The Multiple Sclerosis Inventory of Cognition for Adolescents (MUSICADO): A brief screening instrument to assess cognitive dysfunction, fatigue and loss of health-related quality of life in pediatric-onset multiple sclerosis

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Abbreviations

ADEM	acute disseminated encephalomyelitis
BICAMS	Brief International Cognitive Assessment for MS
BNBC	Brief Neuropsychological Battery for Children
BVMTR	Brief Visual Memory Test-Revised
CI	cognitive impairment
HCs	healthy controls
HRQoL	Health-Related Quality of Life
MUSIC	Multiple Sclerosis Inventory of Cognition
MUSICADO	Multiple Sclerosis Inventory of Cognition for Adolescents
MS	multiple sclerosis
PedsQL™ 4.0	Pediatric Quality of Life Inventory™ version 4.0
POMS	pediatric-onset multiple sclerosis
ROF	Rey-Osterrieth Figure
RWT	Regensburger Wortflüssigkeitstest
SDMT	Symbol Digit Modalities Test
TMT	Trail Making Test
VLMT	Verbaler Lern-und Merkfähigkeitstest

1. Introduction

Neurocognitive dysfunction, fatigue and loss of HRQoL have become a new focus in the care of patients with pediatric-onset multiple sclerosis (POMS) as they occur in a substantial amount of patients with POMS at an early stage of the disease.[1–3] As they have an impact on academic performance, social interactions and development,[2,4,5] they should be evaluated in clinical routine. One possibility is to perform a comprehensive neuropsychological evaluation and specific questionnaires, which would require substantial time resources with additional burden on patients and caregivers. A more targeted approach would be to use a brief screening tool covering the most affected domains in patients with POMS. There is, however, currently no gold standard for cognitive screening of patients with POMS. Several instruments, such as the Symbol Digit Modalities Test (SDMT),[6] the Brief Neuropsychological Battery for Children (BNBC),[7] the Brief International Cognitive Assessment for MS (BICAMS)[8] and the SDMT in combination with the Brief Visual Memory Test-Revised (BVMTR)[9,10] have been recommended as screening tools. However, the use of these screening tools in patients with POMS are limited by missing validation,[6–9] missing of cut-scores,[6–9] not covering important cognitive domains, such as executive functioning and language[6–9] and by a relative long administration time.[7] Furthermore, interpretation of the results of these published studies is limited by small and heterogeneous sample sizes.[6,8,9]

On the basis of the aforementioned considerations, the aim of our study was to design a brief and easy to use screening instrument "MUSICADO" for patients with POMS in order to assess cognitive dysfunction, fatigue and loss of HRQoL on the basis of established test paradigms and to provide cut-scores for dysfunctions in these areas. For this purpose, patients with POMS and HCs underwent a neuropsychological test battery, that included MUSIC,[11] a screening instrument developed for adults and eight standardized and validated neuropsychological tests for children. Additionally, fatigue and HRQOL were evaluated with a well-known pediatric questionnaire.

2. Methods

2.1. *Subjects*

In this cross-sectional study, patients with POMS were enrolled by 20 German and 2 Austrian Neuropediatric Departments of University Hospitals and HCs by 6 German centers. Inclusion criteria for the patients were diagnosis of MS according to the McDonald criteria 2010[12] and age between 12 and 18 years. HCs were included if they were between 12 and 18 years old. Patients were excluded if they had any other demyelinating disease than MS such acute disseminated encephalomyelitis (ADEM). Patients and HCs were also excluded if they didn't speak or understood the German language, if they had a temperature > 37.5 °C, a history of any other neurological or psychiatric disease or neurological or psychiatric symptoms or illness that would preclude them from testing or if they had been subjected to a neuropsychological testing up to one year before the study.

Recruitment for HCs was stratified for age (12–18 years) and education (secondary school and grammar school). In each age level, 15 HCs were recruited who attended secondary school and 15 HCs who attended grammar school ($n = 210$, 7 groups).

Ethical approval was obtained on all sites and written consent was obtained from all subjects and parents.

2.2. *Measures*

Cognition was evaluated with the MUSIC[11,13] and an elaborate cognitive test battery of eight standardized and validated tests in German language. The cognitive part of the MUSIC consists of 5 subtests assessing verbal short- and long-term memory [immediate recall of word list A (MUSIC word list A), immediate recall of word list B (MUSIC word list B), delayed recall of word list A (MUSIC World list A delayed)], fluency of language, attention, working memory, and cognitive flexibility (alternating semantic verbal fluency task; MUSIC verbal fluency), naming and speed of processing [Stroop-Test with naming (MUSIC Stroop Test) and susceptibility to interference (MUSIC Stroop–Interference Test)]. Scores of each test are presented as raw data.

Verbal short- and long-term memory were assessed with the Verbaler Lern-und Merkfähigkeitstest (VLMT),[14] verbal short-term span and working memory with the Digit Span Forward and Backward and non-verbal short-term span and working memory with the Corsi Block Tapping Test both from the revised version of the German version of the Wechsler Memory Scale.[15] Executive functioning and phonemic and semantic verbal fluency were evaluated with the subtests "s-words" and "animals" of the Regensburger Wortflüssigkeitstest (RWT).[16] Cognitive speed and attention were evaluated with the Trail Making Test A (TMT-A) and set-shifting as an executive function with the Trail Making Test B (TMT-B).[17] For better handling, we decided to use the adult version of the TMT-A and TMT-B for all participants and generated new reference values according to the scores of HCs. Divided attention and motor speed was evaluated with the SDMT[18] and visuo-constructive abilities and non-verbal long-term memory with the Rey-Osterrieth Figure (ROF and ROF delayed), respectively.[17]

For the VLMT,[14] RWT,[16] the SDMT,[18] ROF[17] and ROF delayed[17] reference scores for children were available. For the Digit Span, Block Tapping test, TMT-A and TMT-B, reference values were obtained from the scores of HCs. For this purpose, raw data were calculated for each age group, analyzed for an age effect and grouped according to the results. On this basis, reference values for the Digit Span and Block Tapping Test were obtained for individuals 12–14 years old and for 15–18 years old, while for the TMT-A and TMT-B they were defined for individuals aged 12–14 years, 15–17 years, and 18 years.

Following previous work, the cut-off score for test failure was determined for a performance of −1.5 SD or below,[1,5] a T-score of 40 or below (VLMT),[14] and the 15th percentile or below age-related reference percentiles (RWT).[16] Cognitive impairment was defined as failing in at least 3 tests on the elaborate test battery, as suggested in previous studies.[1,2,5]

Quality of life was measured with the German version of the Pediatric Quality of Life Inventory™ version 4.0 [PedsQL™ 4.0] Generic Core Scale child and adolescent self-report form (8–12 years, 13–18 years).[19,20] All questionnaires were evaluated according to the PedsQL-scoring guidelines and have been reported previously.[21] The questions ask how much of a problem each item has been during the past four weeks on a 5-point-likert-scale. The scores were linearly transformed to a 0–100 scale, higher scores indicating a better HRQoL.

Fatigue was evaluated with the German version of the PedsQL™ Multidimensional Fatigue Scale using the child and adolescent self-report form (8–12 years, 13–18 years).[22] The format, instructions and scoring algorithm are identical to the PedsQL™ 4.0 Generic Core Scale with higher scores indicating lower fatigue symptoms.

Dimensions to screen fatigue and HRQoL were extracted from the PedsQL™ Multidimensional Fatigue Scale and from the PedsQL™ Generic Core Scale, respectively.

The cut-off scores for the screening version of the PedsQL™ Multidimensional Fatigue Scale and for the PedsQL™ 4.0 Generic Core Scale were done by face validity. In a first step the dimensions with the highest effect size of each scale were extracted from the original tests. In a second step, cut-scores were calculated among all participants according to the classifications of mild and severe fatigue and mild and severe loss of HRQoL.[3]

The testing was administered on a single day by a neuropsychologist and was conducted in the same order for all subjects. The total administration time for the full assessment was approximately 2 h.

2.3. *Statistics*

Data are indicated as means and *SD* or median with range. Comparisons of subject's characteristics and cognitive functions were analyzed by Student's *t*-test or Mann-Whitney-U test depending on data distribution tested with the Kolmogorov–Smirnov test. Effects of school type on cognition were also tested with the student's *t*-test within the two groups. Comparisons of relative frequencies were done with Chi-square analysis.

Construction of the cognitive part of the MUSIC*ADO* was performed according to published statistical steps that are required for the development of such a screening instrument with an age and education correction (Kalbe 2013). Relationships between cognitive test data including tests for construct validity and between cognitive performance, age and education were analyzed with Pearson correlations.

Effect sizes for the dimensions of the fatigue and the HRQoL scales were calculated as published previously.[23]

Data analysis was conducted using the IBM SPSS version 25.0 (IBM Corp.,Armonk, NY, USA, 2013).

3. Results

3.1. *Sample characteristics*

Between June 2012 und January 2015 a total of 106 patients with POMS and 210 HCs were enrolled. Characteristics of the sample are summarized in Table 1. All patients presented with a relapsing-remitting disease course. Neuropsychological test performance in patients with POMS was significantly lower

Table 1 – Characteristics of the study sample.

Characteristics	MS, $n = 106$	HCs, $n = 210$	p
Mean age (SD)	15.71 (1.63)	15.00 (2.0)	0.003*
Female gender, n (%)	76 (71.7)	95 (45.2)	0.000***
Type of school			
Secondary school	55 (51.9%)	97 (46.2)	0.343***
Grammar school	51 (46.2%)	113 (53.8%)	
Self-reported fatigue			
Mean general fatigue scale score (SD)	63.15 (25.73)	77.64 (17.83)	0.000*
Mean sleep/rest fatigue scale score (SD)	55.46 (21.69)	63.15 (19.16)	0.000*
Mean cognitive fatigue scale score (SD)	65.99 (26.36)	74.52 (20.76)	0.000*
Self-reported HRQoL			
Mean physical health scale score (SD)	74.62 (22.1)	86.67 (13.64)	0.000*
Mean emotional functioning scale score (SD)	63.35 (24.89)	71.9 (21.21)	0.000*
Mean social functioning scale score (SD)	88.73 (17.01)	91.96 (12.66)	0.000*
Mean school functioning scale score (SD)	58.15 (24.74)	71.88 (19.14)	0.000*
Mean age at onset in years (SD)	14.1 (2.4)		
Range	(4–18)		
Mean MS-duration (SD)	18.6 (23.7)		
Range, months	(0–152)		
Mean number of relapses since onset (SD)	1.9 (2.0)		
Range	(0–10)		
Mean EDSS score (SD)	0.65 (1.09)		
Range	(0–7.5)		
Disease modifying drug, n (%)	77 (72.6%)		

MS: multiple sclerosis; HCs: healthy controls; SD: standard deviation; Fatigue scores were derived from the PedsQL™ Multidimensional Fatigue Scale (HCs:$n = 209$). HRQoL scores were derived from the PedsQL™ Generic Core Scale (HCs: $n = 209$). *Mann–Whitney U-test; **t-test; ***χ^2-test.

than in HCs for the phonemic verbal fluency tasks (MUSIC verbal fluency, RWT "s-words"), for the TMT-A and the Digit Span Forward (Table 2). Interestingly, patients performed significantly better in the MUSIC Stroop Test than HCs (Table 2). Patients with POMS experienced significant more fatigue and loss of HRQoL across all self-reported scales (Table 1).

Table 2 – Neuropsychological testing.

	MS, $n = 106$, mean (SD)	HCs, $n = 210$, mean (SD)	p
MUSIC word list A	14.2 (2.6)	13.9 (2.6)	n.s
MUSIC word list B	5.5 (1.4)	5.3 (1.4)	n.s.
MUSIC verbal fluency	13.7 (3.1)	14.5 (1.9)	n.s.
MUSIC stroop (s)	22.1 (4.4)	23.3 (3.8)	n.s.
MUSIC stroop-interference (s)	27.9 (7.4)	29.4 (6.9)	n.s.
MUSIC word list A delayed	5.4 (2.1)	5.4 (2.1)	n.s.
VLMT-total sum of word list A (T-score)	54.65 (12.23)	54.35 (13.92)	n.s
VLMT-list A delayed recall (T-score)	55.02 (11.43)	55.77 (12.72)	n.s.
Digit span forward (z-score)	−0.57 (1.01)	0.00 (1.05)	0.000*
Digit span backward (z-score)	−0.03 (1.01)	−0.00 (1.0)	n.s.
Digit span total (z-score)	−0.35 (1.04)	0.00 (0.99)	0.004*
Block tapping test forward (z-score)	0.06 (1.07)	−0.001 (0.99)	n.s.
Block tapping test backward (z-score)	−0.17 (1.11)	0.00 (1.03)	n.s
Block tapping test total (z-score)	−0.045 (1.10)	−0.00 (1.0)	n.s.
ROF-copy (z-score)	−0.69 (1.74)	−0.32 (1.24)	n.s
ROF-delayed copy (z-score)	−0.32 (1.24)	−0.57 (1.03)	n.s.
TMT-A (z-score)	−0.5 (1.52)	0.000 (0.99)	0.000*
TMT-B (z-score)	−0.23 (1.36)	0.0001 (0.99)	n.s.
SDMT (z-score)	0.34 (1.38)	0.52 (1.34)	n.s.
RWT "s-words" at 2 min (percentile rank)	40.4 (28.64)	53.04 (28.99)	0.000**
RWT "animals" at 2 min (percentile rank)	28.65 (24.29)	34.43 (22.53)	n.s.

Results of the single tests of the elaborate neuropsychological battery. MS: multiple sclerosis; MUSIC: Multiple Sclerosis Inventory of Cognition; VLMT-total word list A: Verbaler Lern-und Merkfähigkeitstest subtest "Total sum of word list A"; VLMT word list A delayed: Verbaler Lern-und Merkfähigkeitstest subtest "Delayed recall of word list A after 30 min"; ROF-Copy: copy of the Rey-Osterrieth figure; ROF-delayed copy: recall of the Rey-Osterrieth figure after 30 min. TMT-A: Trail Making Test-A; TMT-B: Trail Making Test-B; SDMT: Symbol Digit Modalities Test; RWT "S-words": Regensburger Wortflüssigkeitstest naming of words with the letter "S"; RWT "animals": Regensburger Wortflüssigkeitstest naming of animals. The alpha level was corrected using the Bonferroni method to $\alpha = 0.003$. *t-test, **Mann–Whitney-U test.

3.2. *Validity of cognitive test scores*

To validate test performance in redundant test paradigms convergent construct validity between the MUSIC subtests and the elaborate test battery was analyzed in the patient group. The results of the MUSIC word list A task and MUSIC word list B task correlated significantly with the T-score of the "total sum of the word list" task of the VLMT (list A: $r = 0.509$, $p < 0.001$; list B: $r = 0.350$, $p < 0.001$) and with T-score of the „delayed recall of word list A task of the VLMT (list A: $r = 0.451$, $p < 0.001$; list B: $r = 0.256$, $p < 0.001$). The results of the MUSIC verbal fluency task correlated significantly with the percentile rank of the RWT "s-words" ($r = 0.320$, $p < 0.001$) and of the RWT "animals" ($r = 0.351$, $p < 0.001$). The results of the MUSIC Stroop Test correlated significantly with the z-score of the TMT-A ($r = -0.310$, $p < 0.001$) and the z-score of the TMT-B ($r = -0.311$, $p < 0.001$). The results of the MUSIC Stroop–Interference Test correlated significantly with the z-score of the Digit Span Backward task ($r = -0.449$, $p < 0.001$).

3.3. *Constructing the MUSICADO*

After dichotomizing test data of all cognitive tests (normal versus impaired), the three tests in which performance was also significantly lower in patients than HC were the most frequently impaired: RWT "s-words" (24.5%), followed by the TMT-A (17.9%) and the Digit Span Forward (15.1%). Therefore, these three tests were selected for the cognitive part of the brief screening tool "MUSIC*ADO*". Following previous developments of screening tests, we defined a scoring procedure in which raw scores were converted into transformed scores with comparable "weights" in terms of maximum scores for all three subtests.[11] It was defined that mean scores of the HCs should be given the maximum score, while 2 SD below the mean score of the HCs should be given 0 point. Therefore, the mean reference score, −0.5 SD, −1 SD, −1.5 SD and −2 SD were assigned 4, 3, 2, 1, and 0 points, respectively, resulting in a total cognitive test score of 0–12 points. Dependency of test scores from age, education or sex was analyzed in HCs.[11] An age correction was necessary for the verbal fluency task with the letter "S" and the TMT-A, as both tests correlated with age (RWT "s-words": $r = 0.271$, $p < 0.001$; TMT-A: $r = -0.306$, $p < 0.001$). Two age groups were defined on the basis of the HC data for the scoring scheme (12–15 years, 16–18 years), which was performed following the scheme described above (Table 3). An education effect was shown for all three tests (RWT "s-words": $p < 0.001$; Digit span: $p = 0.009$; TMT-A: $p = 0.021$), thus that it was decided to define an education correction for the final total score. As the descriptive difference for individuals with lower (secondary school) versus higher education (grammar school) was around 1 point, it was decided to operationalize the education correction by adding 1 point for individuals with lower education (secondary school). The analysis of the resulting total score showed that correction for age (TMT-A: $r = -0.38$, $p = 0.58$; Digit Span Forward: $r = 0.088$, $p = 0.205$; RWT "s-words": $r = 0.036$, $p = 0.608$) and correction for education was finally successful (patients: $p = 0.138$; HCs: $p = 0.066$), as significant correlations were not found any more.

The cut-off score for impairment for the total test score was defined to be set at 1.5 SD below the mean score of HCs,[11] which was a score of ≤8. The resulting final transformed total score was significantly lower in patients with POMS (M: 9.01, SD: 2.80) in comparison to the score of HCs (M: 10.55, SD: 1.87; $p = 0.000$). 35.8% of patients with POMS were identified to be cognitively impaired compared to 11% of HCs (Table 4). In comparison 28.5% of patients with POMS were deemed cognitively impaired compared to 15.2% of HCs ($p = 0.007$) based on all 8 standardized tests. The resulting specificity of the MUSIC*ADO* was 88.6%. It was not possible to analyze sensitivity in the strict sense, as the neuropsychological battery included the tests, which are now part of the MUSIC*ADO* and no (non-circular) external standardized criterion was available. The evaluation reliability of the MUSIC*ADO* was analyzed in 30 patients and was $r = 0.998$ ($p < 0.001$).

We extracted all 6 questions of the "General Fatique Scale" from the PedsQL™ Multidimensional Fatigue Scale questionnaire for the MUSIC*ADO* screening version for fatigue on the basis of the highest effect size of 0.81. For interpretation of the screening version, raw scores (0–4) of all 6 answers are added (max. 24 points). Scores lower than ≤4 indicate no fatigue, scores between 5 and 9 mild fatigue and scores between 10 and 24 severe fatigue. With the screening version patients with POMS were diagnosed significantly more often with mild and severe fatigue than HCs (mild: 18.1% vs. 9.8%, severe: 19.0% vs. 2.0%; $\chi^2 = 36.543$, $p < 0.000$). The Total Scale Score of the PedsQl™ Multidimensional Fatigue Scale correlated significantly with the score of the screening version ($r = 0.764$,

Table 3 – MUSIC*ADO* transforming procedure for the individual cognitive tests.

Verbal fluency, s-words (12–15 years)					
Raw scores	≤9	10–11	12–14	15–17	≥18
Transformed scores	0	1	2	3	4
Verbal fluency, s-words (16–18 years)					
Raw scores	≤10	11–13	14–16	17–19	≥20
Transformed scores	0	1	2	3	4
TMT-A (12–15 years)					
Raw scores	≥47	42–46	38–41	33–37	≤32
Transformed scores	0	1	2	3	4
TMT-A (16–18 years)					
Raw scores	≥37	33–36	30–32	27–29	≤26
Transformed scores	0	1	2	3	4
Digit span forward (12–18 years)					
Raw scores	≤4	5	6	7	≥8
Transformed scores	0	1	2	3	4

Table 4 – Rates of cognitive impaired individuals according to the MUSIC*ADO* and the neuropsychological battery.

	Diagnosis of cognitive impairment	
	MS, *n* (%)	HCs, *n* (%)
MUSIC*ADO*		
Cut-off ≥ 8	38 (35.8%)	24 (11.4%)
Neuropsychological battery		
≥3 tests under 1.5 SD	30 (28.5%)	32 (15.2%)

SD: standard deviation.

$p < 0.001$). The cut-off point ≥ 4 yielded a specificity of 0.94 (95% CI: 0.90–0.97). The positive predictive value for the screening version of fatigue is 0.87 (95% CI: 0.72–0.95) and the negative predictive value is 0.88 (95% CI: 0.77–0.94) for patients, respectively.

We extracted all 13 questions of the dimensions "Physical Health" and "School functioning" from the PedsQL™ Generic Core Scale for the HRQoL screening version as they showed the highest effect sizes of 0.88 and 0.72, respectively. Scores of all 13 questions were added (max. 52 points). Scores lower than 19 indicate no loss of HRQoL, scores between 19 and 25 mild loss of HRQoL and scores between 26 and 52 severe loss of HRQoL. According to the HRQoL screening version patients with POMS experienced more often mild loss and severe loss of HRQoL compared to HCs (mild: 21.4% vs. 12.2%, severe: 20.4% vs. 2.4%; $\chi^2 = 35.441$, $p < 0.000$). The Total Scale Score of the PedsQl™ Generic Core Scale correlated significantly with the score of the HRQoL screening version ($r = 0.955$, $p < 0.001$). The cut-off score lower than 19 yielded a specificity of 0.96 (95% CI: 0.91–0.98). The positive predictive value is 0.98 (95% CI: 0.86–0.99), the negative predictive value is 0.93 (95% CI: 0.83–0.98) for patients.

4. Discussion

Cognitive dysfunction, fatigue and loss of HRQoL in patients with POMS are common and can have considerable effects on school performance, activities of daily living and disease management. Therefore, assessment of these relevant domains should be part of the clinical routine.

The aim of this study was to identify test paradigms that are highly sensitive to detect cognitive dysfunction in patients with POMS, to combine them to a cognitive screening instrument, provide a well-balanced total score which is independent from age- and education and to provide a cut-off score for impairment according to previously published standardized procedures.[11] Furthermore, we aimed to extract questions from well-known pediatric scales to be able to screen for fatigue and loss HRQoL and present cut scores in order to classify patients as not, mildly and severely fatigued and with no loss, mild loss and severe loss of HRQoL. In addition, these data were examined in a cohort of patients with similar clinical characteristics to those reported in the literature.[3,24]

Regarding the cognitive screening, we identified three neuropsychological tests, the phonemic verbal fluency task with the letter "S", the TMT-A and the Digit Span Forward, from an elaborate test battery that were suitable to indicate cognitive impairment well and that were selected for the cognitive part of the MUSIC*ADO*. According to the well balanced sensitivity of the tests, all three of them were weighted equally. As the sociodemographic variables age and education were related to cognitive performance, we also defined a correction for both variables. To our knowledge, aspects of balanced weighting of subtests and correction for age and education have not been considered in any of the other reported screening instruments for patients with POMS.

Importantly, all three cognitive tests selected for the MUSIC*ADO* cover the most important cognitive domains that are possibly affected in patients with POMS even at an early stage of the disease: phonemic verbal fluency, executive functioning, attention, cognitive speed, verbal span and working memory. Deficits in these domains may have an impact on activities such as listening to lengthy instructions, organization of unstructured assignments, and generation of novel ideas. These skills are increasingly needed in higher academic grades and correlate with clinical observations of declining school performance.[25]

We decided to choose the phonemic verbal fluency task with the letter "S" as it was sensitive and evaluates expressive language as well as cognitive speed and executive function. Language impairment is the most peculiar finding in POMS compared to adult MS.[2] This might be explained by the fact, that children's developing brains are still cultivating necessary linguistic skills.[26] Besides difficulties with complex language functions, difficulties in language skills involving speed such as verbal fluency seem to be evident in patients with POMS.[27,28] Furthermore, executive function in terms of cognitive flexibility and planning is also affected in patients with POMS[2,5] and is covered by the phonemic verbal fluency task with the letter "S". Not surprisingly, we identified more than one fourth of patients with POMS that showed impairment in the verbal fluency task. This underlines the importance of including this test in our screening tool. Until now, none of the published screening instruments considered measurement of verbal fluency in order to cover a broad spectrum of important domains in POMS.

As a second subtest for the cognitive part of the MUSIC*ADO* we included the TMT-A as performance in this test differed significantly between patients and HCs. The TMT-A evaluates attention and information processing, domains that are also frequently affected in patients with POMS.[28,29] It has been hypothesized that deficits appear to emerge very early in the course of the disease, which might be explained by an early onset of disruption of white matter structure by ongoing inflammation and demyelination in patients with POMS.[1,30] Almost one fifth of all patients failed this test, a rate that has also been reported previously.[29]

As a third cognitive subtest of the MUSIC*ADO*, the Digit Span Forward was included. Poor Digit Span performance may reflect a core deficit in verbal span and working memory. Verbal span, defined as memory capacity, recruits the phonological loop, involves short-term storage and rehearsal.[31] Performance in this test also differed significantly from that of HCs and indicated impairment in 15% of the patients. In adults with MS, Digit Span deficits are also observed in only mildly disabled MS patients who are early in the course of the disease and may be absent in other patients who are much more seriously disabled.[32] Until now, only one pediatric study reported a lower rate of failure, which might be due to a small study population.[29]

Interestingly, we did not observe any deficits in verbal and visual memory, both immediate and delayed, measured with the VLMT, ROF and the MUSIC subtests. Impairment of these domains seems to occur with longer disease duration and is therefore discussed controversially with different rates in patients with POMS.[2,27,28,33,34] Therefore, evaluation of memory seems not to be an appropriate domain to screen cognitive impairment at an early stage of the disease.

Despite the wide use of the SDMT as a cognitive assessment tool in pediatric MS patients,[1,6,7,35] the SDMT did not differentiate between MS patients and HCs in our study. This indicates that certain characteristics of the study population, such as young age or short disease duration, might have an impact on SDMT performance and its discriminative effect to detect cognitive impairment. Nonetheless, our results are in accordance with the results of other studies.[2,36] One can assume that after a longer period of illness this test is more suitable for identifying a cognitive deficit.

35% of patients were identified to be cognitively impaired according to our screening tool. This proportion is within the reported range for cognitive impairment in patients with POMS.[1,2,4]

However, sensitivity in the strict sense could not be calculated for the cognitive part, as there would have been a considerable overlap of tests included in the MUSIC*ADO* with the extensive battery, which was implemented to derive reliable information. Therefore, although it is evident that the most sensitive tests were used for the screening tool, further studies will have to confirm the high sensitivity and specificity of the instrument.

We were able to identify fatigue with the screening version in a significant proportion of patients with POMS in comparison to HCs, which is consistent with published rates of self-reported fatigue in POMS.[35] The screening version extracted questions of the General Fatigue Scale that covers the most important questions to detect fatigue in patients with POMS. For the first time, we also provide cut-off scores to classify the severity of fatigue. Classification of fatigue might help to decide for possible treatment interventions. On this basis, non-pharmacological and pharmacological interventions can be considered and monitored.

Measurement of HRQoL has been suggested to constitute a more comprehensive measure than disability scales in assessing the burden of disease.[36] For the screening version we extracted the physical dimension and school dimension from the PedsQL™ Generic Core Scale as these scales are predominantly affected in patients with POMS in comparison to the social and emotional dimension.[37,38] We were able to detected loss of HRQOL in patients which is within the reported range.[3,29,37–40] We also provide cut-off scores for the HRQoL questionnaire in order to classify patients with POMS according to the severity level for the first time. This might help clinicians to estimate the extent of the disease burden better.

Some limitations have to be mentioned when interpreting the results of our study. Most importantly, no external validation criteria for the three parts of the MUSIC*ADO* were available, so that future studies will have to confirm the sensitivity of the tool in German MS patients and even in other cohorts with different languages. Since screening tools for MS patients have just been independently developed within a respective consortium, the longer term objective in developing such a screening instrument is that it can be used in a wider cohort and across countries in order to screen MS patients or be part of drug trials.

Furthermore, as there is a lack of neuropsychological tests with reference scores that cover the age span of 12–18 years, we had to obtain reference values for the Digit span, Block-tapping test, TMT-A and TMT-B from values of our own HCs with a rather limited number of individuals for each age and education group.

The strength of this study is that we were able to include a large cohort of patients with POMS and one of the largest cohort of age and education matched HCs. Furthermore, we present a screening tool specifically tailored for MS-specific deficits in patients with POMS at the age 12–18 that provides age and education corrected scoring with clear cut-off values for impairment.

5. Conclusion

In summary, the results of our study show that MUSIC*ADO* is a valid and useful assessment tool to detect cognitive impairment, fatigue and loss of quality of life in patients with POMS in the age range from 12 to 18 years. Importantly, we present age and education corrected scores to define cognitive impairment for the first time. Patients with POMS that are early identified with CI should be further assessed and confirmed by an extensive neuropsychological testing. According to the questionnaires of the MUSIC*ADO*, we are also able to classify patients' fatigue and loss of HRQoL. MUSIC*ADO* fulfills all criteria of a screening tool, as it is easy to administer, does not take longer than 15 min, is easy to score, tests important domains of cognition and is independent of age and education.[11] Furthermore this screening tool is objective and valid. Further studies are needed in order to validate MUSI*CADO* by other external criteria and to evaluate its clinical feasibility. Finally, longitudinal assessment with this instrument may provide more information on the patient's disease course regarding cognition, fatigue and HRQoL.

Authors's contributions

KSVG, PC, AB, VM, PH, JK, EK designed the study. KSTVG performed data collection. KSVG, LR, JK and EK performed data analyses. KSVG and EK drafted the manuscript. All authors interpreted the data and contributed to editing the manuscript.

Declaration of conflicting interests

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Ethics approval and consent to participate

Ethical approval was received from the ethical committees of all participating study-sites and written consent was obtained from all subjects and parents.

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Appendix A. Colaborators

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REFERENCES

1. Till C, Ghassemi R, Aubert-Broche B, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. *Neuropsychology* 2011;**25**(3):319–32.
2. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 2008;**70**(20):1891–7.
3. MacAllister WS, Christodoulou C, Troxell R, et al. Fatigue and quality of life in pediatric multiple sclerosis. *Mult Scler* 2009;**15**(12):1502–8.
4. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. *Neurology* 2005;**64**(5):891–4.
5. MacAllister WS, Christodoulou C, Milazzo M, Krupp LB. Longitudinal neuropsychological assessment in pediatric multiple sclerosis. *Dev Neuropsychol* 2007;**32**(2):625–44.
6. Charvet LE, Beekman R, Amadiume N, Belman AL, Krupp LB. The symbol digit modalities test is an effective cognitive screen in pediatric onset multiple sclerosis (MS). *J Neurol Sci* 2014;**341**(1–2):79–84.
7. Portaccio E, Goretti B, Lori S, et al. The brief neuropsychological battery for children: a screening tool for cognitive impairment in childhood and juvenile multiple sclerosis. *Mult Scler* 2009;**15**(5):620–6.
8. Charvet LE, Shaw M, Frontario A, Langdon D, Krupp LB. Cognitive impairment in pediatric-onset multiple sclerosis is detected by the brief international cognitive assessment for multiple sclerosis and computerized cognitive testing. *Mult Scler* 2018;**24**(4):512–9.
9. Smerbeck AM, Parrish J, Serafin D, et al. Visual-cognitive processing deficits in pediatric multiple sclerosis. *Mult Scler* 2011;**17**(4):449–56.
10. Smerbeck AM, Parrish J, Yeh EA, et al. Regression-based pediatric norms for the brief visuospatial memory test: revised and the symbol digit modalities test. *Clin Neuropsychol* 2011;**25**(3):402–12.
11. Kalbe E, Calabrese P, Fengler S, Kessler J. DemTect, PANDA, EASY, and MUSIC: cognitive screening tools with age correction and weighting of subtests according to their sensitivity and specificity. *J Alzheimer's Dis* 2013;**34**(4):813–34.
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;**69**(2):292–302.
13. Calabrese P, Kalbe E, Kessler J. Ein neuropsychologisches Screening zur Erfassung kognitiver Störungen bei MS-Patienten. Das Multiple Sklerose Inventarium Cognition (MUSIC). *Psychoneuro* 2004;**30**(7):384–8.

14. Helmstaedter C, Lendt M, Lux S. *Verbaler Lern- und Merkfähigkeitstest*. Göttingen: Beltz Test GmBH; 2001.
15. Härting C, Markowitsch HJ, Neufeld H, Calabrese P, Dreisinger K, Kessler J. *Wechsler Gedächtnistest-Revidierte Fassung (WMS-R)*. Bern: Huber; 2000.
16. Aschenbrenner S, Tucha O, Lange KW. *RWT Regensburger Wortflüssigkeits-test*. Göttingen: Hogrefe; 2000.
17. Strauss E, Sherman EMS, Spreen O. *A compendium of neuropsychological tests: administration, norms, and commentary*. New York: Oxford University Press; 2006.
18. Smith A. *The symbol digit modalities test manual*. Los Angeles: Western Psychological Services; 1982.
19. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;**39**(8):800–12.
20. Felder-Puig R, Frey E, Proksch K, Varni JW, Gadner H, Topf R. Validation of the German version of the pediatric quality of life inventory (PedsQL) in childhood cancer patients off treatment and children with epilepsy. *Qual Life Res* 2004;**13**(1):223–34.
21. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;**3**(6):329–41.
22. Varni JW, Burwinkle TM, Szer IS. The PedsQL multidimensional fatigue scale in pediatric rheumatology: reliability and validity. *J Rheumatol* 2004;**31**(12):2494–500.
23. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 generic core scales. *Health Qual Life Outcomes* 2007;**5**:2.
24. Charvet LE, O'Donnell EH, Belman AL, et al. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US pediatric multiple sclerosis network. *Mult Scler* 2014;**20**(11):1502–10.
25. Suppiej A, Cainelli E. Cognitive dysfunction in pediatric multiple sclerosis. *Neuropsychiatr Dis Treat* 2014;**10**:1385–92.
26. Tan A, Hague C, Greenberg BM, Harder L. Neuropsychological outcomes of pediatric demyelinating diseases: a review. *Child Neuropsychol* 2018;**24**(5):575–97.
27. MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005;**64**(8):1422–5.
28. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology* 2010;**75**(13):1134–40.
29. Holland AA, Graves D, Greenberg BM, Harder LL. Fatigue, emotional functioning, and executive dysfunction in pediatric multiple sclerosis. *Child Neuropsychol* 2014;**20**(1):71–85.
30. Longoni G, Brown RA, MomayyezSiahkal P, et al. White matter changes in paediatric multiple sclerosis and monophasic demyelinating disorders. *Brain* 2017;**140**(5):1300–15.
31. Baddeley A. Working memory: theories, models, and controversies. *Annu Rev Psychol* 2012;**63**:1–29.
32. Beatty WW, Paul RH, Blanco CR, Hames KA, Wilbanks SL. Attention in multiple sclerosis: correlates of impairment on the WAIS-R digit span test. *Appl Neuropsychol* 1995;**2**(3–4):139–44.
33. Fuentes A, Collins DL, Garcia-Lorenzo D, et al. Memory performance and normalized regional brain volumes in patients with pediatric-onset multiple sclerosis. *J Int Neuropsychol Soc* 2012;**18**(3):471–80.
34. Amato MP, Goretti B, Ghezzi A, et al. Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. *Neurology* 2014;**83**(16):1432–8.
35. Carroll S, Chalder T, Hemingway C, Heyman I, Moss-Morris R. Understanding fatigue in paediatric multiple sclerosis: a systematic review of clinical and psychosocial factors. *Dev Med Child Neurol* 2016;**58**(3):229–39.
36. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology* 1999;**53**(5):1098–103.
37. Self MM, Fobian A, Cutitta K, Wallace A, Lotze TE. Health-related quality of life in pediatric patients with demyelinating diseases: relevance of disability, relapsing presentation, and fatigue. *J Pediatr Psychol* 2018;**43**(2):133–42.
38. Mowry EM, Julian LJ, Im-Wang S, et al. Health-related quality of life is reduced in pediatric multiple sclerosis. *Pediatr Neurol* 2010;**43**(2):97–102.
39. Toussaint-Duyster LC, Wong YYM, Van der Cammen-van Zijp MH, et al. Fatigue and physical functioning in children with multiple sclerosis and acute disseminated encephalomyelitis. *Mult Scler* 2018;**24**(7):982–90.
40. Ketelslegers IA, Catsman-Berrevoets CE, Boon M, et al. Fatigue and depression in children with multiple sclerosis and monophasic variants. *Eur J Paediatr Neurol* 2010;**14**(4):320–5.