The Value of Self-Reported Cognitive Performance in low, medium and high EDSS

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Abstract

Background: The inconsistent association of patient-reported Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) scores with performance-based cognitive tests in MS could be related to the degree of disability, due to certain MSNQ-questions assuming some self-dependence and intact instrumental ADLs.

Objectives: To test whether the relation between subjective and objective cognitive performance could be moderated by physical disability as measured by the Expanded Disability Status Scale (EDSS), we assessed the correlation between MSNQ and Symbol Digit Modalities Test (SDMT) scores in different EDSS groups.

Methods: From 288 MS patients who completed the patient-report MSNQ and a two-question screening tool for depression, we also collected SDMT and EDSS scores. We analysed correlations in the total group and three EDSS subgroups: Low 0.0 – 3.0, Medium 3.5 – 6.0 and High 6.5 – 9.5.

Results: We found a significant and negative correlation between patient-reported MSNQ scores and SDMT scores in the low EDSS (r = -.225, p = .044), but not in the medium and high EDSS groups, and significant positive correlations between MSNQ and depression in all subgroups.

Conclusions: Our data suggest that the patient-report MSNQ has potential as a measure of cognition in patients with low EDSS-scores but not in the medium and high EDSS ranges.
Introduction

Multiple sclerosis (MS), the most common inflammatory and neurodegenerative disease presenting in young adults, affects more than two million people worldwide. While the clinical heterogeneity is substantial, between 34 and 65% of persons with multiple sclerosis (PwMS) suffer from cognitive impairment (CI). The most frequently affected areas of cognition are cognitive processing speed and memory, with impairment of visuospatial abilities and executive functions found less commonly.2-5

Because neuropsychological test batteries6,7 are time-consuming and require professional expertise for application and interpretation, single screening and monitoring tools are proposed. The Symbol Digit Modalities Test (SDMT), a sensitive measure of cognitive processing speed,8 is considered the best rapid assessment tool of cognition in clinical practice.9 The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) was developed as a survey to assess perceived cognitive and to a lesser extent neuropsychiatric problems, using 15 questions that are scored by frequency of symptoms, with a patient-report and an informant-report version.10

Further studies revealed that correlation patterns for the patient-report and informant-report version of the MSNQ differed. First of all, only the patient-report version correlated with screening measures for depression.10-14 Second, even though the patient-report questionnaire frequently weakly correlated with objective cognitive test results, this correlation was consistently more pronounced in the informant-report version.10-13,15 These observations resulted in the interpretation that elevated scores obtained with the patient-report version are rather explained by depression whereas the informant-report version is considered a sensitive and validated screening tool for CI.11 Regardless of its link with depression, the impact of subjective cognitive complaints in MS may be substantial, taking into consideration its associations with reduced employment and work performance,16-17 health-related quality of life,16 health-promoting behaviours16,18 and reduced thalamic and cortical grey matter volumes.19

While Kurtzke Expanded Disability Status Scale (EDSS)20 scores were not taken into account when selecting questions for the MSNQ,10 later studies included patients with a wide variety of neurological disability, with EDSS scores ranging from 0 to 9.5 and median EDSS values ranging between 2.5 and 5.0.10,12,14,15 In this context, the characteristics of the study population could potentially explain the discrepancy in correlations between MSNQ scores and objective test results.

We hypothesise that the patient-report MSNQ performs worse as a cognitive screening measure in patients with higher EDSS scores. This is based on the assumption that some questions of the MSNQ may not be relevant for patients with high EDSS scores and restricted autonomy. Furthermore, when assessing discrepancies between self- and informant-reported cognitive performance with the MSNQ, overestimators performed worse on neuropsychological test batteries than underestimators and accurate estimators.21 Since higher EDSS scores have been associated with an increased risk of objective cognitive decline,22,23 overestimating cognitive performance when completing the patient-report MSNQ, resulting in lower MSNQ scores, can be expected to occur in a higher proportion of patients with moderate to severe disability.

To evaluate our hypothesis, we investigate correlations between MSNQ and SDMT scores in low, medium and high EDSS groups with and without correcting for other variables. As a secondary line of questioning, we investigate the correlations of individual questions of the MSNQ with SDMT scores in low, medium and high EDSS groups and calculate the ability of these questions of the MSNQ to predict the total test score.
Methods

MS patients, aged 18 years or older, who were diagnosed with definite MS according to the McDonald criteria and registered in the EDMUS database from the University Hospital Brussels and the National Multiple Sclerosis Center, were included. 1908 patients received a postal survey, including the patient-report MSNQ and two-question screening tool for depression in MS, a reliable tool for identifying depression in PwMS. Sex, age, onset date (date of first symptoms), phenotype at onset, years of education, SDMT score within the last six months before or after the survey and EDSS score were retrieved from the database. For a more detailed description of the methods used, we refer to previous publications on this data set.

Patients were included if there was a full data set for the screening for depression, EDSS, MSNQ and SDMT scores. One missing value in the MSNQ was imputed by the mean item score. When more than one question of the MSNQ was not answered, this patient was excluded. The cohort was divided into three subcohorts according to EDSS scores: Low 0.0 – 3.0, Medium 3.5 – 6.0 and High 6.5 – 9.5.

Results were reported as means with 95% confidence intervals (CI 95%), medians with ranges or as percentages. The relations between MSNQ, SDMT, EDSS and depression and between SDMT scores and the individual MSNQ-questions were investigated through Pearson correlations in the total population and EDSS subgroups. Significance is reported before and after correction for multiple testing through use of the Bonferroni correction. Multiple linear regression analyses were performed to estimate the contribution of the above-mentioned variables to the SDMT score in the total population and EDSS subgroups. The performance of the model was assessed based on R² and adjusted R² and a t-test was used to identify the significantly contributing explanatory variables. The relation between individual MSNQ-questions and the total MSNQ score was assessed using an item response analysis. A two-sided test with a type I error probability of 0.05 was used.
Results

Population characteristics

In Table 1 the characteristics of the three subgroups and the total population are listed.

| Baseline characteristics | All         | Low EDSS    | Medium EDSS | High EDSS   |
|--------------------------|-------------|-------------|-------------|-------------|
|                          | 288/751 (38.35%) | 81/751 (10.79%) | 123/751 (16.38%) | 84/751 (11.19%) |
| Age                      | 52.5 [51.4 - 53.6] | 46.1 [44.3 - 48.0] | 53.5 [52.1 - 55.0] | 57.0 [55.0 - 59.1] |
| Female, n/N (%)          | 187/288 (64.9 %)  | 58/81 (71.6 %)   | 83/123 (67.5 %)   | 46/84 (54.8 %)    |
| Pediatric, n/N (%)       | 101/288 (35.1 %)  | 23/81 (28.4 %)   | 40/123 (32.5 %)   | 38/84 (45.2 %)    |
| Sex                      | 213/288 (74.0 %)  | 72/81 (88.9 %)   | 92/123 (74.8 %)   | 49/84 (58.3 %)    |
| Disease duration         | 19.2 [18.2 - 20.1] | 14.3 [12.8 - 15.8] | 19.1 [17.8 - 20.5] | 23.8 [21.8 - 25.9] |
| Depressed, n/N (%)       | 158/288 (54.9 %)  | 44/81 (54.3 %)   | 67/123 (54.5 %)   | 47/84 (56.0 %)    |
| EDSS                     | 4.8 [4.5 - 5.0]   | 2.0 [1.9 - 2.2]  | 4.9 [4.7 - 5.0]   | 7.2 [7.1 - 7.4]   |
| MSNQ                     | 22.3 [21.1 - 23.5] | 21.9 [19.7 - 24.1] | 22.4 [20.7 - 24.1] | 22.5 [20.2 - 24.8] |
| Depressed, n/N (%)       | 130/288 (45.1 %)  | 37/81 (45.7 %)   | 56/123 (45.5 %)   | 37/84 (44.0 %)    |
| SMDT                     | 4.68 [4.5 - 48.2] | 55.0 [52.9 - 57.1] | 47.1 [45.3 - 49.0] | 38.5 [36.0 - 41.0] |

Table 1: Population characteristics.

Correlations

As listed in Table 2 and shown in Figure 1-2, the negative correlation between MSNQ and SDMT scores in the low EDSS group is not present in the medium and high EDSS groups and the total population. An adverse correlation between EDSS and MSNQ scores was found in the high EDSS group only (Figure 4).

| Var1 | Var2 | r   | p-value | r   | p-value | r   | p-value | r   | p-value |
|------|------|-----|---------|-----|---------|-----|---------|-----|---------|
| MSNQ | SDMT | -0.114 | 0.054 | -0.225* | 0.044* | -0.129 | 0.160 | -0.025 | 0.820 |
| EDSS | MSNQ | -0.010 | 0.870 | 0.211 | 0.058 | -0.126 | 0.170 | -0.220* | 0.044* |
| EDSS | SDMT | -0.507 | < 0.001 | -0.357 | 0.001 | -0.322 | < 0.001 | -0.137 | 0.220 |
| MSNQ | Depression | 0.329 | < 0.001 | 0.360 | 0.001 | 0.376 | < 0.001 | 0.242* | 0.027* |

Table 2: Pearson correlations: Correlations that are significant are marked in green, those that are significant before correction (p<0.05) but become insignificant after correction for multiple testing (p<0.05/16) are marked with *.
Figure 1-6: Scatter plots of MSNQ-SDMT, EDSS-MSNQ and EDSS-SDMT in total population and EDSS subgroups.
When analysing correlations between SDMT scores and individual questions of the MSNQ (see Table 3 for the themes of the different questions), we found significant correlations for the different EDSS groups (see Table 4).

| Question number | Descriptors                          |
|-----------------|--------------------------------------|
| 1               | Distractibility                      |
| 2               | Problems listening to others         |
| 3               | Slowed processing                    |
| 4               | Forgetting appointments              |
| 5               | Forgetting what is read              |
| 6               | Forgetting shows or programs         |
| 7               | Forgetting instructions              |
| 8               | Needing frequent reminders           |
| 9               | Failing to follow through on planned activities |
| 10              | Failing to answer questions coherently |
| 11              | Failing to track two things at once  |
| 12              | Failing to follow conversations      |
| 13              | Problems controlling impulses        |
| 14              | Laughing or crying without cause     |
| 15              | Excessive egocentric speech          |

Table 3: Themes of the MSNQ questions.10

| MNSQ question | All | Low EDSS | Medium EDSS | High EDSS |
|---------------|-----|----------|-------------|-----------|
|               | r   | p-value  | r           | p-value   | r         | p-value   |
| 1             | -0.02 | 0.734  | -0.05 | 0.651 | -0.10 | 0.290 | -0.07 | 0.531 |
| 2             | 0.01 | 0.925  | -0.04 | 0.731 | -0.06 | 0.532 | -0.08 | 0.473 |
| 3             | -0.22 | <0.001 | -0.18 | 0.112 | -0.24* | 0.011* | -0.11 | 0.324 |
| 4             | -0.05 | 0.381  | -0.18 | 0.110 | -0.11 | 0.238 | 0.11 | 0.321 |
| 5             | -0.07 | 0.248  | -0.22 | 0.052 | -0.06 | 0.503 | -0.03 | 0.801 |
| 6             | -0.10 | 0.097  | -0.26* | 0.021* | -0.14 | 0.135 | 0.03 | 0.794 |
| 7             | -0.10 | 0.111  | -0.12 | 0.274 | -0.13 | 0.154 | -0.05 | 0.630 |
| 8             | -0.12* | 0.0499* | -0.18 | 0.101 | -0.16 | 0.083 | -0.03 | 0.802 |
| 9             | -0.05 | 0.452  | -0.12 | 0.285 | -0.16 | 0.088 | 0.05 | 0.683 |
| 10            | -0.18 | 0.003  | -0.31* | 0.005* | -0.14 | 0.144 | -0.08 | 0.475 |
| 11            | -0.20 | 0.001  | -0.21 | 0.058 | -0.26* | 0.004* | -0.08 | 0.460 |
| 12            | -0.15* | 0.015* | -0.34 | 0.002 | -0.07 | 0.485 | -0.08 | 0.494 |
| 13            | -0.14* | 0.024* | -0.19 | 0.093 | -0.10 | 0.291 | -0.12 | 0.261 |
| 14            | 0.06  | 0.321  | -0.13 | 0.258 | 0.14  | 0.126 | 0.12 | 0.300 |
| 15            | 0.00  | 0.976  | 0.00  | 0.985 | -0.08 | 0.412 | 0.02 | 0.857 |

Table 4: Correlations between the SDMT and individual MSNQ questions in the total population and EDSS subgroups. Correlations that are significant are marked in green, those that are significant before correction (p<0.05) but become insignificant after correction for multiple testing (p<0.05/16) are marked with *. 
Multiple linear regression

To estimate the combined contribution of different variables to the SDMT score in the total population and the EDSS subgroups, multiple regression analyses were performed. The analysis for the total population is shown in Figure 7-8. EDSS and MSNQ both significantly and negatively contributed to the predicted value of the model, with an increase of 1 EDSS-point corresponding to a decrease of 2.72 points and an increase of 1 MSNQ-point corresponding to a decrease of 0.14 points in the predicted SDMT score respectively. None of the correction variables significantly contributed. The contribution of MSNQ scores was no longer significant in the EDSS subgroup analyses (data not shown).

![Multiple linear regression model of SDMT in the total population](image)

**Figure 7-8:** Multiple linear regression model of SDMT in the total population: in the graph on the left side the output variable, namely the SDMT, is plotted against the predicted output variable of the model. In case of a perfect prediction all data points would fall on the first bisector indicated by the black dotted line. To evaluate the prediction statistically the univariate regression line between prediction and actual value is plotted in red, which indicate the average predicted value. The light red area indicates the uncertainty of this prediction. In the graph on the right side the regression coefficients of the input variables are plotted as bars. Additionally, the uncertainty intervals for each coefficient is indicated by the black whiskers on top of the bars. Coefficients with an individual significant contribution are plotted as a blue bar, coefficients that are not significant are plotted as a red bar.

Item response analysis

An item response analysis calculates the ability of a single question to predict the total test score. The lower the response strength, the worse this question performs as a predictor of the total score. This analysis was carried out for the MSNQ for the whole group and each EDSS subgroup. The last two questions in the total and medium EDSS group and the last three questions in the high EDSS group scored below 0.5 in response strength, with a tendency to decrease in the higher EDSS groups. No questions performed below 0.5 in response strength in the low EDSS group (see Figure 9-10).

![Item response analysis of the MSNQ in the total population and EDSS subgroups](image)

**Figure 9-10:** Item response analysis of the MSNQ in the total population and EDSS subgroups.
Discussion

We found a negative correlation between the patient-reported MSNQ and SDMT scores in the low EDSS group, not in the medium and high EDSS groups. This suggests that patient-reported MSNQ scores reflect cognitive functioning, at least to some degree in the low EDSS group. Also, MSNQ scores contributed significantly and negatively to the prediction of SDMT scores when correcting for several variables. This finding is in line with the original research finding by Benedict et al. that processing speed is a significant predictor of MSNQ scores.10 The significant correlation between MSNQ and SDMT scores was lost after correction for multiple testing, when using a very conservative method of correction for multiple testing.16 There was no significant contribution of the MSNQ in the subgroup analysis of the regression model for SDMT, probably reflecting the smaller sample sizes in each subgroup.

In previous studies investigating the relationship between the MSNQ and objective cognitive tests, a significant relationship between patient-report MSNQ and SDMT scores was only found in patient samples with a median EDSS ≤ 3.0,12,15 not in samples with a higher median EDSS.10,11,14 Of note, all studies, except one,14 had a sample size of less than 100 subjects. The different pattern of correlations between individual questions of the MSNQ and SDMT scores across the EDSS groups and the decreasing number of questions correlating with SDMT scores from low to medium to high EDSS group, support our conclusion that the MSNQ behaves differently in the low EDSS group compared to the medium and high groups.

The absent correlation between MSNQ and SDMT scores in the medium and high EDSS groups and the negative correlation between MSNQ and EDSS in the high EDSS group suggest that the patient-report MSNQ performs worse as a cognitive screening measure in higher EDSS ranges. In the introduction we proposed two possible explanations. First of all, we expected that questions such as ‘Do you forget appointments?’ or ‘Do you forget errands that were planned?’ (questions 4 and 9) would be less relevant in the higher EDSS ranges. Unexpectedly, these questions had an acceptable and comparable response strength with the item response analysis in all EDSS groups. While in the low EDSS group, all 15 questions had an acceptable response strength, we found a relatively homogeneous pattern of response strengths in the first twelve questions and significantly lower response strengths for the last three questions in the medium and high EDSS groups. The first twelve questions focus on cognitive issues and the last three questions assess behavioural changes. Finding the last three questions to be less predictive of the total MSNQ score, is in line with the inconsistent relationship between the presence of behavioural changes as measured by the Frontal Systems Behavior Scale and CI in MS reported in two small studies.27,28 The reduced response strength of the last three questions in the higher EDSS ranges could explain why the MSNQ performs worse as a cognitive screening measure in the higher EDSS ranges. Our second hypothesis to explain the worse performance of the MSNQ in the higher EDSS ranges related to the overestimation of cognitive functioning, resulting in lower MSNQ scores, being associated with more severe cognitive impairment,22 more frequently seen in the higher EDSS ranges.22,23 The inverse correlation between MSNQ and EDSS scores observed in the high EDSS group only supports this explanation. In case of an accurate patient-reported assessment of cognition, we would have expected a positive correlation due to the presumably higher prevalence of CI in higher EDSS ranges.

Nevertheless, even when considering patients with a low EDSS score, the correlation between the MSNQ and SDMT scores remains weak, limiting its use in daily practice as a cognitive screening measure. The most important criticism on the patient-report MSNQ is its association with depression.10-14 It was found that underestimators by the patient-report MSNQ relative to the
informant-report MSNQ had higher scores on the Beck Depression Inventory (BDI) than overestimators and accurate estimators.\textsuperscript{21} We confirmed the association of MSNQ scores with depression across all EDSS subgroups in our study. The prevalence of depression was also similar in all subgroups. As a consequence, we do not expect the presence of depression to explain the difference in correlations between the MSNQ and SDMT in the three groups. Moreover, it is important to note that depression plays an important role in processing speed,\textsuperscript{29,30} the first and most widely affected cognitive domain in MS,\textsuperscript{31} as well as memory and executive functions in PwMS.\textsuperscript{31} Since there is also a link between depression and performance-based cognitive tests, the link between patient-reported cognitive complaints and depression should not negate its role as a cognitive screening test. Indeed, Marrie et al. found that, independent of mood, fatigue, and physical impairment, subjective CI as measured by the Perceived Deficits Questionnaire reflects subtle declines in cognitive processing speed and memory and that patient-reported cognitive complaints should therefore not be discounted due to depression.\textsuperscript{32}

In the general population, patients with subjective memory complaints are twice as likely to develop dementia compared to patients without complaints. Long-term studies showed that 14\% of these patients developed dementia and 27\% developed mild CI over a period of four years.\textsuperscript{33} According to a recent review of the literature,\textsuperscript{34} multiple possible underlying causes and risk factors of subjective cognitive decline should be considered (e.g. depression, medication side-effects, normal aging), as some are potentially modifiable. Biomarker studies in Alzheimer’s disease are indicating that this decline may correspond to preclinical dementia, with perceived cognitive impairment being the first symptom of neurodegenerative disease. Since depression and subjective cognitive impairment often co-occur, the authors recommend to not immediately attribute these symptoms to mood disorders. Moreover, a wide array of strategies to promote brain health can be recommended in patients with subjective cognitive symptoms. These strategies include controlling cardiovascular risk factors, promoting an active and healthy lifestyle, treating mood disorders, engaging in cognitive and social activities, stress reduction and sleep hygiene.\textsuperscript{34} Based on the associations of subjective cognitive concerns with reduced thalamic and cortical grey matter volumes in PwMS,\textsuperscript{19} subjective CI could likewise predict further cognitive decline in PwMS. In this context, we recommend that these complaints be monitored in addition to the current neuropsychological screening batteries used in daily practice. These patients could be candidates for early interventions in the future.

Important strengths of our study are that, as far as we know, we are the first to assess the relationship between measures of objective and subjective cognitive performance in different EDSS groups, as well as the first to analyse the relationship between the different MSNQ questions and an objective measure of processing speed. Participants were recruited from two centres, representing a broad range of EDSS scores. A limitation is the cross-sectional study design. Furthermore, as already discussed,\textsuperscript{14,16} there was a moderate response rate to the survey, with a possibility of selection bias. Another weakness is that the MSNQ was sent by post and performed by the patient at home, which makes completion of the survey in a controlled environment impossible. The SDMT was assessed within six months before or after the survey, which could introduce bias since SDMT and MSNQ scores were not obtained at the same time. Finally, another limitation is that only one objective cognitive test was carried out.

As a recommendation for future research, we propose to investigate the value of the patient-report MSNQ as a predictive measure of cognition, through a prospective study investigating serial tests of MSNQ and SDMT over several years. Furthermore, it is worth assessing whether the relationship between subjective cognitive performance (as measured by the MSNQ, as well as other scales) and
neuropsychological tests assessing other cognitive domains, such as memory and executive functioning, is also moderated by physical disability.

In summary, we found evidence that the patient-report MSNQ has potential as a cognitive measure in patients with a low EDSS score, not in the medium and high EDSS ranges, regardless of its link with depression. Since the correlations with objective measures of cognition are weak, its use as a single cognitive screening measure is limited in daily practice. Nevertheless, there is emerging evidence that subjective cognitive performance has important implications for the patient’s daily life and that it may predict future cognitive decline. Overall, the patient-report MSNQ could have an added value to the neuropsychological screening batteries that are currently used when assessing cognitive performance.

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