision since high-contrast visual acuity, the only visual measure available in the clinical trial data sets used to develop the MSFC, did not detect changes over time. Routine clinical tests of high-contrast visual acuity, typically assessed by wall-mounted Snellen charts (and as adjudicated in the EDSS), do not maximally capture visual dysfunction in adult patients (Rudick et al. 1997). Pediatric MS patients with optic neuritis typically recover high contrast visual acuity. In one study of 38 pediatric MS patients with optic neuritis, 95% of patients demonstrated complete recovery (Snellen visual acuity of 20/20) (Taimur et al. 2014). As expected, high-contrast (Early Treatment Diabetic Retinopathy Scale [ETDRS]) scores also do not differ between pediatric MS subjects with optic neuritis and controls (Waldman et al. 2014). Low-contrast letter acuity (LCLA), where the subject views letters of progressively smaller size as well as reduced contrast to the background (ie: grey letters as opposed to black) is a more sensitive tool to detect subtle visual impairment (Balcer et al. 2000). In adult clinical trials of natalizumab, LCLA, in comparison to high-contrast acuity, differentiated treated patients from those patients in the placebo arms and identified patients with worsening visual impairments despite no change in the EDSS (Balcer et al. 2012; Chahin et al. 2015).

We have recently demonstrated the ability of LCLA to capture visual dysfunction in 22 pediatric MS patients, although only the more stringent 1.25% contrast distinguished patients from controls (Waldman et al. 2014). With the recent launch of several clinical trials of new therapies in pediatric MS populations, and with the imperative to better appreciate the impact of MS onset during childhood, we evaluated the MSFC and its components, the SDMT and LCLA in a cohort of pediatric MS patients in order to determine which combination of tests best captured measurable neurological impairment.

2. Methods

2.1 Study eligibility

Children with relapsing-remitting MS (presenting with a first attack prior to age 18 years) were recruited from the Pediatric MS Program at the Children's Hospital of Philadelphia as

a convenience sample between 2007 and 2012. The diagnosis of MS was established using the 2007 International Pediatric MS Study Group criteria (Krupp et al. 2007). Healthy children without neurologic, ocular, or systemic disease were recruited by local advertisement, and were required to have normal corrected visual acuity.

For MS subjects, all testing was performed at least 30 days after a relapse and 6 months or more from an attack of optic neuritis. The children were assessed for a history of optic neuritis in one or both eyes. We considered optic neuritis to have occurred if detailed chart review identified documentation of: decreased high-contrast letter acuity, pain with eye movement, color desaturation, and/or visual field abnormalities lasting at least 24 hours, with or without optic nerve swelling or enhancement visualized on magnetic resonance imaging. EDSS scores were obtained retrospectively from neurology office notes using a standardized, reliable algorithm developed by one of the authors (SC).

2.2 MSFC, SDMT, and LCLA

The MFSC was administered according to the Administration and Scoring Manual (Fischer et al. 2001), including two timed trials of both the T25FW and 9HPT (dominant and non-dominant hand). The PASAT was replaced with the ChiPASAT, which was administered via a computerized program (Dr. Robert J. McInerney & Associates, Canada). The written SDMT was completed using a standardized protocol (Smith 1973) in 90 seconds, and the number of correct responses was recorded. High (Early Treatment Diabetic Retinopathy Study [ETDRS] 3.2 meter charts, Lighthouse Low Vision Products, Long Island, NY) and low-contrast letter acuity (Sloan 1.25% contrast 2 meter charts, Precision Vision) were recorded using the patient's own correction, standardized testing protocols at the appropriate viewing distance, and a retroilluminated viewing cabinet. Cycloplegic refraction was not performed. Binocular acuity scores, rather than monocular scores with each eye separately, were included to capture visual function with both eyes together. This is analogous to testing arm and leg function using performance measures of T25FW and 9HPT.

2.3 Analyses

Summary scores for function tests were calculated as follows. For the T25FW, the times for the 2 trials were averaged; for the 9HPT, the times for the 4 trials (2 trials each of the dominant and non-dominant hands) were averaged. The number of correct responses in the allotted time was determined for the ChiPASAT (3 minutes) and the SDMT (90 seconds). For the binocular LCLA (1.25% contrast) charts, the number of letters identified correctly (maximum 70) was recorded. Each functional test was compared between MS subjects and disease-free controls using logistic regression. The analyses were repeated adjusting for age (and height for the T25FW). Z-scores were also created for the MS patients on each performance measures using the data from the disease-free controls as the reference population; Z-scores in this study represent the standard deviation from the control group mean.

Composite Z-scores were also created to allow for comparisons of combinations of tests with regard to capacity to distinguish MS patients vs. controls, although we acknowledge that the composite Z-score is less widely used than perhaps originally anticipated. The

composite Z-scores for each patient were calculated using the methodology proposed in the MSFC manual (Fischer et al. 2001). The MSFC composite Z-score was calculated as follows: $MSFC\ Z\text{-score} = (zT25FW + z9HPT + zChiPASAT)/3.0$; this score is referred to herein as the MSFC-3. The ChiPASAT was replaced with the SDMT to create the MSFC-3-SDMT $(zT25FW + z9HPT + zSDMT)/3.0$. Another substitution was made, omitting the cognitive testing and inserting a visual function test (binocular low-contrast letter acuity) to create a 3-component MSFC, referred to as the MSFC-3-BinLCLA $1.25(zT25FW + z9HPT + zBinLCLA)/3.0$. Vision was also added to the traditional MSFC $(zT25FW + z9HPT + zChiPASAT + zBinLCLA)/4.0$ to create the MSFC-4. In addition, the ChiPASAT was substituted with the SDMT in the MSFC-4 to create the MSFC-4-SDMT: $(zT25FW + z9HPT + zSDMT + zBinLCLA)/4.0$. Finally, all 5 tests were included for the MSFC-5: $(zT25FW + z9HPT + zChiPASAT + zSDMT + zBinLCLA)/5.0$. Logistic regression analyses were performed to determine whether MS vs. control status was a significant predictor of Z-scores, accounting for age and height.

The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Written informed consent and child assent were provided for all participants.

3. Results

Twenty children with pediatric MS and thirteen controls participated in the study. Demographics are included in Table 1. The mean age of children with MS was slightly older than controls; age was accounted for in all regression analyses. The median EDSS was 2 (range 0–4.5) in these pediatric MS subjects.

Sixty percent of children with MS (N=12 patients) had a history of acute optic neuritis in one or both eyes (17 eyes). The mean binocular high-contrast letter acuity score at 3.2 meters for healthy eyes was 62 letters correct (standard deviation [SD] of 5 letters or 1 line on the eye chart). For reference, 55 letters correctly identified on the ETDRS chart is the Snellen equivalent of 20/20; 60 letters is equivalent to 20/16; and 65 letters equals 20/12.5. For MS eyes individually, the mean was 59 letters (SD 13), with the same Snellen equivalent (20/16). When evaluating MS eyes with a history of acute optic neuritis, the mean was 53 (SD 17), compared to a score of 63 (SD 5) in the MS eyes without a history of optic neuritis.

A comparison of the raw scores for individual test components is presented in Table 2. The average score for the T25FW, adjusted for age and height, did not differ between the groups. The 9HPT adjusted for age was a significant discriminator of MS subjects vs. controls with longer times to complete the task demonstrated in the MS group (OR 1.35, $p=0.004$). The ChiPASAT did not differ between the groups. Children with MS performed less well on the SDMT compared to controls (OR 0.84, $p=0.001$). Decreased binocular low-contrast letter acuity (as measured by total correct letters identified) was also noted in the MS group (OR 0.92, $p=0.03$ unadjusted; and OR 0.93, $p=0.08$, adjusted for age).

The Z-scores for the five outcome measures were grouped into various composite measures (Table 3). The original 3-MSFC (MSFC: T25FW, 9HPT, and ChiPASAT), adjusted for age and height, did not differ between children with MS and controls ($p=0.28$). Similarly, when

binocular visual acuity was added to the traditional MSFC (MSFC-4: T25FW, 9HPT, ChiPASAT, and binocular 1.25% LCLA), there was no difference in the composite Z-score between the groups ($p=0.25$). When the ChiPASAT was replaced with the SDMT or binocular acuity, the composite Z-scores better differentiated between the groups (MSFC-SDM: T25FW, 9HPT, SDMT [$p=0.05$]; MSFC-LCLA: T25FW, 9HPT, binocular LCLA 1.25% [$p=0.08$]). By replacing the ChiPASAT with the SDMT and adding binocular low-contrast letter acuity (MSFC-4-SDMT: T25FW, 9HPT, SDMT, and binocular 1.25% LCLA), the composite score best distinguished pediatric MS patients from healthy controls ($p=0.04$). The addition of LCLA and SDMT to the traditional 3-component MSFC did not improve the model ($p=0.18$).

Among the pediatric MS patients, composite Z-scores for the MSFC decreased with increased (worse) EDSS scores, although the relationship was not significant ($p=0.3$, Figure).

4. Discussion

Relapsing-remitting MS in both adults and children leads to episodic neurological impairment with variable recovery and poses a risk for progressive disability. Quantification of MS impact would ideally capture impairments in physical functioning, vision, and cognition- all domains commonly involved in MS over time and all relevant to patient quality of life. We demonstrate that a modified MSFC, which replaces the ChiPASAT with the SDMT and includes 1.25% binocular LCLA, had the greatest capacity to distinguish MS from healthy controls.

While the original MSFC was a composite measure, the MSFC components are now often considered separately to allow several dimensions that distinguish MS patients vs. controls. Of the five measures evaluated (T25FW, 9HPT, ChiPASAT, SDMT and LCLA), the SDMT best discriminated MS patients from controls. The SDMT was more sensitive than the ChiPASAT. Thus, similar to considerations for adult-onset MS, we propose that the SDMT replace the ChiPASAT as a brief, screening tool for cognitive impairment. While the PASAT and ChiPASAT capture information processing speed, working memory, and sustained attention, (Forn et al. 2008) the SDMT does not evaluate computational attention and thus some authors propose that both the PASAT and SDMT should be evaluated in adults in order to provide complimentary information (Brochet et al. 2008; Drake et al. 2010; Williams et al. 2006). However, the PASAT has been criticized due to practice effects and skipping numbers in order to enhance performance on the task (Fisk & Archibald 2001; Wingenfeld et al. 1999). The ChiPASAT utilizes smaller numbers than the PASAT, with answers only adding up to 10 in the pediatric version. The ChiPASAT has been criticized as being too easy for children and adolescents with strong mathematical skills. The sensitivity of the ChiPASAT to identify cognitive impairment in pediatric MS patients is not well established.

In recognition of the challenges of the PASAT in adult MS studies, the SDMT has been administered in pediatric MS studies and detects impairment in pediatric MS compared to age-matched healthy youth. In one study of 18 pediatric MS subjects, 28% scored less than the 5% for age-matched controls (Amato et al. 2010); and another study of 33 pediatric MS

patients demonstrated that 12% of subjects scored less than 1.5 standard deviations below controls (Till et al. 2011). Performance on the SDMT also correlates with specific areas of brain volume, such as the corpus callosum and the thalamus in adults (Batista et al. 2012) and children (Till et al. 2011) with MS. In a longitudinal study, 28 pediatric MS patients failed to show expected improvements in the SDMT over 1-year as seen in 26 age- and sex-matched controls, suggesting minimal developmental gain or a smaller practice effect in the MS group (Till et al. 2013). The ability of the SDMT to discriminate pediatric MS from healthy youth longitudinally over a short-duration further supports the inclusion of this test in future pediatric treatment trials.

The 9HPT discriminated MS patients from healthy controls and was retained as a valuable component of the composite. The 9HPT is a practical, efficient test that takes seconds to complete and is a measure of upper limb dexterity. In contrast to the T25FW (discussed below), the 9HPT has normative data for children (Smith et al. 2000; Wang et al.; Poole et al.). Mean completion time and standard deviation varies with age (decreasing times to complete the task with increasing age), sex (faster times in females), and hand dominance (slower times for the nondominant hand). The 9HPT is recommended as part of the NIH toolbox for assessment of neurologic and behavioral function for children and adults and has been used to assess therapeutic interventions in other neurologic diseases in children such as Friedrich's ataxia, Charcot-Marie Tooth disease, and cerebral palsy (Lynch et al. 2006; Pareyson et al. 2006; Estilow et al. 2012; Mannil et al. 2014; Karaca et al. 2015). Of note, adult MS patients with worsening on the 9HPT also experienced change in fatigue, mood, sexual function, and lower limb function, in addition to arm function, suggesting that the 9HPT may capture impairment in more global domains than just upper extremity function (Kragt et al. 2006).

The timed 25-foot walk did not discriminate MS patients from controls. The T25FW in adults is slower among those with worse (higher) EDSS summary scores, although this has not been demonstrated in children (Cohen et al. 2001; Hoogervorst et al. 2002; Polman & Rudick 2010). The median EDSS in our patient group was 2, with none of our patients having gait impairment. We anticipate that the T25FW would identify patients with gait impairment, however, and thus feel it is reasonable to maintain this as a core measure. As the T25FW is a quick assessment of the patient's ability to walk a short distance, future studies are required to determine whether a more taxing assessment of gait would be more sensitive to subtle impairment in children. It will be of interest to also determine whether pediatric MS patients self-report limitations in physical activity, such as sports, and whether these patient-relevant outcomes can be better captured through creation of a more vigorous examination.

It is notable that inclusion of LCLA improved the discriminatory capacity of the proposed MFSC-4-SDMT. In two adult MS studies, the addition of 1.25% LCLA to the MSFC identified impairment not captured by the MSFC-3 or the EDSS (Balcer et al. 2003; Schinzel et al. 2014). This is not surprising given that the EDSS uses Snellen acuity. In the present study, sixty percent of the pediatric MS subjects had a history of optic neuritis; however, all had excellent high-contrast binocular visual acuity (20/20 or better), indicative of apparent clinically-meaningful recovery. However, LCLA may be identifying more subtle deficits

described by patients as “fuzzy vision” or difficulty with routine activities. In adults with MS (N=167, 50% of whom also had a history of optic neuritis in one or both eyes), lower binocular LCLA scores were associated with reduced vision-related quality of life after accounting for the high-contrast letter score (Mowry et al. 2009). Contrast sensitivity affects driving, face and object recognition (Owsley & Sloane 1987; Freeman et al. 2006), and LCLA reflects general vision, near and distance tasks, limitations in daily activities, and driving (Mowry et al. 2010). It is now of interest to determine whether pediatric MS patients with reduced LCLA also perceive impairments in activities of daily living, and importantly, whether such difficulties have any functional limitations (such as visualization of computer-based school assignments, higher risks during night-driving).

Our study clearly needs to be replicated in a larger pediatric MS population. Our cohort across the pediatric age span is challenged by age-expected maturation of performance in gross motor, fine motor, and cognitive function. For example, performance of the dominant hand on the 9HPT is approximately 8 seconds faster in young adulthood (18–29 years) compared to 6 year old children, although most of this change occurs prior to puberty with only a 1.5 second improvement between ages 12 and adulthood (18–29 years) (Poole et al.; Wang et al.). Mean scores on the ChiPASAT for children ages 14–15 years increased by 3 additional correct numbers compared to the 9–10 year old group (Johnson et al. 1988; Dyche & Johnson 1991). The difference between the groups extended to 6 letters with subsequent testing (performed at a mean interval of 25 days) due to practice effects; however, the present study only tested patients at a single time point; therefore, practice effects would not have influenced our results. Regarding the SDMT, the oral form was administered to 92 healthy children ages 6–17 years, and older children correctly identified 37 more letters than the youngest group further supporting age-related changes improvement on this test (Smerbeck et al. 2011); however, the written, not the oral, form of the SDMT was used for the present study so this normative data is not directly comparable to our raw scores. Similar to the 9HPT, the SDMT scores reported by Smerbeck et al. plateaued between ages 14 and 17 years (Smerbeck et al. 2011) which is the age range for most of our MS subjects. Nevertheless, due to these age-expected differences, comparisons of the group means for each test between MS and healthy controls (Table 2) were adjusted for age. To account for age when combining these metrics into a composite score, we used the control data to create Z-scores, which allow comparisons across age groups by determining the standard deviations for MS subjects from an age-expected means.

The median EDSS in our patient group was low with a narrow range. As such, we could not evaluate the relative utility of our proposed 4-component MFSC in pediatric patients with differing levels of physical impairment, although we were encouraged that the tool was able to distinguish our mildly-affected patients from controls. We anticipate that the MSFC-4-SDMT would perform well in patients with greater deficits, although few pediatric MS patients are anticipated to have marked physical disability prior to adulthood. Very few pediatric MS patients enter secondary-progressive MS during this age range, and our cross-sectional analysis does not permit us to confirm that the MSFC-4-SDMT is sensitive to change. Our study did not include an assessment for depression or fatigue, which may influence the individual test scores, especially cognition.

5. Conclusion

A modified MSFC (T25W, 9-HPT, SDMT and binocular 1.25% LCLA) is more sensitive than the traditional MSFC to capture the subtle impairments that characterize pediatric MS and should be considered for further validation. More sensitive measures for physical impairment, such as exercise limitations, would be of value. Longitudinal studies in pediatric MS are needed to determine whether changes in the MSFC capture patient-reported outcomes, disability, and quality of life over time.

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Highlights

- The Multiple Sclerosis Functional Composite (MSFC) includes three components: a timed 25-foot walk (T25FW), 9-hole peg test (9HPT), and the Paced Auditory Serial Addition Task (PASAT). Only the 9HPT differentiated children with MS from healthy children.
- Scores on the Symbol Digit Modalities Test (SDMT), adjusted for age, were significantly lower in pediatric MS vs. controls whereas no difference was found between the groups using the children version of the PASAT.
- As a composite metric, the T25FW, 9HPT, SDMT, and binocular low-contrast letter acuity (1.25%) together had the greatest capacity to capture the subtle impairments that characterize pediatric MS.

Figure. Modified MSFC Z-scores compared to the EDSS in pediatric MS patients

The Z-scores of a modified MSFC (including the T25FW, 9-HPT, SDMT, and BinLCLA-1.25%) were compared to the EDSS in pediatric MS patients. Pediatric patients with higher EDSS (scores >3) demonstrated the greatest changes from the mean, although for the entire group the relationship between the EDSS and composite MSFC scores were not significant ($p=0.3$).

Table 1

Demographics

	MS (N=20)	Controls (N=13)
Age, years (SD)	15.4 (3.7)	11.3 (3.6)
Sex, number female (%)	10 (50)	7 (54)
Race, number Caucasian (%)	13 (65)	12 (92)
Ethnicity, number Hispanic	0	0
Mean disease duration, years (range)	3.6 (0.12–14.5)	N/A
Receiving disease modifying therapy at the time of the testing, number (%)	15 (75)	N/A
History of optic neuritis, number of patients (%)	12 (60)	N/A
Mean binocular high contrast letter acuity at 3.2 meters, number of letters correct (SD)	65 (4)	65 (8)

Table 2

Capacity for individual tests to distinguish MS vs. control status

Test	Not accounting for age			Accounting for age		
	OR	95% CI	p-value	OR	95% CI	p-value
Timed 25-foot walk	1.09	0.90–1.31	0.39	1.05 [*]	0.86–1.28 [*]	0.63 [*]
9 hole peg test	0.99	0.88–1.12	0.93	1.35	1.10–1.65	0.004
Children's Paced Auditory Serial Addition Task	0.95	0.88–1.03	0.23	0.53	0.25–1.13	0.10
Symbol Digit Modalities Test	0.99	0.96–1.03	0.68	0.84	0.75–0.93	0.001
Binocular low-contrast letter acuity (Sloan, 1.25% contrast)	0.92	0.85–0.99	0.03	0.93	0.86–1.01	0.08

^{*} Also adjusted for height

Table 3

Ability of the MSFC to distinguish patients pediatric MS vs. healthy controls

Test	Components	OR	CI	P value
MSFC	T25W, 9-HPT, ChiPASAT	0.56	0.19–1.60	0.23
MSFC-3-SDMT	T25W, 9-HPT, SDMT	0.72	0.51–1.00	0.05
MSFC-3-LCLA	T25W, 9-HPT, BinLCLA-1.25%	0.72	0.50–1.04	0.08
MSFC-4	T25W, 9-HPT, ChiPASAT, BinLCLA-1.25%	0.81	0.57–1.16	0.25
MSFC-4-SDMT	T25W, 9-HPT, SDMT, BinLCLA-1.25%	0.89	0.80–1.00	0.04
MSFC-5	T25W, 9-HPT, ChiPASAT, SDMT, BinLCLA-1.25%	0.31	0.06–1.74	0.18