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Predictive value of different conventional and non-conventional MRI-parameters for specific domains of cognitive function in multiple sclerosis

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ABSTRACT

Objective: While many studies correlated cognitive function with changes in brain morphology in multiple sclerosis (MS), few of them used a multi-parametric approach in a single dataset so far. We thus here assessed the predictive value of different conventional and quantitative MRI-parameters both for overall and domain-specific cognitive performance in MS patients from a single center.
Methods: 69 patients (17 clinically isolated syndrome, 47 relapsing–remitting MS, 5 secondary-progressive MS) underwent the "Brief Repeatable Battery of Neuropsychological Tests" assessing overall cognition, cognitive efficiency and memory function as well as MRI at 3 Tesla to obtain T2-lesion load (T2-LL), normalized brain volume (global brain volume loss), normalized cortical volume (NCV), normalized thalamic volume (NTV), normalized hippocampal volume (NHV), normalized caudate nuclei volume (NCNV), basal ganglia R2* values (iron deposition) and magnetization transfer ratios (MTRs) for cortex and normal appearing brain tissue (NABT).
Results: Regression models including clinical, demographic variables and MRI-parameters explained 22–27% of variance of overall cognition, 17–26% of cognitive efficiency and 22–23% of memory. NCV, T2-LL and MTR of NABT were the strongest predictors of overall cognitive function. Cognitive efficiency was best predicted by NCV, T2-LL and iron deposition in the basal ganglia. NTV was the strongest predictor for memory function and NHV was particularly related to memory function.
Conclusions: The predictive value of distinct MRI-parameters differs for specific domains of cognitive function, with a greater impact of cortical volume, focal and diffuse white matter abnormalities on overall cognitive function, an additional role of basal ganglia iron deposition on cognitive efficiency, and thalamic and hippocampal volume on memory function. This suggests the usefulness of using multiparametric MRI to assess (micro)structural correlates of different cognitive constructs.

1. Introduction

Cognitive function may be impaired in 43–70% of all multiple sclerosis (MS) patients (Chiaravalloti and DeLuca, 2008; Filippi et al., 2010). Magnetic resonance imaging (MRI) is a valuable tool to investigate the pathophysiology of MS in vivo and to monitor disease evolution (Filippi and Rocca, 2010), and therefore also is expected to aid in enhancing the cerebral correlates of cognitive (dys)function in MS.

However, prior studies focused primarily on brain atrophy or T2 lesion load to predict cognitive function in MS (Langdon, 2011; Pinter et al., 2014; Sumowski et al., 2010). T2 lesion load appears to be an important predictor of cognitive function in MS (Lazeron et al., 2005; Sperling et al., 2001), but also volume decrease of the whole brain and selected regions (i.e. thalamus, hippocampus) provide robust correlates of MS-associated cognitive dysfunction (Filippi and Rocca, 2010; Grassiot et al., 2009; Tiemann et al., 2009).

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Beyond that, advanced MRI-techniques may explain additional variance of overall cognitive function and specific cognitive domains, as they allow assessing microstructural cerebral changes in a more refined manner. More specifically such quantitative MRI-measures, as R2* mapping (iron deposition) and magnetization transfer ratios (MTRs) have further contributed to our understanding of pathophysiologic changes in MS (Khalil et al., 2009; Rovaris et al., 2001).

In particular, magnetization transfer ratio (MTR) of normal appearing brain tissue (MTR-NABT) and MTR of the cortex have been frequently related to cognitive function (Comi et al., 2000; Cox et al., 2004; Deloire et al., 2011; Filippi et al., 2000), especially in early stages of the disease (Amato et al., 2008; Khalil et al., 2011a).

As a growing body of literature indicates that cognitive impairment in MS is related to damage of subcortical gray matter (Benedict et al., 2004; Houtchens et al., 2007) and increased iron deposition has previously been linked to impaired cognitive performance in MS (Brass et al., 2006; Ge et al., 2007), we here also examined the influence of basal ganglia R2* values assessed with a novel quantitative approach on cognition and specific domains of cognitive function.

Another largely neglected aspect refers to the fact that MRI-correlates could be domain-specific for different cognitive functions. In MS, cognitive impairment is typically characterized by domain-specific deficits rather than global cognitive decline (Amato et al., 2010). The hippocampus has been commonly related to memory function (Hulst et al., 2012; Roosendaal and Hulst, 2010), whereas thalamic volumes have been frequently related to overall cognitive function in MS (Benedict et al., 2004; Houtchens et al., 2007; Minagar et al., 2013), specifically to slowed cognitive processing (Batista et al., 2012; Van Der Werf et al., 2001). There is also evidence that atrophy of the caudate nuclei might be related to cognitive function in MS (Batista et al., 2012; Benedict et al., 2004; Modica et al., 2015).

However, frequently a composite cognitive score or performance of a specific subtest has been used in prediction models, not comparing the predictive value of different MRI-parameters for specific domains (e.g. cognitive efficiency and memory) of cognitive function. Furthermore, while many studies correlated cognitive function with changes in brain morphology in multiple sclerosis (MS), few of them used a multi-parametric approach.

Thus, we assessed the predictive value of conventional and quantitative MRI-parameters for overall cognition and specific domains of cognition in a large sample of MS patients from a single center (Graz), using an extended set of MRI-metrics.

Although, various additional parameters might be important for the prediction of cognitive function in MS, we here focused on the compartments most frequently mentioned in relation to cognition and MS. The choice of the presented parameters is selective and not exhaustive.

2. Materials and methods

2.1. Patients

We included 69 patients with a diagnosis of a clinically isolated syndrome (CIS) suggestive of MS, or diagnosis of relapsing–remitting or secondary progressive MS in our study (see Table 1 for characteristics; Polman et al., 2011). Study participants were enrolled from our MS outpatient department. All patients underwent clinical and neuropsychological testing, and a comprehensive 3 T MRI examination of the brain. Subjects had no current relapse, had not received corticosteroids 6 weeks prior to inclusion, and had no history of serious psychiatric illness (e.g. depression) or other neurologic disorders. The study was approved by the ethics committee of the Medical University of Graz. All participants gave written informed consent.

Table 1
Descriptive statistics and scores of neuropsychological and clinical testing for MS patients; means and standard deviations (in parentheses).

	All	CIS	RRMS	SPMS	*p*
N	69	17	47	5	
Sex female (%)	43 (62%)	12 (70%)	29 (61%)	2 (40%)	.04
Age (years)	35.6 (10.2)	33.1 (9.1)	35.8 (10.5)	41.8 (9.3)	.24
Education (years)	13.1 (2.5)	13.1 (2.4)	13.0 (2.6)	13.2 (2.3)	.98
Disease duration (years)	7.1 (8.3)	0.4 (0.8)	9.0 (8.7)	11.3 (6.0)	**.00**
EDSS	2.0 (1.5)	1.1 (0.9)	2.0 (1.2)	5.4 (0.9)	**.00**
Cognition					
SRT	55.7 (10.4)	60.7 (9.3)	54.0 (10.6)	53.8 (8.2)	.07
SPART	22.7 (4.9)	23.8 (3.5)	22.6 (5.4)	20.8 (4.1)	.42
PASAT	48.4 (10.0)	50.5 (9.2)	48.1 (10.0)	52.0 (4.5)	.52
SDMT	48.11 (12.7)	53.1 (10.3)	47.2 (13.0)	44.4 (5.9)	.17
WLG	25.8 (7.0)	29.0 (8.2)	24.8 (6.4)	24.0 (6.6)	.09

CIS = clinically isolated syndrome; RRMS = relapsing–remitting MS; SPMS = secondary progressive MS; EDSS = Expanded Disability Status Scale; SRT = Selective Reminding Test; SPART = 10−36-Spatial Recall Test; PASAT = Paced Auditory Serial Addition Test (3-s version); SDMT = Symbol Digit Modalities Test; WLG = Word List Generation. Disease duration: $p = 0.001$; EDSS: $p = 0.002$.

2.2. Clinical and neuropsychological assessment

Disability was measured using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). Cognition was assessed by the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao, 1990), comprising the following subtests: 1) Selective Reminding Test (SRT), to assess verbal learning and memory, 2) 10/36-Spatial Recall Test (SPART), to measure visuospatial learning; 3) the Symbol Digit Modalities Test (SDMT), to measure information processing speed, sustained attention, and concentration; 4) the Paced Auditory Serial Addition Test (3-s version; PASAT), to examine sustained attention and concentration; and 5) Word List Generation (WLG), to assess semantic verbal fluency (WLG). We used a composite Z-score (calculated on raw data) of all subtests as a measure of overall cognitive function. In subsequent analyses we used constructs of cognitive efficiency (composite Z-score of SDMT and PASAT, comprising attention, processing speed, concentration), memory (composite Z-score of SRT and SPART, comprising verbal and spatial learning and memory) and semantic verbal fluency (Z-score WLG) to assess the relationships between MRI-parameters and specific cognitive domains (Langdon, 2011; Sumowski et al., 2013).

2.3. MRI

MRI was performed on a 3 Tesla TimTrio scanner (Siemens Healthcare, Erlangen, Germany) using a 12-element receiver head coil and GRAPPA as parallel imaging technique with an acceleration factor of 2. High-resolution structural 3D images were acquired by a T1-weighted MPRAGE sequence with 1 mm isotropic resolution (TR = 1900 ms, TE = 2.19 ms, 176 slices), to assess normalized brain volume (NBV in cm^3), normalized regional volumes (thalamus, hippocampus, caudate nucleus) and normalized cortical volume (NCV in cm^3). A fluid-attenuated inversion recovery (FLAIR) sequence with $1 \times 1 \times 3$ mm^3 resolution served for the assessment of T2-LL (TR = 9000 ms; TE = 69 ms, 44 slices). FLAIR MRI is a highly sensitive sequence for lesion detection and literature suggests that observer performance of lesion detection is superior on FLAIR images than on T2 images (Woo et al., 2006).

R2* relaxation data were acquired with a spoiled 3D gradient echo sequence (FLASH) with 12 equally spaced echoes (TR = 68 ms; TE = 4.92 ms, interecho spacing = 4.92 ms, flip angle = 20°, resolution = $0.9 \times 0.9 \times 4$ mm^3, 32 slices). Magnetization transfer data were acquired with a spoiled 3D gradient-echo sequence (TR = 40 ms; TE = 7.38 ms; flip angle = 15°; resolution = $1 \times 1 \times 3$ mm^3; 44 slices) which was performed with and without a Gaussian shaped saturation pre-pulse. The total imaging time was approximately 23 min.

2.4. Image analysis

All image analyses were performed by trained and experienced analysts, blinded to clinical information T2-lesion load was assessed by a semi-automated region growing algorithm (DispImage; Plummer, 1992). High-resolution T1 scans served to determine NBV, normalized thalamic volume (NTV), normalized hippocampal volume (NHV), normalized caudate nuclei volume (NCNV) and normalized cortical volume (NCV), using SIENAX (Structural Image Evaluation using Normalization of Atrophy; Version v 2.6, part of fMRIB's Software Library; FSL). T1-weighted anatomical images from the MPRAGE sequence served for structural segmentation and volume measurement of the thalamus, hippocampus and caudate nucleus, using FIRST (FMRIB's Integrated Registration and Segmentation Tool; part of FSL). Gradient echo and magnetization transfer ratio (MTR) images were registered to the MPRAGE images using affine registrations as implemented in FLIRT (FSL). R2* maps were obtained by mono-exponentially fitting of the multi-echo gradient data and overlaid with the 3D segmentations to obtain mean R2* rates for the individual structures. Additionally, bilateral R2* rates of the globus pallidus, putamen, and caudate nuclei were utilized to calculate mean R2* values of the basal ganglia (BG). MTR images were calculated by normalizing the MR images with saturation pulses to the non-saturated images. After affine registration of the MPRAGE to the MTR images, cortical areas from SIENAX analysis were utilized to calculate mean MTR values of the entire cortex. Also, MTR of normal appearing brain tissue (NABT; brain volume minus lesion volume and volume of the ventricles) was calculated.

2.5. Statistical analysis

Clinical and neuropsychological data were analyzed with the Statistical Package of Social Science (IBM SPSS Statistics 20). The level of significance was set at 0.05. Exploratory analyses (Pearson correlation, point-biserial correlation) examined the relationship between demographic and clinical variables (e.g. sex, age, disease duration) and cognition (overall cognitive function, cognitive efficiency, memory). We then controlled for any demographic and clinical variable significantly correlated with cognition in further analyses. Assumptions for regression analyses (e.g. linearity, homoscedasticity, auto-correlation (Durbin–Watson-test), multicollinearity (Variance Inflation Factor)) were checked. Hierarchical regression models served to assess the predictive value of individual MRI-parameters for overall cognitive function and specific cognitive domains. Therefore, we included sex, age and disease duration in our first step and individual MRI metrics in a second step. Standardized beta-values (βj), adjusted R^2 (explanation of variance) and delta (Δ) adjusted R^2 (displaying incremental explanation of variance) in percent are presented for each model in the Results section. A multivariate model including the three strongest predictors for overall cognitive function and specific subdomains served to assess a potential additional value of multiple MRI-parameters for prediction of cognitive function. For the multivariate models we centered predictor variables.

3. Results

Table 1 gives information on the descriptive variables, the cognitive and clinical profile of the study cohort.

3.1. Prediction of overall cognitive function: comparison of individual MRI-parameters

A regression model including clinical, demographic variables, and NCV explained 27.0% of the variance of overall cognitive function. There was a positive effect of NCV on overall cognition ($\beta j = 0.39$; $p < 0.05$). A regression model including clinical, demographic variables, and T2-LL explained 26.7% of the variance of overall cognitive function. There was a positive effect of sex ($\beta j = 0.24$; $p < 0.05$; male = 1; female = 2; women performed better than men) and a negative effect of T2-LL ($\beta j = -0.32$; $p < 0.001$). A regression model including clinical, demographic variables and MTR of NABT explained 26.7% of the variance of overall cognitive function. There was a positive effect of sex ($\beta j = 0.25$; $p < 0.05$; male = 1; female = 2; women performed better than men) and MTR of NABT ($\beta j = 0.33$; $p < 0.05$). A regression model including clinical, demographic variables and NTV explained 23.5% of overall cognition ($\beta j = 0.28$; $p < 0.05$). Similar explanation of variance for overall cognition was found for NBV (22.4%; $\beta j = 0.26$; $p < 0.05$) and MTR values of the cortex (22.5%; $\beta j = 0.24$; $p < 0.05$), when controlled for clinical and demographic variables. Iron deposition in the basal ganglia (R2* BG), NCNV and NHV did not significantly explain incremental variance of overall cognition. Results of prediction models of overall cognitive function are presented in Table 2.

3.2. Prediction of specific cognitive functions: comparison of individual MRI-parameters

3.2.1. Cognitive efficiency

Cognitive efficiency was operationalized by the composite Z-score of SDMT and PASAT, comprising attention, processing speed and concentration.

A regression model including clinical, demographic variables, and NCV explained 26.3% of the variance of cognitive efficiency ($\beta j = 0.50$; $p < 0.001$). A regression model including clinical, demographic variables, and T2-LL explained 23.1% of the variance of cognitive efficiency. There was a negative effect of age ($\beta j = -0.28$; $p < 0.05$) and T2-LL on cognitive efficiency ($\beta j = -0.38$; $p < 0.001$). Iron deposition in the basal ganglia (R2* BG) explained 22.4% of variance of cognitive efficiency ($\beta j = -0.41$; $p < 0.05$). MTR values of the cortex explained 19.9% of variance of cognitive efficiency ($\beta j = 0.33$; $p < 0.05$). A regression model including clinical, demographic variables, and MTR of NABT explained 18.9% ($\beta j = 0.31$; $p < 0.05$) of the variance of cognitive efficiency. Similar explanation of variance for cognitive efficiency was found for NTV (17.1%; $\beta j = 0.30$; $p < 0.05$) and NBV (17.7%; $\beta j = 0.32$; $p < 0.05$), when controlled for clinical and demographic variables. NCNV and NHV did not significantly explain incremental variance of cognitive efficiency.

3.2.2. Memory

Memory was operationalized by the composite Z-score of SRT and SPART, comprising verbal and spatial learning and memory.

Table 2
Prediction of overall cognition (*Z*-scores of BRB-N) and the subdomains cognitive efficiency (SDMT + PASAT) and memory (SRT + SPART). Adjusted R^2 in percent (if controlled for age, sex, disease duration) of individual models including individual MRI − parameters (N = 69). Explanation of incremental variance due to MRI-parameter (delta of adjusted R^2) in parentheses.

R^2 MR-metrics	Cognition 18.8% explained by age, sex, DD	Cogn. eff. 11.8% explained by age, sex, DD	Memory 16.9% explained by age, sex, DD
T2-LL	26.7 (7.9)%	23.1 (11.3)%	23.1 (6.2)%
NBV (cm^3)	22.4 (3.6)%	17.7 (5.9)%	ns
NCV (cm^3)	27.0 (8.2)%	26.3 (14.5)%	ns
NTV	23.5 (4.7)%	17.1 (5.8)%	23.4 (6.5)%
NHV	ns	ns	22.1 (5.2)%
NCNV	ns	ns	ns
MTR cortex	22.5 (3.7)%	19.9 (8.1)%	ns
MTR-NABT	26.7 (7.9)%	18.9 (7.1)%	22.4 (5.5)%
R2*-BG	ns	22.4 (10.6)%	ns

DD = disease duration; T2-LL = T2-lesion load; NBV = normalized brain; NCV = normalized cortical volume; NTV = normalized thalamic volume; NHV = normalized hippocampal volume; NCNV = normalized caudate nuclei volume; R2*-BG = basal ganglia R2* values (iron deposition); MTR cortex = magnetization transfer ratio for the cortex; MTR-NABT = magnetization transfer ratio for normal appearing brain tissue; ns = not significant.

A regression model including clinical, demographic variables, and NTV explained 23.4% of the variance of memory ($\beta j = 0.32$; $p < 0.05$). A regression model including clinical, demographic variables and T2-LL explained 23.1% of the variance of memory. Sex had a positive effect ($\beta j = 0.22$; $p < 0.05$) and T2-LL had a negative effect ($\beta j = -0.29$; $p < 0.05$) on memory. Similar explanation of variance for memory was found for NHV (22.4%; $\beta j = 0.25$; $p < 0.05$) and MTR of NABT (22.4%; $\beta j = 0.28$; $p < 0.05$). NBV, NCV, NCNV, R2* values of the basal ganglia and MTR values of the cortex did not significantly explain variance of memory.

None of the MRI-parameters did significantly explain incremental variance over and above clinical and demographic variables for semantic verbal fluency. Results of individual prediction models of cognitive efficiency and memory are presented in Table 2.

3.3. Multivariate models

A multivariate model including the strongest predictors for overall cognition (T2-LL, NCV and MTR-NABT) and memory function (NTV, T2-LL and MTR-NABT) did not explain incremental variance, compared to the model with the strongest predictor. The only retained predictor for overall cognition was NCV (27%) and the only retained predictor for memory function was NTV (23.4%). A multivariate model including the strongest predictors for cognitive efficiency (NCV, T2-LL, and R2*-BG) explained 29.5% of variance, R2*-BG explaining 22.4% of variance, T2-LL explaining incremental 3.5% and NCV explaining incremental 3.6% (see Table 3).

Based on the small number of SPMS patients and on the considerations that this reflects a different stage of disease, we also ran all analyses after exclusion of the 5 SPMS patients. Major results did not change. Minor deviations of the explanation of variance (delta of adjusted R^2) by 1–2% were found (data not shown). We did not find an effect of disease phenotype on the findings.

4. Discussion and conclusions

Regression models including clinical, demographic variables and individual MRI-parameters explained 22–27% of variance of overall cognition, 17–26% of cognitive efficiency and 22–23% of memory. Cortical volume was the strongest predictor of overall cognitive function and cognitive efficiency. The specific role of cortical volume changes in relation to cognitive function in MS has also been repeatedly highlighted in prior studies (Amato et al., 2004, 2007, 2008; Benedict et al., 2006; Calabrese et al., 2010; Khalil et al., 2011b). In contrast to other studies (Amato et al., 2004; Benedict et al., 2006), cortical volume did not significantly predict memory function in our sample.

In line with previous work T2-lesion load was identified as an important predictor for overall cognition, cognitive efficiency and memory function (Penny et al., 2010; Pinter et al., 2014). In general, greater lesion burden has been associated with more severe cognitive dysfunction (Chiaravalloti and DeLuca, 2008; Filippi and Rocca, 2010; Summers et al., 2008; Tiemann et al., 2009).

MTR of the NABT, i.e. diffuse microstructural white matter changes, was the third-strongest predictor of overall cognitive function and explained additional variance of cognitive efficiency and memory function. MTR allows detecting abnormalities outside MS-lesions, related to diffuse astrocytic hyperplasia, patchy edema, perivascular cellular infiltration, and abnormally thin myelin and axonal damage (Filippi et al., 2000). MTR of the NABT has been related to overall cognitive dysfunction (Filippi et al., 2000) and impairment of attention and information processing speed (Deloire et al., 2005). Furthermore, a longitudinal study found baseline MTR of NABT to be associated with subsequent changes of memory and processing speed over 7 years (Deloire et al., 2011). Also, cortical MTR has been related to impairment of overall cognitive function (Amato et al., 2008).

Besides normalized cortical volume and T2-lesion load, iron deposition of the basal ganglia best predicted cognitive efficiency. In contrast, iron deposition of the basal ganglia did not significantly explain overall cognition or memory function in our sample, suggesting a domain-specific influence of iron in the basal ganglia on cognitive efficiency. Increased iron deposition has been previously related to cognitive dysfunction in the elderly and MS (Brass et al., 2006; Daugherty and Raz, 2013; Ge et al., 2007; Khalil et al., 2009). Previous own work found a correlation between iron deposition in the basal ganglia and processing speed (Khalil et al., 2011a), but processing speed did not predict iron deposition in the brain. Here, we investigated whether iron deposition of the basal ganglia was predictive for cognitive function. Hence, the inverse significant prediction suggests that iron deposition negatively affects cognitive efficiency (comprising attention, processing speed, concentration) in MS patients, even when controlled for age.

In general, memory scores were more strongly explained by demographic and clinical variables while lower predictive scores were found for MR-metrics. Predictors of memory function were normalized thalamic volume, lesion load, MTR of NABT and normalized hippocampal volume. Hippocampal volume may provide high domain-specificity, as it was only significantly predicting memory in our cohort. This is in line with existing studies highlighting that the hippocampus is a key region for memory function and damage to this critical and specialized brain region may result in particular alterations of memory (Battaglia et al., 2011; Hulst et al., 2012; Roosendaal and Hulst, 2010; Sumowski et al., 2013).

The thalamus relays sensory information to the higher cortical centers that influence cognition (Minagar et al., 2013). Thalamic volumes have been previously linked to overall cognitive function, processing speed (cognitive efficiency) and memory function (Batista et al., 2012; Benedict et al., 2013; Houtchens et al., 2007; Minagar et al., 2013). Consistent with these findings, also in our study overall cognition and subdomains could be predicted by normalized thalamic volume.

Overall, explanation of variance was comparable for individual models. Prediction of overall cognition and memory did not improve when multiple MR-metrics were included in the model. Only minor increases (17.7% vs 14.5%) of explanation of variance were observed including multiple MR-parameters for prediction of cognitive efficiency. Markers of MS-related brain pathology can be detected in the earliest phases of MS, and are associated with each other, e.g. iron deposition and atrophy of deep gray nuclei are closely related to the magnitude of inflammation (Minagar et al., 2013). Therefore for prediction of overall cognition in large samples, investigation of brain volume or lesion load may be sufficient, whereas for individual exploration of MRI-parameters related to domain-specific deficits, a clear selection of MRI-parameters (e.g. iron deposition for cognitive efficiency) seems to be essential. This suggests the usefulness of using multiparametric MRI to assess (micro)structural correlates of different cognitive constructs.

There are several limitations that have to be considered regarding our study. First of all, the choice of included MRI-parameters is selective and not exhaustive. As this study represents a first attempt to assess the usefulness of multiparametric MRI to assess structural correlates of cognitive function in MS, we included the (in our opinion) most crucial parameters in this context. Various additional parameters might be important for prediction of cognitive function in MS. Secondly, we did

Table 3
Multivariate model for cognitive efficiency. Adjusted R^2 in percent (if controlled for age, sex, disease duration). Explanation of incremental variance due to MRI-parameter (delta of adjusted R^2) in parentheses.

R^2 MR-metrics	Cognitive efficiency 11.8% explained by age, sex, DD
R2*-BG	22.4 (3.5)%
T2-LL	25.9 (3.5)%
NCV	29.5 (3.6)%

DD = disease duration; R2*-BG = basal ganglia R2* values (iron deposition); T2-LL = T2-lesion load; NCV = normalized cortical volume.

not perform lesion filling prior to atrophy quantification as increasingly used to improve brain tissue volume measurement (Battaglini et al., 2012; Valverde et al., 2014). Furthermore, the maximum variability explained by this multiple MRI-approach was 29.5%, indicating that various other parameters have to be considered regarding cognitive function in MS. In this study, we controlled for any demographic and clinical variable significantly correlated with cognition. We included sex, age and disease duration in our models. Clinical phenotype did not have an effect on our findings. However, additional scores, e.g. EDSS or education might be included in the future, but the inclusion of further predictors requires a larger sample size to ensure sufficient statistical power. Furthermore, it should be mentioned that based on a commonly used stringent definition of cognitive impairment (Rocca et al., 2010; the patient scores = 0 in at least 3 tests), only seven of our patients would be classified as cognitively impaired. As also evident from the title, we therefore focused on prediction of cognitive function in MS. In addition, in our sample SPMS patients performed unexpectedly well in the PASAT subtest. As this might have had an effect on our findings, and based on the small number of SPMS patients, we also ran all analyses after exclusion of the 5 SPMS patients. However, major results did not change.

Further studies in larger cohorts and longitudinal setting are thus needed to better clarify the relevance of distinct MRI-parameters for specific domains of cognitive function.

Conflicts of interest

D. Pinter has received funding from Genzyme/Sanofi-Aventis and speaking honoraria from Merck Serono.

M. Khalil has received funding for travel/speaker honoraria from Bayer Schering Pharma, Novartis Genzyme, Merck Serono, Biogen Idec, and Teva Pharmaceutical Industries.

A. Pichler, C. Langkammer, and P. Marschik report no disclosures.

S. Fuchs serves on scientific advisory boards for Biogen Idec and Novartis; and has received funding for travel and speaker honoraria from Bayer-Schering Pharma, Biogen Idec, Sanofi-Aventis, and Merck Serono.

F. Fazekas serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, D-Pharm Ltd., and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis; serves on the editorial boards of Cerebrovascular Diseases, multiple sclerosis, the Polish Journal of Neurology and Neurosurgery, Stroke, and the Swiss Archives of Neurology and Psychiatry; and has received speaker honoraria from Biogen Idec, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis.

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