Spatial distribution of white matter degenerative lesions and cognitive dysfunction in relapsing-remitting multiple sclerosis patients

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ABSTRACT

Aim. The aim of this study was to assess degenerative lesion localisation in the course of relapsing-remitting multiple sclerosis (RRMS) and to identify the association between localisation and the frequency of T1-hypointense lesions (black holes) with cognitive dysfunction. We also searched for neuroradiological predictors of cognitive dysfunction in patients. The clinical rationale for the study was previous research, and our own findings suggest that lesion localisation plays an important role in cognitive performance and neurological disability of MS patients.

Material and methods. Forty-two patients were included in the study. All subjects underwent neuropsychological examination using Raven's Coloured Progressive Matrices, a naming task from the Brief Repeatable Battery of Neuropsychological Tests, and attention to detail tests. Magnetic resonance imaging (MRI) was acquired on 1.5 Tesla scanner and black holes were manually segmented on T1-weighted volumetric images using the FMRIB Software Library. Linear regression was applied to establish a relationship between black hole volume per lobe and cognitive parameters. Bonferroni correction of voxelwise analysis was used to correct for multiple comparisons.

Results. The following associations between black hole volume and cognition were identified: frontal lobes black hole volume was associated with phonemic verbal fluency (t = –4.013, p < 0.001), parietal black hole volume was associated with attention (t = –3.776, p < 0.001), and parietal and temporal black hole volumes were associated with nonverbal intelligence (p < 0.001). The volume of parietal black holes was the best predictor of cognitive dysfunction.

Conclusions. Our approach, including measurement of focal axonal loss based on T1-volumetric MRI sequence and brief neuropsychological assessment, might improve personalised diagnostic and therapeutic decisions in clinical practice.

Key words: relapsing-remitting multiple sclerosis (RRMS), T1-hypointense lesions, black holes, magnetic resonance imaging (MRI), cognitive dysfunction

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Introduction

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS) in young adults. It is defined as a chronic neuroinflammatory and neurodegenerative disease, which in its most typical course leads to relapses and remissions of various neurological symptoms, resulting from focal demyelinating lesions of the CNS [1]. Magnetic resonance imaging (MRI) is a key tool in MS diagnosis, monitoring, measuring treatment response and predicting disability. While disease activity is usually related to T2 or FLAIR hyperintense white matter lesions, or gadolinium enhancing T1 lesions, the neurodegenerative aspect of MS is represented by T1 hypointense lesions with high water content. These are called black holes [2]. Depending on the degree of neuronal damage, black holes can be classified as persistent, transitional or slowly evolving lesions [3–4]. Some of the focal degenerative changes may be transformed into persistent black holes [2, 5–6]. Early evolution of severe neurodegenerative lesions indicates more aggressive and rapidly disabling disease [7].

Currently, treatment guidelines do not address the occurrence of new black holes as an indication to escalate therapy, despite the fact that those lesions are irreversible and over time are followed by brain atrophy. Black holes represent complete demyelination with irreversible axonal damage on the focal level. As such, they are likely to contribute to disease progression, which has been shown in several studies [8–9]. Also, their clinical relevance may be reflected by their associations with other MRI parameters (lower supratentorial and infratentorial brain volume) [10], clinical data (disease duration, score of EDSS) [10–11] and cognitive impairment [12].

In the course of multiple sclerosis, 40–70% of patients develop cognitive dysfunction [13]. The most commonly observed deficits related to MS include executive dysfunction, low verbal fluency, and difficulties in visuospatial performance, short-term memory, abstract reasoning and attention [14–15]. These may be accompanied or related to depression or general fatigue. Several MRI parameters have been correlated with cognitive dysfunction in MS patients. While total white matter T2 lesion volume load is a modest correlate for MS- related cognitive impairment [16], measures of neurodegeneration, including brain atrophy, are stronger predictors of cognitive dysfunction [17–18]. These measures include black holes, but also other MRI parameters that correlate with cognitive dysfunction and clinical markers of disability, such as fractional anisotropy (FA) or mean diffusivity (MD) coefficient, derived from diffusion tensor imaging (DTI) methods [19]. Similar results have been obtained by using functional MRI or magnetisation transfer (MT) imaging [20]. These techniques, although potentially superior, require additional scanning time and advanced post-processing, which makes black holes assessment a more feasible yet reliable method.

The purpose of the present study was to assess the spatial distribution of MS-related white matter neurodegenerative lesions and its association with cognitive impairment, focusing on the following domains: nonverbal intelligence, attention, and phonemic verbal fluency. We hypothesised there is an association between localisation and the frequency of black holes and examined cognitive functions, and that black holes in the brain lobes are predictors of cognitive functioning.

Clinical rationale for the study

Early detection of neurodegenerative changes in multiple sclerosis should prompt a change in patient therapy. However, current treatment guidelines do not indicate any specific actions based on detection of new black holes. We evaluated the relationship between black holes in selected cortical regions of the brain and the severity of cognitive deficits.

The complete extent of brain damage cannot be estimated without a precise neurocognitive assessment. Neglecting the cognitive component of patient dysfunction might result in missing an important insight into disease progression, and the main reason behind the decline of quality of life in young individuals with MS.

Materials and methods

Cohort characteristics

Forty-two patients (25 women, 17 men) with relapsing-remitting multiple sclerosis fulfilling the 2010 McDonald criteria [21] at the time of diagnosis were recruited for the study. The mean disease duration was 5.6 years (range 0–24). Four patients were diagnosed at the time of inclusion into the study, while the longest time since diagnosis was 24 years in one patient. Age and EDSS measures are presented in Table 1. Thirty six percent of patients had obtained higher education. Significant comorbidities were found in three subjects: bronchial asthma (n = 2) and ulcerative colitis (n = 1). Beck Depression Inventory (BDI) scores ranged from 0 to 39 (median = 7, interquartile range, IQR = 1-12). Exclusion criteria included: current relapse stage or relapse within the last eight weeks, immunomodulatory therapy in the last year, age older than 65 years, concomitant psychiatric disease, current use of neuroleptics or antiepileptic drugs, alcohol or drug abuse, diagnosis of another autoimmune or neoplastic pathology, relevant motor deficit in the dominant hand, upper limb ataxia or loss of visual acuity, and dementia. The neurological, MRI and neuropsychological examinations were all performed within a one month period. Patients treated with intravenous steroids within the previous three months, or immunomodulation at any point before baseline assessment, were not included in the study.

Procedure

All subjects underwent a neurological examination, psychometric assessment and MRI examination. Psychometric tests used for the assessment of cognition included:

— Raven's Coloured Progressive Matrices (RCPM; non-verbal intelligence) [22]

— Attention to detail test (attention) [23]

— Spontaneous word list generation test, which is a modified version of phonemic naming task from Brief Repeatable Battery of Neuropsychological Tests (phonemic verbal fluency).

Structural MRI was performed on 1.5 Tesla MRI scanner (Siemens Avanto, Erlangen, Germany), with the use of Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE, TR = 2400 ms, TE = 3.61 ms, IR = 1000 ms, slice thickness 1.2 mm, pixel band width 180 Hz, FOV 240 × 240 mm, voxel size 1.25 × 1.25 × 1.20 mm) and FLAIR space sequence (TR = 6000 ms, TE = 359 ms, IR = 2200ms, slice thickness 1.5 mm, pixel band width 930 Hz, FOV 227 × 260 mm, voxel size 1.01 × 1.01 × 1.50 mm).

Structural analysis of T1-weighted sequences was performed with the use of FSL (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk/fsl; version 5.0.6) [24] installed on Linux (Ubuntu 16.04 LTS). The analysis included: manually segmenting black holes by a reader blinded to clinical status, reproduction of manual segmentation after four weeks, and Bland-Altman assessment of intra-rater reproducibility. Probabilistic brain MNI152 atlas included in the FSL package was registered to each patient using *flirt* and black hole volume from each lobe was extracted using the *fslstats* tool.

Manual segmentation allowed the creation of masks of the black holes (dark area in T1-weighted sequences). Detailed detection of images was possible with the use of the *fslview* tool. Before the brain extraction procedure, the masks of degenerative changes in white matter were created by using the *fslview* and *fslmerge* (to concatenate the images) technique.

Secondly, brain and structure extraction were performed by the *fslroi* command and Brain Extraction Tool (BET) of FSL. *Fslroi* command allows extraction of a selected region of the brain based on the determination of the size values of individual axes. BET methods were needed to delete non-brain tissue from images of the whole head. We also estimated the inner and outer skull surfaces, and outer scalp surfaces, for good quality T1 input images. Two parameters were used: the force threshold (f = 0.44) and the gradient threshold (g = 0). The level of the force threshold was optimised. The duration of the brain extraction process was up to one minute.

A registration process was necessary to fit extracted scans and masks to the MN152 atlas of the FSL program. Before masks registration, the binarisation procedure (masks value = 1, other brain structure = 0, default value of threshold) was conducted using the *fslmaths* technique. In our linear registration, the parameters were set on 12 degrees of freedom (three rotations, three translations, three scales, and three warps), the cost function (such as mutual information), and three-linear interpolation. The result of this affine transformation process was a linear transformation matrix needed to receive standard images nearing to the atlas template. After the registration, the masks and scans were matched using the *ApplyXFM* option.

Brain lobes were selected based on the structural atlas MN152 of brain template images. Automated image registration algorithms were used to align brain MRI images with the target image [25]. By using the MN152 brain atlas (the volumetric coordinate system created by averaging MRI scans of 152 people) it was possible to analyse nine anatomical structures: frontal, parietal, occipital and temporal lobes, thalamus, insula, caudate, putamen and cerebellum. For the result of linear registration for each scan, see Figure 1.

Statistical analysis

Non-parametric mapping software (NPM) was used to analyse all scans with fitted plaques' masks in the MNI152 atlas. In cases of binarised masks, we used a Voxel Based Morphometry (VBM) technique in MRICRON ver. 2012 software. We calculated statistical maps for each cognitive dysfunction and black hole spatial distribution. Each variable was evaluated using a Shapiro-Wilk normality test. Normally distributed variables
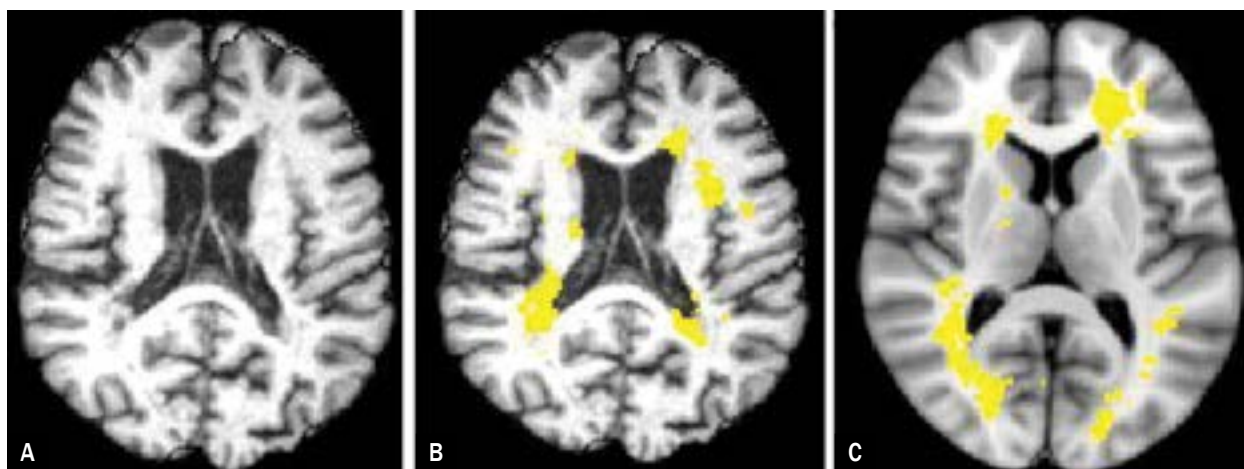

Figure 1. A linear registration of multiple sclerosis plaques and scans of axial brain section in magnetic resonance imaging (MRI): (**A**) extracted brain, (**B**) extracted brain after linear registration with prepared masks, (**C**) previous image fitted to the MNI152 atlas

were summarised using mean and standard deviation. For non-normally distributed continuous variables, median and interquartile range (IQR) were calculated. Finally, linear regression analysis and stepwise regression analysis were conducted to identify associations between black hole volume per lobe and cognitive dysfunctions. BPF was calculated according to the formula: grey and white matter volume / total intracranial volume derived from FSL FAST. We applied Bonferroni correction for multiple comparisons. We also calculated Spearman's correlation coefficients for BPF and global black hole volume. Statistical analyses were performed using the RCRAN statistical environment (www.r-project.org) and the RStudio 1.1.453 graphical interface.

Results

Descriptive statistics for variables in the study

The descriptive statistics for all the measured variables are presented in Table 1.

Spatial distribution of degenerative lesions

Lesion distribution maps for nonverbal intelligence, phonemic verbal fluency and attention are represented in Figure 2.

Lobar black hole lesion load

Spatial heterogeneity of black hole location limits the clinical interpretation of the VBM results. Therefore, we calculated black hole lesion load for each lobe and conducted stepwise regression to identify the lobe where the lesion load was the best predictor of cognitive dysfunction.

Stepwise linear regression performed using black hole lesion load identified parietal lobe damage as the main predictor of cognitive dysfunction for each domain. Parietal lesion load predicted 2 to 29% of variance in the cognitive functioning. Detailed results are presented in Table 2. BPF did not correlate with total black hole lesion load (rho = -0.161, p = 0.348), but there was a correlation with the temporal black hole load (rho = -0.344, p = 0.040). No significant differences (p > 0.05) of the volumetric parameters were found for gender or level of education in the studied MS cohort.

Discussion

We found that in RRMS cohort parietal lobe black hole lesion load was predicting cognitive dysfunction for each evaluated domain: attention, phonemic verbal fluency, and nonverbal intelligence. The role of the parietal lobe is focused on multimodal information integration, which is crucial for intelligence and attention control. Both these functions are frequently impaired in multiple sclerosis patients [26]. We observed the highest lesion load in parietal lobes, and the lowest in occipital lobes. The results of voxel-wise analysis identified lesions associated with dysfunction in other structures as well. Specifically, attention

Table 1. Descriptive statistics for clinical data of the examined group

Variable	Median(IQR) or *Mean(SD)	Range
Age	*39.55 (11.3)	18–63
EDSS	1.00 (0–2.0)	0–6
Cognitive functions		
Phonemic verbal fluency	*20.05 (4.38)	12–31
Nonverbal intelligence	33 (30–35)	20–36
Attention	7 (5–8)	1–8
Volumetric measurements		
BPF	*0.77 (0.03)	0.70–0.85
Spatial distribution of black hole load per lobe [cm³]		
Frontal lobes	0.62 (0.18–2.39)	0.00–15.23
Parietal lobes	1.10 (0.09–3.45)	0.00–15.63
Temporal lobes	0.06 (0.00–0.63)	0.00–17.21
Occipital lobes	0.26 (0.00–1.71)	0.00–10.00
All MS plaques	7.02 (1.82–16.48)	0.21–87.05

deficit was associated with caudate lesions, and nonverbal intelligence and phonemic verbal fluency deficits were associated with frontal lobe lesions.

In previous studies, the incidence of black holes explained disharmonious cognitive and emotional processing in MS [27]. The location of degenerative white matter lesions can be associated with subsequent development of atrophy in distant brain regions [28–31].

Most of the published studies have focused on the relationship between black holes and neurological disability measured with the EDSS scale [32]. However, black holes are also associated with cognitive dysfunction [33]. This aspect has been underestimated and only a few studies have provided detailed analysis of this association [16]. In one study, T1 hypointense lesions were shown to correlate with Stroop test performance [34]. In another study, which analysed cognitive event-related potentials (ERPs), white matter degenerative lesion volume was associated with semantic and phonemic verbal fluency [14]. Both the Stroop test and the verbal fluency test require high performance in executive functions. This suggests that spatial distribution of degenerative white matter lesions could influence executive functions and other cognitive domains, including attention or auditory processing [35]. Similar results were found by Hojjat et al. [12]. According to their study, there were regional perfusion associations with cognitive dysfunction.

As for the choice of the psychometric tests, we used easily accessible tools that could be applied in everyday clinical practice. Following the literature, we decided to assess cognitive functions that had already been described as being affected in the course of MS [36], namely attention, which we measured with the use of an attention to detail test [23], and non-verbal intelligence (involving the visuo-spatial processes), which we assessed with Raven's Coloured Progressive Matrices [22]. To assess the
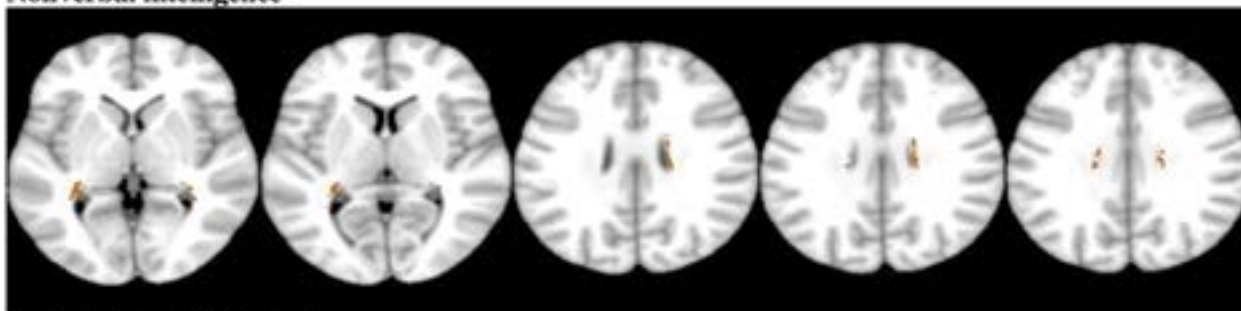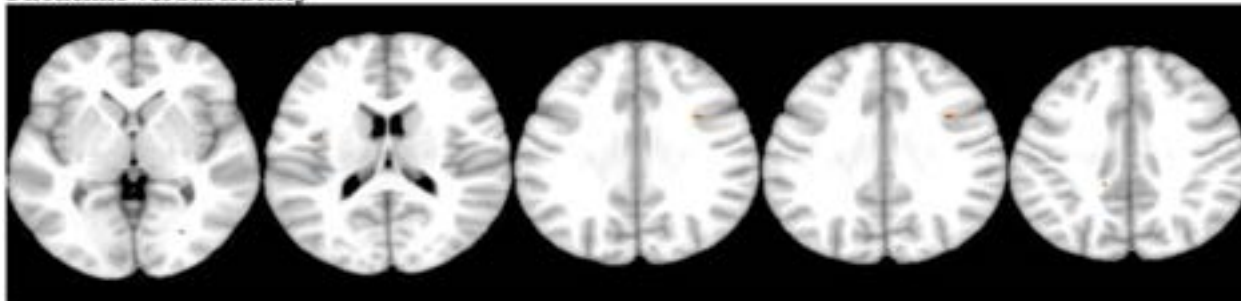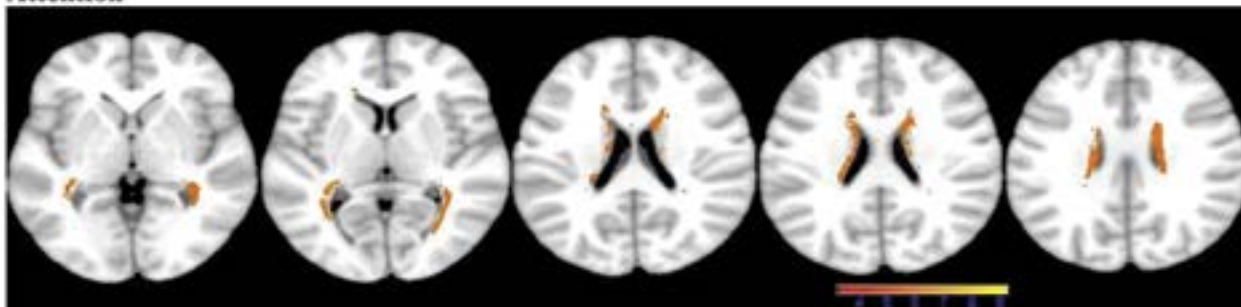
Nonverbal intelligence

Phonemic verbal fluency

Attention

Figure 2. Statistical maps of black hole distribution for each cognitive function computed using Voxel Based Morphometry (VBM) analysis (Brunner-Munzel z statistics). Lesions are overlaid on the Montreal Neurological Institute (MNI) brain in axial slices. Colored voxels were -log of the p value ($p < 0.05$). The equivalent of Bonferroni-corrected threshold was 5.112 and the equivalent of BM threshold was 3.1734.

phonemic verbal fluency we used a modified version of the Word List Generation (WLG), which is a phonemic naming task in the original BRB-N [37]. WLG is a semantic verbal fluency test. In our study, we decided to measure one type of verbal fluency. Phonemic verbal fluency, which consists in generating words for a given letter in a minute, requires higher efficiency of executive functions than semantic fluency [38–40].

Individual lesions in multiple sclerosis always run the chance of damaging critical infrastructure and causing widespread dysfunction of structures distant to the lesion. This is often hard to prove because of low lesion burden per studied group. To solve that problem, grouping lesions based on atlas information might confer meaningful and easy-to-obtain information for every clinician. Modern image processing software is perfectly capable of producing a black hole lesion report per lobe, which in turn conveys the risk of cognitive dysfunction.

As for our methodological approach, the advantage of conducting linear registration using FMRIB's Linear Image Registration Tools (FLIRT) is that it may be fully automated, although it is significant to analyse the default values of the parameters. Also, according to Tam et al. [41] the assessment of the association between black holes volume and clinical parameters will be more precise if unpaired segmentation and paired registration methods are used. Literature data confirm that both fully-automated [42] and semi-automated [43] segmentation methods are justified. Manual lesion segmentation, such as we applied in the current study, is time consuming, and so in clinical practice its usefulness may be limited. Automated methods of black holes analysis are more likely to be used in everyday practice.

In the current study we chose to investigate white matter black holes. While it would be interesting to relate cognitive dysfunction also to cortical lesions in our cohort, this was not possible due to the sequence protocol and magnet field that we

Table 2. Linear regression analysis of T1- weighted black holes in multiple sclerosis patients

Volumes of black holes in brain structures	R² adjusted	F	β	t	p
Phonemic verbal fluency					
Frontal lobes	0.269	16.108	-0.536	-4.013	.000
Parietal lobes	0.233	13.476	-0.502	-3.671	.001
Temporal lobes	0.132	7.221	-0.391	-2.687	.010
Occipital lobes	0.039	2.679	-0.251	-1.637	.109
Attention					
Frontal lobes	0.100	5.542	-0.349	-2.354	.024
Parietal lobes	0.244	14.257	-0.513	-3.776	.001
Temporal lobes	0.107	5.895	-0.358	-2.428	.020
Occipital lobes	0.088	4.940	-0.332	-2.223	.032
Nonverbal intelligence					
Frontal lobes	0.195	10.954	-0.464	-3.310	.002
Parietal lobes	0.290	17.732	-0.554	-4.211	.000
Temporal lobes	0.283	17.157	-0.548	-4.142	.000
Occipital lobes	0.098	5.456	-0.346	-2.336	.025

used. Cortical pathology is difficult to visualise in a conventional MRI protocol. Although the value of grey matter pathology has been increasing, as shown by the inclusion of cortical localisation in the latest version of MS criteria [44], it is still largely underestimated due to technical difficulties in their visualisation. Neither T2*-weighted gradient echo nor Double Inversion Recovery (DIR) sequences are routinely available. Also, high-field magnets, which are also more sensitive to cortical pathology, are not at a routine disposal. Nevertheless, cortical lesions have in fact been shown to be associated with cognition and disability in MS patients [45].

Our study is limited by its small, relatively heterogeneous sample size and relatively long and differential disease duration. The sample size was limited by the exclusion criteria, including immunomodulation therapy, which is currently widely available for RRMS and thus the sample size is limited. However, we wanted to avoid the possible influence of immunomodulatory drugs on brain volumetry results. Also, we focused solely on degenerative white matter lesions without taking into account FLAIR lesions and atrophy accumulated over time. This reductionist approach stemmed from the context of this work, which was primarily a masters' thesis of the first author. Another limitation is the choice of basic psychometric tests to assess cognitive dysfunction. However, this could also be a potential advantage, as they can be used without charge or time consumption in an everyday clinical practice setting.

Clinical implications and future directions

The pathophysiological substrate of cognitive dysfunction in MS is not fully understood. Several MRI markers have been suggested as predictors of cognitive impairment. Over recent years, attention has shifted to more and more sophisticated parameters derived from advanced image analysis. In this paper, we are revisiting the aspect of traditional and relatively easily identified T1 hypointense lesions detected on volumetric T1-weighted images as predictors of poor cognitive performance. We suggest that modern image processing software should be used to obtain a black hole lesion mapping report. Such a report could aid in assessing the individual risk of cognitive dysfunction in MS patients, and in selecting the patients for detailed neuropsychological assessment. Also, linking cognitive dysfunction to degenerative white matter lesions could be an important predictor of MS patients' quality of life. It may aid in selecting patients in need of neuropsychological rehabilitation [46].

Studies on a larger sample size and using standardised batteries of neuropsychological tests are needed to enable the use of black hole spatial distribution analysis in everyday clinical practice.

Ethics: *This study was approved by the Internal Review Board at the Poznan University of Medical Sciences. Written informed consent was obtained from all the study participants.*

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