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Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire

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Background Brief cognitive performance tests and self-report measures of neuropsychological symptoms have been proposed for screening purposes in multiple sclerosis (MS) clinics. To better understand the reliability of screening methods, two tests, the Symbol Digit Modalities Test (SDMT) and the MS Neuropsychological Screening Questionnaire (MSNQ), were administered to 76 patients with MS and 25 healthy controls, matched on demographic characteristics.

Methods Tests were administered at monthly intervals, over 6 months. In addition, the Beck Depression Inventory Fast Screen for medical patients (BDIFS) was administered to monitor for changes in depression. Our objectives were to determine the reliability of these measures and the relative contribution of cognitive impairment and depression in predicting self-report MSNQ scores.

Results Results showed that both the SDMT and MSNQ have good to excellent reproducibility over repeated testing. In MS, there are minimal practice effects over successive tests, in the order of 0.2 SD for SDMT and minimal change in the MSNQ. Regression analyses modeled to predict MSNQ based on SDMT and BDIFS showed significant contribution for both, but with the majority of variance being accounted for depression.

Conclusions We conclude that these brief screening tests provide some independent information about the mental status of patients with MS and are reliable, even when used in monthly, successive examinations. *Multiple Sclerosis* 2008; **14:** 940–946. http://msj.sagepub.com

Key words: cognition; depression; multiple sclerosis; screening

Introduction

The efficiency of screening tests for detecting patients at risk for neuropsychological impairment continues to be a topic of great interest in the multiple sclerosis (MS) literature. Many patients with MS complain of cognitive or psychiatric problems, and in large-sample, cross-sectional studies, roughly 50% showed impairment on objective cognitive tests [1,2]. Such impairment has important implications in the clinical management of patients with MS. Deficits on neuropsychological testing are associated with work disability [2–5], poorer rehabilitation outcomes [6], and social maladjustment [3,7,8]. Recent studies that report potential medical treatments for processing speed [9] and memory [10] deficits in MS emphasize the importance of early identification and monitoring of MS-associated cognitive disorder.

Two tests have shown particular promise in efforts to screen for cognitive impairment in MS, the Symbol Digit Modalities Test (SDMT) [11] and the MS Neuropsychological Screening Questionnaire (MSNQ) [12]. The SDMT is a performance measure that requires patients to visually scan a key of number/symbol pairings and then voice the

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correct number for randomly presented symbols as rapidly as possible. This neuropsychological test requires about 5 min to administer. There is a single outcome measure – the total number of correct responses in 90 s. Test–retest reliability was very good over 1 week in a recent study of 34 patients with MS [13]. SDMT performance is strongly associated with lesion burden [14], ventricle enlargement [15–17], cortical atrophy [18], deep gray matter atrophy [14], collateral reported cognitive problems [19], and unemployment [5]. The test has reasonable sensitivity and specificity in predicting performance on a larger battery of cognitive tests and is easily implemented in the clinical setting [20].

In contrast to the SDMT, the MSNQ is a self-report measure of cognitive and neuropsychiatric problems that may be encountered in everyday living circumstances. There are 15 statements describing difficulty with attention, processing speed, memory, emotional control, and social skills. Each item is ranked from 0 [does not occur] to 4 [very often, very disruptive] such that the total score reflects the degree of perceived impairment. There are two MSNQ forms, self- and informant-report. The latter is more strongly correlated with neuropsychological testing, brain imaging, and neuropsychiatric symptoms [19]. The self-report form is significantly correlated with cognitive performance in most studies but more so with self-reported depression [12]. In one study examining self/informant report discrepancies [21], depression was most prominent in patients who reported markedly greater cognitive problems than informants. Thus, in general, we have concluded that the self-report MSNQ informs the clinician that the patient is at high risk for cognitive or psychiatric involvement [22].

Both the SDMT and MSNQ are brief and could be quite useful for screening purposes, but little is known about their reliability and feasibility when used repeatedly in the clinic setting. The purpose of this study was to investigate these tests in patients with MS seen at monthly intervals. We hypothesized that reliability coefficients would be good to high and that practice effects would be evident but not significant when compared with normal control participants. In addition, we hypothesized that the validity of the MSNQ as a measure of both cognitive and emotional status would be maintained across all time points.

Methods

Participants

We recruited 85 patients with MS agreeing to undergo 90–120 min of neuropsychological testing, neurologic evaluation, and five monthly follow-up examinations lasting about 15 min. All were recruited from a single MS care center in the eastern United States. Informed consent was obtained as per institutional review board requirements. The subjects were paid $50 USD for each clinic visit. The study was conducted as a pilot study in parallel with an ongoing international, multi-center, open-label study of the effects of natalizumab in MS. The primary goal was to generate comparative data for monthly administration of SDMT and MSNQ in patients with MS not treated with natalizumab, and to use the data to explore possible thresholds for detecting mild changes in cognitive function in natalizumab-treated patients. The patients recruited for this study were not involved in any other research protocol. Three of the 85 patients withdrew from the study after the second assessment, voicing a desire to change disease modifying therapy, and six did not return to the clinic for unknown reasons. Exclusion criteria were: 1) current or past medical or psychiatric disorder other than MS that could affect cognitive function, 2) substance abuse, 3) neurological impairment that might interfere with psychometric testing, 4) change in psychotropic or disease modifying medication, and 5) MS relapse or corticosteroid pulse within the past 6 weeks. For the 76 patients completing the study, the mean (±SD) age was 47.6 ± 8.4 years and mean education was 14.7 ± 2.2 years. The majority (74%) of the sample was female and Caucasian (91%). Mean disease duration was 11.6 ± 7.6 years. Expanded Disability Status Scale (EDSS) [23] scores were available for all participants (median = 3.0, range = 1.0–7.0). Diagnoses [24] and MS course [25] were based on established guidelines for research protocols in MS (relapsing–remitting [RR] = 63, secondary progressive [SP] = 11, primary progressive [PP] = 2). The disease modifying therapy was as follows: 39 interferon β-1a, 3 interferon β-1b, 15 glatiramer acetate, and 19 untreated. These subgroups did not differ on SDMT or MSNQ by Kruskal–Wallis test.

Also assessed were 25 healthy volunteers, free of neurological and psychiatric history. These subjects also signed informed consent forms and were paid at the same rate as the patient group. Controls were group-matched to the patients with MS as follows: age 44.5 ± 10.9 years, education 15.5 ± 1.6 years, 84% female, 88% Caucasian.

Tests and procedures

Baseline evaluation

Prospective patients and controls were initially screened for entrance criteria via telephone

interview and chart review. Those agreeing to participate were seen initially in both the neurology clinic and the neuropsychology testing area of the MS Center. On the first visit, in the clinic, a structured neurological evaluation [BWG] was used to derive the EDSS [23] score.

Monthly assessments

The patients then underwent neuropsychological testing using the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery [2,26]. The MACFIMS has been described previously and includes the following tests: Controlled Oral Word Association Test [27], Judgment of Line Orientation Test [27], California Verbal Learning Test, second edition [28], Brief Visuospatial Memory Test – Revised [29], Paced Auditory Serial Addition Test [30,31], SDMT [11,31], and the DKEFS Sorting Test [32]. Using a normal control sample from our previous work [2], *z* scores were calculated for each test measure. From the 10 measures, we calculated a mean MACFIMS *z* score for each participant. The SDMT was administered using the method of Rao, *et al*. [31], thus, omitting the written response form of the test. Subjects were presented with symbol–number pairings at the top of an 8.5 × 11-inch page and asked to voice the digit for each unpaired symbol as quickly as possible. The variable of interest was the number of correct responses in 90 s.

The MSNQ was administered before objective testing. As noted above, the MSNQ is a paper and pencil test that includes 15 statements concerning cognitive problems that may arise in the course of day-to-day life. Participants were asked to designate a number from 0 to 4 for each statement with higher numbers indicating greater intensity and frequency of the perceived problem (range of possible scores is 0–60). Participants also completed the Beck Depression Inventory Fast Screen (BDIFS), a questionnaire including seven items assessing mood, self-evaluation, anhedonia, and suicidal ideation, with the degree of symptom gauged on a 0–3 scale. This self-report measure of depression avoids symptoms that may have a neurological or medical basis (e.g., insomnia, fatigue, anergia) and is frequently used in medical populations. It has been recently validated in an MS sample [33].

The SDMT, MSNQ, and BDIFS were all administered at monthly intervals beginning 30 days (±7 days) after the initial evaluation. Nursing and research staff, having no previous training in neuropsychological testing, were taught to administer these tests in accordance with published instructions. In brief, for the self-report questionnaires, testing staff were merely on hand to answer questions that the participant may have about a specific question. For the SDMT, testing staff reviewed a training video demonstration developed by the first author and then practiced the testing under his direction. Questionnaires were always administered before the SDMT. Staff administering these monthly assessments were blind to baseline evaluation results.

Statistical analysis

As in previous studies [20,21,34], Kolmogorov–Smirnov testing showed that the SDMT and MSNQ tests conformed with a Gaussian distribution at all time points, in both MS patients and controls. On the contrary, as would be expected, BDIFS was skewed positively, as there were many 0 scores, especially among normal controls. For the regression analyses, we attempted to control for differences in the sample distribution across tests via $\log_{10}$ transformation. General linear models were used to construct mixed-factor ANOVAs, where time was treated as a repeated factor and group as a between factor. Throughout the study, we adopted an α criterion of $P < 0.05$. As MSNQs were not obtained from 17 patients during the initial examination, the MSNQ model was limited to the last five time points. Effect sizes were calculated according to the Cohen's *d* statistic, representing the difference between the means divided by the pooled SD. Cognitive impairment was defined as a mean MACFIMS *z* score less than –1.0. The regression models were used to determine whether SDMT and BDIFS predict MSNQ scores at each time point. Each model used a forward selection procedure with age entered as a covariate in step one, followed by BDIFS, MSNQ, disease duration, and EDSS in step two.

Results

The ANOVA for the SDMT showed a significant group × trial interaction ($F = 3.0$, $P = 0.015$). As shown in Figure 1, the most parsimonious explanation for the interaction is a steeper learning curve in normal controls versus MS. Both within-groups main effects were significant as were the individual group comparisons at each time point. However, visual inspection of the data clearly showed that the degree of change was more notable in the normal control group. Controls improved from 62.0 ± 11.3 to 71.4 ± 13.2, a total change of $d = 0.8$. On the other hand, the degree of improvement among patients with MS was far less, from 49.8 ± 12.4 to 52.5 ± 14.3 ($d = 0.2$).

A similar analysis was conducted to determine whether learning effects would differ between cogni-

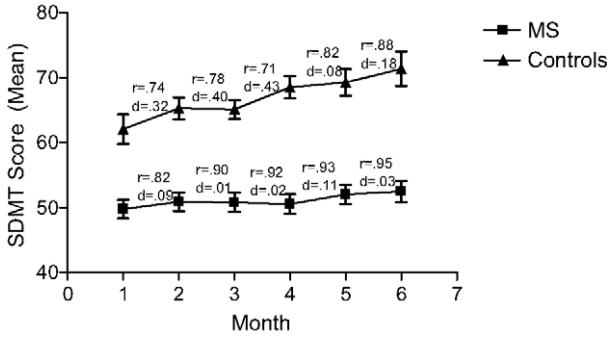

Figure 1 Presented are the Symbol Digit Modalities Test (SDMT) raw scores for 76 patients with MS and 25 healthy volunteers, along with the test–retest correlation between each time point, and the degree of change as measured by Cohen's *d*. The data were analyzed using a general linear model, which showed a significant group × time interaction. Both within-groups main effects were significant as were the individual group comparisons at each time point. However, visual inspection of the data clearly shows that the degree of change is more notable in the normal control group. The data further show that the SDMT is reliable across all time points in both groups.

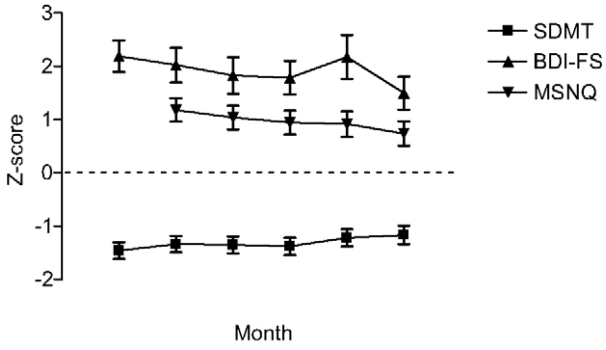

Figure 2 Presented are the *z* scores of the MS group based on normal controls studied previously. Lower *z* scores for SDMT represent impairment in that patients responding to fewer stimuli than controls. For the self-report BDIFS and MSNQ, the elevated *z* scores represent a greater frequency of reported cognitive and emotional problems. The mean *z* scores at each time point are generally outside a 1 SD demarcation showing significant impairment. In addition, there is minimal change over 6 months on all three tests.

tively impaired and preserved MS patients. Patients with MS had a significantly lower mean MACFIMS *z* score than controls [MS mean = –0.83 ± 0.83, control mean = –0.10 ± 0.60; $P < 0.001$], and 40% of the patients with MS were impaired. When the impaired and normal MS patient subgroups were compared on SDMT learning effects, the ANOVA showed significant main effects for group and time, but no significant interaction, indicating that the learning effect did not differ between more severely affected versus minimally affected patients.

The ANOVAs for the BDIFS and MSNQ failed to reveal a significant interaction with both analyses showing only a group difference. In each case, patients with MS showed greater pathology as evidenced by significantly higher scores throughout the 6-month interval [BDIFS between group main effect $F = 20.9$, $P < 0.001$; MSNQ between group main effect $F = 31.4$, $P < 0.001$]. For comparison, the *z*-score equivalents for patients with MS, based on the normal control group, are presented in Figure 2. It can be seen that for all three tests, mean MS patient scores over about 1 SD from the normal mean.

The test–retest correlations comparing the results of one test with the preceding test showed that all three tests were moderately to strongly reproducible in patients with MS. As can be seen in Figure 1, SDMT test–retest correlations were consistently above 0.80 and ranged from 0.82 to 0.95. Test–retest correlations ranged from $r = 0.74$ [test 4 to test 5] to 0.85 [test 3 to test 4] for BDIFS and from 0.86 [test 2 to test 3] to 0.90 [test 3 to test 4] for MSNQ.

Finally, linear regression models were calculated for MSNQs at each time point to determine whether SDMT and/or BDIFS would account for significant variance in self-reported neuropsychiatric symptoms. As can be seen in Table 1, bivariate correlations showed stronger correlation between the MSNQ and the BDIFS than with SDMT at each time point. Three of the five linear regression models were additive; however, with both SDMT and BDIFS accounting for significant variance. The

Table 1 Regression models predicting MSNQ at each of five monthly time points

Time point	SDMT *r*	BDIFS *r*	Variable in model step one	R^2 step one	Variable entering step two	Final model R^2	*P*
Month 2	–0.33	0.58	BDIFS	0.35	SDMT	0.40	0.016
Month 3	–0.33	0.61	BDIFS	0.37	None	0.37	<0.001
Month 4	–0.24	0.61	BDIFS	0.38	None	0.38	<0.001
Month 5	–0.30	0.48	BDIFS	0.24	SDMT	0.28	0.044
Month 6	–0.38	0.58	BDIFS	0.34	SDMT	0.38	0.049

Each model used a forward selection procedure with age entered as a covariate in step one, followed by Beck Depression Inventory Fast Screen (BDIFS), Symbol Digit Modalities Test (SDMT), disease duration, and Expanded Disability Status Scale (EDSS) in step two.

final R^2 values ranged from 0.28 to 0.40, suggesting that SDMT and BDIFS combined account for roughly 1/3 of the variance in MSNQ.

Discussion

The primary purpose of the study was to investigate the stability of neuropsychological screening tests in MS. The SDMT is a well-known cognitive performance measure emphasizing processing speed and visual working memory. The MSNQ is a self-report screening questionnaire shown to correlate with cognitive impairment in some studies but more robustly with emotional status [12,21,34]. It may be possible to effectively screen for the neuropsychological complications of MS by using these tests in combination, on a routine basis. Our results clearly show that both the SDMT and the MSNQ are reliable when administered by nursing staff at monthly intervals. The data also indicate that these tests provide some independent information regarding the mental status of patients with MS.

Test–retest coefficients were acceptable to strong for both tests and showed very little variation over the course of the study. There were no test–retest correlations below the commonly accepted threshold of $r = 0.80$ [35]. Moreover, several test–retest coefficients approached or surpassed the 0.90 level. The current findings parallel previous work showing good test–retest reliability with these measures using a weekly assessment schedule [12,13]. Good reliability is a critical psychometric principle when developing tests used to screen for clinical compromise. Confidence intervals (also known as the Reliable Change Index) surrounding follow-up mean values, used to gauge the clinical significance of deviations from expectation, are based on the standard deviation and reliability of the outcome measure [36]. When tests lack reliability, large deviations from expected performance may be due to chance variability. The high reliability for the SDMT and MSNQ when used on a monthly basis means that these tests can be used to identify patients at high risk for neuropsychological compromise with minimal error, in the clinic setting.

An entirely different question is whether the meaning of the test scores is valid both at baseline and on monthly follow-ups. Both tests significantly discriminated between patients with MS and controls, and the degree of difference between the groups did not change over time (Figures 1 and 2). The validity of the SDMT is well established in MS cross-sectional research. Within the MACFIMS, the SDMT is the most sensitive test in distinguishing between patients with MS and controls [2,19,20] and RR versus SP course [18]. It is significantly associated with vocational disability after accounting for EDSS and depression [5]. Factor analysis of the MACFIMS finds the SDMT loading on either a unique processing speed factor or splitting contributions between a general cognitive factor and visual memory [2]. In several studies, the SDMT has been the most strongly correlated cognitive test with a wide range of MRI variables [15–17,37]. We have also shown that the SDMT has good sensitivity and specificity when predicting neuropsychological impairment as assessed with portions of the MACFIMS battery [20]. The SDMT takes less time than the Paced Auditory Serial Addition Test [30], is more sensitive [2], and can be administered easily in the clinic by nursing or research staff without electronic or computer equipment. These studies suggest that the SDMT is a good choice when clinicians or researchers need a sensitive test for measuring some limited aspect of cognitive impairment in MS. In this study, we find that the SDMT remains valid for discriminating patients from controls even when it is administered six times on a monthly basis.

The question of validity was also examined in the regression models where we attempted to determine the most significant correlate of the MSNQ. From its inception [34], it was understood that correlations between the MSNQ and tests of depression were higher than with neuropsychological testing. Such a finding makes sense as it is well known that depression is associated with complaints of poor memory [38,39]. In a study of metamemory in MS [40], patients were asked to estimate their cognitive ability and then tested neuropsychologically. Cognitive abilities were overestimated by non-depressed patients, underestimated by mildly depressed patients, and accurately estimated by moderately depressed patients. Using the MSNQ, Carone, *et al.* [21] classified patients into over-estimators and under-estimators of their cognitive ability, relative to informant ratings. Over-estimators were characterized by greater degrees of cognitive impairment, euphoric behavioral disinhibition, and unemployment, whereas under-estimators were more likely to be depressed. This research shows how self-reports and informant reports of cognitive capacity in MS are differentially influenced by patient depression. The current data are consistent with these findings in that BDIFS was a stronger predictor of self-report MSNQ than SDMT.

However, we also note that a majority of the regression models were additive, retaining both BDIFS and SDMT. We interpret this to suggest that combining the SDMT and MSNQ may be a useful approach to routine screening. The MSNQ relies on the patient's self-perception of cognitive and neuropsychiatric vulnerability. Studies show that the patient-reported MSNQ is modestly correlated with neuropsychological testing and, unlike the

informant-report MSNQ, is more strongly correlated with depression than cognitive functioning [12,21,34,41]. Therefore, the utility of this screening measure when used alone is limited. However, like investigators in other diseases [42,43], we find that although depression accounts for the majority of variance in self-reported cognitive impairment, objective performance does contribute smaller but statistically significant variance. Thus, when combined with the SDMT, these tests may be effective because they supply independent sources of data, patient self-report, and cognitive capacity. Both tests can be completed in less than 5 min and require minimal experience for administration. In this study, the tests were reliably administered by nursing and research staff with minimal neuropsychological testing experience.

There are a number of limitations in this study. Repeated experience with these subjects probably led to nursing and research staff testers becoming unblinded to the patients versus control status of some subjects. Because the MACFIMS was only administered at baseline, and there was no inclusion of brain imaging or repeated independent psychiatric interview, we have no independent criterion of cognitive disorder or depression at each time point. The only validity criterion available consistently over 6 months was the discrimination of MS and normal controls. Therefore, we were unable to assess the sensitivity and specificity of the SDMT or the MSNQ over time. The monthly time interval was selected to match the needs of the Safety of TYSABRI® Re-dosing and Treatment (STRATA) study – monthly assessments were deemed necessary to screen for possible neuropsychiatric complications of natalizumab, a medication that is administered on a monthly basis. It would have been preferable, perhaps, to use a test–retest interval more closely aligned with the more usual clinical follow-up schedule, for example, every 6 months.

These concerns notwithstanding, we provide evidence supporting the reproducibility and validity of these tests over six monthly exams. Both the SDMT and MSNQ can be administered very quickly with minimal equipment. Future work will investigate these properties in a much larger sample of patients with MS participating in the STRATA study.

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