



Can we predict cognitive decline after initial diagnosis of multiple sclerosis? Results from the German National early MS cohort (KKNMS)

Andreas Johnen¹ · Paul-Christian Bürkner² · Nils C. Landmeyer¹ · Björn Ambrosius³ · Pasquale Calabrese⁴ · Jeremias Motte³ · Nicole Hessler⁵ · Gisela Antony⁶ · Inke R. König⁵ · Luisa Klotz¹ · Muna-Miriam Hoshi^{7,8} · Lilian Aly^{7,8} · Sergiu Groppa⁹ · Felix Luessi⁹ · Friedemann Paul¹⁰ · Björn Tackenberg¹¹ · Florian Then Bergh¹² · Tania Kümpfel¹³ · Hayrettin Tumani^{14,15} · Martin Stangel¹⁶ · Frank Weber^{17,18} · Antonios Bayas¹⁹ · Brigitte Wildemann²⁰ · Christoph Heesen²¹ · Uwe K. Zettl²² · Frauke Zipp⁹ · Bernhard Hemmer^{7,8} · Sven G. Meuth¹ · Ralf Gold³ · Heinz Wiendl¹ · Anke Salmen^{3,23} on behalf of German Competence Network Multiple Sclerosis (KKNMS)

Received: 25 September 2018 / Revised: 14 November 2018 / Accepted: 26 November 2018 / Published online: 4 December 2018
© The Author(s) 2018

Abstract

Background Cognitive impairment (CI) affects approximately one-third of the patients with early multiple sclerosis (MS) and clinically isolated syndrome (CIS). Little is known about factors predicting CI and progression after initial diagnosis.

Methods Neuropsychological screening data from baseline and 1-year follow-up of a prospective multicenter cohort study (NationMS) involving 1123 patients with newly diagnosed MS or CIS were analyzed. Employing linear multilevel models, we investigated whether demographic, clinical and conventional MRI markers at baseline were predictive for CI and longitudinal cognitive changes.

Results At baseline, 22% of patients had CI (impairment in ≥ 2 cognitive domains) with highest frequencies and severity in processing speed and executive functions. Demographics (fewer years of academic education, higher age, male sex), clinical (EDSS, depressive symptoms) but no conventional MRI characteristics were linked to baseline CI. At follow-up, only 14% of patients showed CI suggesting effects of retesting. Neither baseline characteristics nor initiation of treatment between baseline and follow-up was able to predict cognitive changes within the follow-up period of 1 year.

Conclusions Identification of risk factors for short-term cognitive change in newly diagnosed MS or CIS is insufficient using only demographic, clinical and conventional MRI data. Change-sensitive, re-test reliable cognitive tests and more sophisticated predictors need to be employed in future clinical trials and cohort studies of early-stage MS to improve prediction.

Keywords Multiple sclerosis · Cognition · Neuropsychology · Cohort study · Longitudinal

Other Members of the German Competence Network Multiple Sclerosis (KKNMS) that acted as collaborators in this study are listed in Acknowledgments.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00415-018-9142-y>) contains supplementary material, which is available to authorized users.

✉ Andreas Johnen
a.johnen@uni-muenster.de

Extended author information available on the last page of the article

Introduction

Cognitive impairment (CI) and associated neurobehavioral symptoms (e.g., fatigue, depression) are frequent and often highly debilitating in multiple sclerosis (MS) [1]. Particularly cognitive processing speed, executive functions such as working memory capacity as well as verbal and figural episodic memory show a disease-related decline with adverse effects on patient's vocational status and quality of life [2, 3]. CI has been shown to be present in the earliest disease stages of MS as well as in clinically isolated syndrome (CIS) [4, 5]. Several studies suggest that CI can be present independent of physical disability and that its development and progression is most pronounced during the first years after disease onset [6, 7]. Despite its increasingly recognized clinical

relevance for patients with early MS, little is known about risk factors that contribute to CI, its short-term course and a potential progression after initial diagnosis of MS [3, 8, 9]. Associations between clinical disease severity markers (e.g., EDSS, number of relapses, disease duration), conventional MRI parameters of disease burden (e.g., number and/or site of lesions, degree of atrophy) and both severity and profiles of CI have been reported in large cross-sectional cohort studies on a group level [8, 10–12]. However, these associations were less evident in patients with early disease stages [13]. A range of studies have also investigated longitudinally risk factors and prediction of long-term outcome of CI in patients with MS mainly based on clinical and MRI parameters [5, 6, 14–16]. Compatible with results from cross-sectional studies, baseline brain volume [14, 15] and to a lesser degree lesion metrics [6, 16] usually contribute to long-term prediction of CI but predictive abilities were generally low and inconsistent for short-term follow-up periods and early disease stages [5, 14]. Both cross-sectional and longitudinal studies, moreover, display a substantial heterogeneity regarding (i) assessments and definitions of CI, (ii) selection and measurement of predictor variables, (iii) homogeneity of sample characteristics (e.g., disease severity, intake of medication, etc.) and (iv) employed MRI techniques and length of follow-up periods. These methodological issues currently impede an integration and extrapolation of results onto individual cases with newly diagnosed MS [6, 8, 10, 11, 14–17]. In turn, this gap in key-knowledge hinders incorporation of cognitive monitoring into standard clinical care which in turn hampers the development and evaluation of specific programs for the prevention and rehabilitation of CI in MS [1].

Here, we aimed to investigate whether CI and its short-term progression can be effectively predicted by a single marker or combinations of conventional demographic, clinical and MRI parameters that are readily available to clinicians at the time of diagnosing MS. We were further interested in the relative importance of these potential risk factors both for CI as well as for its longitudinal change. To this end, we analyzed cognitive screening data from the German National MS cohort (NationMS) of patients with initial diagnosis of either MS or CIS [18]. We assumed standard sociodemographic data, established clinical markers of MS disease burden and/or conventional MRI parameters at baseline to be predictive for CI. We further analyzed whether changes in cognitive test performance during the first year after diagnosis may be effectively predicted using these baseline parameters.

Materials and methods

NationMS cohort study

The German National MS cohort is a prospective longitudinal observational study comprising (a) detailed assessment of patients with first diagnosis of MS or CIS and (b) yearly follow-up assessment with a standardized protocol across 22 centers in Germany. It was approved by the ethics committee of Ruhr-University Bochum (Registration no. 3714-10), and consecutively, by all local committees of the participating centers. All patients provided written informed consent. Inclusion and exclusion criteria as well as assessment plans are laid out in detail elsewhere [18]. In short, inclusion required a recent diagnosis of either CIS or RRMS according to Barkhof [19] or 2005 McDonald [20] criteria, respectively; exclusion criteria implied previous intake of disease-modifying therapies (DMTs), other neurological or psychiatric conditions as well as progressive courses of MS. Assessment involved sociodemographic data, detailed neurological status, medication status regarding DMTs, standardized cranial MRI evaluation regarding signs of disease burden, collection of biomaterial as well as neuropsychological screenings and self-report questionnaires. Datasets from $N=1123$ patients were included for baseline statistics. Data from $N=958$ patients were available for follow-up assessment at an average of 12.13 (SD=1.54) months after baseline.

Cognitive screening data

MUSIC: Multiple Sclerosis Inventory for Cognition

The MUSIC is a brief multiple-domain cognitive screening test geared towards rapid assessment of the most frequently impaired cognitive domains in MS [21]. It is widely used as a screening for CI in German-speaking countries and consists of six subtests, in the following order: (1) Word List Learning (number of words learned over two consecutive trials out of a list with 10 words), (2) Interference Word List Learning (number of words learned from a 10 word interference list), (3) Category Fluency Switch Condition (number of correctly associated words within 1 min from two continuously alternating semantic categories), (4) Modified Stroop Task (speed of correctly naming animal silhouettes either in a congruent or incongruent condition with printed animal names on them), (5) Word List Recall (number of correctly recalled words from the initially learned word list after a short delay). For easier inter-test and inter-subject comparisons, individual test scores were z standardized

based on normative data from $N = 158$ German-speaking healthy young adults as laid out in detail elsewhere [21].

PASAT: Paced Auditory Serial Addition Test

The PASAT 3-s version is a widely used cognitive screening test in MS tapping into processing speed, divided attention and working memory. PASAT data were extracted from the Multiple Sclerosis Functional Composite (MSFC) [22]. Participants are asked to add numbers in a 1-back-like fashion during a continuous auditory presentation (one number presented every 3 s) and verbally state the correct sums continuously. Outcome measure is the number of correct calculations during a fixed time period. Administration was carried out in accordance with the manual including a preceding training trial and the use of a parallel version at follow-up. Analogous to the MUSIC data, individual PASAT test scores were z standardized, stratified for age and education based on normative data from a German sample of $N = 241$ healthy controls [23].

Across all cognitive tests (i.e., subtests of MUSIC and PASAT), a normative z score of -1.645 was used as a

cut-off for “impaired performance” as this value approximately represents the 5th percentile rank. Following the criterion put forth by Amato et al., impaired performance in two or more subtests was required to classify individual patients as having CI [6]. Additionally, an unweighted mean z score of all cognitive tests was calculated for each patient as a proxy for overall severity of CI.

Prediction parameters

A priori-considered predictors for CI and longitudinal change are depicted in Table 1. Besides general sociodemographic factors known to influence cognitive status, we examined a range of previously discussed disease-specific risk factors for CI in MS [9]. In total, we considered 17 predictor variables assessed at baseline pertaining to the domains demographics, clinical disease severity markers, MRI ratings of disease burden and self-reports on psychopathology (depressive symptoms and fatigue).

Table 1 Baseline predictors and sample characteristics (total $N = 1123$)

| Predictor | Available N | Mean (SD) |
|--|-------------------|-------------------|
| Demographic characteristics | | |
| Age, years | 1123 | 34.12 (9.67) |
| Sex, m:w | 1123 | 348:775 |
| Education, years | 1103 | 14.41 (2.57) |
| Clinical characteristics | | |
| Time since symptom onset, years | 1123 | 0.57 (0.61) |
| EDSS | 1120 | 1.49 (0.99) |
| Total number of relapses | 958 | 1.39 (0.62) |
| Type of disease, RRMS:CIS | 1123 | 622:501 |
| Type of first relapse, mono-:polysymptomatic | 1122 | 831:291 |
| Start of DMT after baseline, yes:no | 958 | 782:176 |
| MRI characteristics | | |
| Number of T2 lesions | 1117 | 7.67 (2.21) |
| Periventricular lesions, yes:no | 1123 | 1081:42 |
| Juxtacortical lesions, yes:no | 1123 | 871:252 |
| Infratentorial lesions, yes:no | 1123 | 666:457 |
| Black holes, yes:no | 822 | 489:333 |
| Visible atrophy, yes:no | 877 | 97:780 |
| Psychopathological characteristics | | |
| Depressive symptoms, BDI-II total | 1077 ^a | 7.61 (7.72):185 |
| Fatigue, FSMC total | 1073 ^b | 39.12 (18.21):390 |

CI cognitive impairment, EDSS Expanded Disability Status Scale, RRMS relapsing–remitting multiple sclerosis, CIS clinically isolated syndrome, DMT disease-modifying therapy, BDI Beck Depression Inventory, FSMC Fatigue Scale for Motor and Cognitive functions

^a $N = 103$ (9.6%) of patients had scores ≥ 19 , the clinical cut-off score suggested for indicating an at least mild depressive episode in patients with MS

^b $N = 390$ (36.3%) of patients had scores ≥ 42 , indicating at least mild fatigue

Statistics

SPSS 25 (IBM Corporation) was used for data preparation and R 3.3.0 (R Foundation, Vienna, Austria) for statistical computations. Descriptive statistics (means and SD as well as frequencies (%) of impaired cases) for baseline and follow-up cognitive data were computed. Change of CI from baseline to follow-up was evaluated using paired *t* tests. Linear multilevel models were applied to predict baseline cognitive test values as well as baseline to follow-up changes in cognitive test values and to control for possible dependency between observations gathered in the same participating center. All predictors were entered into the multiple regression model simultaneously so that co-variance between predictors was controlled for. Models were fitted adopting a Bayesian multilevel approach with the *brms* package [24] using the probabilistic programming language Stan. For all analyses, a 5% significance level was used and Bonferroni correction was applied within each regression model (that is over 18 regression coefficients per model). Prior to analyses, dichotomous variables (e.g., sex, presence of brain atrophy) were dummy-coded to include them into the regression models. Missing values in predictor variables were imputed by means of 20-fold multiple imputation by chained equations using the *mice* package [25]. The full analysis is available within the Open Science Framework (<https://osf.io/wznca/>).

Results

Frequencies of patients with and without CI are depicted in Fig. 1a for baseline and follow-up for each cognitive subtest/domain separately. At baseline, a total of 245 (22%) of patients were classified as having CI with the highest frequencies observed in the interference subscore of the Modified Stroop Task ($N=185$; 17%) of the MUSIC followed by the PASAT ($N=135$, 12%). Other subtests (e.g., verbal learning and memory) were substantially less frequently impaired. At follow-up, the general profile of relatively frequent impairments in processing speed and executive functions compared to other cognitive domains was similar to baseline. However, substantially less frequent impairments were observed across all tests at follow-up (overall CI in $N=120$; 14%).

Regarding the severity of deficits, normative *z* scores of baseline cognitive tests and significances of changes from baseline to follow-up are presented in Fig. 1b and Table 2.

Additionally, spaghetti plots depicting individual cognitive changes from baseline to follow-up can be found in Supplementary Figure 1 for each subtest.

Compared to normative data, the sample's average overall cognitive ability was not pathological with a mean of all cognitive tests of $z=-0.06$ at baseline. Compatible

with frequency data, processing speed (PASAT, $z=-0.20$) and executive functions (modified Stroop Test interference seconds, $z=-0.40$) were the domains with the lowest performances on average. At follow-up, patients performed significantly better on the mean cognitive *z* score ($z=0.16$ $p<0.0001$). Likewise, significant gains from baseline to follow-up were observed in the majority of subtests with the exception of the Stroop Inhibition Quotient and the Learning trial of the Interference word list for which no change occurred.

Results of the multilevel linear regression models are presented for the mean *z* score of all cognitive tests representing a proxy for overall CI. Regression coefficients of the model including all predictors for baseline CI are provided in Table 3.

The proportion of variance explained by this model was $R^2=0.27$ when including the variance explained by the participating center and $R^2=0.21$ without it. The predictors that remained significant after Bonferroni correction were age (“more CI in older patients”), years of education (“more CI in patients with fewer years of academic education”), EDSS score (“more CI in patients with higher EDSS”), BDI-II score (“more CI in patients with more self-reported depressive symptoms”), and sex (“more CI in males”). Other MS-specific clinical or MRI characteristics did not significantly contribute to the prediction of baseline CI. Regression coefficients of the model including all predictors for the baseline to follow-up changes in cognitive test scores are provided in Table 4.

No predictor remained significant after Bonferroni correction indicating that longitudinal cognitive change could neither be effectively predicted by the considered baseline variables nor the additional variable of DMT initiation after baseline (yes vs. no). The proportion of variance explained was $R^2=0.06$ when including the variance explained by participating center and $R^2=0.05$ without it. Likewise, results for each separate cognitive subtest were non-significant regarding the prediction of cognitive change from baseline to 1-year follow-up. These and other additional analyses are provided as supplementary material on <https://osf.io/wznca/>.

Discussion

Despite the increasingly recognized burden of CI in MS, little is known about an increased individual risk for CI after initial diagnosis of MS, hampering research on early prevention and treatment. In the current study, we aimed to characterize CI and identify risk factors for its severity and short-term course in a large, clinically homogeneous cohort of patients with first diagnosis of MS or CIS. To this end, neuropsychological screening data from $N=1123$ patients enrolled in the multicentric German National MS cohort

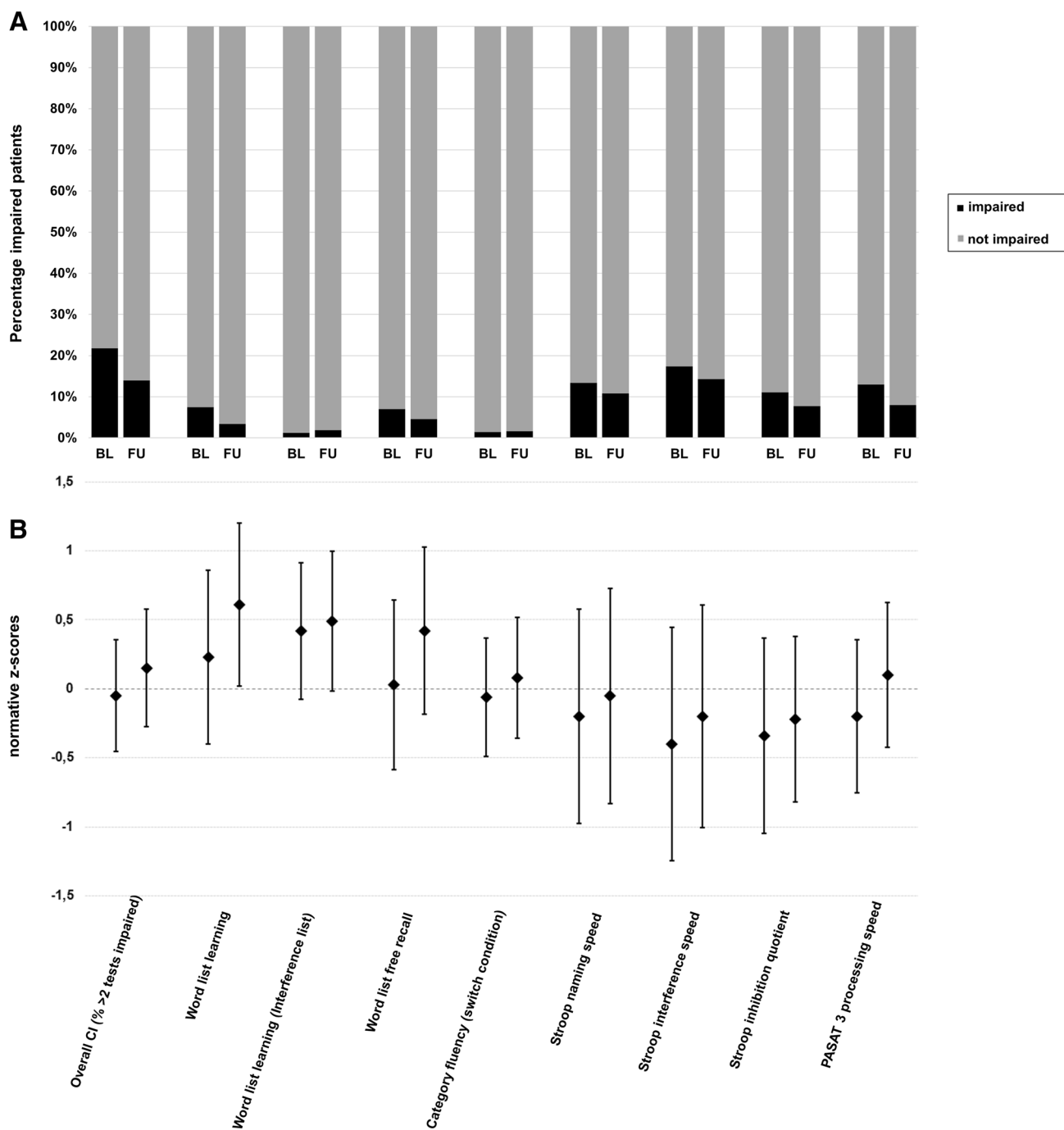


Fig. 1 **a** Frequencies of patients with overall CI (≥ 2 tests impaired compared to age- and education-corrected normative data) and of patients with impairments (z score < -1.645) in single cognitive tests for baseline (BL) and follow-up (FU) assessments. **b** Mean normative

z scores stratified for age and education for overall CI (mean z score of all tests) and for each cognitive test separately for baseline (BL, left) and follow-up (FU, right)

study were analyzed. We used linear multilevel regression models to predict CI and the short-term progression of CI from conventional MRI characteristics and other clinical and demographic parameters that are usually accessible to clinicians at the time of diagnosis.

Frequency, severity and profile of CI

Adopting conventional criteria of overall CI, we found 22% of patients to be impaired at baseline, with largest deficits in subtests for processing speed and executive function and lowest impairments in verbal learning and memory. The

Table 2 Mean (SD) of unstandardized raw scores and mean normative z scores of cognitive tests for baseline, follow-up and longitudinal change

| Cognitive test | <i>N</i> | Baseline | | Follow-up | | | Longitudinal change | |
|------------------------------------|----------|---------------|---------------|-----------|---------------|---------------|---------------------|-----------|
| | | Raw mean (SD) | Mean z (SD) | <i>N</i> | Raw mean (SD) | Mean z (SD) | Raw change (SD) | p_{Bon} |
| Word list learning (max 20) | 1067 | 15 (3) | 0.23 (1.26) | 913 | 16 (3) | 0.61 (1.18) | 0.81 (2.70) | <0.001 |
| Interference list (max 10) | 1067 | 6 (2) | 0.42 (0.99) | 913 | 6 (2) | 0.49 (1.01) | 0.13 (1.70) | 0.028 |
| Word list free recall (max 10) | 1065 | 6 (2) | 0.03 (1.23) | 913 | 7 (2) | 0.42 (1.21) | 0.74 (2.16) | <0.001 |
| Category fluency switch | 1067 | 15 (5) | −0.06 (0.86) | 913 | 15 (5) | 0.08 (0.88) | 0.77 (4.82) | <0.001 |
| Stroop naming speed seconds | 1066 | 22 (5) | −0.20 (1.55) | 910 | 21 (5) | −0.05 (1.56) | −0.55 (4.51) | <0.001 |
| Stroop interference seconds | 1066 | 28.6 (8.3) | −0.40 (1.69) | 910 | 27.6 (7.9) | −0.20 (1.61) | −1.12 (7.81) | <0.001 |
| Stroop inhibition quotient | 1066 | 7 (6) | −0.34 (1.42) | 910 | 6 (5) | −0.22 (1.20) | −0.57 (6.70) | 0.012 |
| MUSIC total score (max 32) | 1067 | 25 (5) | N/A | 913 | 26 (4) | N/A | 1.02 (3.87) | <0.001 |
| PASAT 3 s (max 60) | 1038 | 46 (11) | −0.20 (1.11) | 876 | 49 (11) | 0.10 (1.05) | 2.75 (9.10) | <0.001 |
| Overall CI (mean z of all tests) | 1038 | N/A | −0.06 | 921 | N/A | 0.16 | 0.21 (0.67) | <0.001 |

MUSIC subscores as well as PASAT test scores and corresponding normative z scores for baseline and follow-up

MUSIC multiple sclerosis inventory for cognition, *Max* maximum raw score, *CI* cognitive impairment, *N/A* not applicable, *PASAT* paced auditory serial addition test, p_{Bon} Bonferroni-corrected p value for paired t test of baseline vs. follow-up mean scores

Table 3 Regression coefficients for baseline mean cognitive test scores

| Coefficient | <i>b</i> | <i>SE</i> | 95% <i>CI</i> | u95% <i>CI</i> | p | p_{Bon} |
|--|----------|-----------|---------------|----------------|-------|-----------|
| Intercept | −0.267 | 0.162 | −0.585 | 0.050 | 0.098 | – |
| Demographic characteristics | | | | | | |
| Age | −0.148 | 0.023 | −0.193 | −0.103 | 0.000 | 0.000 |
| Sex (female vs. male) ^a | 0.279 | 0.047 | 0.186 | 0.372 | 0.000 | 0.000 |
| Education, years | 0.188 | 0.023 | 0.144 | 0.233 | 0.000 | 0.000 |
| Clinical characteristics | | | | | | |
| Years since symptom onset | −0.012 | 0.026 | −0.063 | 0.039 | 0.637 | 1.000 |
| EDSS | −0.112 | 0.025 | −0.161 | −0.064 | 0.000 | 0.000 |
| Total number of relapses | 0.040 | 0.047 | −0.052 | 0.133 | 0.399 | 1.000 |
| Type of disease (RRMS vs. CIS) ^a | 0.064 | 0.051 | −0.036 | 0.166 | 0.214 | 1.000 |
| Type of 1st relapse (poly- vs. monosymptomatic) ^a | −0.046 | 0.051 | −0.145 | 0.053 | 0.368 | 1.000 |
| Start of DMT after baseline ^a | 0.079 | 0.061 | −0.041 | 0.200 | 0.196 | 1.000 |
| MRI characteristics | | | | | | |
| Number of T2 lesions | −0.045 | 0.022 | −0.088 | −0.002 | 0.040 | 0.681 |
| Periventricular lesions present ^a | 0.018 | 0.116 | −0.208 | 0.247 | 0.877 | 1.000 |
| Juxtacortical lesions present ^a | −0.051 | 0.054 | −0.156 | 0.055 | 0.345 | 1.000 |
| Infratentorial lesions present ^a | −0.059 | 0.044 | −0.144 | 0.027 | 0.175 | 1.000 |
| Black holes present ^a | −0.013 | 0.056 | −0.123 | 0.097 | 0.823 | 1.000 |
| Visible atrophy present ^a | −0.094 | 0.075 | −0.241 | 0.049 | 0.209 | 1.000 |
| Psychopathological characteristics | | | | | | |
| Depressive symptoms (BDI-II) | −0.111 | 0.031 | −0.170 | −0.050 | 0.000 | 0.006 |
| Fatigue (FSMC total) | 0.006 | 0.031 | −0.056 | 0.067 | 0.853 | 1.000 |

Coefficients in bold indicate a significant influence on the outcome variable (mean z of cognitive test performance at baseline). Negative regression coefficients indicate that larger values in the predictor have a negative influence on the outcome variable and vice versa

b regression coefficient, *SE* standard error, *95% CI* lower bound of the 95% credible interval, *u95% CI* upper bound of the 95% credible interval, p uncorrected two-sided p value, p_{Bon} Bonferroni corrected two-sided p value

^aDichotomous variables that have been dummy-coded prior to analysis

Table 4 Regression coefficients for baseline to follow-up changes in mean cognitive test scores

| Coefficient | b | SE | l95% CI | u95% CI | <i>p</i> | <i>p</i> _{Bon} |
|--|--------|-------|---------|---------|----------|-------------------------|
| Intercept | −0.273 | 0.228 | −0.723 | 0.174 | 0.234 | – |
| Demographic characteristics | | | | | | |
| Age | −0.073 | 0.035 | −0.141 | −0.005 | 0.034 | 0.580 |
| Sex (female vs. male) ^a | 0.141 | 0.072 | 0.001 | 0.283 | 0.049 | 0.826 |
| Education (years) | −0.031 | 0.035 | −0.099 | 0.036 | 0.372 | 1.000 |
| Clinical characteristics | | | | | | |
| Years since symptom onset | 0.044 | 0.040 | −0.034 | 0.124 | 0.266 | 1.000 |
| EDSS | 0.086 | 0.037 | 0.013 | 0.157 | 0.022 | 0.370 |
| Total number of relapses | −0.045 | 0.066 | −0.176 | 0.085 | 0.497 | 1.000 |
| Type of disease (RRMS vs. CIS) ^a | −0.037 | 0.079 | −0.192 | 0.117 | 0.642 | 1.000 |
| Type of 1st relapse (poly- vs. monosymptomatic) ^a | 0.106 | 0.077 | −0.044 | 0.258 | 0.173 | 1.000 |
| Start of DMT after baseline ^a | −0.125 | 0.088 | −0.299 | 0.048 | 0.158 | 1.000 |
| MRI characteristics | | | | | | |
| Number of T2 lesions | −0.006 | 0.034 | −0.072 | 0.059 | 0.850 | 1.000 |
| Periventricular lesions present ^a | 0.211 | 0.176 | −0.134 | 0.553 | 0.231 | 1.000 |
| Juxtacortical lesions present ^a | 0.149 | 0.083 | −0.015 | 0.311 | 0.076 | 1.000 |
| Infratentorial lesions present ^a | 0.072 | 0.068 | −0.061 | 0.204 | 0.294 | 1.000 |
| Black holes present ^a | −0.114 | 0.087 | −0.286 | 0.055 | 0.188 | 1.000 |
| Visible atrophy present ^a | 0.124 | 0.113 | −0.093 | 0.348 | 0.271 | 1.000 |
| Psychopathological characteristics | | | | | | |
| Depressive symptoms (BDI-II) | 0.080 | 0.051 | −0.020 | 0.181 | 0.118 | 1.000 |
| Fatigue (FSMC total) | −0.106 | 0.053 | −0.212 | −0.003 | 0.042 | 0.715 |

Coefficients in bold indicate a significant influence on the outcome variable (mean z of baseline to follow-up change of cognitive test performance). Negative regression coefficients indicate that a larger value in the predictor has a negative influence on the outcome variable and vice versa

b regression coefficient, *SE* standard error, *l95% CI* lower bound of the 95% credible interval, *u95% CI* upper bound of the 95% credible interval, *p* uncorrected two-sided *p* value, *p*_{Bon} Bonferroni corrected two-sided *p* value

^aDichotomous variables that have been dummy coded prior to analysis

result of a relatively larger impairment in attention and processing speed as compared to other cognitive domains is well in line with previous studies on the cognitive profile of patients with early MS [6, 8] and CIS [1, 3]. Overall frequency and mean severity of CI was lower in our sample than commonly reported: the majority of previous studies found approximately one-third of patients with CI in early MS or CIS [3, 6, 7], although reported frequencies range from < 15 to > 50% [5, 26]. One explanation for this discrepancy may be that the current sample is unique in terms of a homogeneous sample in a very early disease stage with a median disease duration of only 0.33 years [18]. Compensatory mechanisms such as cognitive reserve may attenuate direct measurability of CI specifically in young patients with low overall disease burden and high formal education resulting in lower frequencies [17]. Hence, patients with larger cognitive reserve capacity may be able to compensate for brain pathology despite suffering from clinically relevant CI [13]. An additional explanation for our finding of a lower prevalence of CI in patients with early MS and CIS may be

that the employed screening tests are less sensitive to detect CI in these early disease stages that might extend beyond executive and speed-related domains. Reports on the prevalence of CI in MS depends on (a) the employed tests (e.g., screening tests only or extensive test batteries), (b) the formal definition of CI (e.g., one or two standard deviations below the norm; comparison to a control group), and (c) the composition of the sample (e.g., patients with progressive MS show a different degree of CI than patients with early MS or CIS [27]). Internationally accepted standards regarding screening for CI have been proposed in terms of the Brief International Cognitive Assessment in MS (BICAMS battery) and may allow a higher sensitivity to detect relevant CI in MS throughout the different disease stages [28]. For instance, the Symbol Digit Modalities Test (SDMT) has been shown to be a more reliable, and sensitive measure of cognitive processing speed than the PASAT employed in this study [29, 30]. More specific cognitive functions like calculation skills may as well influence individual PASAT results. Thus, while the Modified Stroop Task of the MUSIC was

able to detect early deficits in processing speed and executive function, the single-trial ten-item list might be insufficient to reveal subtle memory changes that might unfold in a multiple-trial learning-paradigm.

Predictors of CI and its progression

We found baseline CI to be significantly associated with three general demographic characteristics: male sex, fewer years of education and higher age. These factors have previously been linked to lower (verbal-)cognitive test performance in healthy adults suggesting influences that are not specific to MS or CIS but may, nevertheless, be of clinical importance for the interpretation of MS patients' test performances [31, 32]. Considering MS-specific clinical characteristics, only EDSS (a marker for mainly physical disease burden) and severity of depressive symptoms (BDI-II) were associated with severity of CI at baseline. These results are in line with previous evidence from large patient samples finding that higher EDSS and depressive symptoms negatively influence cognitive status [10, 27, 33]. Surprisingly, none of the conventional MRI (e.g., visual inspection of atrophy, number of T2 lesions) or other clinical predictors (e.g., type of disease CIS/RRMS, total number of relapses) that have previously been directly linked to CI and its long-term course contributed to prediction. This result may again cast doubts on the sensitivity of the employed screening tests to reliably detect CI in early disease stages. In the current sample, however, brain pathology and disease severity were also homogeneously low and relationships between CI and conventional markers for structural brain damage may be generally weak in early MS, even when using more sophisticated neuropsychological assessments. In a recent large cohort study, lack of association between brain pathology (as measured by voxel-based morphometry) and performance in the BICAMS test battery was termed a "clinico-radiological paradox" and attributed to both, stronger compensatory mechanisms (e.g., cognitive reserve) and a statistical restriction of range within a homogeneous sample of patients in early disease stages [13]. Despite the large sample size and the numerous considered clinical, demographic and conventional MRI baseline parameters as well as the variable of DMT initiation after baseline, the longitudinal change of cognition over the course of 1 year could not be sufficiently predicted. One explanation may be that, for instance, for the considered MRI parameters and DMT initiation, the categorization was too broad (e.g., dichotomization DMT start yes vs. no, visible MRI atrophy yes vs. no). On the other hand, the follow-up interval of 1 year may be too short to detect clinically relevant changes. However, significant gains in cognitive performance were observed in the majority of patients and in most cognitive subtests. This strongly suggests that test performances in both, MUSIC and

PASAT, were substantially influenced by practice effects, potentially masking clinically relevant longitudinal changes after 1 year. A recent review has estimated the average effect size of cognitive retesting in a 12-month interval to be as high as 0.25 while some standard neuropsychological tests reached effect sizes of 0.73 [34]. Likewise in patients with MS, carryover effects from one testing session to another is a frequent problem in longitudinal test designs and common to a range of neuropsychological tests including the PASAT and to lesser degrees also the SDMT [29, 35, 36]. Although alternate test versions matched for difficulty and modern regression-based normative data (including estimates for retesting effect-sizes) may attenuate the influence of practice effects, few standardized cognitive tests employed in testing patients with early MS provide these features. Moreover, despite the use of an alternate version in the PASAT in this study, patients on average performed significantly better at follow-up, highlighting a likely influence of familiarity that is not dependent on the particular stimuli. Practice effects may endure for approximately 1 year after a baseline assessment and are most pronounced between the first and second evaluations [37, 38]. This is, particularly, true for tests assessing memory, learning and executive functions while visuo-perceptive tasks are less prone to practice effects [39]. Hence, the difference of some cognitive tests in their resilience against practice effects has to be considered more rigorously when planning re-evaluation schedules. Moreover, additional cognitive testing (performed outside of the study or by patient self-assessment and training) needs to be controlled for.

Conclusions

In patients first diagnosed with MS or CIS, demographic characteristics (male sex, higher age, lower education) as well as more severe depressive symptoms (BDI-II) and higher physical disability (EDSS) are significantly associated with severity of CI. In patients with these characteristics, neuropsychological monitoring and potentially cognitive rehabilitation should be considered. No other disease-specific clinical or conventional MRI parameters from clinical routine were significantly related to the presence of CI in this large cohort of patients in earliest disease stages. Moreover, longitudinal prediction of short-term cognitive change over the course of 1 year was insufficient despite the large number of patients and the inclusion of numerous conventional yet disease-specific and previously discussed predictor variables. These findings indicate that three branches of research are highly needed to increase our understanding of CI, its clinical relevance and its risk factors in early MS to blaze the trail for early interventions: (1) establishment and

evidence-based proof of sensitive and change-sensitive cognitive outcome parameters providing free-to-use longitudinal normative data. (2) Evidence that these assessments are able to detect disease-specific and clinically relevant CI (i.e., by validation with patient-centered outcomes) from the earliest to advanced disease stages. (3) Improving the prediction of these measurements by the development of refined clinical scales and standardized automation of MRI parameters for use in clinical routine [40].

Acknowledgements The authors and representatives of the KKNMS express their deep gratitude to all contributors of the study, especially the study nurses, for their motivated collaboration and recruitment efforts, all the patients and relatives for their participation and support, and the data monitoring and administrative personnel of the study. Other members of the KKNMS that acted as collaborators in this study: Seray Demir: Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany. Christoph Schröder: Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Germany. Lisa A. Voithenleitner: Dept. of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. Achim Berthele: Dept. of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. Sarah Haars: Dept. of Neurology, University of Leipzig, Germany. Sandra Nischwitz: Neurology, Max-Planck-Institute of Psychiatry, Munich, Germany. Matthias J. Knop: Neurology, Max-Planck-Institute of Psychiatry, Munich, Germany. Susanne Rothacher: Dept. of Neurology, Klinikum Augsburg, Germany. Jana Pöttgen: Institut für Neuroimmunologie und Multiple Sklerose, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany. Clemens Warnke: Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany; Department of Neurology, University Hospital Köln, Cologne, Germany. Ralf A. Linker: Department of Neurology, University Hospital Erlangen, Germany. Ulf Ziemann: Department of Neurology and Stroke, and Hertie Institute for Clinical Brain Research, Eberhard-Karls-University Tübingen, Tübingen, Germany.

Funding The German National MS cohort and KKNMS are supported by grants from the German Federal Ministry for Education and Research (BMBF), Grant no. 01GI0914 (Bochum), 01GI0916, 01GI1601G (Lübeck), and 01GI1601B (Marburg).

Compliance with ethical standards

Conflicts of interest Paul-Christian Bürkner, Nils C. Landmeyer, Nicole Hessler, Gisela Antony, Inke R. König, Lilian Aly, Sergiu Groppa and Pasquale Calabrese report no disclosures. Andreas Johnen received speaker's honoraria and reimbursement of travel expenses from Actelion Pharmaceuticals unrelated to this work. Björn Ambrosius received travel grants from Novartis, not related to this work. He is now an employee of Celgene Corporation (not during the work of this project). Jeremias Motte received travel grants from Biogen idec, his research is funded by Klaus Tschira Foundation and Ruhr-University, Bochum (FoRUM-Program); none related to this work. Luisa Klotz received honoraria for lecturing and serving on advisory boards, as well as travel expenses for attending meetings and financial research support from Novartis, Biogen, Roche, Merck, Sanofi Genzyme, the BMBF and the Deutsche Forschungsgemeinschaft (DFG; German Research Society). Muna-Miriam Hoshi received travel expenses from Bayer Health Care and honoraria for an advisory board from Merck Serono GmbH. Felix Lüssi serves as an advisory board member for

Roche Pharma and has received travel grants from Teva Pharma. Friedemann Paul serves on the scientific advisory board for Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an academic editor for PLoS One; is an associate editor for Neurology® Neuroimmunology & Neuroinflammation; consulted for SanofiGenzyme, Biogen Idec, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA; none related to this work. Björn Tackenberg received personal speaker honoraria and consultancy fees as a speaker and advisor from Bayer Healthcare, Biogen, CSL Behring, GRIFOLS, Merck Serono, Novartis, Octapharma, Roche, Sanofi Genzyme, TEVA und UCB Pharma. His University received unrestricted research grants from Biogen-idec, Novartis, TEVA, Bayer Healthcare, CSL-Behring, GRIFOLS, Octapharma, Sanofi Genzyme und UCB Pharma; none related to this work. Florian Then Bergh received travel support to attend scientific meetings, personal speaker honoraria, and consultancy fees as a speaker and advisor from Actelion, Bayer Healthcare, Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. He received, through his institution, unrestricted research grants from Novartis, TEVA, Bayer Healthcare, and Actelion; none related to this work. He received funding from the DFG and, through TRM Leipzig, from the BMBF. Tania Kümpfel received travel expenses and personal compensations from Bayer Healthcare, Teva Pharma, Merck-Serono, Novartis, Sanofi-Aventis/Genzyme, Roche and Biogen as well as grant support from Bayer-Schering AG, Novartis and Chugai Pharma; none related to this work. Hayrettin Tumani received speaker honoraria from Bayer, Biogen, Fresenius, Genzyme, Merck, Novartis, Roche, Siemens, Teva; serves as section editor for the Journal of Neurology, Psychiatry, and Brain Research; and receives research support from Fresenius, Genzyme, Merck, and Novartis; none related to this work. Martin Stangel received honoraria for scientific lectures or consultancy from Bayer Healthcare, Biogen, Baxter/Baxalta, CSL Behring, Euroimmune, Grifols, Merck-Serono, Novartis, Roche, Sanofi-Aventis, and Teva. His institution received research support from Bayer Healthcare, Biogen Idec, Genzyme, Merck-Serono, Novartis, and Teva; none related to this work. Frank Weber received honoraria from Genzyme, Novartis TEVA and Biogen for speaking or for serving on a scientific advisory board, a travel grant for the attention of a scientific meeting from Merck-Serono and Novartis and grant support from Merck-Serono, Novartis and from the Federal Ministry of Education and Research (BMBF, Projects Biobanking and Omics in ControlMS as part of the Competence Network Multiple Sclerosis). Antonio Bayas received personal compensation from Merck Serono, Biogen, Bayer Vital, Novartis, TEVA, Roche and Sanofi/Genzyme and grants for congress trips and participation from Biogen, TEVA, Novartis, Sanofi/Genzyme, and Merck Serono; none related to this work. Brigitte Wildemann received grants from the German Ministry of Education and Research, Dietmar Hopp Foundation and Klaus Tschira Foundation, grants and personal fees from Biogen, Merck Serono, Sanofi Genzyme, Novartis pharmaceuticals, Teva Pharma, and personal fees from Bayer Healthcare; none related to this work. Christoph Heesen received research grants and speaker honoraria from Biogen, Genzyme, Roche, and Merck; none related to this work. Uwe K. Zettl received speaker fees from Aventis, Almirall, Biogen, Bayer, Merck, Novartis, Roche, and Teva. Frauke Zipp received funds for scientific consultation or research of DFG, BMBF, Novartis, Octapharma, Merck Serono, ONO Pharma, Biogen, Genzyme, and Sanofi Aventis within the past 3 years. Bernhard Hemmer served on scientific advisory boards for F. Hoffmann-La Roche Ltd, Novartis, Bayer AG, and Genentech; he has served as DMSC member for Allergycare; he

or his institution have received speaker honoraria from Biogen Idec, Teva Neuroscience, Merck Serono, Medimmune, Novartis, Desitin, and F. Hoffmann-La Roche Ltd; his institution has received research support from Chugai Pharmaceuticals; holds part of two patents; one for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and one for genetic determinants of neutralizing antibodies to interferon during the last 3 years. Sven G. Meuth received honoraria for lecturing, travel expenses for attending meetings, and/or financial research support from Almirall, Bayer Health Care, Biogen, Diamed, Fresenius Medical Care, Genzyme, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis and Teva. Ralf Gold serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, and Novartis; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Novartis; serves as editor for *Therapeutic Advances in Neurological Diseases* and on the editorial boards of *Experimental Neurology* and the *Journal of Neuroimmunology*; and receives research support from Teva Pharmaceutical Industries Ltd., Biogen Idec, Bayer Schering Pharma, Genzyme, Merck Serono, and Novartis; none related to this work. Heinz Wiendl receives honoraria for acting as a member of Scientific Advisory Boards and as a consultant for Biogen, Evgen, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, TEVA, and WebMD Global. Prof. Wiendl is acting as a paid consultant for Abbvie, Actelion, Biogen, IGES, Novartis, Roche, Sanofi-Genzyme, and the Swiss Multiple Sclerosis Society. His research is funded by the BMBF, DFG, Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, Biogen GmbH, GlaxoSmith-Kline GmbH, and Roche Pharma AG, Sanofi-Genzyme. Anke Salmen received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme; none related to this work. Collaborators: Seray Demir, Christoph Schröder, Susanne Rothacher, Lisa A. Voithenleitner and Jana Pöttgen report no disclosures. Achim Berthele reports personal fees from Bayer Healthcare, Biogen, Merck Serono, Mylan, Roche, and Sanofi Genzyme, and his institution received compensations for clinical trials from Alexion Pharmaceuticals, Biogen, Chugai, Novartis, Roche, Sanofi Genzyme, and Teva - all outside the submitted work. Sarah Haars received, through her institution, travel compensation to attend scientific meetings from Merck, Bayer, Novartis and Actelion, unrelated to this work. Sandra Nischwitz received honoraria for serving on scientific Adboards and as a speaker from Merck Serono, Novartis, Genzyme and Roche and grant support from Novartis. Matthias J. Knop received honoraria for serving on scientific Adboards and as a speaker from Biogen, Merck, Genzyme, Novartis and Roche. Clemens Warnke received honoraria and/or research funding from Bayer, Biogen, Novartis, and TEVA; none related to this work. Ralf A. Linker received Research Support and/or personal compensation for activities with Bayer Health Care, Biogen, Genzyme/Sanofi, Merck, Novartis Pharma, Roche, and TEVA Pharma; none related to this work. Ulf Ziemann received speaker honoraria and/or travel compensation from Biogen Idec GmbH, Bayer Vital GmbH, Bristol Myers Squibb GmbH, CorTec GmbH, Medtronic GmbH, and grants from Biogen Idec GmbH, Servier, and Janssen Pharmaceuticals NV; none related to this work.

Informed consent Informed consent was obtained from all individual participants included in the study.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Sumowski JF, Benedict R, Enzinger C et al (2018) Cognition in multiple sclerosis. *Neurology* 90:278–288. <https://doi.org/10.1212/WNL.0000000000004977>
2. Rao SM, Leo GJ, Ellington L et al (1991) Cognitive dysfunction in multiple sclerosis.: II. Impact on employment and social functioning. *Neurology* 41:692–696. <https://doi.org/10.1212/WNL.41.5.692>
3. Amato MP, Zipoli V, Portaccio E (2006) Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *J Neurol Sci* 245:41–46. <https://doi.org/10.1016/j.jns.2005.08.019>
4. Hynčicová E, Vyhnálek M, Kalina A et al (2017) Cognitive impairment and structural brain changes in patients with clinically isolated syndrome at high risk for multiple sclerosis. *J Neurol* 264:482–493. <https://doi.org/10.1007/s00415-016-8368-9>
5. Uher T, Blahova-Dusankova J, Horakova D et al (2014) Longitudinal MRI and neuropsychological assessment of patients with clinically isolated syndrome. *J Neurol* 261:1735–1744. <https://doi.org/10.1007/s00415-014-7413-9>
6. Amato MP, Portaccio E, Goretti B et al (2010) Relevance of cognitive deterioration in early relapsing-remitting MS: a 3-year follow-up study. *Mult Scler* 16:1474–1482. <https://doi.org/10.1177/1352458510380089>
7. Reuter F, Zaaraoui W, Crespy L et al (2011) Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 82:1157–1159. <https://doi.org/10.1136/jnnp.2010.213744>
8. Borghi M, Cavallo M, Carletto S et al (2013) Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. *PLoS One* 8:1–9. <https://doi.org/10.1371/journal.pone.0069820>
9. Benedict RHB, Zivadinov R (2011) Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nat Rev Neurol* 7:332–342. <https://doi.org/10.1038/nrneurol.2011.61>
10. Ruano L, Portaccio E, Goretti B et al (2017) Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Mult Scler* 23:1258–1267. <https://doi.org/10.1177/1352458516674367>
11. Patti F, Amato M, Trojano M et al (2009) Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing–remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Mult Scler J* 15:779–788. <https://doi.org/10.1177/1352458509105544>
12. Ozakbas S, Turkoglu R, Tamam Y et al (2018) Prevalence of and risk factors for cognitive impairment in patients with relapsing-remitting multiple sclerosis: multi-center, controlled trial. *Mult Scler Relat Disord* 22:70–76. <https://doi.org/10.1016/j.msard.2018.03.009>
13. Uher T, Krasensky J, Sobisek L et al (2018) Cognitive clinicoradiological paradox in early stages of multiple sclerosis. *Ann Clin Transl Neurol* 5:81–91. <https://doi.org/10.1002/acn3.512>

14. Deloire M, Ruet A, Hamel D et al (2011) MRI predictors of cognitive outcome in early multiple sclerosis. *Neurology* 76:1161–1167. <https://doi.org/10.1212/WNL.0b013e318212a8be>
15. Benedict RHB, Weinstock-Guttman B, Fishman I et al (2004) Prediction of neuropsychological impairment in multiple sclerosis. *Arch Neurol* 61:226–230. <https://doi.org/10.1001/archneur.61.2.226>
16. Summers M, Swanton J, Fernando K et al (2008) Cognitive impairment in multiple sclerosis can be predicted by imaging early in the disease. *J Neurol Neurosurg Psychiatry* 79:955–958. <https://doi.org/10.1136/jnnp.2007.138685>
17. Rimkus CM, de IMB Avolio, Miotto EC et al (2018) The protective effects of high-education levels on cognition in different stages of multiple sclerosis. *Mult Scler Relat Disord* 22:41–48. <https://doi.org/10.1016/j.msard.2018.03.001>
18. von Bismarck O, Dankowski T, Ambrosius B et al (2018) Treatment choices and neuropsychological symptoms of a large cohort of early MS. *Neurol Neuroimmunol Neuroinflamm* 5:e446. <https://doi.org/10.1212/NXI.0000000000000446>
19. Barkhof F, Filippi M, Miller DH et al (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069. <https://doi.org/10.1093/brain/120.11.2059>
20. Polman CH, Reingold SC, Edan G et al (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the ‘McDonald Criteria’. *Ann Neurol* 58:840–846. <https://doi.org/10.1002/ana.20703>
21. Calabrese P, Kalbe E, Kessler J (2004) Das Multiple Sklerose Inventarium Cognition (MUSIC). *Psychoneuro* 30:384–388
22. Cutter GR, Baier ML, Rudick RA et al (1999) Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 122(Pt 5):871–882
23. Scherer P, Baum K, Bauer H et al (2004) Normierung der Brief Repeatable Battery of Neuropsychological Tests (BRB-N) für den deutschsprachigen Raum. *Nervenarzt* 75:984–990. <https://doi.org/10.1007/s00115-004-1729-0>
24. Bürkner P-C (2017) brms: an R package for Bayesian multilevel models using Stan. *J Stat Softw* 80:1–28. <https://doi.org/10.18637/jss.v080.i01>
25. Buuren S van, Groothuis-Oudshoorn K (2011) mice: multivariate imputation by chained equations in R. *J Stat Softw*. <https://doi.org/10.18637/jss.v045.i03>
26. Feuillet L, Reuter F, Audoin B et al (2007) Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler* 13:124–127. <https://doi.org/10.1177/1352458506071196>
27. Johnen A, Landmeyer NC, Bürkner P-C et al (2017) Distinct cognitive impairments in different disease courses of multiple sclerosis—a systematic review and meta-analysis. *Neurosci Biobehav Rev* 83:568–578. <https://doi.org/10.1016/j.neubiorev.2017.09.005>
28. Langdon DW, Amato MP, Boringa J et al (2012) Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Mult Scler J* 18:891–898. <https://doi.org/10.1177/1352458511431076>
29. Sonder JM, Burggraaff J, Knol DL et al (2014) Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Mult Scler J* 20:481–488. <https://doi.org/10.1177/1352458513501570>
30. López-Góngora M, Querol L, Escartín A (2015) A one-year follow-up study of the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT) in relapsing-remitting multiple sclerosis: an appraisal of comparative longitudinal sensitivity. *BMC Neurol* 15:40. <https://doi.org/10.1186/s12883-015-0296-2>
31. Rannikko I, Jääskeläinen E, Miettinen J et al (2016) Predictors of long-term change in adult cognitive performance: systematic review and data from the Northern Finland Birth Cohort 1966. *Clin Neuropsychol* 30:17–50. <https://doi.org/10.1080/13854046.2015.1128000>
32. Munro CA, Winicki JM, Schretlen DJ et al (2012) Sex differences in cognition in healthy elderly individuals. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 19:759–768. <https://doi.org/10.1080/13825585.2012.690366>
33. Patel VP, Walker LAS, Feinstein A (2018) Revisiting cognitive reserve and cognition in multiple sclerosis: a closer look at depression. *Mult Scler* 24:186–195. <https://doi.org/10.1177/1352458517692887>
34. Goldberg TE, Harvey PD, Wesnes KA et al (2015) Practice effects due to serial cognitive assessment: implications for preclinical Alzheimer’s disease randomized controlled trials. *Alzheimer’s Dement Diagnosis Assess Dis Monit* 1:103–111. <https://doi.org/10.1016/j.dadm.2014.11.003>
35. Roar M, Illes Z, Sejbaek T (2016) Practice effect in Symbol Digit Modalities Test in multiple sclerosis patients treated with natalizumab. *Mult Scler Relat Disord* 10:116–122. <https://doi.org/10.1016/j.msard.2016.09.009>
36. Benedict RHB, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R (2017) Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler J* 23:721–733
37. Baird BJ, Tombaugh TN, Francis M (2007) The effects of practice on speed of information processing using the Adjusting-Paced Serial Addition Test (Adjusting-PSAT) and the Computerized Tests of Information Processing (CTIP). *Appl Neuropsychol* 14:88–100. <https://doi.org/10.1080/09084280701319912>
38. Bartels C, Wegrzyn M, Wiedl A et al (2010) Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC Neurosci* 11:118. <https://doi.org/10.1186/1471-2202-11-118>
39. Basso MR, Bornstein RA, Lang JM (1999) Practice effects on commonly used measures of executive function across twelve months. *Clin Neuropsychol* 13:283–292. <https://doi.org/10.1076/clin.13.3.283.1743>
40. Rummel C, Aschwanden F, McKinley R et al (2018) A fully automated pipeline for normative atrophy in patients with neurodegenerative disease. *Front Neurol* 8:1–16. <https://doi.org/10.3389/fneur.2017.00727>

Affiliations

Andreas Johnen¹ · Paul-Christian Bürkner² · Nils C. Landmeyer¹ · Björn Ambrosius³ · Pasquale Calabrese⁴ · Jeremias Motte³ · Nicole Hessler⁵ · Gisela Antony⁶ · Inke R. König⁵ · Luisa Klotz¹ · Muna-Miriam Hoshi^{7,8} · Lilian Aly^{7,8} · Sergiu Groppa⁹ · Felix Luessi⁹ · Friedemann Paul¹⁰ · Björn Tackenberg¹¹ · Florian Then Bergh¹² · Tania Kümpfel¹³ · Hayrettin Tumani^{14,15} · Martin Stangel¹⁶ · Frank Weber^{17,18} · Antonios Bayas¹⁹ · Brigitte Wildemann²⁰ · Christoph Heesen²¹ · Uwe K. Zettl²² · Frauke Zipp⁹ · Bernhard Hemmer^{7,8} · Sven G. Meuth¹ · Ralf Gold³ · Heinz Wiendl¹ · Anke Salmen^{3,23} on behalf of German Competence Network Multiple Sclerosis (KKNMS)

- ¹ Department of Neurology, University Hospital Münster, Westfälische-Wilhelms-University Münster, Münster, Germany
- ² Department of Statistics, Faculty of Psychology, Westfälische-Wilhelms-University, Münster, Germany
- ³ Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany
- ⁴ Department of Neuropsychology and Behavioral Neurology, University of Basel, Basel, Switzerland
- ⁵ Institute of Medical Biometry and Statistics, University of Lübeck, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany
- ⁶ Central Information Office (CIO), Philipps-University Marburg, Marburg, Germany
- ⁷ Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
- ⁸ Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
- ⁹ Department of Neurology and Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network (rmn2), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
- ¹⁰ NeuroCure Clinical Research Center and Experimental and Clinical Research Center, Charité, University Medicine Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany
- ¹¹ Department of Neurology, Philipps-University Marburg, Marburg, Germany
- ¹² Department of Neurology, University of Leipzig, Leipzig, Germany
- ¹³ Institute of Clinical Neuroimmunology, Ludwig Maximilian University of Munich, Munich, Germany
- ¹⁴ Department of Neurology, University of Ulm, Ulm, Germany
- ¹⁵ Clinic of Neurology Diätenbronn, Schwendi, Germany
- ¹⁶ Department of Neurology, Hannover Medical School, Hannover, Germany
- ¹⁷ Neurology, Max-Planck-Institute of Psychiatry, Munich, Germany
- ¹⁸ Neurological Clinic, Sana Kliniken des Landkreises Cham, Cham, Germany
- ¹⁹ Department of Neurology, Klinikum Augsburg, Augsburg, Germany
- ²⁰ Department of Neurology, University of Heidelberg, Heidelberg, Germany
- ²¹ Institut für Neuroimmunologie und Multiple Sklerose, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
- ²² Department of Neurology, Neuroimmunological Section, University of Rostock, Rostock, Germany
- ²³ Department of Neurology, Inselspital Bern, Bern University Hospital and University of Bern, Bern, Switzerland