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Original article

Correlations of health status indicators with perceived neuropsychological impairment and cognitive processing speed in multiple sclerosis

Marie B. D'hooghe[a,b,c,1,*], Alexander De Cock[a,b,1], Ann Van Remoortel[a], Ralph H B Benedict[d], Piet Eelen[a], Erika Peeters[a], Miguel D'haeseleer[a,b,c], Jacques De Keyser[b,c,e], Guy Nagels[a,b,c,f]

[a] Neurology, National MS Center, Vanheylenstraat 16, 1820 Melsbroek, Belgium
[b] Center for Neurosciences, Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussel, Belgium
[c] Neurology, UZ Brussel (VUB), Laarbeeklaan 101, 1090 Brussel, Belgium
[d] Neurology, SUNY Buffalo, BGH 100 High Street Suite D6, Buffalo, NY, USA 14226
[e] Neurology, Universitair Medisch Centrum Groningen (UMCG), Groningen, the Netherlands
[f] St Edmund Hall, Oxford University, Queen's Ln, Oxford OX1 4AR, UK

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ABSTRACT

Background: Comorbidity and health behaviours may explain heterogeneity regarding cognitive performance in multiple sclerosis. Patient-reported cognitive difficulties have impact but do not consistently correlate with objective cognitive performance.

Our study aims to investigate whether health status indicators including comorbidities, body mass index, physical activity, smoking, sleeping behaviour and consumption patterns for fish, alcohol and caffeinated drinks are associated with measures of subjective and objective cognitive performance.

Methods: Survey data on self-reported cognitive performance, assessed with the MS Neuropsychological Screening Questionnaire (MSNQ), were related to the presence of arterial hypertension, diabetes mellitus, cardiovascular and chronic renal diseases, hypercholesterolemia, depression based on 2-question screening tool, health and consumption behaviors. We included the Symbol Digit Modalities Test when available within 6 months as an objective, performance-based metric of cognitive processing speed. We investigated the interrelation between all variables with a Spearman correlation matrix and corrected for multiple testing. Regression models were built and controlled for age, sex and phenotype.

Results: We used available data from 751 patients with definite MS, including 290 SDMT scores within a time window of 6 months, to study relations between variables. MSNQ and SDMT scores were not significantly correlated. Correlation patterns for subjective and objective performance differed. Age, disease duration and physical disability correlated with SDMT scores only.

Regression analyses could be performed for MSNQ scores in 595/751 (79.2%) and for SDMT scores in 234/751 (31.2%) participants. After restricting variables to avoid collinearity and adjusting for the number of variables, regression models explained 15% of the variance for subjective and 14% of the variance for objective cognitive performance. A higher number of physical comorbidities, reporting depressive symptoms, sleeping 9 h or more and daily use of sleeping medication were associated with lower subjective cognitive performance, whereas increasing age was associated with reduced processing speed. These associations persisted after correction for multiple testing.

Conclusion: Increasing age is associated with reduced cognitive processing speed whereas comorbidities and sleep behaviors contribute to subjective cognitive performance.

1. Introduction

MS, a chronic inflammatory and neurodegenerative disease, is characterized by substantial clinical heterogeneity. While demographic and disease-specific variables explain part of the variability, the disease course remains largely unpredictable.

Comorbidities, smoking and cardiovascular risk factors have been related to increased disease progression (Marrie et al., 2010;

* Corresponding author at: Neurology, National MS Center, Vanheylenstraat 16, 1820 Melsbroek, Belgium.
E-mail address: marie.dhooghe@mscenter.be (M.B. D'hooghe).
[1] Shared first authorship.

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Moccia et al., 2015; Hempel et al., 2017). Lower education levels and lower neighbourhood socioeconomic status have also been associated with increased disability progression (Harding et al., 2019; D'Hooghe M et al., 2016). These observations suggest that factors amenable to modification, including lifestyle or comorbidity could be involved. Most studies focussed on the disability, as measured with the Expanded Disability Status Scale (EDSS). However, because the EDSS scale is heavily weighted towards physical disability, the impact of cognitive impairment may be underestimated. Despite having low EDSS scores, patients may perceive cognitive difficulties and have mild to moderate cognitive impairment (Migliore et al., 2017). While patient-reported cognitive difficulties are frequent and have impact on patient's lives, they do not consistently correlate with objective cognitive performance as currently measured (Ruet and Brochet, 2018). Whether this relates to the heterogeneity of cognitive impairment, depression or difficulties in measuring cognition, remains to be clarified. Information processing speed appears to be a key deficit in MS. Cognitive monitoring with the Symbol Digit Modalities Test (SDMT), a valid measure of latent processing speed, has been highly recommended (Benedict et al., 2017).

We used an extensive questionnaire assessing comorbidities, health and consumption behaviour and subjective cognitive performance in a large group of MS patients to correlate health variables with perceived neuropsychological impairment assessed with the MS Neuropsychological Screening Questionnaire (MSNQ) scores (Benedict et al., 2004). In a subset of participants, we correlated oral SDMT scores obtained during clinical follow up within a predefined time window. We included questions assessing fish intake frequency and preference based on studies suggesting a protective effect of a diet rich in fish in inflammatory diseases (Fetterman and Zdanowicz, 2009), including MS (D'Hooghe M et al., 2011), and a benefit of n-3 fatty acids on attention and processing speed in cognitive impaired older subjects (Mazereeuw et al., 2012).

The goal of our project is to investigate whether comorbidities and health behaviours as indicators of the patient's health status are associated with perceived neuropsychological impairment, assessed with the MS Neuropsychological Screening Questionnaire (MSNQ) (Benedict et al., 2003) and reduced information processing speed (Costa et al., 2017), as measured with the oral version of the SDMT.

2. Materials and methods

2.1. Study design and population

This cross-sectional, multicenter study collected data about comorbidities, health and consumption behaviours, MS treatment status (never, ever, current), self-reported neuropsychological functioning and depressive symptoms. The study protocol, survey, patient information and informed consent obtained approval by the ethical committees at the university hospital Brussel and the National MS Center, Melsbroek. All MS patients from both centres, registered in the EDMUS database, a protected database containing information on clinical and treatment data, were invited to participate. Sex, age, MS onset date (defined as date of first manifestations of clinical symptoms), MS phenotype at onset and Expanded Disability Status Scale (EDSS) scores were retrieved from the database. If no neurological assessment was available in a time window of 6 months before or after the survey, we used the self-reported scale of disability developed for the European study on costs and quality of life in MS (Kobelt, 2006), based on the validated description in the EDSS (Kurtzke, 1983) and on the patient determined disease steps instrument (Hohol et al., 1999).

The primary outcomes were the MSNQ (Benedict et al., 2003), obtained as part of the survey and the oral version of the SDMT, a valid measure of cognitive processing speed (Costa et al., 2017), obtained during neuropsychological testing and/or clinical follow up within a time period of 6 months before or after the survey in a subset of participants at the National MS Center, Melsbroek.

2.2. Outcome variables

The MSNQ is a brief, validated, self-administered test with 15 questions reflecting neuropsychological competence during activities of daily living (Benedict et al., 2003). The 15 MSNQ items have 5 response options, from 0 (does not occur) to 4 (very often, very disruptive). A total score is calculated with a range from 0 to 60 with imputation of one missing value by a mean item score (Sonder et al., 2012). In case of 2 missing values, subject data are excluded (Sonder et al., 2012). A cutoff value of > 23 has been proposed to classify patients correctly as affected, either depressed or cognitive impaired, versus not depressed or impaired (Benedict et al., 2004).

The SDMT is sensitive to information processing speed deficits, the most prevalent cognitive difficulty in MS (Costa et al., 2017). It is the first cognitive deficit to emerge in MS and has been proposed as a sentinel test for cognitive impairment in MS (Van Schependom et al., 2014). A cut-off value of 40 has been proposed to predict outcome based on an extensive Neuropsychological Screening Battery for MS (Van Schependom et al., 2014).

2.3. Explanatory variables

We based the survey on a questionnaire used in 2009 (D'Hooghe M et al., 2011) and considered the following health status indicators as explanatory variables: education level (<12, 12–15 and > 15 years), comorbidity count and a range of health behaviours including smoking, physical activity, sleep duration, sleeping medication and consumption patterns for alcohol (combining frequency and dose in units per month), caffeine (combining frequency and dose of caffeine containing drinks in units per day) and fish including frequency (3 categories < 1 monthly, between 1 monthly and 1 weekly, and at least 2 weekly) and fish preference (lean fish, no preference, fatty preference). Smoking status included the possibilities never (or max 100 cigarettes ever), ever (not current, > 100 cigarettes) and daily. Hours of sleep per night (8 h or less, 9 h or more), use of sleeping medication (never, ever and daily) and physical activity score (0–8) based on Marshall et al. (2005) were requested. Weight and height were used to calculate BMI. The co-existence of comorbidities such as arterial hypertension, diabetes mellitus, cardiovascular and chronic renal diseases, and hypercholesterolemia were questioned and summed, resulting in a comorbidity count (Marrie et al., 2016). To assess depressive symptoms, we included the 2-question screening tool for depression. These questions are possible effective to identify individuals with major depressive disorder (level C evidence). An affirmative response to either question results in a positive screen for depression (Minden et al., 2014).

2.4. Statistics

The Spearman correlation matrix was computed to study the interrelation between all variables. To reduce the likelihood of false positives associated with a large number of statistical tests, the significance level was corrected for multiple testing by dividing by the number of tests ($p<0.05/210$).

Because correlations consider two variables at the time, and may therefore fail to account for confounding effects, we also performed a multiple linear regression analysis to estimate the contribution of age, sex, onset phenotype, education, the number of comorbidities, depression, health and consumption variables to MSNQ and SDMT scores. The set of explanatory variables was constructed such that the highest correlation was lower than 0.40 and the highest variance inflation factor (VIF) was lower than 5, ensuring a sufficiently low collinearity between the explanatory variables to warrant an interpretation of the individual contribution of the explanatory variables. The overall performance of the linear regression models was evaluated based on R^2 and adjusted R^2. A *t*-test was used to identify the explanatory variables that contributed significantly to the outcome, both before (p-value $<$

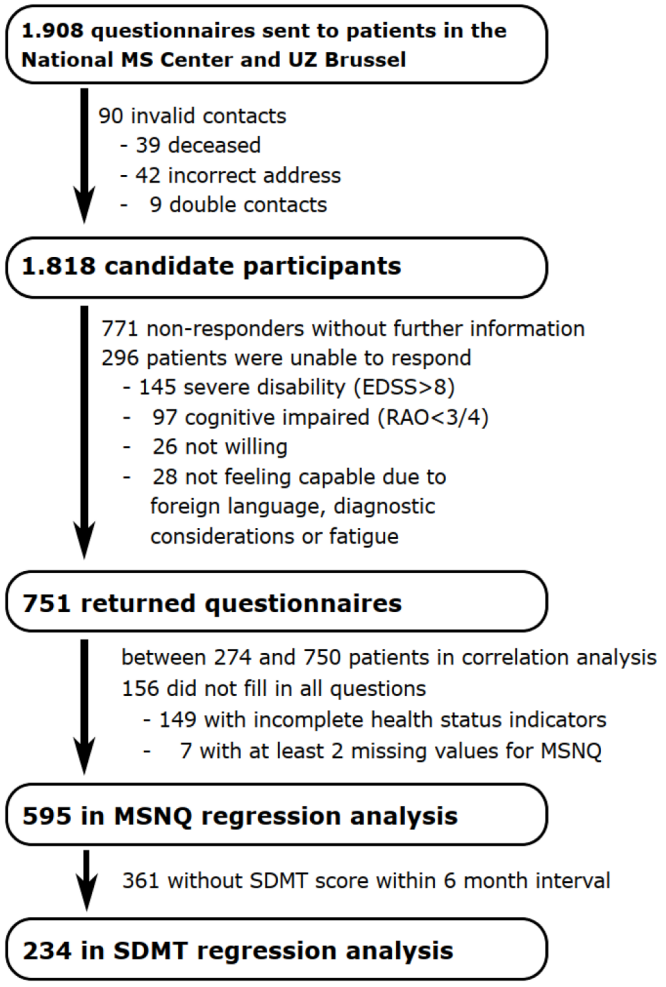

Fig. 1. Flow chart.

0.05) and after adjustment for the number of explanatory variables (p-value $< 0.05/22$).

3. Results

3.1. Descriptive characteristics

As shown in Fig. 1, a final response from 751 patients with definite MS was obtained. A substantial number of surveys (156/751) had missing values leading to a variable number of data for each analysis depending on the variables used. SDMT scores within a time window of 6 months were available in 290 participants. Sample sizes for the correlation analysis ranged from 274 to 750 samples. Regression analyses were performed for MSNQ scores in 595/751 (79.2%) and for SDMT scores within 6 months in 234/751 (31.2%) participants. Demographic, MS, explanatory and outcome variables in the total population, the MSNQ and SDMT regression subsets are presented in Table 1. The most common reported comorbidities were hypercholesterolemia (n = 195), arterial hypertension (n = 134), heart disease (n = 87), diabetes mellitus (36) and renal disease (n = 15).

3.2. Correlation between explanatory variables

Spearman correlations between all variables are graphically represented in Fig. 2. The significant correlations between explanatory variables that persist after multiple testing (see green diamonds in Fig. 2) are given in Table 2, including the number of data available for each combination of variables.

Age significantly correlated with disease duration (rho = 0.59), EDSS (rho 0.49), treatment status (rho −0.45) and progressive onset phenotype (rho = 0.29), as well as comorbidity (rho 0.34), physical activity score (rho −0.30) and BMI (rho = 0.16).

3.2.1. Univariate relations between explanatory and outcome variables

As shown in Table 3, reporting depressive symptoms (rho 0.30), more hours of sleep (rho 0.15) and sleeping medication (rho 0.16) were significantly correlated with MSNQ scores, after correction for multiple testing. The significant correlations of age (rho −0.36), disease duration (rho −0.34) and EDSS (rho −0.50) with SDMT scores survived multiple testing.

SDMT and MSNQ scores were not significantly correlated whereas SDMT and EDSS scores were strongly correlated (Fig. 3)

3.3. Regression analysis with MSNQ and SDMT scores as outcome variables

We restricted the set of explanatory variables to age, sex, onset phenotype, education, the comorbidity count, depression, behavioral and consumption variables to reduce collinearity. We omitted disease duration due to its strong correlation with age and EDSS due to its strong correlation with age and physical activity score. Treatment status was not taken into account because of its correlation with age.

The highest correlation between the remaining explanatory variables was 0.31 for age and comorbidity count, while the highest VIF score was 2.91 for the highest category of education.

The regression models explained 15% of the variance of MSNQ scores and 14% of the variance of SDMT scores (Table 4). After adjustment for the number of predictors (see table 3), higher MSNQ scores were associated with a higher comorbidity count, reporting depressive symptoms, 9 h of sleep or more and using sleeping medication on a daily basis. The associations of reduced MSNQ scores with reporting at least once weekly fish intake (when compared with less than once monthly) and higher age did not persist after correction. For the SDMT, only age contributed substantially after adjustment for the number of predictors. Associations with physical activity score and reporting no preference or fatty fish preference and the adverse association with using sleeping medication on a daily basis were not confirmed after correction for the number of variables.

4. Discussion

Based on the correlation analyses, reporting depressive symptoms, on average 9 h or more of sleep and daily use of sleeping medication were associated with higher MSNQ scores whereas increasing age, EDSS and disease duration correlated with lower SDMT scores. These results were confirmed by the regression analysis after accounting for age, sex, onset phenotype and other explanatory variables.

The difference in associations between the MSNQ, a patient-reported experience measure of perceiving neuropsychological impairment and the SDMT, an information processing speed assessment, is in line with the absence of a significant correlation between MSNQ and SDMT scores, an observation also reported by others (Sonder et al., 2012). While SDMT scores worsened with age and physical disability, subjective cognitive complaints assessed with the MSNQ did not. This finding is in accordance with previous studies assessing subjective cognitive performance (Benedict et al., 2003; O'Brien et al., 2007) and consistent with the modest correlations of SDMT with EDSS scores (Strober et al., 2018). Taken together with the recently reported relationship between aerobic capacity and processing speed in MS (Langeskov-Christensen et al., 2018), these findings suggest that SDMT scores, as a measure of cognitive processing speed, decrease with age and impaired motor function, an observation which does not hold for perceived neuropsychological impairment, assessed with the MSNQ.

The comorbidity number did significantly contribute to the variance of MSNQ scores in the regression model. To the best of our knowledge,

Table 1
Study population with patient characteristics, explanatory and outcome variables for full sample and subsets used for the MSNQ and SDMT regression analysis. The mean, 95% confidence interval of the mean, median and range are shown for continuous variables. Fractions are shown for the categorical variables.

Baseline characteristics	Total study population		MSNQ regression subset		SDMT regression subset	
	751/751	(100.00%)	589/751	(78.43%)	231/751	(30.76%)
Age						
Mean [CI 95%]	53.4	[52.6 - 54.1]	52.7	[51.9 - 53.5]	52.0	[50.8 - 53.1]
Median [range]	54.0	[20.0 - 83.0]	53.0	[20.0 - 83.0]	53.0	[25.0 - 78.0]
Sex						
Female, n/N (%)	497/751	(66.2%)	373/589	(63.3%)	147/231	(63.6%)
Male, n/N (%)	254/751	(33.8%)	216/589	(36.7%)	84/231	(36.4%)
Years of education						
Less than 12 years, n/N (%)	94/750	(12.5%)	66/589	(11.2%)	20/231	(8.7%)
Between 12 and 15 years, n/N (%)	336/750	(44.8%)	267/589	(45.3%)	105/231	(45.5%)
More than 15 years, n/N (%)	320/750	(42.7%)	256/589	(43.5%)	106/231	(45.9%)
Onset Type						
Relapsing, n/N (%)	546/751	(72.7%)	442/589	(75.0%)	177/231	(76.6%)
Progressive, n/N (%)	205/751	(27.3%)	147/589	(25.0%)	54/231	(23.4%)
Disease duration						
Mean [CI 95%]	20.3	[19.6 - 20.9]	19.5	[18.8 - 20.2]	18.6	[17.6 - 19.7]
Median [range]	19.0	[0.0 - 61.0]	19.0	[0.0 - 61.0]	18.0	[2.0 - 54.0]
EDSS						
Mean [CI 95%]	4.8	[4.7 - 4.9]	4.7	[4.5 - 4.8]	4.7	[4.4 - 4.9]
Median [range]	5.0	[0.0 - 9.5]	4.5	[0.0 - 9.0]	4.5	[0.0 - 9.0]
Treatment Status						
Never Treated, n/N (%)	145/751	(19.3%)	105/589	(17.8%)	38/231	(16.5%)
Ever Treated, n/N (%)	209/751	(27.8%)	161/589	(27.3%)	62/231	(26.8%)
Currently Treated, n/N (%)	397/751	(52.9%)	323/589	(54.8%)	131/231	(56.7%)
Depressed						
Not depressed, n/N (%)	391/748	(52.3%)	309/589	(52.5%)	125/231	(54.1%)
Depressed, n/N (%)	357/748	(47.7%)	280/589	(47.5%)	106/231	(45.9%)
Comorbidity						
Mean [CI 95%]	0.6	[0.6 - 0.7]	0.6	[0.6 - 0.7]	0.6	[0.6 - 0.7]
Median [range]	0.0	[0.0 - 4.0]	0.0	[0.0 - 4.0]	0.0	[0.0 - 4.0]
BMI						
Mean [CI 95%]	24.8	[24.5 - 25.1]	24.8	[24.5 - 25.1]	24.7	[24.3 - 25.2]
Median [range]	24.2	[11.4 - 46.2]	24.2	[14.5 - 46.2]	24.2	[14.5 - 38.7]
Monthly alcohol score						
Mean [CI 95%]	9.3	[8.3 - 10.4]	9.7	[8.5 - 10.9]	8.4	[6.9 - 9.9]
Median [range]	3.0	[0.0 - 192.0]	3.0	[0.0 - 192.0]	3.0	[0.0 - 89.0]
Daily caffeine score						
Mean [CI 95%]	2.3	[2.2 - 2.4]	2.3	[2.2 - 2.4]	2.5	[2.3 - 2.6]
Median [range]	2.0	[0.0 - 10.0]	2.0	[0.0 - 10.0]	2.0	[0.0 - 9.0]
Physical activity score						
Mean [CI 95%]	2.5	[2.4 - 2.6]	2.6	[2.4 - 2.7]	2.7	[2.4 - 2.9]
Median [range]	2.0	[0.0 - 8.0]	2.0	[0.0 - 8.0]	2.0	[0.0 - 8.0]
Smoking status						
Never Smoker, n/N (%)	326/744	(43.8%)	251/589	(42.6%)	91/231	(39.4%)
Ever Smoker, n/N (%)	267/744	(35.9%)	213/589	(36.2%)	84/231	(36.4%)
Daily Smoker, n/N (%)	151/744	(20.3%)	125/589	(21.2%)	56/231	(24.2%)
Daily exposure to smoke						
No, n/N (%)	547/729	(75.0%)	435/589	(73.9%)	157/231	(68.0%)
Yes, n/N (%)	182/729	(25.0%)	154/589	(26.1%)	74/231	(32.0%)
Fish intake frequency						
Less than once a month, n/N (%)	114/746	(15.3%)	69/589	(11.7%)	26/231	(11.3%)
Between once a month and once a week, n/N (%)	519/746	(69.6%)	430/589	(73.0%)	175/231	(75.8%)
More than twice a week, n/N (%)	113/746	(15.1%)	90/589	(15.3%)	30/231	(13.0%)
Fish preference						
Lean fish, n/N (%)	202/715	(28.3%)	155/589	(26.3%)	66/231	(28.6%)
No preference, n/N (%)	336/715	(47.0%)	279/589	(47.4%)	108/231	(46.8%)
Fatty fish, n/N (%)	177/715	(24.8%)	155/589	(26.3%)	57/231	(24.7%)
Average hours of sleep						
8 h or less, n/N (%)	520/743	(70.0%)	414/589	(70.3%)	165/231	(71.4%)
9 h or more, n/N (%)	223/743	(30.0%)	175/589	(29.7%)	66/231	(28.6%)
Use of sleeping medication						
Never, n/N (%)	491/744	(66.0%)	392/589	(66.6%)	158/231	(68.4%)
Ever, n/N (%)	123/744	(16.5%)	100/589	(17.0%)	39/231	(16.9%)
Daily, n/N (%)	130/744	(17.5%)	97/589	(16.5%)	34/231	(14.7%)
MSNQ						
Mean [CI 95%]	22.3	[21.6 - 23.0]	22.0	[21.2 - 22.8]	21.5	[20.3 - 22.7]
Median [range]	21.0	[0.0 - 54.0]	21.0	[0.0 - 54.0]	21.5	[0.0 - 52.0]
SDMT						
Mean [CI 95%]	47.0	[45.7 - 48.3]	47.7	[46.1 - 49.2]	47.7	[46.1 - 49.2]
Median [range]	47.5	[15.0 - 98.0]	48.0	[15.0 - 98.0]	48.0	[15.0 - 98.0]

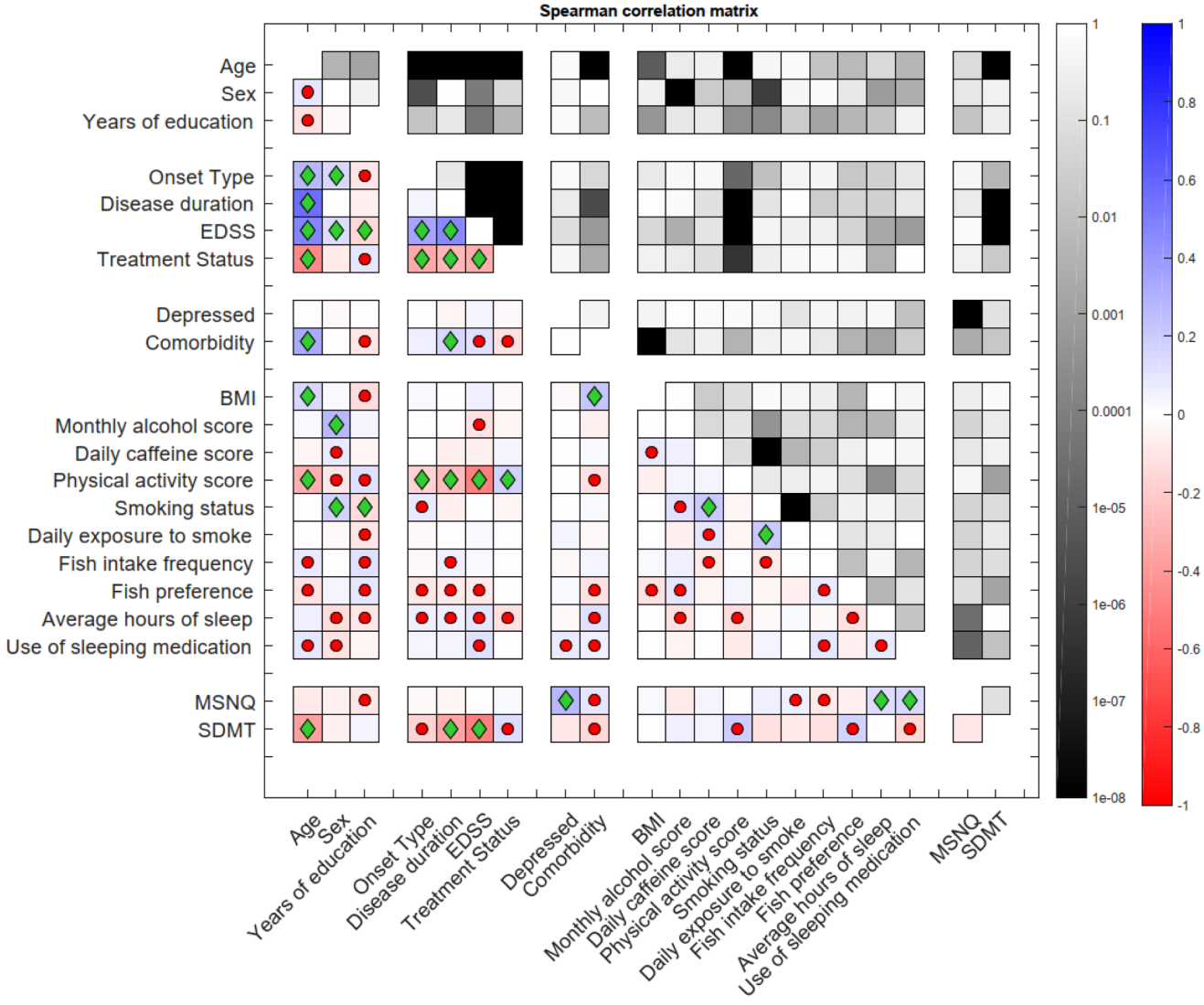

Fig. 2. Spearman correlation matrix with red dots indicating significant correlations before correction ($p < 0.05$) and green diamonds indicating significant correlations after correction for multiple testing ($p < 0.05/210$). Blue-red color scale shows the strength of correlations with blue representing perfect positive correlation and red perfect negative correlation. Black and white color scale shows significance level of the correlations on a logarithmic scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the observed association between physical comorbidity and MSNQ scores (independently from depression and sleep variables) has not been reported before. Because the nature of the requested comorbidities primarily related to cardiovascular diseases, including hypercholesterolemia, arterial hypertension, heart disease and diabetes mellitus, its contribution to MSNQ scores reminds us of the association of vascular comorbidity with increased disability progression when focusing on ambulation in MS (Marrie et al., 2010) and the increased risk of cognitive decline in patients with type 2 diabetes mellitus in non-MS populations (Bellou et al., 2017).

Our findings confirm the widely recognized association of perceived neuropsychological impairment with depression (Benedict et al., 2004; Sonder et al., 2012). This observation also explains why subjective cognitive complaints are frequently being discounted. The absence of a strong correlation between depression and SDMT scores is in line with previous reports (Golan et al., 2018). While depression has been associated with increased disease burden in MS (Feinstein, 2004), decreased SDMT scores (Patel and Feinstein, 2018) and reduced leisure activities, thereby affecting cognitive reserve (Patel et al., 2018), it remains to be elucidated whether depression serves as a risk factor or an early expression of cognitive impairment.

Daily use of sleeping medication and sleeping 9 h or more were related to a significant increase in MSNQ score. While this association has not been reported in MS yet, there is substantial evidence that benzodiazepine use is associated with cognitive decline in non-MS populations (Bellou et al., 2017). Sleeping medication was reported to be taken daily by 17.5% of our study population, and ever taken by another 16.5%. These proportions are high, which is probably related to medicalization of sleep problems in European countries (van de Straat et al., 2018). As sleeping problems have been reported in 60% of subjects with MS, disrupted sleeping patterns might be the reason for taking sleeping medication and explain this association. Increased sleeping problems have also been associated with an increased risk of subjective cognitive decline over time in MS (Hughes et al., 2018).

We did not find a direct relationship of BMI and smoking with self-reported cognitive functions, as reported recently (Jelinek et al., 2019). However, BMI correlated with comorbidity, and comorbidity was associated with MSNQ scores. A healthy lifestyle and health promoting behaviour in general have been related to reduced disability accumulation in several cross-sectional studies (D'Hooghe M et al., 2011, 2013).

The SDMT is highly recommended as a monitoring tool in clinical

Table 2
Significant Spearman correlations between explanatory variables after correction for multiple testing ($p < 0.05/210$), sorted from strong to weak. N refers to the number of data available for this analysis.

Variable 1	Variable 2	rho	p-value	N
Age	Disease duration	0,59	6,18E-71	749
EDSS	Physical activity score	−0,50	1,96E-47	739
Age	EDSS	0,49	1,14E-46	747
Disease duration	EDSS	0,47	1,09E-42	747
Age	Treatment Status	−0,45	2,17E-38	750
Onset Type	EDSS	0,36	3,64E-24	748
Age	Comorbidity	0,34	3,53E-21	738
Onset Type	Treatment Status	−0,33	7,65E-21	751
EDSS	Treatment Status	−0,31	8,45E-18	748
Age	Physical activity score	−0,30	5,84E-17	741
Sex	Monthly alcohol score	0,29	2,12E-15	707
Age	Onset Type	0,29	4,84E-16	750
Disease duration	Treatment Status	−0,28	6,26E-15	750
Disease duration	Physical activity score	−0,26	9,32E-13	741
Comorbidity	BMI	0,24	1,86E-10	716
Daily caffeine score	Smoking status	0,22	2,98E-09	706
Smoking status	Daily exposure to smoke	0,21	7,77E-09	727
Treatment Status	Physical activity score	0,18	5,59E-07	742
Sex	Smoking status	0,18	1,07E-06	744
Disease duration	Comorbidity	0,17	2,53E-06	738
Sex	Onset Type	0,17	3,44E-06	751
Age	BMI	0,16	8,46E-06	723
Onset Type	Physical activity score	−0,16	2,00E-05	742
Years of education	EDSS	−0,15	5,33E-05	747
Sex	EDSS	0,14	6,95E-05	748
Years of education	Smoking status	−0,14	1,97E-04	743

Table 3
Spearman correlation between explanatory variables and outcomes.

Variables	MSNQ scores			N	SDMT scores			N
	rho	p-value			rho	p-value		
Age	−0,06	8,42E-02		733	−0,36	3,03E-10	◆	290
Sex	−0,05	1,79E-01		734	−0,05	4,09E-01		290
Years of education	−0,09	1,49E-02	●	733	0,06	3,22E-01		290
Onset Type	−0,02	5,88E-01		734	−0,16	5,29E-03	●	290
Disease duration	−0,04	2,71E-01		733	−0,34	2,64E-09	◆	290
EDSS	−0,01	8,08E-01		731	−0,50	1,33E-19	◆	288
Treatment Status	0,03	4,29E-01		734	0,14	2,00E-02	●	290
Depressed	0,30	1,76E-16	◆	732	−0,09	1,45E-01		289
Comorbidity	0,11	2,37E-03	●	723	−0,14	1,79E-02	●	286
BMI	0,04	2,89E-01		709	0,02	7,94E-01		277
Monthly alcohol score	−0,07	5,22E-02		692	0,07	2,69E-01		274
Daily caffeine score	0,05	1,90E-01		701	0,05	4,03E-01		276
Physical activity score	0,02	5,87E-01		726	0,19	1,05E-03	●	287
Smoking status	0,07	5,04E-02		727	−0,10	7,54E-02		289
Daily exposure to smoke	0,07	4,99E-02	●	713	−0,07	2,16E-01		284
Fish intake frequency	−0,07	5,00E-02	●	732	−0,10	8,87E-02		289
Fish preference	−0,06	9,99E-02		702	0,19	1,41E-03	●	278
Average hours of sleep	0,15	3,27E-05	◆	727	0,00	9,75E-01		287
Use of sleeping medication	0,16	1,25E-05	◆	727	−0,15	1,34E-02	●	287
MSNQ	—	—		—	−0,09	1,18E-01		285
SDMT	−0,09	1,18E-01		285	—	—		—

N refers to the number of data available for this analysis.
● *significant correlations before correction $p < 0.05$.*
◆ *significant correlations after correction for multiple testing ($p < 0.05/210$).*

practice (Sumowski et al., 2018) and particularly sensitive to slowed information processing. Nevertheless, the question remains how well it reflects neurocognitive capacities that are related to activities of daily life important to patients (Benedict et al., 2017; D'Hooghe M et al., 2019). Furthermore, there is no consensus in how we measure and define cognitive impairment (Ruet and Brochet, 2018; Sumowski et al., 2018). Non-linear relationships between subjective and objective measures of cognition, independent of mood and physical impairment, and modified by age, suggest that self-reported cognitive impairment may reflect changes in cognition whereas the absence of subjective impairment does not predict the absence of objective cognitive impairment (Marrie et al., 2005). Furthermore, we may have to leave a dichotomous classification in either being cognitively impaired or not and adopt a novel taxonomy for cognitive phenotypes, as recently proposed (Leavitt et al., 2018). Recent associations between subjective cognitive concerns, based on a continuous score, and reduced thalamic and cortical gray matter volumes lend support to the relevance of these concerns in MS patients (Kletenik et al., 2019). Altogether, increasing evidence suggests to assess subjective cognitive performance in a multidimensional approach with the aim of providing us a better insight in the nature of perceived changes.

Our findings suggest that strategies to interfere with these complaints might be offered by targeting health status indicators, including cardiovascular risk factors, vascular comorbidity, depression, sleeping behaviour and medication. In line with the shifting concepts for brain aging in non-MS populations, we speculate that multiple processes might combine idiosyncratically which could result in a multiplication of individual relative risks for each comorbid disease related to cognitive impairment or dementia (Montine et al., 2019).

The strengths of our study relate to the use of validated questionnaires, the incorporation of all available data and the correction for potential confounders and multiple testing. We used a survey in a large group of patients to address a topic that is difficult to assess using other approaches. Nonetheless, there are limitations. First, we focussed on current comorbidities, health and consumption behaviours and did not include information from the past. This might explain the rather weak correlation of current health behaviour factors with comorbidity and perceived neuropsychological impairment. We assume that comorbidities are, at least partially, the result of health behaviours in the past. This could explain the correlation of these factors with education levels even though education did not independently contribute to cognitive functioning. Second, health status indicators are self-reported and estimates. These measurements inevitably have some degree of imprecision. Third, we treated all comorbidities equally and did not take into account interactions. As participants may have focused on coexisting conditions which impact their daily life without being aware of hypercholesterolemia, the reported comorbidity count may actually balance the consequences of this limitation. Fourth, we have to consider sample bias. Fifth, the SDMT sample size was smaller and scores were obtained within a time window of 6 months.

In conclusion, our study findings encourage researchers and clinicians to include perceptions of cognitive performance in people with MS and investigate whether strategies focusing on preventing and treating comorbidities, depression and sleep disturbances might be useful and effective in improving subjective and objective cognitive performance.

5. Author declaration template

We wish to confirm that there are no known conflicts of interest associated with thïs publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no ïmpediments to publication, including the timing of publication, with respect to intellectual property. In 50 doing we confirm that we have

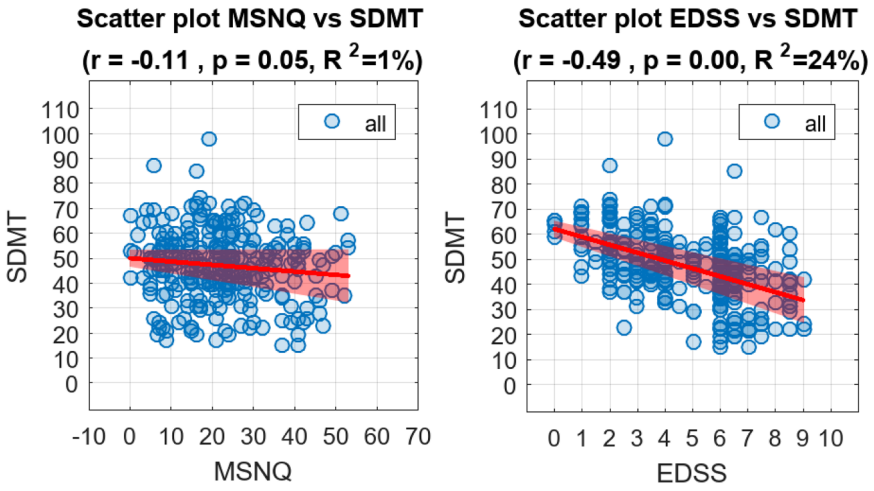

Fig. 3. Pearson correlations between MSNQ and SDMT scores, and between EDSS and SDMT scores.

followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Table 4
Regression analysis for MSNQ and SDMT scores.

	MSNQ				SDMT			
	R2	R2adj	N		R2	R2adj	N	
	0.18	0.15	595		0.22	0.14	234	
	b (CI 95%)	b0 (CI 95%)	p-value		b (CI 95%)	b0 (CI 95%)	p-value	
Age	−0.09 ± 0.07	−0.09 ± 0.07	5,0E-02	●	−0.31 ± 0.16	−0.24 ± 0.12	1,1E-03	◆
BMI	0.12 ± 0.17	0.05 ± 0.07	2,4E-01		0.30 ± 0.35	0.09 ± 0.11	1,6E-01	
Monthly alcohol score	−0.05 ± 0.05	−0.08 ± 0.07	6,0E-02		−0.02 ± 0.11	−0.02 ± 0.11	8,0E-01	
Daily caffeine score	0.12 ± 0.55	0.01 ± 0.06	7,2E-01		0.54 ± 1.07	0.05 ± 0.11	4,0E-01	
Physical activity score	0.07 ± 0.33	0.01 ± 0.07	7,2E-01		0.91 ± 0.63	0.15 ± 0.11	1,8E-02	●
Comorbidity	1.88 ± 0.93	0.14 ± 0.07	1,0E-03	◆	−0.42 ± 1.82	−0.03 ± 0.11	7,0E-01	
Intercept	22.48 ± 6.62	0.00 ± 0.31	3,6E-08	◆	51.17 ± 13.97	−0.15 ± 0.53	7,5E-09	◆
Sex (Ref: Female)								
- Male	0.25 ± 1.66	0.02 ± 0.14	8,02E-01		−3.02 ± 3.37	−0.22 ± 0.24	1,41E-01	
Years of education (Ref: Less than 12 years)								
- Between 12 and 15 years	−1.32 ± 2.47	−0.11 ± 0.21	3,79E-01		3.55 ± 5.30	0.25 ± 0.38	2,72E-01	
- More than 15 years	−1.53 ± 2.52	−0.13 ± 0.21	3,19E-01		1.57 ± 5.38	0.11 ± 0.38	6,32E-01	
Depressed (Ref: Not depressed)								
- Depressed	6.07 ± 1.49	0.51 ± 0.13	5,21E-11	◆	−1.30 ± 2.90	−0.09 ± 0.21	4,63E-01	
Onset Type (Ref: Relapsing)								
- Progressive	−0.69 ± 1.82	−0.06 ± 0.15	5,32E-01		1.20 ± 3.74	0.09 ± 0.27	5,97E-01	
Smoking status (Ref: Never Smoker								
- Ever Smoker	1.16 ± 1.73	0.10 ± 0.15	2,69E-01		−1.27 ± 3.54	−0.09 ± 0.25	5,56E-01	
- Daily Smoker	1.36 ± 2.16	0.12 ± 0.18	2,99E-01		−0.70 ± 4.11	−0.05 ± 0.29	7,80E-01	
Daily exposure to smoke (Ref: No)								
- Yes	1.06 ± 1.78	0.09 ± 0.15	3,26E-01		−1.85 ± 3.26	−0.13 ± 0.23	3,52E-01	
Fish intake frequency (Ref: Less than once a month)								
- between once a month and once a week	−4.08 ± 2.38	−0.35 ± 0.20	5,02E-03	●	0.06 ± 4.78	0.00 ± 0.34	9,82E-01	
- more than twice a week	−4.12 ± 2.97	−0.35 ± 0.25	2,27E-02	●	−4.95 ± 6.20	−0.35 ± 0.44	1,90E-01	
Fish preference (Ref: Lean fish)								
- No preference	−2.02 ± 1.84	−0.17 ± 0.16	7,19E-02		4.82 ± 3.52	0.34 ± 0.25	2,56E-02	●
- Fatty fish	−0.80 ± 2.09	−0.07 ± 0.18	5,30E-01		7.40 ± 4.01	0.53 ± 0.29	2,72E-03	●
Average hours of sleep (Ref: 8 h or less)								
- 9 h or more	4.02 ± 1.67	0.34 ± 0.14	8,37E-05	◆	−1.46 ± 3.34	−0.10 ± 0.24	4,73E-01	
Use of sleeping medication (Ref: Never)								
- Ever	2.05 ± 2.03	0.17 ± 0.17	9,81E-02		1.99 ± 4.01	0.14 ± 0.29	4,16E-01	
- Daily	4.28 ± 2.06	0.36 ± 0.18	6,99E-04	◆	−6.73 ± 4.26	−0.48 ± 0.30	9,96E-03	●

Regression analysis for MSNQ and SDMT scores.
N refers to the number of data available for this analysis.
● *significant coefficients before correction $p<0.05$.*
◆ *significant coefficients after correction for multiple testing ($p<0.05/22$).*

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CRediT authorship contribution statement

Marie B. D'hooghe: Conceptualization, Investigation, Funding acquisition, Methodology, Writing - original draft, Writing - review & editing. **Alexander De Cock:** Methodology, Data curation, Formal analysis, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ann Van Remoortel:** Methodology, Resources, Data curation, Project administration. **Ralph H B Benedict:** Supervision, Writing - review & editing. **Piet Eelen:** Resources. **Erika Peeters:** Resources. **Miguel D'haeseleer:** Resources. **Jacques De Keyser:** Supervision, Writing - review & editing. **Guy Nagels:** Conceptualization, Investigation, Methodology, Supervision, Writing - review & editing.

Declaration of competing interest

No competing interests.

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