European Journal of Neurology 2014, 21: 1219–1225 doi:10.1111/ene.12463

The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis

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Keywords:
assessment of cognitive disorders, cognitive impairment, multiple sclerosis, sentinel test

Received 14 January 2014
Accepted 7 April 2014

Background and purpose: Cognitive impairment (CI) is found in about half of the multiple sclerosis (MS) population and is an important contributor to employment status and social functioning. CI is encountered in all disease stages and correlates only moderately with disease duration or Expanded Disability Status Scale scores. Most present neuropsychological test batteries are time-demanding and expensive. The Symbol Digit Modalities Test (SDMT) has been suggested as a screening tool for CI in MS. In this paper, we aim to assess the performance of the SDMT in predicting the outcome of an extensive battery.

Methods: Neuropsychological test results from 359 patients were assessed in a multidisciplinary MS center (National MS Center Melsbroek, Belgium). Using receiver operating characteristic curves, the performance of the SDMT in predicting the general cognitive outcome of the extensive Neuropsychological Screening Battery for MS (NSBMS) could be assessed. The performance of the SDMT was assessed for different levels of CI and compared with other cognitive tests. Finally, useful covariates were included in a logistic regression model.

Results: At a specificity of 0.60 a high sensitivity (0.91) was obtained indicating the potential of the SDMT as a sentinel test for CI in MS. The SDMT outperformed the individual tests included in the NSBMS, used as benchmark. As the logistic regression model did not result in a relevant improvement, it is concluded that most clinical variables influence both the SDMT and the NSBMS in a similar way. Excluding patients with possible practice effects, an optimal cutoff of 40 was found for the SDMT.

Conclusion: As the SDMT is an easy, low-cost and fast test, this result may help to detect CI in everyday clinical practice.

Introduction

Multiple sclerosis (MS) is the most frequently encountered disease of the central nervous system in young and middle-age adults [1] and affects about 2 million people worldwide. MS has a prevalence varying between 1 per 100 000 in equatorial countries up to 30–80 per 100 000 in Canada, northern Europe and the northern USA [2].

The prevalence of cognitive impairment in MS is estimated at 43%–47% in community based surveys [3,4] and between 54% and 65% in clinic based studies [5]. Most patients show cognitive impairment on information processing speed, sustained attention, memory and visuospatial perception [6,7]. Next to physical disability, cognitive impairment impacts significantly and independently on employment and social functioning [8–10].

Several batteries have been developed to detect cognitive impairment in MS. The Neuropsychological Screening Battery for MS (NSBMS) and the related Brief Repeatable Battery for Neuropsychological Testing [3] are probably the best known and most widely used batteries to detect cognitive impairment in MS. In 2002 a team of experts was convened which resulted in the development of the Minimal Assessment of Cognitive Functioning in MS (MACFIMS) [11], and recently the Brief International Cognitive Assessment for MS (BICAMS) has been developed [12,13]. These batteries test the different cognitive domains commonly affected by MS like recent memory, sustained attention, verbal

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fluency, visuospatial learning and information processing speed.

The disadvantage, however, is that most test batteries require a lot of time (0.5–2 h) to be administered. The BICAMS recommends the use of the Symbol Digit Modalities Test (SDMT) when only 5 min are available [13]. The SDMT is designed to measure mainly information processing speed. In many studies this test emerged as the test with the highest ability to discriminate healthy controls from MS patients [7,14–17]. However, only one paper was found to report the accuracy of detecting cognitive impairment within MS [18].

The results obtained by the SDMT are in concordance with other studies showing that information processing speed is a primary deficit in MS [19]. Parmenter *et al*. [18] were also the only ones to report receiver operating characteristic (ROC) curves which give a better sense of discriminability of the two groups (cognitively impaired, CI; cognitively preserved, CP). However, they did not compare the performance of the SDMT to other tests.

Although the SDMT has been reported as the most sensitive test when comparing healthy controls and MS patients, only little is known about its performance in detecting cognitive impairment within an MS population. In this paper the results (sensitivity, specificity, area under the curve) obtained by the SDMT when predicting the NSBMS on a large cohort of patients (358) are reported and compared with the results obtained by the other tests included in the NSBMS. It was the first SDMT measurement for all patients, and the influence of possible practice effects on the NSBMS was assessed by comparing the results obtained on the total cohort with the results obtained on the subgroup of patients who had not yet been assessed by the NSBMS.

Methods

Patient population

Patients with MS who attend inpatient and outpatient rehabilitation programs in the National MS Center Melsbroek (Belgium) are seen at regular time intervals for evaluation of their neuropsychological and neurological status and their medical treatment as well as for multidisciplinary care and/or rehabilitation. At the first visit, baseline demographic and clinical data are collected. During follow-up, functional assessments and Expanded Disability Status Scale (EDSS) measurements are repeatedly performed. All patients fulfilled the diagnosis of MS according to the Poser criteria [20]. The medical records of these patients were scrutinized for year and type of disease onset, time course (relapsing/progressive) and EDSS. The year of the first manifestation of neurological symptoms suggestive of MS was taken as the year of onset. These data are all stored in the Melsbroek EDMUS database [21].

Neuropsychological tests

The most important neuropsychological test included in this research was the SDMT, a test designed to assess information processing speed [22]. The more extensive battery was the NSBMS as proposed by Rao [23] and consists of the Paced Auditory Serial Addition Test (PASAT), the Controlled Oral Word Association Test (COWAT), the Selective Reminding Test (Controlled Long Term Retrieval, CLTR) and the 7/24 Spatial Recall Test (SPART).

Failure on one test was defined as obtaining a score under the 5th percentile of a normal population as reported in [23]. The NSBMS score was defined as the total number of tests passed by the subject (range 0–4). Failure on the NSBMS was defined as failing two or more tests of the battery. The data introduced in the analyses are the raw data (i.e. not corrected for age, education or gender). The effects of introducing confounding clinical parameters were investigated by logistic regression models.

Receiver operating characteristic curves

When predicting the outcome of a dichotomized scale (like a patient's cognitive status) using a continuous predictor, a frequently used method is the construction of an ROC curve. For every possible value of the predictor, the group of patients is divided into two groups. Those with a score below that cutoff will be denoted CI, above as CP patients. In this way one can calculate for every cutoff the true positives (CI patients who are also denoted CI), the true negatives (CP patients who are denoted CP), the false positives (CP patients who are falsely classified in the CI group) and the false negatives (the CI patients who are falsely classified in the CP group). Subsequently, for each cutoff, the sensitivity (the number of true positives divided by the total number of CI patients) and specificity (the number of true negatives divided by the total number of CP patients) can be calculated. Plotting sensitivity and specificity in one graph results in the ROC curve. An important parameter is the area under the curve (AUC). An AUC of 0.5 denotes mere chance, an AUC of 1 denotes that the predictor used can perfectly discriminate between CI and CP patients.

In general the AUC will be between 0.5 and 1. An optimal cutoff at which the predictor best predicts the cognitive state, however, is difficult to determine as higher cutoffs will always lead to higher sensitivity

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and lower specificity and maximizing the percentage of correctly classified patients is not always the main goal. Therefore the results obtained on the test set on sensitivity, specificity and percentage correctly classified for the cutoff that obtained a specificity of 0.6 and 0.65 in the training group are reported. This choice was made as it was desired to assess the ability of the SDMT as a sentinel test for cognitive impairment in MS. For the definition of the test and training groups, see the Statistics section.

Predicting the NSBMS outcome using the SDMT and the NSBMS tests

In a first analysis the performance of the SDMT and the performance of the tests included in the NSBMS battery in predicting a patient's cognitive status were compared.

Predicting adjusted NSBMS outcomes to avoid a positive bias effect

It is clear that the tests included in the NSBMS are positively biased as they also determine a patient's cognitive status. Therefore for each patient four additional NSBMS scores were calculated omitting one test at a time. Then, the performance of the SDMT was compared with the performance of the omitted test in predicting the adjusted NSBMS score.

Predicting different levels of cognitive impairment

Although our main aim was to investigate the performance of the SDMT in predicting the generally used definition of cognitive impairment (failing two or more tests on the NSBMS), it was also considered worthwhile to assess how this performance changes when different levels of cognitive impairment (as defined by the possible NSBMS outcome, i.e. 0–3) are used.

Confounding variables

When including other variables such as age, disease duration, onset type and EDSS score, the ROC curve cannot be calculated in the same way anymore. Therefore, these variables were included in a logistic regression model to see whether their inclusion could significantly influence our results.

Statistics

Cross-validation is an important tool for generalization of the results. Ten-fold cross-validation was applied, i.e. the total cohort was randomly divided into approximately 10 equal groups, the optimal cutoff score was calculated based on nine of the 10 groups (the so-called training data) and that cutoff was evaluated on the separate and independent group (the test group). All 10 groups were used as test data once and both test and training groups were assured to contain the same percentage of CI and CP patients (stratification). This procedure allows for an estimation of the accuracy of our results.

Ethics

According to the Belgian law of 7 May 2004 informed consent or approval by a local ethics committee is not needed for a study that concerns the review of clinical files under supervision of a member of the clinical team responsible for the patient, which was the case for our study.

Results

Patient population

A database was constructed restricted to complete neuropsychological measurements. There are currently 860 patients in our database who have been tested at least once. However, not all individual neuropsychological tests are repeated at every visit. Reasons are that the patient already failed a certain test several consecutive times or to avoid the influence of practice effects. Our neuropsychological team aims at assessing every patient every 2 years in order to be able to follow the patients' neuropsychological status whilst avoiding practice effects. From 2000 to 2012, complete data for 359 patients who underwent at least one complete neuropsychological testing (NSBMS and SDMT) could be obtained. The patient characteristics are summarized in Table 1. For all patients it was the first time to be administered the SDMT; 238 patients had had no previous NSBMS testing. The 359 patients were used for all analyses; when the results change by using only those 238 patients who have their first NSBMS assessment included this will be specified.

Predicting the NSBMS outcome using the SDMT and the NSBMS tests

The calculated ROC plots are shown in Fig. 1. The SDMT shows very high sensitivity (approximately 90%) at a low (but acceptable) specificity of 0.60. The SDMT outperformed the different tests in predicting the cognitive status even though the latter tests were positively biased.

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Table 1 Patient characteristics

	Total	RR	SP	PP
No. of subjects	359	144	132	60
Women/men	227/132	95/49	87/45	30/30
Age (SD)	49.4 (11.9)	44.2 (11.1)	52.3 (10.9)	55.9 (11.3)
Age at onset (SD)	34.0 (10.5)	33.7 (10.6)	32.0 (9.63)	39.6 (10.8)
Disease duration (SD)	16.0 (10.7)	10.5 (8.8)	20.3 (11.0)	16.3 (9.9)
EDSS score (SD)	5.5 (1.8)	2.8 (2.4)	3.2 (2.2)	2.9 (2.5)
NSBMS score (SD)	2.9 (1.2)	3.1 (1.1)	2.8 (1.2)	2.7 (1.2)
Education (SD)	12.7 (2.7)	12.8 (2.8)	12.7 (2.7)	12.3 (3.2)

Clinical data of this patient cohort. RR, relapsing–remitting; SP, secondary progressive; PP, primary progressive.

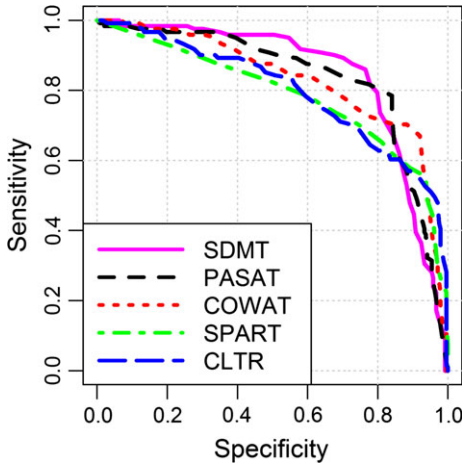

Figure 1 Comparing the receiver operating characteristic curves obtained by the Symbol Digit Modalities Test and the different subtests of the Neuropsychological Screening Battery for MS in the prediction of a patient's cognitive status.

Predicting adjusted NSBMS outcomes to avoid a positive bias effect

In Fig. 2, the ROC analyses were repeated for different adjusted NSBMS scores. The denoted P values are obtained when comparing the complete curves. In Table 2 additional numerical information is provided: sensitivity obtained at specificities of 0.60 or 0.65, the respective AUCs and the statistical significance when comparing the complete curve or only a part (0.60–0.65 region).

Predicting different levels of cognitive impairment

The results obtained by 10-fold stratified cross-validation are shown in Fig. 3. The AUC rises slightly when defining cognitive impairment more and more strictly (AUC = 0.82 for NSBMS cutoff 4, AUC = 0.84 for NSBMS < 2). It can be seen that it is most difficult to predict the lowest level of cognitive impairment (NSBMS < 4). Although the results obtained on the subgroup of 238 patients are very similar, it is important to note that the optimal cutoffs for the SDMT are 46–43–40 instead of 44–41–37 for the total group.

In Table 3, the sensitivity (mean and SD), specificity and percentage correctly classified obtained in the test groups when the SDMT cutoff value was optimized at a specificity level of 65% are reported. The cutoffs used and the AUC are also shown. N_{Imp} is the number of patients failing that specific cutoff.

Assessment of practice effect

A practice effect can never be excluded from neuropsychological data that have been repeatedly assessed. It was possible to investigate this effect because a subset of our patient group (238) had not undergone a previous NSBMS testing, whereas 121 patients had already undergone one NSBMS test. When only those 238 patients were analyzed, the results obtained were very similar although the cutoffs used for the SDMT were consistently higher for the different levels of cognitive impairment (46–43–40) compared with patients who had already undergone an NSBMS assessment (but no SDMT). This reflects a practice effect, i.e. patients with relatively low SDMT scores who had already undergone NSBMS testing still pass the NSBMS due to this practice effect.

Inclusion of covariates

As a first step the EDSS score was correlated with the total NSBMS score (NSBMS = 4.11–0.232*EDSS, $r = 0.33$, $P < 0.001$). The AUC obtained with the EDSS was 0.658.

Including SDMT, age, age at onset, disease duration, gender, level of education and EDSS into a logistic regression model and applying the Akaike information criterion to exclude uninformative variables, SDMT, disease duration, age and level of education were found to be significant contributors for cognitive status. An ROC analysis performed on the

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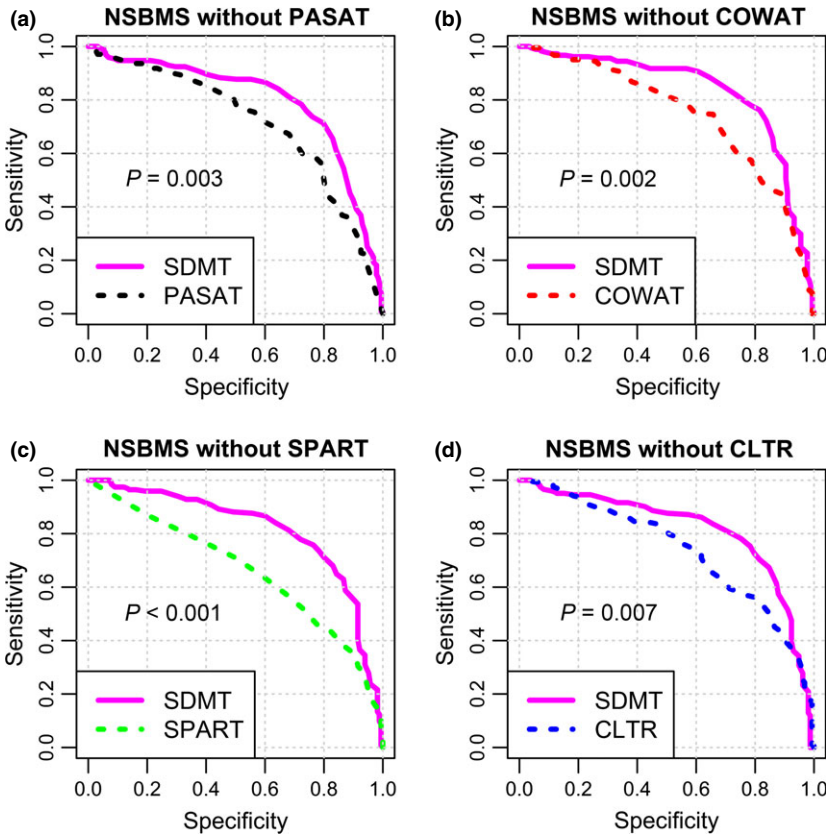

Figure 2 Comparison of the individual Neuropsychological Screening Battery for MS (NSBMS) tests with the Symbol Digit Modalities Test in predicting unbiased NSBMS scores. The *P* values denoted in the figures are calculated using the pROC package [36] and denote the statistical significance between the two plotted curves.

Table 2 Statistical comparison ROC curves

		Sensitivity (0.60)	Sensitivity (0.65)	AUC	*P* value	*P* value
Full NSBMS	SDMT	0.91	0.90	0.85	–	–
NSBMS w. PASAT	SDMT	0.87	0.81	0.80	0.003	<0.001
	PASAT	0.70	0.67	0.71		
NSBMS w. COWAT	SDMT	0.91	0.86	0.83	0.002	<0.001
	COWAT	0.75	0.75	0.74		
NSBMS w. SPART	SDMT	0.87	0.81	0.81	<0.001	<0.001
	SPART	0.57	0.57	0.66		
NSBMS w. CLTR	SDMT	0.86	0.84	0.81	0.007	0.004
	CLTR	0.73	0.63	0.71		

Results of the performance of the SDMT and the different subtests of the NSBMS to predict the NSBMS or adjusted NSBMS outcome. *P* values are the outcomes of the statistical comparisons between the different ROC curves (SDMT vs. one of the tests included in the NSBMS). The first column of *P* values represents the outcomes of the comparisons of the total curves. For the last column, the AUC was compared for the interval 0.60–0.65. w., without.

outcome of the logistic regression model returned an AUC of 0.86 and a sensitivity of 0.90 at a specificity of 0.60. The results are therefore comparable to the results obtained by using only the SDMT. This strengthens our confidence that these covariates influence both the SDMT and the general cognitive outcome equally.

Based on a central database, Zung scores could be retrieved for 175 MS patients. The scale consists of a response on 20 questions on which a score of 1 (= normal) to 4 (= indicative of depression) can be obtained. The total is divided by 0.80 leading to a range of 25–100 [24]. The logistic regression model was rebuilt on this subset of patients using the same

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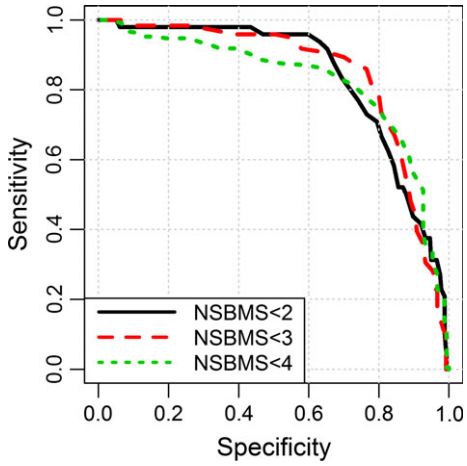

Figure 3 Evolution of the receiver operating characteristic curves when predicting different levels of cognitive impairment using the Symbol Digit Modalities Test.

variable selection procedure. Depression was not included in the final model, which did include SDMT, age and education. As an explanation it is proposed that depression affects the SDMT and general cognitive functioning in a comparable way. Therefore, it was hypothesized that the effect of depression is included in the model through the SDMT.

Discussion

This study shows that the SDMT is a promising sentinel test to screen for cognitive impairment in MS. Although this finding might seem well known, many studies have limited themselves to detecting cognitive changes between an MS population and healthy controls [7,14–17,25,26], whereas only one study was found assessing the value of the SDMT within an MS population [18]. A recent long-term study also showed better psychometric properties for the SDMT compared with the PASAT [27].

Our classification results are better than the sensitivity (0.74) and specificity (0.77) reported by Deloire *et al.*[28] and the sensitivity (0.82) and specificity (0.60) reported by Parmenter *et al.*[18]. However, the optimal point in the ROC curve was chosen based on our ambition to assess the performance of the SDMT as a sentinel test for cognitive deterioration in MS. The application of 10-fold stratified cross-validation assures us that this is not just a chance finding.

Comparing with other studies assessing the SDMT as a sentinel test, the cutoff was optimized in order to assess its ability to detect cognitive impairment in MS. Our results were compared with the tests included in the NSBMS and the SDMT was shown to outperform these tests even though the tests were clearly positively biased. Furthermore the possible gain in classification accuracy was assessed by adding several covariates in a logistic regression model. This analysis showed that no clinically relevant gain is to be expected, i.e. only the SDMT suffices to determine a patient's cognitive status. This study also shows that one has to be careful when defining a cutoff score for the SDMT under which a patient will be denoted cognitively impaired. The cutoff scores found in the subgroup of patients not previously assessed can be recommended for clinical practice.

Several reasons can be proposed that may serve as an explanation for this performance. One may be that the SDMT is simple and reliable to test. Another may be that the SDMT focuses on slowed (visual) information processing speed, which has been suggested as being the core cognitive deficit in MS [13,14,29,30]. Another possible explanation was offered by Drake *et al.* [26] who proposed the inclusion of afferent visual processing next to higher cognitive functions as an explanation why the (visual) SDMT is sensitive to cognitive impairment in MS.

Our finding that the SDMT is the best predictor of general cognitive impairment is consistent with results showing that the SDMT shows higher correlations with brain magnetic resonance imaging metrics than other tests included in the NSBMS [31–33]. These findings led some researchers to propose the replacement of the PASAT in the Multiple Sclerosis Functional Composite by the SDMT [26,34]. On the other hand, similar correlations were found between corpus callosum atrophy parameters and PASAT, SDMT and a test of verbal fluency [35].

Next to its high sensitivity to cognitive impairment and its correlation to magnetic resonance imaging

Table 3 Evolution of classification results for different levels of cognitive impairment

		Sensitivity		Specificity	PCC	CO	AUC	
Cutoff NSBMS	N_{Imp}	Mean	SD	Mean	Mean	Mean	Mean	SD
<4	209	0.84	0.04	0.67	0.76	44	0.82	0.03
<3	121	0.90	0.03	0.67	0.79	41	0.85	0.03
<2	48	0.87	0.11	0.68	0.77	37	0.84	0.05

PCC, percentage correctly classified; CO, cutoff.

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metrics, the SDMT has several other advantages. It is an easy test that does not cause a significant amount of stress amongst patients [26] and does not have to be administered by a trained neuropsychologist. All these arguments contribute to the practical application of this test in peripheral neurological assessment, where cognitive impairment is mostly not assessed.

Our study has some limitations. First, our study sample is recruited in a large MS center where patients are referred to for multidisciplinary care. These patients may not be representative of the general MS population, which possibly limits the validity of these results. Secondly, possible confounders including psychotropic medication or fatigue were not taken into account. A comparable influence of these factors on both the NSBMS and the SDMT was assumed, but a differential effect cannot be excluded.

The generalizability of our results was increased by using 10-fold stratified cross-validation on a large number of patients. The robustness of our results is ensured by the use of different analysis techniques and the comparison with other neuropsychological tests used as a benchmark.

A sensitivity of 0.91 means that, if 100 CI patients are tested, only nine will seem to be CP based on the SDMT results. The corresponding specificity of 0.60 means that if 100 CP patients are screened by the SDMT, 60 will pass the test and 40 – in reality CP – patients will be referred for further testing. The latter is not considered a big problem though, as the SDMT is an easy and quick test which does not necessarily have to be administered by a neuropsychologist. This result clearly demonstrates the applicability of the SDMT in everyday clinical practice.

Conclusion

In this paper the SDMT has been shown to outperform other neuropsychological tests in predicting the outcome of a complete neuropsychological test battery (the NSBMS). As the SDMT is an easy and low-cost test that can be easily assessed by a nurse instead of a neuropsychologist or in standard neurological examination, these findings could lead to a higher detection rate for cognitive impairment in MS and could lead to improved patient management.

Despite our promising results, assessing a patient's cognitive status based on a single test remains rather blunt. Therefore the use of the SDMT in peripheral neurological examinations and the use of a more extensive neuropsychological battery in specialized centers is suggested. When only one test is to be chosen, the SDMT seems to be the best option.

Acknowledgements

We gratefully acknowledge the assistance of Mrs Ann Van Remoortel and the other MS research nurses from the National MS Center Melsbroek, who participated in this study. JVS was holder of a grant funded by UMons (50%) and Biogen (50%) between October 2011 and October 2012 and holds a grant funded by Fonds Wetenschappelijk Onderzoek (FWO) since October 2012 (FWO-aspirant). The Melsbroek ED-MUS database effort is supported by a grant from Teva Belgium.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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