

Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis

Ralph HB Benedict, John DeLuca, Glenn Phillips, Nicholas LaRocca, Lynn D Hudson, Richard Rudick and Multiple Sclerosis Outcome Assessments Consortium

Multiple Sclerosis Journal

1–13

DOI: 10.1177/
1352458517690821

© The Author(s), 2017.



Reprints and permissions:
<http://www.sagepub.com/uk/journalsPermissions.nav>

Abstract: Cognitive and motor performance measures are commonly employed in multiple sclerosis (MS) research, particularly when the purpose is to determine the efficacy of treatment. The increasing focus of new therapies on slowing progression or reversing neurological disability makes the utilization of sensitive, reproducible, and valid measures essential. Processing speed is a basic elemental cognitive function that likely influences downstream processes such as memory. The Multiple Sclerosis Outcome Assessments Consortium (MSOAC) includes representatives from advocacy organizations, Food and Drug Administration (FDA), European Medicines Agency (EMA), National Institute of Neurological Disorders and Stroke (NINDS), academic institutions, and industry partners along with persons living with MS. Among the MSOAC goals is acceptance and qualification by regulators of performance outcomes that are highly reliable and valid, practical, cost-effective, and meaningful to persons with MS. A critical step for these neuroperformance metrics is elucidation of clinically relevant benchmarks, well-defined degrees of disability, and gradients of change that are deemed clinically meaningful. This topical review provides an overview of research on one particular cognitive measure, the Symbol Digit Modalities Test (SDMT), recognized as being particularly sensitive to slowed processing of information that is commonly seen in MS. The research in MS clearly supports the reliability and validity of this test and recently has supported a responder definition of SDMT change approximating 4 points or 10% in magnitude.

Keywords: Multiple sclerosis, cognition, processing speed, performance outcome, psychometric validity, Symbol Digit Modalities Test

Date received: 17 July 2016; revised: 12 December 2016; accepted: 15 December 2016

Overview and historical perspective

Slowed cognitive processing was identified as a core symptom of multiple sclerosis (MS) in 1877 by Charcot¹ who presciently observed that in many patients, “conceptions are formed slowly and the intellectual and emotional faculties are blunted in their totality.” It would take a century for psychometric methods to be rigorously applied to this population, confirming Charcot’s hypothesis that bradyphrenia is a core MS deficit. Beginning with the work of Stephen Rao in the 1980s,^{2–4} cognitive processing speed (CPS) was formally quantified using primarily two neuropsychological tests, the Paced Auditory Serial Addition Test (PASAT)⁵ and the Symbol Digit Modalities Test (SDMT).⁶ When other,

more complicated, timed executive function tests were applied to MS samples, more often than not the processing speed component accounted for the test’s sensitivity.^{7–8} Subsequently, due to its ease of administration and other factors (e.g. reliability and validity, predictive validity, sensitivity, and specificity), the SDMT has risen to the forefront of neuropsychological evaluation in MS. Over the last 5 years, it has become the most commonly used neuropsychological test of processing speed in MS.¹⁰

While the SDMT was first published as a commercially available test in 1982,⁶ the idea of measuring information processing speed and efficiency using a symbol/digit substitution task dates to the early 20th

Correspondence to:

RHB Benedict
Department of Neurology
and Buffalo General Medical
Center, University at Buffalo,
Suite E2, 100 High Street,
Buffalo, NY 14226 USA.
benedict@buffalo.edu

Ralph HB Benedict
Department of Neurology
and Buffalo General Medical
Center, University at Buffalo,
Buffalo, NY, USA

John DeLuca
Kessler Foundation, West
Orange, NJ, USA; Rutgers
New Jersey Medical School,
Newark, NJ, USA

Glenn Phillips
Richard Rudick
Biogen, Cambridge, MA,
USA

Nicholas LaRocca
National Multiple Sclerosis
Society, New York, NY,
USA

Lynn D Hudson
Critical Path Institute,
Tucson, AZ, USA

**Multiple Sclerosis Outcome
Assessments Consortium**
Multiple Sclerosis Outcome
Assessments Consortium
(MSOAC), Critical Path
Institute, Tucson, AZ, USA

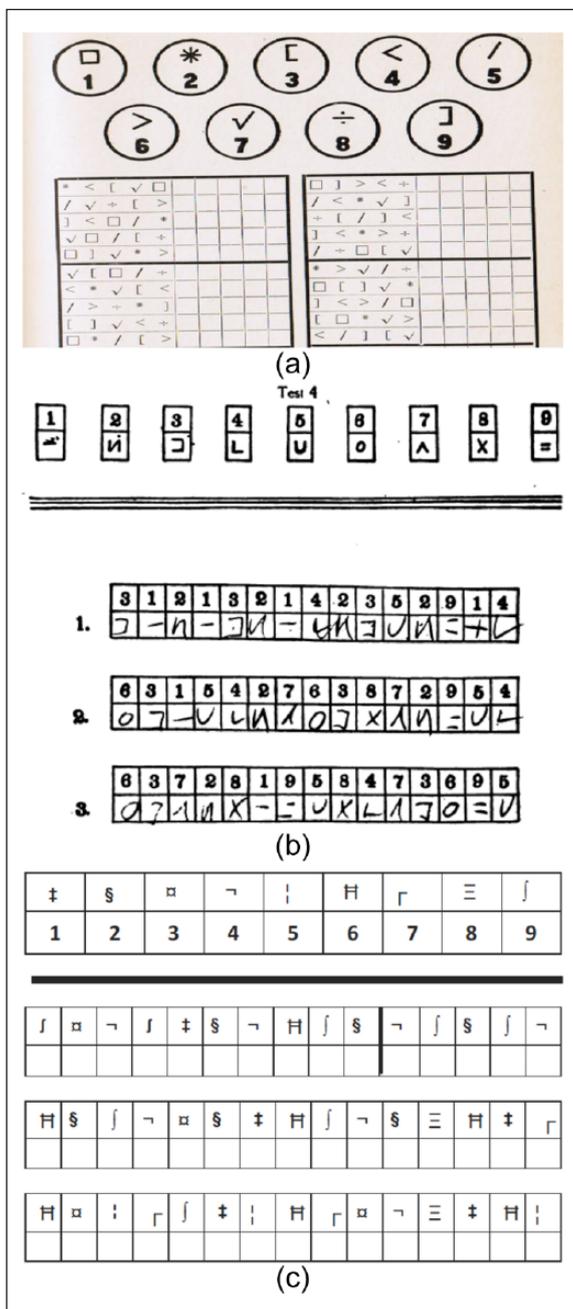


Figure 1. (a) The Symbol Digit Modalities Test as originally developed by Whipple¹³ and Pyle¹¹ in the early 20th century. This is the earliest description of a symbol/number coding task we are able to locate, and neither source refers to a prior version of the task. (b) A scored version of the Digit Symbol Substitution Test as developed for the US Army in the early 1920s, subsequently adapted by the Wechsler intelligence scales. (c) A faux version of the Symbol Digit Modalities Test (SDMT) as presented in an earlier publication on the Brief International Cognitive Assessment for MS (BICAMS).

century. In 1913, a symbol digit substitution task was described in a manual of psychometric scales for the examination of school children (Figure 1(a)).¹¹ Writing

in 1927, Lemmon¹² credited both Guy Montrose Whipple¹³ and William Henry Pyle¹¹ for developing this procedure. By then, the task had been adopted by the United States Army in their efforts to screen incoming recruits for mental deficiency (Figure 1(b)).¹⁴ However, the stimulus/response pairing had shifted from the reporting of numbers associated with the correct symbol to that of writing symbols in accordance with the target numbers. This form would evolve into the digit symbol coding (aka digit symbol substitution test) test co-opted by the Wechsler adult and children intelligence tests, in the 1930s¹⁵ and 1940s.¹⁶ The Coding Test Version, wherein the participant writes symbols corresponding to the target key at the top of the page, is a core test of processing speed in current versions of the Wechsler intelligence scales. It seems that the original number response method lay quiescent for decades until the 1960s when Smith and colleagues began to pilot their SDMT method in studies of cognitive aging and neuropsychology.¹⁷⁻¹⁹

The SDMT is presently owned by Western Psychological Services and to protect the copyright and conform with ethical principles, we present a faux rendering²⁰ of the test in Figure 1(c). The subject is presented with a page headed by a key that pairs the single digits 1-9 with nine symbols. Rows below contain only symbols, the subject's task is to write or orally report the correct number in the spaces below. After completing the first 10 items with guidance, the subject is timed to determine how many responses can be made in 90 seconds. In the standard administration of the SDMT, the written response task is conducted first, followed by an oral response task, using the same stimuli. However, the vast majority of MS studies skip the written response administration and only utilize the oral version, to diminish the sensory motor impact of using the written version. Thus, the examiner uses a scorer form on which he or she records the subject's voiced responses. The correct answers appear on the examiner's form making scoring quick, with minimal chance for error. In total, the test requires no more than 5 minutes to complete.

Recognizing the importance of the processing speed domain for MS research, Rao and colleagues included both the PASAT and SDMT in the Brief Repeatable Battery of Neuropsychological Tests (BRB),²¹ and for the past 25 years, the vast majority of studies have utilized either or both of these measures. Both tests are included in the Minimal Assessment of Cognitive Function in MS (MACFIMS),²² a consensus opinion battery developed in 2002. The PASAT gained considerable favor after its inclusion in the Multiple Sclerosis Functional Composite (MSFC).^{23,24} However, in the

Table 1. Neuropsychological tests used in common consensus standard assessment batteries, by cognitive domain.

Cognitive domain	MACFIMS	BRNB	NINDS CDE	MS-Cog	BICAMS
Processing speed	Symbol Digit Modalities Test	Symbol Digit Modalities Test	Symbol Digit Modalities Test	Symbol Digit Modalities Test	Symbol Digit Modalities Test
	Paced Auditory Serial Addition Test	Paced Auditory Serial Addition Test	Paced Auditory Serial Addition Test	Paced Auditory Serial Addition Test	
Auditory verbal memory	California Verbal Learning Test 2	Selective Reminding Test	California Verbal Learning Test 2	Selective Reminding Test	Selective Reminding Test
Visual spatial memory	Brief Visuospatial Memory Test Revised	10/36 Spatial Recall Test	Brief Visuospatial Memory Test Revised	Brief Visuospatial Memory Test Revised	Brief Visuospatial Memory Test Revised
Expressive language	Controlled Oral Word Association Test	Controlled Oral Word Association Test	Controlled Oral Word Association Test		
Visual spatial processing	Benton Judgment of Line Orientation Test	Benton Judgment of Line Orientation Test			
Executive Function	DKEFS Card Sorting Test	DKEFS Card Sorting Test			
<p>Minimal Assessment of Cognitive Function in MS (MACFIMS) by consensus meeting in 2001. The Brief Repeatable Neuropsychological Battery (BRNB) for MS was developed by Rao and colleagues in 1991. The National Institute of Neurological Disorders and Stroke (NINDS) has a series of recommended assessments across multiple clinical domains for several neurological diseases, called Common Data Elements (CDE) www.nlm.nih.gov/cde. The MS-Cog is a composite outcome measure proposed for MS clinical trials. The Brief International Cognitive Assessment for MS (BICAMS) is a proposed cognitive monitoring tool based on a consensus panel opinion paper with recommended procedures for international validation. BVMTR: Brief Visuospatial Memory Test Revised; CVLT2: California Verbal Learning Test Second Edition; SRT: Selective Reminding Test; COWAT: Controlled Oral Word Association Test.</p>					

early 2000s, we and others began to take note of what seemed to be superior reliability and sensitivity of the SDMT as well as greater patient acceptance, suggesting that it may be a superior test due to better psychometric validity and ease of administration. Consequently, as shown in Table 1, the SDMT is the single test common to all recommended cognitive batteries for MS patients, including the BRB, MACFIMS, NINDS Common Data Elements,²⁵ MS-Cog,²⁶ and the Brief International Cognitive Assessment for MS (BICAMS).^{27,28}

Review objective

The SDMT was selected for this review due to its prominent role in discussions emanating from the Multiple Sclerosis Outcome Assessments Consortium (MSOAC). This effort to adopt a clinical outcome assessment tool for clinical trials to better capture MS-related disability was born out of a consensus paper by the International Advisory Committee on Clinical Trials in Multiple Sclerosis.²⁹ The MSOAC includes representatives from the National

MS Society as well as 6 other MS advocacy organizations, Food and Drug Administration (FDA), European Medicines Agency (EMA), National Institute of Neurological Disorders and Stroke (NINDS), 21 academic institutions, and 9 industry partners, along with persons living with MS. The goals of the consortium are acceptance and qualification by regulators of performance outcomes that reflect core MS impairments that are highly reliable and valid, practical, cost-effective, and meaningful to persons with MS. This review benefitted from a formal MSOAC sponsored literature search, conducted in Embase, Medline, PsycINFO, and Cumulative Index of Nursing and Allied Health Literature, followed by an enrichment technique (key papers identified by MSOAC members added and informed search criteria) including work identified from prior reviews. Like the companion reviews in this issue of the Timed 25-Foot Walk, Nine-Hole Peg Test, and Low-Contrast Letter Acuity, this article begins with psychometric characteristics and concludes with an appraisal of the clinical meaningfulness of the measure.

Psychometric validity

Reliability. The SDMT manual reports that in a healthy sample, the test–retest reliability coefficient is 0.76 for the oral response version. The r was considerably higher, 0.97, in a sample of 34 MS patients tested over 2 weeks.³⁰ Satisfactory reliability was maintained at 1-month³¹ and 2-year intervals (an epoch that encompasses both reliability and maturation effects).³² Through the BICAMS^{27,28} initiative, the reliability of SDMT remains good to excellent at short intervals following translation of the test instructions into Persian (0.79),³³ Portuguese (0.86),³⁴ and Spanish (0.95).³⁵

Alternate forms were developed by a National MS Society Cognitive Function Study Group,²¹ but subsequently, these forms were found to be non-equivalent.³⁶ For these alternate forms, the same symbols were employed, but the alternative forms used different symbol–digit pairings. On the standard SDMT, however, the first 26 items utilize only the first six symbols in the key, a subtlety apparently missed when alternate forms were first developed. Accommodating this idiosyncrasy while generating new forms resulted in alternate versions that yield data nearly identical with the standard form,³⁷ while maintaining good test–retest reliability in healthy controls (HCs) with r varying from 0.84 to 0.90. Drake et al.³² reported that the test–retest reliability of the SDMT in 115 MS patients over 2 years is $r=0.74$.

Construct and predictive validity. The construct validity of SDMT was investigated in 278 MS patients.³⁸ The MACFIMS was administered in total. SDMT loaded on a general processing factor in the relapsing–remitting multiple sclerosis (RRMS) analysis and showed a split loading in the secondary-progressive multiple sclerosis (SPMS) group, loading on a speed/executive function factor and a memory factor. This latter observation is important. The SDMT was originally developed^{11–13} as a learning and processing efficiency test, under the assumption that as the test proceeds, individuals will tend to learn the symbol/digit associations. Subsequent research showed that symbol search coding tests in general load on a processing speed factor.^{15,39} Nevertheless, there is likely some degree of learning involved, and this multimodal aspect of the SDMT may account for its very high sensitivity to cognitive impairment. Within a brief battery of cognitive tests, the SDMT was found to be the test that best predicted future cognitive decline.⁴⁰

Discriminative validity. An oft-repeated observation is that the SDMT frequently discriminates MS and

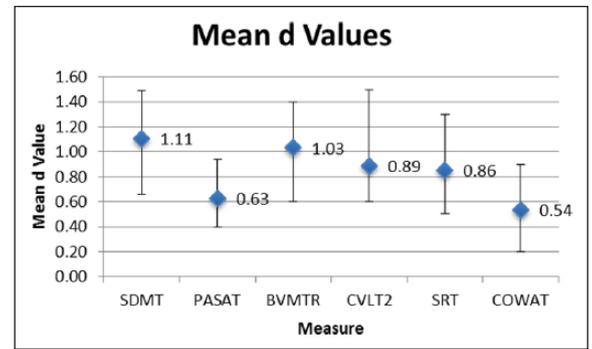


Figure 2. Mean effect sizes and ranges for each of the more commonly used neuropsychological tests in consensus standard batteries. Figure shows the mean effect size as calculated by the Cohen d method where d is the difference between group means divided by the average SD. All d values reflect MS and healthy control group comparisons. SDMT has a larger mean effect size as compared to others depicted.

control groups as well as, if not better than, other neuropsychological tests.^{32,38,41–49} In a study using an extended battery of tests,⁴¹ SDMT loaded first in regression models discriminating MS patients and HCs.³⁸ While all MACFIMS tests significantly discriminated these groups, the effect size was largest for SDMT ($d=1.3$). In Figure 2, the mean effect size d and the range of smallest to largest effects sizes are depicted. The analysis is derived from 15 studies^{26,33,38,41,44,46,50–57} that compared MS patients and HCs and included the SDMT, PASAT, a consensus opinion memory test, and the Controlled Oral Word Association Test.

Criterion validity, correlation with brain MRI. Neuropsychological testing is frequently employed as a clinical benchmark for interpreting the meaningfulness of MRI abnormalities. In MS, early work in the late 1980s showed that cognitive impairment is correlated with lesion burden and ventricle enlargement.^{58,59} The next decade witnessed the advent of many MRI metrics including spectroscopy, diffusion, whole brain atrophy, and gray versus white matter volume. Two early studies^{44,60} used linear regression with multiple MRI measures to determine the most robust predictor of cognitive impairment and in both studies MRI accounted for most variance in SDMT, the strongest predictor being central atrophy ($r = 0.70$ or 0.71), as measured by ventricle enlargement. Compared to other MACFIMS cognitive tests, SDMT accounted for more variance in gray matter volume,⁶¹ whole brain diffusion abnormalities,⁶² and lesion burden at both 1.5 and 3.0 T.⁶³ Consequently, SDMT has become a standard for

measuring cognition in recent efforts to understand clinical correlations of regional gray matter atrophy, within-structure diffusivity, and connectivity.^{55,64–67} In a recent meta-analysis, the SDMT was found to have the strongest relationship with various MRI metrics among tests of processing speed.⁶⁸

Summary. The SDMT has proven to be quite useful in neuropsychological MS research. It has excellent test–retest reliability, and alternate forms have been developed that are equivalent in difficulty. When the alternate forms are used, reliability is maintained. Validity research shows that SDMT is a good measure of processing speed or efficiency. SDMT is the neuropsychological test most sensitive to MS cognitive disorder and correlates very well with MRI measures of atrophy, lesion burden, and microstructural pathology. The test very effectively represents the core neuropsychological domain of processing speed. Thus, it is no surprise that the SDMT is the only neuropsychological test included in all MS cognitive test batteries developed in recent years (Table 1).^{21,22,25,26,28}

Clinical relevance of the SDMT

How well does the SDMT reflect neurocognitive capacities that are related to activities of daily life important to patients? On the surface, the test may not seem to be very relevant. Unlike the T25FW, for example, patients are not asked to perform a task ordinarily undertaken in daily life. In fact, when a person takes the test for the first time, the chances are there that he or she has never seen anything like it before. One may have some appreciation for the observation that a person who used to walk 25 feet in 4 seconds and now requires 6 seconds to cover the same distance is affected or in some way meaningfully compromised. In contrast, there is little inherent meaning in a SDMT raw score change of 60 to 45. Why then should a relative deficit on the SDMT compared to a healthy person, or SDMT decline over time, be of concern to patients or clinicians?

Group studies. Slower performance on the SDMT is correlated, at the group level, with activities of daily living (ADLs) and employment status. Some research⁶⁹ suggests that cognition is the most important domain for employability, although a recent study found that the T25FW is just as closely linked to this particular limitation of daily functioning.⁷⁰

Strober *et al.*⁷¹ assessed cognition and Expanded Disability Status Scale (EDSS) in 101 patients and defined employment as employed/volunteer, disabled,

or retired. Disease duration, MS course, EDSS, and cognitive performance all distinguished the groups, and a regression analysis retained EDSS, SDMT, and the personality trait of persistence as the strongest predictors. In this, and a subsequent study carried out with an independent sample,⁷² SDMT was the most robust neuropsychological predictor of employment from a comprehensive test battery. The effect size was large, on the order of $d=0.80–0.90$. This effect size was recently replicated by an independent group in Australia.⁷³

SDMT is similarly related to other daily activities, even when measured in controlled or relatively standardized conditions. All of the cognitive outcomes in the BICAMS²⁸ battery were correlated with errors when patients were asked to use a desktop computer to access the Internet and purchase an airplane ticket or food.⁷⁴ The correlation between performance errors and SDMT was $r=-0.48$, slightly lower than with the Brief Visuospatial Memory Test—Revised (BVMT-R)⁷⁵ ($r=-0.59$). In a similar setting, MS patients were asked to prepare a dish from a standard recipe.⁷⁶ Across a comprehensive test battery, SDMT showed the largest, albeit modest, correlation with cooking efficiency ($r=0.29$). Furthermore, the SDMT was the only neuropsychological test which predicted impaired money management in MS patients.⁷⁷

Benchmarks for clinically relevant levels of SDMT performance. Group studies showing significant positive correlations between SDMT and employment status and various ADLs support the test's ecological validity. MS patients performing poorly on the SDMT are more likely to lose employment and struggle while carrying out ADLs. However, within-sample correlations do not determine when SDMT performance becomes relevant for a particular patient—we do not know how any specific score corresponds to a patient's adaptive functioning.

Unfortunately, as is the case for neuropsychological performance in general, the correlation between SDMT and self-reported cognitive difficulty is poor.^{43,78–83} Largely subjective symptoms, such as depression, pain, and fatigue, tend to correlate with one another and with quality of life measures. In contrast, cognitive performance tests tend to correlate poorly with such symptoms but are robustly related to ADLs and employability. Therefore, it is within these functional domains that we must search for benchmarks to aid in the interpretation of SDMT scores.

Following the work of Goldman *et al.*,⁸⁴ multiple employment-related anchors were recently captured

to compare with SDMT performance. SDMT scores were obtained from MS adults who were fully employed and free of work problems, employed but work-challenged, or unemployed due to disease-related factors.⁷⁰ The analysis established benchmark SDMT scores associated with these varying levels of vocational disability. Of the tests under study, T25FW and SDMT were most discriminating of these groups, and the SDMT benchmarks (MS work disabled=45, MS employed but work challenged=55, MS employed and stable=63) were offered to complement previously established, meaningful levels of slowed ambulation.⁸⁴

Clinically meaningful change. In an effort to correlate discrete changes in SDMT with functional status, Morrow et al.⁸⁵ examined a sample of persons with MS who were all employed full time 3.5 years earlier. Those persons who had declined in status over the interim were compared on the MACFIMS with those maintaining employment. SDMT maximally discriminated the groups. Depending on how work disability was defined, conservatively or liberally, SDMT raw score decline of 3 or 4 points maximally separated the employment status groups.

Another way of documenting clinically meaningful change is to consider how the test reflects a clearly discernible change in clinical condition apparent to the person with MS, caregiver, and/or a clinician observer. If the test declines during an acute neurologic episode, that is, a relapse, and then recovers, the degree of change that is observed could be construed as clinically meaningful.

The STRATA study⁸⁶ was a long-term observational safety study of natalizumab (Tysabri) for relapsing MS. STRATA provided a unique opportunity to study SDMT in a large cohort of patients undergoing monthly screenings (SDMT, Beck Depression Inventory Fast Screen for Medical Patients,⁸⁷ MS Neuropsychological Screening Questionnaire (MSNQ)⁴³) for progressive multifocal leukoencephalopathy (PML). The SDMT was reliable over the course of the investigation, showing an anticipated learning or treatment effect, as scores improved. While no PML was observed, the evaluation of patients undergoing relapse provided the opportunity to isolate the effects of such an overt clinical state on SDMT performance. This analysis⁸⁸ revealed that in comparison with the scores in non-relapsing patients where improvement was observed, those in relapse declined by roughly 2–3 points, followed by recovery to nearly the level of the control group.

MS relapses involve a range of sensory/motor deficits that could compromise SDMT performance. In a prospective study,⁸⁹ these factors were controlled in a comparison of 24 relapsing and 24 non-relapsing MS patients. All participants had a retrospective baseline evaluation and were examined again prospectively at the time of relapse, before steroid treatment, and again 3 months later. Importantly, all patients enrolled in the relapse group either reported or were suspected of cognitive impairment on the basis of clinician or observer impression. At relapse, the groups differed on SDMT by 5 points, and at 3 months, the difference had been reduced to roughly 3.

These SDMT findings suggest that it may be possible to identify MS patients experiencing cognitive changes as part of a relapse, independent of other factors. Pardini et al.⁹⁰ attempted to validate the concept by examining patients free of relapse, and having no clinical change by EDSS, but based on prior work⁸⁵ showing at least a 4-point decline on SDMT from baseline. Of 99 patients, 17 were so identified and labeled as having an “isolated cognitive relapse” with a stable EDSS. This group evidenced positive gadolinium enhancement on MRI concordant with the SDMT decline and showed only a partial recovery of function at 6 months and 1 year follow-up.

These findings have a bearing not only on the issue of benchmarks for clinically meaningful change but also on the MS disease activity in general. It has recently been shown that the frequency of “no evidence of disease activity” or NEDA is significantly reduced when cognitive function is monitored.⁹¹ Were SDMT or similar tests employed on a routine basis,⁹² transient deficits may explain, in part, some of the discrepancy between MRI disease activity and clinical activity, which is typically defined as positive findings on a traditional neurologic exam, which heavily emphasizes motor and sensory testing.

Summary. SDMT, a valid measure of cognitive processing speed (CPS), is robustly correlated with instrumental ADLs in MS patients. In studies including multiple cognitive or motor performance tests, it stands out as among the best or the single most robust predictor of employability and overall ADLs. One retrospective, longitudinal study comparing work-stable versus work-disabled patients showed that a 3- or 4-point decline over 42 months maximally separated the groups. There are now three controlled studies revealing changes in SDMT that are associated with functional decrements during relapses or acute

Table 2. Changes in SDMT correlated with acute clinical changes.

			Pre Relapse	Relapse	Change	Raw	%
			Score	Score		Change	Change
Morrow et al. ⁸⁸	Conventional relapse	Relapse	53.6	52.4	Within group	1.2	2.2
		Control	53.4	54.7	Between group	2.3	4.3
Benedict et al. ⁸⁹	Relapse with cognitive impairment	Relapse	53.6	50.3	Within group	3.3	6.2
		Control	53.1	55.3	Between group	5.0	9.4
Pardini et al. ⁹⁰	Isolated cognitive relapse	Relapse	54.7	46.4	Within group	8.3	15.2
		Control	54.3	55.0	Between group	8.6	15.8

disease activity, as a proxy for readily observable decline in clinical status (Table 2). The percentage of change relative to controls ranges from 4% to 16%. A general interpretation of the data suggests that a raw score change of 4 points, or a 10% change, is clinically meaningful.

Conclusion and future directions

A century ago, psychologists in the United States developed a cognitive test requiring subjects to process symbol/digit associations as rapidly as possible, believing the task to be related to processing speed and efficiency. Work in MS dates to the early 1990s when Smith's SDMT was incorporated in the Rao Brief Repeatable Neuropsychological Battery. In the early 2000s, researchers began to take note^{22,43,44,60} of the repeated observation that the SDMT is the most reliable and sensitive neuropsychological test, leading to the idea that it may serve as a screen for neuropsychological impairment.⁴² In 2008, Brochet et al.⁴⁶ questioned whether the SDMT should replace the PASAT as the cognitive component of the MSFC, compelling Drake et al. to publish *z* score calculation tables for the SDMT versions of the MSFC.^{29,32,46} This work was paralleled by experimental neuropsychological research reinforcing the core contributions of processing speed in MS.^{93–95} The SDMT is now the leading cognitive test candidate for the more recent MSOAC effort to qualify performance scales for MS clinical trials with the FDA and EMA.²⁹

One should bear in mind that while the SDMT is a published psychometric test protected by copyright, the task, in general, comes in many administration formats and dates to the early 20th century. There are many similar tasks in the psychological and medical literature, and virtually any computer-based test found on the Internet includes a variant of the original digit/symbol substitution test. The MATRICS Consensus Cognitive Battery,^{96–98} endorsed by the FDA for

labeling in cognitive impairment associated with schizophrenia, includes the Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding Test. An adaptation of the SDMT has been used in professional sports concussion management for years.^{99,100} An iPad version of the MSFC¹⁰¹ will likely include the Processing Speed Test, a digit symbol task wherein the participant presses a button corresponding to the correct number for each stimulus. It remains to be seen how important it is to use the same task across studies and if there are any differences in reliability, sensitivity, and validity across many versions of the test.

In our opinion, the SDMT is the best psychometric measure available for assessing CPS in MS patients. That said, the test is not without its problems and limitations. There are very little longitudinal data that would permit us to draw conclusions about how sensitive SDMT is to changes in cerebral function over time. Interestingly, even though decline in SDMT over 3 years was associated with morphological abnormalities in the thalamus;¹⁰² as a group, MS patients were stable on the test compared to HCs.^{103,104} Most notably, the SDMT is not a pure test of processing speed. SDMT performance can be influenced by visual acuity and ocular motor functions,^{10,105} and while SDMT is correlated with other processing speed tests, there is undoubtedly some incidental learning of symbol–digit associations, and hence the need for alternate forms.¹⁰⁶ Although not likely the major contributor to measuring processing speed, these factors should be taken into account when interpreting SDMT performance.

Processing speed is a basic elemental cognitive function required by, and therefore influencing downstream processes such as learning, memory, word retrieval, and executive function.¹⁰ In MS, processing speed has been shown to account for impairments in working memory, executive functions, and learning and memory.^{107–111} As such,

higher cognitive processes in MS can be influenced by impaired processing speed and may be the primary reason that impaired performance on tests of higher cortical function may be compromised. This has significant implications as the choice of treatment may influence the effectiveness of the cognitive intervention. For example, MS patients with impaired learning and memory and a co-morbid deficit in processing speed may not benefit from memory retraining compared to those without impaired processing speed.

As noted in a prior topical review,¹¹² cognitive performance is not reliably correlated with patient self-reports of cognitive symptoms. Patient self-reports of cognitive functioning (cognition patient-reported outcomes (PROs)) are less related to actual cognitive performance than to other subjective symptoms such as depression and fatigue.^{81,113,114} While the linear relationship between SDMT and real-life activities within groups is well established, identifying definitive anchors has been challenging. This and the earlier review identify two potential anchors, unwanted job loss and employment problems, and mental status changes during relapses. In general, the available work suggests that a 10% change in SDMT is clinically relevant. Others have already proposed that a 4-point change is relevant,⁹⁰ which may also serve as a responder definition in clinical trials.¹¹⁵

The relapse anchor is interesting from several perspectives. The notion of a cognitive relapse has been discussed in the literature^{116–118} but until recently mental status was not quantified and compared to baseline levels. In the available studies, SDMT was measured in three gradations: (a) all relapsing patients, ignoring mental status as is typically the case,⁸⁸ (b) patients meeting commonly accepted criteria for relapse but with some clinical evidence of mental status change,⁸⁹ and (c) relapse defined by actual change in cognition without other clinical evidence of acute disease activity but with radiological evidence of relapse.⁹⁰ As is evident in Table 2, changes in SDMT are uniformly greater in the relapsing patients. While an SDMT definition of relapse based on only three studies may be premature, it is clear that SDMT is the most useful metric discovered thus far for studying this phenomenon.

Another issue is whether or not these studies challenge our conceptions of disease activity in MS. As cognitive changes are documented, it begs the question of how we define disease activity-free status, also termed NEDA.^{119,120} If cognition were to be

routinely monitored in all patients, regardless of their clinical presentation or subjective complaints, deterioration in cognitive status might serve as an additional indicator of disease activity. Damasceno and colleagues⁹¹ recently reported that accounting for neuropsychological test abnormalities significantly lowers estimates of NEDA over 2 years. Cognitive status and processing speed in particular influence everyday functions such as employment, household activities, money management, and use of the Internet to perform everyday tasks. Clearly, expanding NEDA beyond sensory motor functions alone and including the influence of cognitive status will result in a more valid and broader understanding of the influence of MS on everyday life. Efforts to bring cognitive assessment into the clinical routine continue, using both conventional in-person^{27,28} and computer-based self-administered tests.¹²¹

Finally, while measuring a construct by a single test such as the SDMT may be practical, such an approach runs the risk that the test does not fully represent the construct in question, that is, processing speed. Future research should be geared toward a greater theoretical understating of the concept of processing speed, as well as etiology and course of the impairment in persons with MS.

Acknowledgements

The authors gratefully acknowledge the expert services of Wendy Kaye (McKing Consulting) and the organizational support from Gary Lundstrom and Alicia West (Critical Path Institute).

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Benedict receives research support from Accordia, Novartis, Genzyme, Biogen, and Mallinckrodt Pharmaceuticals; is on the speakers' bureau for EMD Serono (designing CME courses); consults for Biogen, Genentech, Genzyme, Novartis, Abbvie, Roche and Sanofi; and receives royalties from Psychological Assessment Resources. Dr DeLuca receives grant funding from Biogen and EMD Serono, serves on an Advisory board for Biogen, and is on the speakers' bureau for EMD Serono.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Multiple Sclerosis Society (grant number RG 4869-A-1 to the Critical Path Institute).

References

1. Charcot JM. Lectures on the *Diseases of the Nervous System*. London: New Sydenham Society, 1877.
2. Rao SM, Leo GJ and St Aubin-Farbert P. Information processing speed in patients with multiple sclerosis. *J Clin Exp Neuropsychol* 1989; 11: 471–477.
3. Peyser JM, Rao SM, LaRocca NG, et al. Guidelines for neuropsychological research in multiple sclerosis. *Arch Neurol* 1990; 47: 94–97.
4. Rao SM, Leo GJ, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41: 685–691.
5. Gronwall DMA. Paced auditory serial addition task: A measure of recovery from concussion. *Percept Mot Skills* 1977; 44: 367–373.
6. Smith A. *Symbol digit modalities test: Manual*. Los Angeles, CA: Western Psychological Services, 1982.
7. Demaree HA, DeLuca J, Gaudino EA, et al. Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *J Neurol Neurosurg Psychiatry* 1999; 67: 661–663.
8. DeLuca J, Chelune GJ, Tulskey DS, et al. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J Clin Exp Neuropsychol* 2004; 26: 550–562.
9. Denney DR, Lynch SG, Parmenter BA, et al. Cognitive impairment in relapsing and primary progressive multiple sclerosis: Mostly a matter of speed. *J Int Neuropsychol Soc* 2004; 10: 948–956.
10. Costa SL, Genova HM, DeLuca J, et al. Information processing speed in multiple sclerosis: Past, present, and future. *Mult Scler*. Epub ahead of print 9 May 2016. DOI: 10.1177/1352458516645869.
11. Pyle WH. *The examination of school children: A manual of directions and norms*. New York: Macmillan, 1913.
12. Lemmon VW. *The relation of reaction time to measures of intelligence, memory and learning*. New York: Archives of Psychology, 1927; 94: 1–39.
13. Whipple GM. *Manual of mental and physical tests*. Baltimore, MD: Warwick & Sons, 1910.
14. Yerkes RM. *Psychological examining in the United States Army*. Washington, DC: Government Printing Office, 1921.
15. Wechsler D. *Wechsler-Bellevue intelligence scale*. New York: Psychological Corporation, 1939.
16. Wechsler D. *Wechsler intelligence scale for children*. New York: Psychological Corporation, 1949.
17. Smith A. Ambiguities in concepts and studies of brain damage and organicity. *J Nerv Ment Dis* 1962; 135: 311–326.
18. Smith A. Mental deterioration in chronic schizophrenia. *J Nerv Ment Dis* 1964; 129: 479–487.
19. Smith A. Consistent sex differences in a specific (decoding) test performance. *Educ Psychol Meas* 1967; 27: 1077–1083.
20. Langdon DW. Cognition in multiple sclerosis. *Curr Opin Neurol* 2011; 24: 244–249.
21. Rao SM. *A manual for the brief, repeatable battery of neuropsychological tests in multiple sclerosis*. New York: National Multiple Sclerosis Society, 1991.
22. Benedict RHB, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: A consensus approach. *Clin Neuropsychol* 2002; 16: 381–397.
23. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1999; 122: 871–882.
24. Fischer JS, Rudick RA, Cutter GR, et al. The Multiple Sclerosis Functional Composite Measure (MSFC): An integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler* 1999; 5: 244–250.
25. Benedict RHB, Krupp L, Francis G, et al. *NINDS common data elements, multiple sclerosis, neuropsychology/cognition recommendations* (ed MCW Group). Washington, DC: National Institute for Neurological Diseases and Stroke, 2012.
26. Erlanger DM, Kaushik T, Caruso LS, et al. Reliability of a cognitive endpoint for use in a multiple sclerosis pharmaceutical trial. *J Neurol Sci* 2014; 340: 123–129.
27. Benedict RHB, Amato MP, Boringa J, et al. Brief International Cognitive Assessment for MS (BICAMS): International standards for validation. *BMC Neurol* 2012; 12: 55.
28. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler* 2012; 18: 891–898.
29. Cohen JA, Reingold SC, Polman CH, et al. Disability outcome measures in multiple sclerosis clinical trials: Current status and future prospects. *Lancet* 2012; 11(5): 467–476.
30. Benedict RHB. Effects of using same vs. alternate form memory tests in short-interval, repeated assessment in multiple sclerosis. *J Int Neuropsychol Soc* 2005; 11: 727–736.

31. Benedict RHB, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Mult Scler* 2008; 940–946.
32. Drake AS, Weinstock-Guttman B, Morrow SA, et al. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: Replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler* 2010; 16: 228–237.
33. Eshaghi A, Riyahi-Alam S, Roostaei T, et al. Validity and reliability of a Persian translation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Clin Neuropsychol* 2012; 26: 975–984.
34. Spedo CT, Frndak SE, Marques VD, et al. Cross-cultural adaptation, reliability, and validity of the BICAMS in Brazil. *Clin Neuropsychol* 2015; 29: 836–846.
35. Vanotti S, Smerbeck A, Benedict RHB, et al. A new assessment tool for patients with multiple sclerosis from Spanish speaking countries: Validation of the Brief International Cognitive Assessment for MS (BICAMS) in Argentina. *Clin Neuropsychol* 2016; 30(7): 1023–1031.
36. Boringa JB, Lazeron RH, Reuling IE, et al. The brief repeatable battery of neuropsychological tests: Normative values allow application in multiple sclerosis clinical practice. *Mult Scler* 2001; 7: 263–267.
37. Benedict RH, Smerbeck A, Parikh R, et al. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: Implications for multiple sclerosis clinical trials. *Mult Scler* 2012; 18(9): 1320–1325.
38. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006; 12: 549–558.
39. Wechsler D. *WAIS-R manual*. New York: Psychological Corporation, 1981.
40. Amato MP, Portaccio E, Goretti B, et al. Relevance of cognitive deterioration in early relapsing-remitting MS: A 3-year follow-up study. *Mult Scler* 2010; 16: 1474–1482.
41. Strober L, Englert J, Munschauer F, et al. Sensitivity of conventional memory tests in multiple sclerosis: Comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. *Mult Scler* 2009; 15: 1077–1084.
42. Parmenter BA, Weinstock-Guttman B, Garg N, et al. Screening for cognitive impairment in MS using the Symbol Digit Modalities Test. *Mult Scler* 2007; 13: 52–57.
43. Benedict RHB, Cox D, Thompson LL, et al. Reliable screening for neuropsychological impairment in MS. *Mult Scler* 2004; 10: 675–678.
44. Benedict RHB, Weinstock-Guttman B, Fishman I, et al. Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol* 2004; 61: 226–230.
45. Nocentini U, Pasqualetti P, Bonavita S, et al. Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. *Mult Scler* 2006; 12: 77–87.
46. Brochet B, Deloire MS, Bonnet M, et al. Should SDMT substitute for PASAT in MSFC? A 5-year longitudinal study. *Mult Scler* 2008; 14: 1242–1249.
47. Deloire MS, Salort E, Bonnet M, et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005; 76: 519–526.
48. Huijbregts SC, Kalkers NF, de Sonneville LM, et al. Cognitive impairment and decline in different MS subtypes. *J Neurol Sci* 2006; 245: 187–194.
49. Huijbregts SC, Kalkers NF, de Sonneville LM, et al. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology* 2004; 63: 335–339.
50. Solari A, Mancuso L, Motta A, et al. Comparison of two brief neuropsychological batteries in people with multiple sclerosis. *Mult Scler* 2002; 8: 169–176.
51. Benedict RHB, Bruce JM, Dwyer MG, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Arch Neurol* 2006; 63: 1301–1306.
52. Sepulcre J, Vanotti S, Hernandez R, et al. Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. *Mult Scler* 2006; 12: 187–195.
53. Parmenter BA, Testa SM, Schretlen DJ, et al. The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2010; 16: 6–16.
54. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011; 77(2):138–144.
55. Batista S, Zivadinov R, Hoogs M, et al. Basal ganglia, thalamus and neocortical atrophy predicting slowed

- cognitive processing in multiple sclerosis. *J Neurol* 2012; 259: 139–146.
56. Dusankova JB, Kalincik T, Havrdova E, et al. Cross cultural validation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Clin Neuropsychol* 2012; 26: 1186–1200.
 57. Caceres F, Vanotti S, Benedict RH, et al. Cognitive and neuropsychiatric disorders among multiple sclerosis patients from Latin America: Results of the RELACCEM study. *Mult Scler Related Dis* 2014; 3: 335–340.
 58. Rao SM, Glatt S, Hammeke TA, et al. Chronic progressive multiple sclerosis: Relationship between cerebral ventricular size and neuropsychological impairment. *Arch Neurol* 1985; 42: 678–682.
 59. Rao SM, Leo GJ, Houghton VM, et al. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology* 1989; 39: 161–166.
 60. Christodoulou C, Krupp LB, Liang Z, et al. Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. *Neurology* 2003; 60: 1793–1798.
 61. Sanfilippo MP, Benedict RH, Weinstock-Guttman B, et al. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 2006; 66: 685–692.
 62. Benedict RHB, Bruce J, Dwyer MG, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. *Mult Scler* 2007; 13: 722–730.
 63. Stankiewicz JM, Glanz BI, Healy BC, et al. Brain MRI lesion load at 1.5T and 3T versus clinical status in multiple sclerosis. *J Neuroimaging* 2011; 21: e50–e56.
 64. Schoonheim MM, Popescu V, Rueda Lopes FC, et al. Subcortical atrophy and cognition: Sex effects in multiple sclerosis. *Neurology* 2012; 79: 1754–1761.
 65. Schoonheim MM, Hulst HE, Brandt RB, et al. Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. *Neurology* 2015; 84(8): 776–783.
 66. Benedict RH, Hulst HE, Bergsland N, et al. Clinical significance of atrophy and white matter mean diffusivity within the thalamus of multiple sclerosis patients. *Mult Scler* 2013; 19: 1478–1484.
 67. Bisecco A, Rocca MA, Pagani E, et al. Connectivity-based parcellation of the thalamus in multiple sclerosis and its implications for cognitive impairment: A multicenter study. *Hum Brain Mapp* 2015; 36(7): 2809–2825.
 68. Rao SM, Martin AL, Huelin R, et al. Correlations between MRI and information processing speed in MS: A meta-analysis. *Mult Scler Int* 2014; 2014: Article 975803. DOI: 10.1155/2014/975803.
 69. Benedict RHB, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci* 2005; 231(1–2): 29–34.
 70. Benedict RHB, Drake AS, Irwin LN, et al. Benchmarks of meaningful impairment on the MSFC and BICAMS. *Mult Scler* 2016; 22(14): 1874–1882.
 71. Strober LB, Christodoulou C, Benedict RH, et al. Unemployment in multiple sclerosis: The contribution of personality and disease. *Mult Scler* 2012; 18: 647–653.
 72. Strober L, Chiaravalloti N, Moore N, et al. Unemployment in multiple sclerosis (MS): Utility of the MS Functional Composite and cognitive testing. *Mult Scler* 2014; 20: 112–115.
 73. Honan CA, Brown RF and Batchelor J. Perceived cognitive difficulties and cognitive test performance as predictors of employment outcomes in people with multiple sclerosis. *J Int Neuropsychol Soc* 2015; 21: 156–168.
 74. Goverover Y, Chiaravalloti N and DeLuca J. Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and performance of everyday life tasks: Actual reality. *Mult Scler* 2016; 22: 544–550.
 75. Benedict RHB. *Brief visuospatial memory test—Revised: Professional manual*. Odessa, FL: Psychological Assessment Resources, Inc., 1997.
 76. Goverover Y, Strober L, Chiaravalloti N, et al. Factors that moderate activity limitation and participation restriction in people with multiple sclerosis. *Am J Occup Ther* 2015; 69: 6902260020p1-9.
 77. Goverover Y, Haas S and DeLuca J. Money management activities in persons with multiple sclerosis. *Arch Phys Med Rehabil* 2016; 97(11): 1901–1907.
 78. Goverover Y, Chiaravalloti N and DeLuca J. The relationship between self-awareness of neurobehavioral symptoms, cognitive functioning, and emotional symptoms in multiple sclerosis. *Mult Scler* 2005; 11: 203–212.
 79. Kalmar JH, Gaudino EA, Moore NB, et al. The relationship between cognitive deficits and everyday functional activities in multiple sclerosis. *Neuropsychology* 2008; 22: 442–449.
 80. Benedict RHB and Zivadinov R. Predicting neuropsychological abnormalities in multiple sclerosis. *J Neurol Sci* 2006; 245: 67–72.

81. Carone D, Benedict RHB, Munschauer FE III, et al. Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. *J Int Neuropsychol Soc* 2005; 11: 574–583.
82. Bruce JM and Arnett PA. Self-reported everyday memory and depression in patients with multiple sclerosis. *J Clin Exp Neuropsychol* 2004; 26: 200–214.
83. Goverover Y, O'Brien AR, Moore NB, et al. Actual reality: A new approach to functional assessment in persons with multiple sclerosis. *Arch Phys Med Rehabil* 2010; 91: 252–260.
84. Goldman MD, Motl RW, Scagnelli J, et al. Clinically meaningful performance benchmarks in MS: Timed 25-foot walk and the real world. *Neurology* 2013; 81: 1856–1863.
85. Morrow SA, Drake A, Zivadinov R, et al. Predicting loss of employment over three years in multiple sclerosis: Clinically meaningful cognitive decline. *Clin Neuropsychol* 2010; 24: 1131–1145.
86. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Mult Scler* 2010; 16: 1385–1392.
87. Beck AT, Steer RA and Brown GK. *BDI-fast screen for medical patients: Manual*. San Antonio, TX: Psychological Corporation, 2000.
88. Morrow SA, Jurgensen S, Forrestal F, et al. Effects of acute relapses on neuropsychological status in multiple sclerosis patients. *J Neurol* 2011; 258(9): 1603–1608.
89. Benedict RH, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. *Mult Scler* 2014; 20(13): 1745–1752.
90. Pardini M, Uccelli A, Grafman J, et al. Isolated cognitive relapses in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014; 85(9): 1035–1037.
91. Damasceno A, Damasceno BP and Cendes F. No evidence of disease activity in multiple sclerosis: Implications on cognition and brain atrophy. *Mult Scler* 2016; 22: 64–72.
92. Langdon D. A useful annual review of cognition in relapsing MS is beyond most neurologists—NO. *Mult Scler* 2016; 22: 728–730.
93. Lengenfelder J, Bryant D, Diamond BJ, et al. Processing speed interacts with working memory efficiency in multiple sclerosis. *Arch Clin Neuropsychol* 2006; 21: 229–238.
94. Leavitt VM, Lengenfelder J, Moore NB, et al. The relative contributions of processing speed and cognitive load to working memory accuracy in multiple sclerosis. *J Clin Exp Neuropsychol* 2011; 33: 580–586.
95. Genova HM, Lengenfelder J, Chiaravalloti ND, et al. Processing speed versus working memory: Contributions to an information processing task in multiple sclerosis. *Appl Neuropsychol Adult* 2012; 19: 132–140.
96. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICES workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull* 2005; 31: 5–19.
97. Kern RS, Green MF, Nuechterlein KH, et al. NIMH-MATRICES survey on assessment of neurocognition in schizophrenia. *Schizophr Res* 2004; 72: 11–19.
98. Green MF and Nuechterlein KH. The MATRICES initiative: Developing a consensus cognitive battery for clinical trials. *Schizophr Res* 2004; 72: 1–3.
99. Lovell M, Collins M and Bradley J. Return to play following sports-related concussion. *Clin Sports Med* 2004; 23: 421–441.
100. Iverson GL, Lovell MR and Collins MW. Interpreting change on ImPACT following sport concussion. *Clin Neuropsychol* 2003; 17: 460–467.
101. Rudick RA, Miller D, Bethoux F, et al. The Multiple Sclerosis Performance Test (MSPT): an iPad-based disability assessment tool. *J Vis Exp* 2014 Jun 30; (88): e51318.
102. Bergsland N, Zivadinov R, Dwyer MG, et al. Localized atrophy of the thalamus and slowed cognitive processing speed in MS patients. *Mult Scler* 2016; 22: 1327–1336.
103. Modica CM, Bergsland N, Dwyer MG, et al. Cognitive reserve moderates the impact of subcortical gray matter atrophy on neuropsychological status in multiple sclerosis. *Mult Scler* 2015; 22(1): 36–42.
104. Roy S, Rodgers J, Drake AS, et al. Stable neuropsychiatric status in multiple sclerosis: A 3-year study. *Mult Scler* 2015; 22(4): 569–574.
105. Bruce JM, Bruce AS and Arnett PA. Mild visual acuity disturbances are associated with performance on tests of complex visual attention in MS. *J Int Neuropsychol Soc* 2007; 13: 544–548.
106. Benedict RH, Smerbeck A, Parikh R, et al. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: Implications for multiple sclerosis clinical trials. *Mult Scler* 2012; 18: 1320–1325.
107. Denney DR and Lynch SG. The impact of multiple sclerosis on patient's performance on the Stroop Test: Processing speed versus interference. *J Int Neuropsychol Soc* 2009; 15: 451–458.

108. Drew MA, Starkey NJ and Isler RB. Examining the link between information processing speed and executive functioning in multiple sclerosis. *Arch Clin Neuropsychol* 2009; 24: 47–58.
109. Owens EM, Denney DR and Lynch SG. Difficulties in planning among patients with multiple sclerosis: A relative consequence of deficits in information processing speed. *J Int Neuropsychol Soc* 2013; 19: 613–620.
110. Genova HM, DeLuca J, Chiaravalloti N, et al. The relationship between executive functioning, processing speed, and white matter integrity in multiple sclerosis. *J Clin Exp Neuropsychol* 2013; 35: 631–641.
111. Chiaravalloti ND, Stojanovic-Radic J and DeLuca J. The role of speed versus working memory in predicting learning new information in multiple sclerosis. *J Clin Exp Neuropsychol* 2013; 35: 180–191.
112. Benedict RH and Walton MK. Evaluating cognitive outcome measures for MS clinical trials: What is a clinically meaningful change? *Mult Scler* 2012; 18(12): 1673–1679.
113. Vanotti S, Benedict RHB, Acion L, et al. Validation of the Multiple Sclerosis Neuropsychological Screening Questionnaire in Argentina. *Multiple Sclerosis* 2009; 15: 244–250.
114. O'Brien A, Gaudino-Goering E, Shawaryn M, et al. Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch Clin Neuropsychol* 2007; 22: 933–948.
115. Benedict RHB, Cohan S, Lynch SG, et al. Improved cognitive outcomes in relapsing-remitting multiple sclerosis with daclizumab HYP in the phase 3 DECIDE study. *Am Acad Neurol* 2016.
116. Foong J, Rozewicz L, Quaghebeur G, et al. Neuropsychological deficits in multiple sclerosis after acute relapse. *J Neurol Neurosurg Psychiatry* 1998; 64: 529–532.
117. Prado FM, Kosac VA and Dib JG. Cognitive relapse in multiple sclerosis: Report of 3 cases. *Mult Scler J* 2012; 18: 1830–1831.
118. Patzold T, Schwengelbeck M, Ossege LM, et al. Changes of the MS functional composite and EDSS during and after treatment of relapses with methylprednisolone in patients with multiple sclerosis. *Acta Neurol Scand* 2002; 105: 164–168.
119. Kieseier BC and Stuve O. A critical appraisal of treatment decisions in multiple sclerosis—Old versus new. *Nat Rev Neurol* 2011; 7: 255–262.
120. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 2015; 72: 152–158.
121. Rudick RA, Miller D, Bethoux F, et al. The Multiple Sclerosis Performance Test (MSPT): An iPad-based disability assessment tool. *J Vis Exp* 2014; 88: e51318.

Visit SAGE journals online
<http://msj.sagepub.com>

 SAGE journals