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Reliable screening for neuropsychological impairment in multiple sclerosis

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In an earlier study, we developed the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) to assist in the screening for neuropsychological (NP) impairments. Self-report MSNQ scores correlated significantly with measures of depression, whereas informant-report MSNQ scores correlated with cognitive performance, but not depression. This study was criticized for use of a small sample and lack of data regarding normal performance and test–retest reliability. The present study was designed to replicate the earlier work with a larger sample of patients and normal controls obtained from multiple sites. We also evaluated the test–retest reliability and predictive validity of the MSNQ. The sample included 85 multiple sclerosis (MS) patients and 40 normal controls, matched on demographic variables. All participants completed the MSNQ and underwent NP testing. Thirty-four patients were re-examined at one week. Pearson and ANOVA techniques were utilized for univariate comparisons. Bayesian statistics were calculated to assess predictive validity. Patient self- and informant-report MSNQ scores differed from normal and test–retest reliability indices were high. Both self- and informant-reports were correlated with cognitive dysfunction and depression scales. Self-report MSNQ scores correlated more strongly with depression than cognitive performance, whereas the opposite pattern was observed with informant-report scores. Bayesian statistics showed that informant-report MSNQ scores predict cognitive impairment and patient self-report scores identify patients with cognitive impairment or depression. It is concluded that the MSNQ is useful, although patient self-reports may be exaggerated in depressed patients or reduced in patients with severe cognitive impairment.
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Introduction

Cognitive dysfunction is common in multiple sclerosis (MS)[1,2] and predictive of vocational disability and poor quality of life.[3] Neuropsychological (NP) testing is useful for monitoring cognition during treatment with either disease-modifying or symptomatic medications.[4] Unfortunately, NP testing is time consuming and costly, thus limiting application in some settings. We therefore developed the MS Neuropsychological Screening Questionnaire (MSNQ) to obviate both the technical and professional components of NP evaluation during the screening process.[5]

In a preliminary study,[5] we reduced a pool of 80 items to 15 via Rasch analysis and created patient self-report and informant-report forms. Patient reports were more strongly correlated with depression than MS cognitive performance. In contrast, informant-report MSNQ scores correlated strongly with cognition. We then investigated the sensitivity and specificity of the MSNQ and found it comparable to the validity of previously reported psychometric screening methods. However, the sample size was small, test–retest reliability was not assessed, and normal controls were not studied.

In the present study, we endeavoured to replicate and extend this earlier work in a multicentre trial that included normal controls and analysis of test–retest effects.

Methods

Subjects

Eighty-five patients were studied, attending one of four MS clinics (Baird MS Center, Buffalo, NY; University of California at San Francisco; University of Colorado Health Sciences Center, Denver, CO; Gimbel Center at Teaneck, NJ). Inclusion criteria were a) diagnosis of clinically definite MS,[6] b) an informant having contact with the patient at least three times per week, c) age 18 or older, d) fluent in English, and e) able to provide informed consent to all procedures. Exclusion criteria were a) current or past

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neurological disorder other than MS, b) history of psychotic disorder, c) current psychiatric disorder[7] other than mood, personality or behaviour changes following the onset of MS, d) medical condition that might influence cognition, e) history of developmental disorder (e.g., ADHD, learning disability), f) history of substance or alcohol dependence, g) current substance abuse, h) motor or sensory defect that might interfere with cognitive test performance, or i) relapse and/or corticosteroid pulse within four weeks of assessment. Expanded Disability Status Scale (EDSS)[8] scores were available for 77 patients and the median was 2.5 (range 0–7.5). Mean age was 42.4 (SD = 9.3) years. Other demographics were as follows: 14.8 years of education (SD = 2.3), 80 (94%) Caucasian, 68 (80%) female. Most patients ($n = 68$ or 80%) had relapsing–remitting rather than progressive ($n = 17$ or 20%) course. Most informants ($n = 53$ or 62%) were spouses: 13 informants were parents, 11 were a 'domestic partner or friend', and the remaining 8 designated 'other family member'. Informants reported an average of 6.5 (SD = 1.6) days of patient contact per week. On average, informants had known their respective patient for 23.3 (SD = 13.1) years.

The normal controls ($n = 40$) were matched to patients on age (mean = 40, SD = 9.1), education (mean = 14.9, SD = 2.0), race/ethnicity (40 Caucasian) and gender ($n =$ 28 or 70% female) as demonstrated by nonsignificant ANOVA and chi-square tests. Control informant characteristics also approximated those of the MS group: 63% spouses, contacts per week = 6.0 (SD = 1.9), years known = 19.3 (SD = 11.6).

Procedure

Patient and informant-report forms of the MSNQ were handed to patients and caregivers at the beginning of each NP exam. Each packet contained explicit instructions and answers to frequently asked questions. Informants completed the questionnaires in a waiting room while patients completed theirs in exam rooms prior to testing. The following tests were then administered: Controlled Oral Word Association Test (COWAT),[9] Judgement of Line Orientation Test (JLO),[10] California Verbal Learning Test second edition (CVLT-II),[11] Brief Visuospatial Memory Test-Revised (BVMT-R),[12] and adapted versions[13] of the Paced Auditory Serial Addition Test (PASAT)[14] and the Symbol Digit Modalities Test (SDMT).[15] The Wisconsin Card Sorting Test (WCST, $n = 57$)[16] and/or D-KEFS Sorting Test (DST, $n = 59$) were also administered to most patients. The 10-item version of the Center for Epidemiologic Studies Depression Scale (CES-D-10)[17] was administered to assess for mood disorder. In addition, patients completed the Beck Depression Inventory – Fast Screen for Medical Patients (BDI-FS),[18] which was recently validated in this population.[19] Test–retest effects were examined at one-week intervals in 34 randomly selected patients.

Analysis

Pearson and ANOVA techniques were utilized to examine correlations and group effects, respectively. A conservative threshold of $p < 0.01$ was selected to control for type 1 error. Internal consistency was tested using Cronbach's alpha analysis. Patient data were converted to Z scores based on control values. Cognitive impairment was defined as a) a mean z score of < -1.5 across the four attention and memory measures believed to be most sensitive to MS-associated cognitive impairment,[20] or b) the presence of one severe ($z < -2.0$) and two mild ($z < -1.5$) defects, or two severe defects, across all cognitive measures. Bayesian statistics predicting cognitively impaired versus normal patients were calculated in the traditional way: sensitivity = no. true positives/no. impaired patients, specificity = no. true negatives/no. intact patients, positive predictive value (PPV) = no. true positives/no. positive MSNQs, negative predictive value (NPV) = no. true negatives/no. negative MSNQs.

Results

Performance was significantly lower in MS patients on nearly all NP measures (CVLT, PASAT and DST $p < 0.01$; all others $p < 0.001$ except WCST $p = 0.23$). Patients also produced elevated scores on the CES-D-10 ($p < 0.001$). Mean MSNQ scores were significantly ($p < 0.001$) higher in patients than controls (mean ± SD, MS self-report = 27.4 ± 11.9, control self-report = 16.0 ± 6.2, MS informant-report = 21.3 ± 12.9; control informant-report = 12.9 ± 7.6).

Cronbach's coefficient alpha values were in the acceptable range[21] for patients (patient form = 0.94; informant form = 0.93) and controls (patient form = 0.84; informant form = 0.89). Test–retest correlations for MS patients were similarly high (patient form = 0.90; informant form = 0.93).

Validity coefficients (Table 1) show that both versions of the test were correlated ($p < 0.01$) with low cognitive performance and elevated CES-D-10. However, whereas the self-report form correlated most strongly with CES-D-10, the opposite was true of the informant-report form.

There were 30 (35%) cognitively impaired patients. We selected cut-off scores yielding maximum classification accuracy and sensitivity values of at least 0.80 (Table 2). For the patient self-report form, scores exceeding 24 classified 68% of patients as cognitively impaired or normal. Bayesian statistics were as follows: sensitivity = 0.83, specificity = 0.60, PPV = 0.53, NPV = 0.87. We noted that of five false negatives, three were patients that achieved z scores less than -2.0 on three or more tests, and were associated with high (> 32) informant-report MSNQ scores.

We then observed that false-positive classification errors often occurred in patients with elevated BDI-FS scores. To address this, patients were reclassified as 'affected' if there was evidence of cognitive impairment *or* depression. In accordance with the BDI-FS manual,[18] patients with scores of 4 or greater were placed in the affected group. There were 45 cases with either cognitive impairment or an elevated BDI-FS score, comprising 53% of the sample. Using a cut-off of > 23, 74% of patients were correctly classified as affected versus normal. The Bayesian statis-

Table 1 Validity coefficients for MSNQ

	Correlation with MSNQ patient self-report form	*Correlation with MSNQ informant-report form*
Controlled Oral Word Association Test	−0.17	−0.33†
Judgement of Line Orientation	−0.44‡	−0.36†
CVLT-II Total Learning	−0.37‡	−0.45‡
CVLT-II Delayed Recall	−0.42‡	−0.50‡
BVMT-R Total Learning	−0.46‡	−0.57‡
BVMT-R Delayed Recall	−0.45‡	−0.55‡
PASAT	−0.38‡	−0.59‡
Symbol Digit Modalities Test	−0.45‡	−0.58‡
WCST Perseverative Responses	0.29	0.35†
D-KEFS Sorting Correct Sorts	0.30	−0.38†
Composite *Z*	−0.49‡	−0.64‡
CESD-10 Depression	0.61‡	0.37‡

Probability values: † = $p < 0.01$, ‡ = $p < 0.001$.

tics were as follows: sensitivity = 0.80, specificity = 0.68, PPV = 0.73, NPV = 0.75.

Finally, a score exceeding 22 on the informant-report form correctly classified 85% of patients on the basis of cognitive impairment (sensitivity = 0.87, specificity = 0.84, PPV = 0.74, NPV = 0.92).

Discussion

The purpose of this study was to replicate previous findings that supported the validity of the MS Neuropsychological Screening Questionnaire (MSNQ), a brief self-administered, 15-item test that reflects NP competence with activities of daily living. In the earlier work, we found that informant-report MSNQ scores predicted cognitive impairment with a high degree of accuracy. However, the sample was small and we did not study normal controls or test–retest effects. The present multicentre study included a healthy control sample, providing normative data for clinical interpretation and a uniform standard for determining impairment on a wide range of cognitive tests. The internal consistency of the MSNQ was supported in both healthy controls and MS patients. Test–retest reliability indices were very high in MS patients reexamined at one-week intervals. In contrast to the earlier work, the MSNQ patient self-report form was correlate with cognitive dysfunction, although to a lesser degree than with self-reported depression. Thus we conclude that when the MSNQ is used to screen for either cognitive or depressive disorders (as indicated by elevated BDI-FS scores), we find reasonable sensitivity and positive predictive values. Bayesian statistics (Table 2) for the informant-report MSNQ are acceptable and similar to preliminary work.[5]

Table 2 Bayesian statistics for MSNQ in comparison to NP test batteries

Screening method	*% Correctly classified*	*Sens*	*Spec*	*PPV*	*NPV*
MSNQ self-report	68	0.83	0.60	0.53	0.87
MSNQ self-report (including depressed pts)	74	0.80	0.68	0.73	0.75
MSNQ informant-report	85	0.87	0.84	0.74	0.92
MSNQ informant-report, Benedict *et al.*[5]	94	0.83	0.97	0.91	0.95
NP screening battery, Franklin *et al.*[25]	nr	0.55	0.94	nr	nr
NP screening battery, Rao *et al.*[26]	nr	0.68	0.85	nr	nr
NP screening battery, Beatty *et al.*[27]	nr	0.80	0.91	nr	nr

Sens = sensitivity, Spec = specificity, nr = not reported.

Screening for cognitive disorders is fraught with threats to validity. Memory complaints are associated with depressive disorder,[22,23] and MS patients with dementia often lack insight and overestimate cognitive capacity.[24] In the present study, three impaired patients with composite *z* scores less than −2.0 had normal self-report MSNQ scores, while their informants generated elevated scores. On the other hand, we found that false-positive classification errors were common in depressed patients. Thus, clinicians should continue to collateral sources of information such as caregiver or informant reports when assessing cognitive complaints in MS patients. The MSNQ is an attempt to accomplish this with maximal standardization, reliability and brevity.

As can be seen in Table 2, the sensitivity and specificity values reported here are comparable to those reported in previous efforts to screen for cognitive impairment using brief psychometric methods.[25–27] These so-called 'screening batteries' require up to 30 minutes of professional time. The MSNQ, particularly when used in conjunction with the BDI-FS, is more cost effective than these psychometric methods because there is no need for additional clinical appointments. Both tests can be administered in a waiting room setting in less than 5 minutes, and tallied by clinicians in a matter of seconds.

Yet, however promising, the MSNQ should not supplant NP testing. Our data indicate that classification errors do occur, particularly when only the self-report form of the test is used. The self-report MSNQ is particularly vulnerable to the influence of depressive disorder. Prevalence estimates place lifetime risk for major depressive disorder in MS from 25 to 50%[28,29] and if subsyndromal depression is considered, prevalence estimates rise considerably.[30] Thus, ambiguity about the interpretation of elevated self-report MSNQ scores in this subpopulation may limit its applicability, especially when patients are seen without a reliable informant. High scores on the patient self-report form only indicate that there is high risk for cognitive impairment *or* depression.

In summary, cognitive impairment is frequently missed during routine neurological evaluation. Identifying patients with early cognitive impairment is important in that defects predict problems with quality of life, and cognitive tests provide a basis for monitoring patients during

treatment. As a brief and cost-effective procedure, the MSNQ shows promise as an effective screening method.

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