Research Paper

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Contribution of cortical and white matter lesions to cognitive impairment in multiple sclerosis

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Abstract

Background: Cortical lesions (CLs) have been reported to be a better predictor for cognitive impairment than white matter (WM) lesions in relapsing–remitting multiple sclerosis (RRMS).

Objectives: The objectives of this article are to investigate the contribution of CLs and WM lesions to cognitive impairment in 91 patients with MS and clinically isolated syndrome, and to test potential associations of CLs and WM lesions with fatigue and depression.

Methods: Lesions were scored and segmented on 3D double inversion recovery sequences, according to their location (cortical, WM). Normalised grey matter volume was also determined. Cognitive performance was assessed with the SDMT and PASAT-3, fatigue with the FSMC and depression with the German version of the CES-D.

Results: CL volume did not correlate with fatigue or depression, but correlated significantly with both neuropsychological outcome measures: PASAT-3 (r = -0.275, p = 0.009) and SDMT (r = -0.377, p < 0.001). Multiple regression analyses with age, WM lesions, CLs and GM volume as independent variables, however, did not reveal CL volume as a significant predictor of neuropsychological outcomes, whereas WM lesion volume significantly predicted SDMT and by trend PASAT performance.

Conclusions: These findings suggest a role of WM lesions in the development of cognitive deficits, especially information-processing speed, which may be higher than previously assumed.

Abbreviations: CES-D: Center for Epidemiologic Studies Depression scale (ADS-L: Allgemeine Depressions Skala-L, German version of CES-D), CIS: clinically isolated syndrome, CL: cortical lesion, DIR: double inversion recovery, EDSS: Expanded Disability Status Scale, FSMC: fatigue scale for motor and cognitive functions, GM: grey matter, MRI: magnetic resonance imaging, MS: multiple sclerosis, PASAT-3: paced auditory serial addition test 3s, PPMS: primary progressive multiple sclerosis, RRMS: relapsing–remitting multiple sclerosis, SDMT: symbol digit modalities test, SPM: statistical parametric mapping, SPMS: secondary progressive multiple sclerosis, WM: white matter

Keywords

Cortical lesions, white matter lesions, cognition, multiple sclerosis

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Introduction

Multiple sclerosis (MS) was for a long time considered a disease affecting mainly the white matter. However, in recent years neuropathological and imaging studies have drawn attention to the involvement of grey matter in MS in terms of focal lesions and atrophy.[1–10] This is especially so since the application of more sensitive magnetic resonance imaging (MRI) sequences, such as double inversion recovery (DIR), have enabled cortical lesions (CLs) to be described in vivo in the majority of patients with MS as well as in one-third of patients with clinically isolated syndrome (CIS).[3,11–13] In

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Table 1. Clinical and demographic characteristics of the 91 patients included in the study.

Patient characteristics	
n	91
Females (%)	58 (63.7%)
Mean age (SD)	49.1 (1.85)
Mean disease duration (SD)	17.4 (9.4)
Disease type (%)	
CIS and RRMS	65 (71.4%)
SPMS and PPMS	26 (28.6%)
Mean EDSS (SD)	3.64 (1.85)

SD: standard deviation; CIS: clinically isolated syndrome; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale.

patients with benign MS, however, CLs seem to be less common.[14] Further, cortical lesion load correlates moderately with clinical disability as measured by the Expanded Disability Status Scale (EDSS).[11,15,16] Cognitive impairment is a frequent (40–65%)[17] and disabling symptom in MS. It is most probably the result of multiple structural and functional disease-related changes in the brain. CL load has been reported to correlate with cognitive dysfunction in MS.[4,15,16,18] Calabrese et al.[4] suggested that the volume of cortical lesions might be an even better predictor for cognitive impairment than white matter lesion volume.

In the present study we aimed at investigating the associations of CLs, white matter (WM) lesions and normalised grey matter volume with cognitive impairment in a cohort of patients with definite MS and CIS. Moreover, we tested the potential associations of CL load with fatigue and depression.

Methods

Patients

The data in this study were acquired in an ongoing prospective observational study on the phenotype-genotype characterisation of MS. Written informed consent was obtained from all patients participating in the study. In this analysis, we included all patients in whom three-dimensional (3D) DIR sequences were acquired in study year three (2008) or four (2009) (n=91). At the time of MRI acquisition, patients were treated with the best individually selected disease-modifying treatments. They were clinically stable and showed in general only minimal signs of inflammatory activity on MRI (mean contrast enhancing lesions 0.1 ± 0.52). The demographic and clinical characteristics of the patients are presented in Table 1.

Analysis of MRIs

The 3D DIR images were obtained with a 1.5 Tesla MRI scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) with the following sequence parameters: repetition time (TR): 7.5 s, echo time (TE): 311 ms, inversion time (TI): 3 s, slice thickness: 1.5 mm and in-plane spatial resolution 1.33 mm × 1.33 mm. All lesions were marked on axial slices by the same rater (AP), who was blinded to the patients' identity and clinical characteristics. The corresponding coronal and sagittal slices were used for verification and better characterisation of the lesions. Based on the DIR images, lesions were assigned to be CL or WM lesions. The marked lesions were reviewed by a second rater, an experienced neuroradiologist (NML), and in case of a discrepancy a decision was made by consensus. For the scoring of CLs, both raters followed the criteria proposed by Geurts et al.[19] Thus, CLs involved strictly intracortical and mixed grey (GM)-WM lesions, they had to be hyperintense compared to the surrounding normal-appearing GM, and they had to occupy at least three pixels (see the Figure for illustration). Moreover, supportive criteria were used to avoid false-positive lesions, according to the consensus recommendations of the Magnetic Resonance in Multiple Sclerosis (MAGNIMS) study group.[19] For example, both raters became acquainted with common artefacts as described in the scientific literature,[3,6,11,19,20] while in cases of debatable lesions, multiple slices and additional T1-, T2- and proton density-weighted images were used to verify lesions or distinguish them from artefacts. After consensus lesion scoring was completed, all lesions were outlined at the voxel level on each of the axial sections of the DIR images by means of the commercially available semi-automatic thresholding contour software AMIRA 3.1.1 (Mercury Computer Systems Inc) in accordance with common practice in brain imaging studies.[21] The volumes of WM lesions and CLs per patient were calculated. Moreover, normalised GM volume, including volume of the cortex and of the deep GM, was assessed on 3D magnetisation-prepared rapid gradient echo (MPRAGE) images using statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neurosciences, University College London, (http://www.fil.ion.ucl.ac.uk/spm), version 958, last updated 13 December 2007), as described previously.[22]

Neuropsychological assessment

Eighty-nine of the 91 patients included in this study were investigated with regard to cognition, fatigue and depression. The neuropsychological screening was performed by a neuropsychologist (IKP) blinded to other clinical and MRI results. The Paced Auditory Serial Addition Test 3s (PASAT-3)[23] and the Symbol Digit Modalities Test (SDMT)[24] were applied as tests of attention, working memory and speed of information processing. In addition, a German short screening battery (Das Multiple Sklerose Inventarium Cognition (MUSIC))[25] was applied that was, however, not followed up further to allow comparison of analysis with the existing literature. For the assessment of

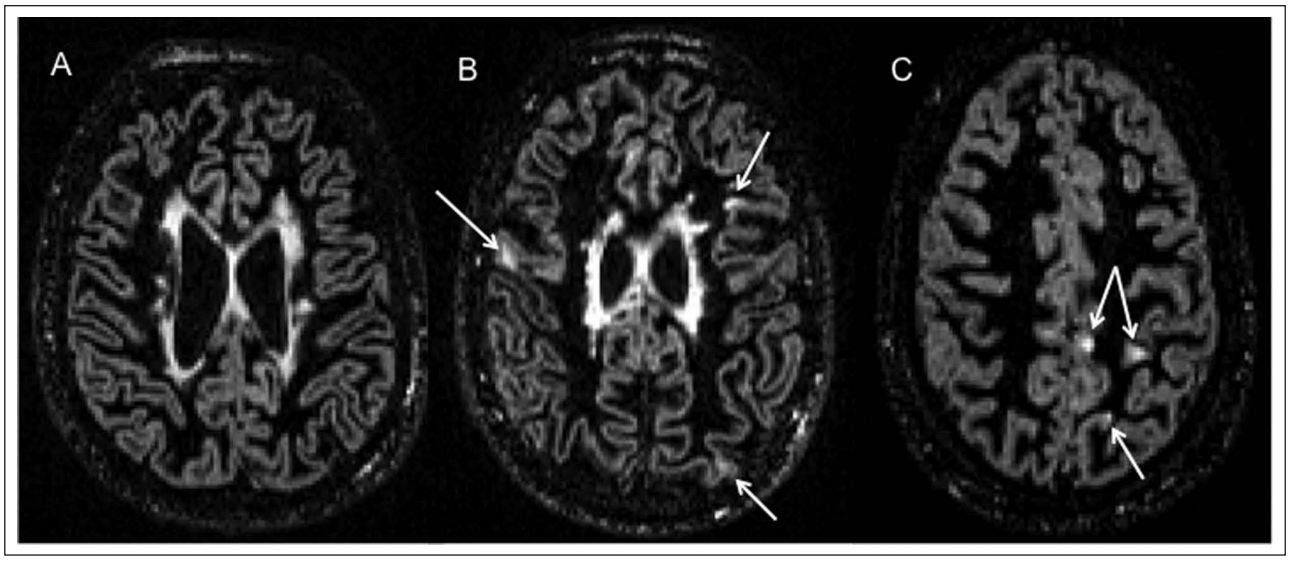

Figure. Examples of double inversion recovery (DIR) images with white matter and cortical lesions. A: patient with mostly white matter lesions, B: patient with white matter and cortical lesions (arrows), C: patient with cortical lesions (arrows).

Table 2. Neuropsychological characteristics of patients.

Psychosocial domains (*n*=91)	Instruments	Mean	SD	**Impairment categorisation**[a]
Fatigue total score	FSMC_tot	56.33	20.62	Moderate
Fatigue physical subscore	FSMC_mot	30.21	10.87	Moderate
Fatigue cognitive subscore	FSMC_cog	26.12	10.62	Mild
Depression	CES-D (German version ADS-L)	13.65	10.52	Normal
Cognitive domains (*n*=89)				
Information processing speed and working memory	SDMT	44.60 (z=-1.15)	13.61 (1.39)	moderate
Information processing speed, working memory, concentration, complex attention	PASAT -3	44.29 (z=-.71)	12.16 (1.19)	mild

FSMC_tot: sum score of the Fatigue Scale for Motor and Cognitive Functions; FSMC_mot: physical subscore of the Fatigue Scale for Motor and Cognitive Functions; FSMC_cog: cognitive subscore of the Fatigue Scale for Motor and Cognitive Functions; CES-D: Center for Epidemiologic Studies Depression Scale (ADS-L: Allgemeine Depressions Skala-L); SDMT: Symbol Digit Modalities Test; PASAT-3: Paced Auditory Serial Addition Test 3 sec Version; [a]impairment categorisation is based on cut-off values for FSMC and CES-D and on z scores for PASAT and SDMT (according to the normative data of the German Brief Repeatable Battery of Neuropsychological Tests[30] (BRB-N)).

fatigue, we used the Fatigue Scale for Motor and Cognitive functions (FSMC).[26] Depressive symptoms were assessed using the German version of the Center for Epidemiologic Studies Depression Scale (CES-D).[27] The neuropsychological characteristics of the patients are illustrated in table 2.

Statistical analysis

For the statistical analysis we used lesion volume instead of lesion number, since the volume can be regarded as a more accurate measure of lesion load. Since lesion volumes were not normally distributed, a logarithmic transformation was used for all further statistical analyses. Bivariate correlations of lesion volumes with demographic, clinical and neuropsychological variables (cognition, fatigue and depression) were calculated using Pearson's correlation coefficient (r). To assess the relative contribution of MRI variables to the outcomes of cognitive tests, a hierarchical regression analysis was performed with age as a nuisance variable in the first block and the three MRI variables in the second block. Bivariate correlations between CL volume and clinical/neuropsychological characteristics as well as the hierarchical regression analysis were also performed in a subgroup of patients with relapsing–remitting MS (RRMS). All statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM, Chicago, IL, USA).

Results

A total of 1040 CLs were scored in 71/91 patients (78% of the patients had ≥ 1 CL, mean CLs per patient 11.43 ± 19.52, range 0–124, median 4). CL volume varied from 0 to 7311.6 µl among patients (mean 697.6 µl). Mean WM lesion volume was 6311.3 µl (range: 21.3–40720.5 µl).

CL volume correlated moderately with WM lesion volume ($r = 0.644$, $p < 0.001$) whereas no correlations were found with normalised GM volume and age.

Correlations of CL volume with disability, cognition, fatigue and depression

CL volume correlated only by trend with EDSS ($r = 0.206$; $p = 0.051$). Concerning the cognitive tests, CL volume correlated significantly with PASAT ($r = -0.275$, $p = 0.009$) and SDMT ($r = -0.377$, $p < 0.001$). It did not correlate with depression, motor or cognitive fatigue.

Table 3. Summary of hierarchical regression analysis for different MRI variables and age predicting PASAT performance (n=87).

Variable	B	SE B	beta
Step 1			
Age	-.360	.110	-.334[c]
Step 2			
Age	-.243	.115	-.226[b]
Cortical lesion volume	-1.602	1.242	-.160
White matter lesion volume	-4.403	2.299	-.241[a]
Normalised grey matter volume	41.225	28.283	.156

$R^2 = .112$ for Step 1; $\Delta R^2 = .156$ for Step 2; B: non-standardised regression coefficient; SE B: standard error of non-standardised regression coefficient B; beta: standardised regression coefficient; MRI: magnetic resonance imaging; PASAT: Paced Auditory Serial Addition Test; [a]trend with $p = 0.059$; [b]$p \leq 0.05$ cp ≤ 0.01(c is indicating that this value is highly significant with p smaller or equal to 0.01)

Correlations of WM lesion volume with disability, cognition, fatigue and depression

WM lesion volume correlated significantly with EDSS ($r = .290$, $p = 0.005$). The correlations of WM lesion volume with the cognitive tests were in general stronger than those of CL volume: PASAT ($r = -0.361$, $p = 0.001$) and SDMT ($r = -0.585$, $p < 0.001$). In addition, WM lesion volume did not correlate with depression and cognitive fatigue, but significantly with motor fatigue ($r = 0.225$, $p = 0.032$).

Predictive properties of CLs, WM lesions, normalised GM volume and age in relation to cognitive impairment

Since we were interested in evaluating which MRI measure is best in predicting cognitive impairment, we decided to compute a hierarchical regression analysis to consider the influence of the factor age on both cognitive performance and brain status. As CLs and WM lesions were correlated, we checked for the problem of multicollinearity with the tolerance factor and the variation inflation factor (VIF). Both factors did not indicate multicollinearity since tolerance with values between .57 and .78 was much higher than the critical value of 0.2, and the VIF with values between 1.27 and 1.73 was much lower than the critical value of 4. Thus, we can assume that the results of our multiple regression analyses are not hampered by multicollinearity of the predictor variables.

The hierarchical regression analysis was performed for both cognitive tests as dependent variables and CL volume, WM lesion volume, normalised GM volume and age as independent variables (Tables 3 and 4). CL load was not a significant predictor for any of the neuropsychological outcome measures. On the contrary, WM lesion load was a significant predictor for SDMT and by trend a predictor for PASAT. In all analyses, age was also found to be a significant predictor for cognitive performance.

Subgroup analysis in patients with RRMS

In order to allow for consistency and comparability with the study of Calabrese et al.,[4] we applied to a subgroup of patients with RRMS (n=60) the identical statistical procedure as described before. CL volume only correlated significantly with SDMT ($r = -0.301$, $p = 0.019$). Similarly to the whole cohort, CL load did not correlate with fatigue or depression in patients with RRMS. On the contrary, WM lesion volume correlated significantly with both neuropsychological outcomes (SDMT: $r = -.609$, $p < 0.001$; PASAT: $r = -.308$, $p = 0.018$) and with motor fatigue ($r = .280$, $p = 0.030$). The results of the multiple regression analysis are summarised in Tables 5 and 6. The main finding was that CL load was again not significantly associated with any cognitive outcome, while WM lesion load turned out to be predictive for SDMT.

Discussion

The main finding of our study was that, despite the moderate bivariate correlations found with neuropsychological outcome measures, CL volume did not predict cognitive performance in a multiple regression model with WM lesion volume, normalised GM volume and age as additional independent variables. In contrast, WM lesion volume turned out to be a significant predictor for SDMT performance and by trend to be predictive for PASAT performance, suggesting a stronger association of WM structural damage with information-processing speed and working memory than of CLs. In line with this, the bivariate correlations of WM lesion load with the cognitive tests were stronger than those of CL load.

There are very few studies that have tried to compare cortical and WM lesions regarding their relation to cogni-

Table 4. Summary of hierarchical regression analysis for different MRI variables and age predicting SDMT performance (*n*=87).

Variable	B	SE B	beta
Step 1			
Age	-.434	.124	-.356[b]
Step 2			
Age	-.275	.113	-.225[a]
Cortical lesion volume	-.971	1.223	-.085
White matter lesion volume	-10.177	2.255	-.488[b]
Normalised grey matter volume	40.542	27.175	.138

R^2 = .126 for Step 1; ΔR^2 = .320 for Step 2; B: non-standardised regression coefficient; SE B: standard error of non-standardised regression coefficient B; beta: standardised regression coefficient; MRI: magnetic resonance imaging; SDMT: Symbol Digit Modalities Test; [a]$p \leq 0.05$; [b]$p \leq 0.01$.

Table 5. Summary of hierarchical regression analysis for different MRI variables and age predicting PASAT performance in a sub-sample of RRMS patients (*n*=60).

Variable	B	SE B	beta
Step 1			
Age	-.362	.132	-.344[a]
Step 2			
Age	-.218	.147	-.207
Cortical lesion volume	-1.127	1.376	-.125
White matter lesion volume	-3.008	2.391	-.193
Normalised grey matter volume	56.015	32.434	.239

R^2 = .118 for Step 1; ΔR^2 = .128 for Step 2; B: non-standardised regression coefficient; SE B: standard error of non-standardised regression coefficient B; beta: standardised regression coefficient; MRI: magnetic resonance imaging; PASAT: Paced Auditory Serial Addition Test; RRMS: relapsing–remitting multiple sclerosis. [a]$p \leq 0.01$.

Table 6. Summary of hierarchical regression analysis for different MRI variables and age predicting SDMT performance in a sub-sample of RRMS patients (*n*=60).

Variable	B	SE B	beta
Step 1			
Age	-.603	.163	-.441[a]
Step 2			
Age	-.413	.153	-.302[a]
Cortical lesion volume	.086	1.438	.007
White matter lesion volume	-11.044	2.499	-.547[a]
Normalised grey matter volume	36.751	33.235	.123

R^2 = .194 for Step 1; ΔR^2 = .309 for Step 2; B: non-standardised regression coefficient; SE B: standard error of non-standardised regression coefficient B; beta: standardised regression coefficient; MRI: magnetic resonance imaging; SDMT: Symbol Digit Modalities Test; RRMS: relapsing–remitting multiple sclerosis; [a]$p \leq 0.01$.

tive impairment in MS. Mike et al.[15] examined 26 MS patients and found similar correlations of cortical (Spearman's Rho = 0.449, $p = 0.008$) and WM lesion volumes (Spearman's Rho = 0.418, $p = 0.014$) with the SDMT score, whereas only CL load predicted verbal learning and memory (CVLT-II test). Calabrese et al.[4] reported a better correlation of cognitive dysfunction with CL ($r = 0.59$, $p < 0.001$) than with WM lesion volume ($r = 0.41$, $p < 0.001$) in 70 patients with RRMS. Furthermore, the regression analysis of this study[4] revealed age, normalised GM volume and CL volume, but not WM lesion volume as independent predictors of a cognitive impairment index.

Our own findings, however, do rather show the opposite picture in that the WM lesion volume contribution to cognitive performance, especially performance on the SDMT, was much stronger. To rule out whether this discrepancy was due to the inclusion of patients with progressive disease forms, we also performed the same statistical analysis in a subgroup of patients with RRMS. Again, CL volume did not show any predictive value for cognitive performance, while WM lesion volume significantly predicted SDMT performance.

The inclusion of mixed GM-WM lesions in our study (according to the consensus recommendations of the MAGNIMS study group[19]), also seems unlikely to explain the diverging results, since intracortical lesions are probably not playing a more important role in the development of cognitive impairment than mixed GM-WM lesions.[16] Thus, further differences between the study populations may account for the different results. First, our patients had on average lower CL volumes than the patients in the study of Calabrese et al. (mean 697.6 µl with a range of 0–7311.6 µl, compared to 7300 µl and 4100 µl in cognitively impaired and unimpaired patients in the study of Calabrese et al., with a range of 0–13200 µl), which could partly explain the weaker correlations in our dataset. However, total number of CLs was higher in our study, suggesting that in our patient group CLs per se did not play the most relevant role in the development of cognitive impairment. Second, our patients were on average older (mean age 49.1 in the total cohort and 46.7 in the RRMS subgroup vs. 34.8 years) and had longer disease duration (17.4 in the total cohort and 16.2 in the RRMS subgroup vs. 8.4 years). It therefore remains to be shown in future studies whether CLs are probably more important for cognitive functioning at the early stages of the disease whereas WM lesions contribute more at later stages. Third, our study population was on average not really cognitively impaired. According to the calculated *z* values, only 18% of the patients (16/89) failed both tests, SDMT and PASAT, and another 18% failed one of them. Furthermore, only two cognitive tests entered the statistical analysis that are not targeted on memory and higher-order executive functions. The SDMT is a measure for information-processing speed and working memory while the PASAT measures complex attention, executive function, working memory and information-processing speed. Thus, from a topographical perspective it can be suggested that the SDMT is more strongly associated with WM lesions while the PASAT might involve both WM and

cortical structures. However, even for the PASAT the beta weights of the multiple regression analysis were lower for CLs than for WM lesions, indicating that WM lesions in direct comparison to CLs may be even more predictive for cognitive performance in tests that do not primarily target processing speed.

Further, in our analysis we included the volume of the entire GM and not the regional GM volume. Considering that the latter might be more sensitive in predicting cognitive impairment, this has to be regarded as an additional limiting factor. The low sensitivity of MRI in the detection of CLs should also be considered in the interpretation of our results. According to comparative MRI-histopathological studies, the sensitivity of DIR is relatively high for mixed GM-WM lesions (83%), but only 18% for intracortical lesions.[9] Moreover, subpial CLs are known to show very low contrast on MRI[2] and cannot be reliably detected in imaging studies using DIR.[19] Thus, the in vivo underestimation of intracortical and subpial lesions could be at least partly responsible for the weak correlations of CLs with clinical and cognitive outcomes, but this would hold true for all studies using this technique.

Our study also provides some insight into the relationship between cortical and WM lesions in MS. This issue has been addressed by several studies, with contradictory results. Some reported correlations between the two lesion types[3,4,11,18] and some did not,[14,28,29] the latter supporting the hypothesis that cortical pathology might be independent of the inflammatory process in WM. Recently, Lucchinetti et al.[8] showed that CLs in the early stages of MS are inflammatory, not supporting a primary neurodegenerative process in the cortical GM. The presence of many mixed GM-WM lesions as well as the relatively strong and significant correlations of CL and WM lesion volumes in our study suggest an association between CL and WM lesions in MS, but future studies are needed to clarify the underlying pathogenic processes of lesion formation in the cortex.

In conclusion, our findings indicate that WM lesion volume contributes more to the development of cognitive dysfunction as measured by the SDMT than CL volume. Whether this result is dependent on the way lesions were categorised and on sample characteristics has to be clarified in future studies.

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Conflicts of interest

Athina Papadopoulou has received honoraria as a consultant for Teva.

Nicole Müller-Lenke has received honoraria from Biogen Idec for consulting services.

Yvonne Naegelin, Gaby Kalt, Kerstin Bendfeldt and Pascal Kuster have nothing to declare.

Achim Gass has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Merck Serono, Novartis and Teva Neurosciences.

Till Sprenger has served on advisory boards for Mitsubishi Pharma, Eli Lilly, Genzyme, Biogen and Allergan. He has received travel support from Pfizer, Bayer Schering, Eli Lilly and Allergan.

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Authors' contributions

AP performed the MRI analysis, contributed to the study design, data analysis and interpretation and drafted the manuscript.

NML contributed to the MRI analysis and the data interpretation and commented on the different drafts of the manuscript.

YN collected the clinical data, contributed to the data interpretation and commented on the different drafts of the manuscript.

MS supervised the statistical analysis and commented on the different drafts of the manuscript.

GK contributed to the MRI analysis and commented on the different drafts of the manuscript.

PK provided essential technical assistance.

KB, AG, TS, EWR and LK contributed to the study design, data analysis and interpretation and commented on the different drafts of the manuscript.

IKP collected the neuropsychological data, performed the statistical analysis, contributed to the study design and data interpretation and commented on the different drafts of the manuscript.

IKP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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