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ORIGINAL COMMUNICATION

Cognitive impairment and structural brain changes in patients with clinically isolated syndrome at high risk for multiple sclerosis

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Abstract Patients with clinically isolated syndrome (CIS), unlike those with multiple sclerosis (MS), have a selective cognitive impairment which is not consistently related to structural brain changes. Our objective was to characterize a profile of cognitive impairment and its association with structural brain changes in patients with CIS who are at high risk of developing MS. Patients with CIS at high risk for MS on interferon-beta ($n = 51$) and age-, gender-, and education-matched controls ($n = 44$) underwent comprehensive neuropsychological testing and MRI brain scan with voxel-based morphometry. The CIS group had lower cognitive performance in verbal and nonverbal memory, information processing speed/attention/working memory, and executive and visuo-spatial functions compared to controls ($p \leq 0.040$). Lower cognitive performance was present in 18–37 and 14–26% of patients with CIS at high risk for MS depending on the criteria used. Brain volume was reduced predominantly in fronto-temporal regions and the thalamus in the CIS group ($p \leq 0.019$). Cognitive performance was not associated with structural brain changes except for the association between worse visuo-spatial performance and lower white matter volume in the CIS group ($\beta = 0.29$; $p = 0.042$). Our results indicated that patients with CIS at high risk for MS may have a pattern of lower cognitive performance and regional brain atrophy similar to that found in patients with MS. Lower cognitive performance may be present in up to one-third of patients with CIS at high risk for MS, but, unlike patients with MS, variability in their cognitive performance may lead to a lack of consistent associations with structural brain changes.

Keywords Clinically isolated syndrome · Cognition · MRI · Multiple sclerosis · Neuropsychology · Voxel-based morphometry

Introduction

Cognitive impairment is present in 43–72% of patients with multiple sclerosis (MS) and influences their quality of life [1]. Patients with MS are impaired in all cognitive functions, predominantly in information processing speed, executive functions, attention, and memory [2]. This pattern of cognitive impairment was consistently found across studies irrespective of the type of a neuropsychological battery and essentially did not vary with respect to the criteria used to define cognitive impairment [3–5]. Structural brain changes associated with MS encompass global and regional cortical atrophy, atrophy of the subcortical structures, especially of the thalamus, and demyelinating lesions [5–9]. These changes were consistently found in studies using voxel-based morphometry (VBM) and region of interest-based analyses [6, 9, 10]. The structural brain changes may be related to a specific cognitive impairment

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in patients with MS. Specifically, global cortical atrophy was related to attentional and verbal memory deficits [4, 11], while regional cortical atrophy of frontal, temporal, prefrontal, parietal, and insular lobes was related to both, verbal and nonverbal, memory deficits in patients with MS [12, 13]. Atrophy of the subcortical structures, especially of the thalamus and the basal ganglia, was found to be related to impairment of information processing speed [8]. Similarly, lower interhemispheric white matter volume was related to impairment of information processing speed but also to visuo-spatial deficit [14]. Association between lesion load and cognitive performance was not consistently found across studies in patients with MS. About half of the studies found an association of lesion load with information processing speed, while the rest of the studies did not find such an association [15–18].

Cognitive impairment may also be present in 12–57% [2, 19] of patients with clinically isolated syndrome (CIS), a heterogeneous population at risk of developing MS [20, 21], where a few selected cognitive functions were found to be affected. Specifically, information processing speed, attention, working memory, and verbal fluency were consistently found to be affected in patients with CIS [6, 9, 22–25]. In addition, some studies found impairment in executive functions and memory, while the other studies found relative sparing of these cognitive functions [2, 19, 22, 26]. Visuo-spatial functions were not found to be affected in patients with CIS [27]. Cognitive impairment in these studies was established when the patients were statistically different from the control group or scored more than a predefined cutoff from a normative data set using cutoff criteria ranging from more than 1 standard deviation (SD) to more than two SDs [23–25, 28]. The various criteria used in the studies to define cognitive impairment did not essentially cause a significant variation in results [2, 29]. To our best knowledge, in the previous studies, an extensive neuropsychological examination was not performed and individual neuropsychological tests or the Brief Repeatable Battery of Neuropsychological Tests were most frequently used to assess cognitive impairment in patients with CIS [2, 9, 23]. Structural brain changes associated with CIS encompass regional cortical atrophy, especially in frontal and temporal lobes, and atrophy of the subcortical structures, especially of the thalamus [6, 23, 29]. These changes were consistently found in studies using VBM analyses [6, 23, 29]. However, only a few studies evaluated association between structural brain changes and cognitive performance in patients with CIS, mostly with negative results [23, 26–28]. A single recent study found association of thalamic atrophy with attention, executive, and visuo-spatial functions [29]. Studies focused on association between normal-appearing white matter volume and cognitive performance in patients with CIS are lacking.

We aimed to characterize a cognitive profile and its association with structural brain changes in a homogeneous cohort of patients with CIS who are at high risk of developing MS using a comprehensive neuropsychological battery and a VBM analysis. The first aim was to evaluate cognitive functions using the comprehensive neuropsychological battery covering major cognitive domains. The second aim was to find a specific pattern of brain atrophy. The third aim was to find associations between cognitive performance, global, and regional brain atrophy and lesion load in patients with CIS at high risk for MS.

Based on the studies of patients with early MS, we hypothesized that patients with CIS at high risk for MS would have lower cognitive performance in information processing speed/attention/working memory, executive functions, and verbal and nonverbal memory compared to healthy control participants. Next, brain atrophy would be most pronounced in cortical grey matter and in the thalamus in patients with CIS at high risk for MS. Finally, cognitive performance would be more associated with brain atrophy than with lesion load in those patients.

Patients and methods

Subjects

51 patients with CIS were recruited between September 2012 and June 2015 at the Multiple Sclerosis Centre, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Czech Republic. The patients with CIS were after the first clinical episode, had an objective clinical evidence of one lesion, did not have a simultaneous dissemination of lesions in space and time on routine clinical brain MRI with gadolinium, and thus did not meet the criteria for MS [30]. In addition, the patients with CIS met the following criteria for eligibility for treatment with disease modifying drugs (DMDs): 18–55 years of age, Expanded Disability Status Scale (EDSS) less than 3.0, 2, or more hyperintensive T2 lesions on brain MRI and 2 or more oligoclonal bands in cerebrospinal fluid [31]. The patients with CIS did not fulfil the criteria of dissemination in time but fulfilled the criteria of dissemination in space [30]. According to the previous studies, these individuals are at high risk of developing clinically definite MS [32]. Only those patients with CIS who were on medication of interferon-beta were recruited to get as homogeneous cohort as possible. The first symptom was treated with 3–5 g of methylprednisolone, and the duration of treatment with interferon-beta was at least 1 month (median 6 months). Neuropsychological battery and time-matched experimental brain MRI (within 4 weeks) were performed more than 30 days after administration of steroids and

between 1 and 12 months from the diagnosis of CIS (median 6 months).

In addition, 44 age-, gender-, and education-matched healthy control participants were recruited from relatives of the Motol University Hospital staff. They underwent neuropsychological examination and time-matched experimental brain MRI. Their performance on neuropsychological battery was normal—they did not score more than 1.5 SDs below the mean of age- and education-adjusted norms in any neuropsychological test.

The subjects with psychiatric disorders (depression, anxiety, obsessive compulsive disorder, and a history of psychotic or schizoaffective disorders), neurological disorders (epilepsy, a history of traumatic brain injury, and a history of stroke), cardiovascular diseases, and a history of alcohol or drug abuse were not included in the study.

Neuropsychology

All participants underwent comprehensive neuropsychological testing, including 12 neuropsychological tests administered by a single-trained neuropsychologist. The tests were focused on verbal (Rey Auditory Verbal Learning Test—RAVLT [33, 34]) and nonverbal memory (Brief Visuo-spatial Memory Test Revised—BVMT-R [35]), information processing speed/attention/working memory (Symbol Digit Modalities Test—SDMT, Paced Auditory Serial Addition Test—PASAT, Digit Forward task—DF, Digit Backward task—DB, and Trail Making Test A—TMT A [36–40]), executive (Trail Making Test B—TMT B and Controlled Oral Word Association Test—COWAT [39–41]), visuo-spatial (Judgment of Line Orientation Test—JLO [42]), and language (Category Fluency Test—CFT—animals and shopping items [41]) functions. The arbitrary assignment of COWAT to executive functions and CFT to language functions was adopted from the previous studies [43, 44]. A self-administered 15-item Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) was used as a self-report screening measure of neuropsychological functioning. The Beck Depression Inventory (BDI) [45] and the Beck Anxiety Inventory (BAI) [46] were also administered. The score for each cognitive function was expressed as a unit-weighted composite z-score from the relevant neuropsychological tests. The score for overall cognitive performance was expressed as a unit-weighted composite z-score from all neuropsychological tests. Lower cognitive performance was established when the subject with CIS scored more than 1.5 SDs below the mean of the control group on any test assigned to each cognitive function. We used the arbitrary criterion of >1.5 SDs as an analogy with studies in patients with mild cognitive impairment [47]. In addition, to provide a more conservative estimate of lower cognitive performance in patients with CIS, we also calculated values for a more stringent criterion of scoring more than two SDs below the mean of the control group.

Magnetic resonance imaging acquisition and analysis

Brain MRI was performed at 1.5 T device (Siemens AG, Erlangen, Germany) in an experimental "lesion load" protocol using 1) T1-weighted three-dimensional high-resolution magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence with the following parameters: TR/TE = 12/4.605 ms, flip angle 15°, 150 continuous partitions, and slice thickness 1.0 mm for volumetric measurement and 2) fluid-attenuated inversion recovery (FLAIR) sequence with the following parameters: TR/TE/TI = 11,000/140/2600 ms, flip angle 90°, 100 continuous partitions, and slice thickness 1.5 mm for lesion load measurement. Scans were visually inspected by a neuroradiologist. The experimental "lesion load" protocol" was available for 45 subjects with CIS and 30 control participants.

Brain tissue volume [normalized brain parenchymal (nBP) volume and separate estimates of normalized grey and white matter (nGM and nWM) volume] was estimated with SIENAX, part of FSL [48] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA. Voxel-based morphometry (VBM) was used to assess focal differences in brain anatomy. VBM was performed with masking of the registration cost function with lesion masks to reduce the impact of white matter lesions on brain segmentation and creation of grey matter template. Lesion masks were obtained by Lesion Segmentation Tool (LST) toolbox version 1.2.3 (http://www.statistical-modelling.de/lst.html) for SPM (http://www.fil.ion.ucl.ac.uk/spm/). The algorithm segmented the T1 images into the three main tissue classes (cerebrospinal fluid, grey matter, and white matter). This information was then combined with the coregistered FLAIR intensities to calculate lesion probability maps. A lesion filling algorithm implemented in FSL SIENAX was adopted [49]. The algorithm uses previously generated lesion masks registered to the image to fill the lesions with intensities matching the surrounding normal-appearing white matter. Next, an optimized VBM approach was adopted with all processing steps carried out using openware FSL version 5.0.7 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Anatomical localization of significant clusters was established using the Harvard-Oxford Structural Atlas. The results of VBM were corrected for familywise error using

an FSL's tool for nonparametric permutation inference ("randomise") [50].

Statistics

Students' independent two-sample t tests evaluated mean differences between groups in demographic and neuropsychological variables, nBP, nWM, and nGM volume. The χ^2 test evaluated differences in gender proportions. Age, gender, education, and disease duration, which may affect cognitive performance, were subsequently controlled in an analysis of covariance, which assessed between-group differences in neuropsychological variables, to provide more conservative estimates of the hypothesized associations. General linear model (GLM) implemented in FSL was used to compare voxelwise between-group differences in regional cortical and subcortical grey matter volume derived from VBM. Correlation coefficients for continuous variables (Pearson) and one ordinal variable—EDSS score (Spearman) were calculated to explore bivariate relationships. The relationships between regional cortical and subcortical grey matter volume derived from VBM and other variables were assessed using GLM parametric and nonparametric correlation models implemented in FSL. If a correlational analysis between cognitive performance and MRI data yielded a significant association, a linear regression model adjusted for age, gender, and years of education was estimated.

All quantitative data were found to be adequate for parametric analysis. Statistical significance was set at two-tailed alpha of 0.05. Effect sizes were reported using Cohen's d for the Students' t tests and Cramér's V for the χ^2 test. All analyses were conducted with the IBM SPSS 20.0 software.

Results

The groups did not differ in age, gender, education, MSNQ, BDI, and BAI scores. The results are presented in Table 1. The median disease duration in the CIS group was 6 months, and a range was 11 months. Higher EDSS score was correlated with lower nBP volume in the CIS group ($r = -0.38$, $p = 0.011$). The correlations between variables are presented in Table 2, Online Resource Table 1 (for each neuropsychological test), Online Resource Table 2, and Online Resource Fig. 1 (for regional brain volumes).

Cognitive functions

The CIS group had worse performance in RAVLT 1–5 ($p = 0.031$; the score of verbal memory learning), RAVLT after 30 min ($p = 0.014$; the score of verbal delayed recall), BVMT-R 1–3 ($p = 0.002$; the score of nonverbal memory learning), and BVMT-R after 25 min ($p = 0.015$; the score of nonverbal delayed recall). Next, the CIS group had worse performance in SDMT ($p = 0.006$), PASAT ($p = 0.008$), DF ($p = 0.014$) (the scores of information processing speed/attention/working memory), TMT B ($p = 0.001$), and COWAT ($p = 0.047$) (the scores of executive functions). Finally, the CIS group had worse performance in JLO ($p = 0.040$; the score of visuo-spatial functions). There were no between-group differences in DB, TMT A (the scores of information processing speed/attention/working memory), and CFT for animals and shopping items (the language scores) (Table 1). Controlling for age and gender did not modify the results. Controlling for education changed the between-group differences in RAVLT 1–5, COWAT, and JLO scores to non-significant. Controlling for disease duration changed the between-group differences in BVMT-R after 25 min and JLO scores to non-significant. The differences between the groups in other neuropsychological scores remained unchanged.

Next, we assigned each neuropsychological test to one of the six cognitive functions. The CIS group had worse performance in verbal ($p = 0.005$; Cohen's $d = 0.59$) and nonverbal ($p = 0.002$; Cohen's $d = 0.65$) memory, information processing speed/attention/working memory ($p = 0.001$; Cohen's $d = 0.73$), executive ($p < 0.001$; Cohen's $d = 0.75$), and visuo-spatial ($p = 0.040$; Cohen's $d = 0.43$) functions compared to the control group. There were no differences in language functions between the groups. Controlling for age and gender did not modify the results. Controlling for education changed the between-group differences in visuo-spatial functions to non-significant. Controlling for disease duration changed the between-group differences in visuo-spatial functions and nonverbal memory to non-significant. The differences between the groups in other cognitive domains remained unchanged. Furthermore, the CIS group had worse overall cognitive performance ($p < 0.001$; Cohen's $d = 0.82$) compared to the control group. Controlling for age, gender, education, and disease duration did not modify this result.

Finally, we estimated proportion of subjects with lower cognitive performance in one or more neuropsychological tests for each cognitive function among the CIS group. Using the criterion of 1.5 SDs, lower cognitive performance was present in verbal memory for 37.3% of CIS subjects, in nonverbal memory for 33.3% of CIS subjects, in information processing speed/attention/working memory for 35.3% of CIS subjects, in executive functions for 23.5% of CIS subjects, in visuo-spatial functions for 19.6% of CIS subjects, and in language functions for 17.6% of CIS subjects. Using a more stringent criterion of two SDs,

Table 1 Characteristics of the study participants

	Controls ($n = 44$)	CIS ($n = 51$)	p values	Effect sizes
Age (years)	30.20 (8.82)	31.61 (9.01)	0.446	0.16[a]
Women, n (%)	24 (54.5)	29 (56.9)	0.821	0.02[b]
Education (years)	16.18 (2.78)	15.12 (2.87)	0.071	0.38[a]
EDSS	NA	1.57 (0.64)	NA	NA
MSNQ (score)	13.18 (7.42)	11.78 (8.61)	0.403	0.18[a]
BDI (score)	4.43 (4.92)	6.06 (5.66)	0.141	0.31[a]
BAI (score)	4.93 (5.06)	7.22 (6.78)	0.070	0.38[a]
RAVLT 1–5 (score)	58.11 (8.24)	54.14 (9.38)	**0.031**	**0.45**[a]
RAVLT delayed (score)	12.43 (2.12)	11.10 (2.93)	**0.014**	**0.52**[a]
BVMT-R 1–3 (score)	29.80 (4.14)	26.90 (4.48)	**0.002**	**0.67**[a]
BVMT-R delayed (score)	10.95 (1.12)	10.29 (1.43)	**0.015**	**0.51**[a]
SDMT (score)	62.48 (11.02)	56.49 (9.80)	**0.006**	**0.57**[a]
PASAT (score)	51.02 (8.33)	45.63 (10.80)	**0.008**	**0.56**[a]
Digit span forward (score; digits)	10.07 (1.91)	9.06 (1.99)	**0.014**	**0.52**[a]
Digit span backward (score; digits)	7.93 (2.86)	7.06 (2.23)	0.099	0.34[a]
TMT A (time in s)	29.91 (21.48)	31.02 (7.58)	0.730	0.07[a]
TMT B (time in s)	54.89 (16.23)	72.37 (30.48)	**0.001**	**0.72**[a]
COWAT (score)	48.36 (14.53)	42.35 (14.47)	**0.047**	**0.42**[a]
JLO (score)	27.57 (3.27)	25.90 (4.34)	**0.040**	**0.43**[a]
CFT animals (score)	26.59 (5.69)	25.27 (6.39)	0.295	0.22[a]
CFT shopping (score)	27.11 (8.50)	26.33 (7.34)	0.632	0.10[a]
nBP (volume; cm^3)	1504.03 (58.79)[c]	1456.69 (78.98)[d]	**0.006**	**0.66**[a]
nWM (volume; cm^3)	702.05 (38.04)[c]	681.90 (38.49)[d]	**0.029**	**0.52**[a]
mGM (volume; cm^3)	801.98 (38.23)[c]	774.79 (57.87)[d]	**0.027**	**0.53**[a]
Lesion load (volume; cm^3)	NA	2.75 (4.49)[d]	NA	NA
Lesion load, median (IQR) (volume; cm^3)	NA	1.20 (1.93)[d]	NA	NA

Demographic, neuropsychological, and MRI characteristics. The values represent mean (SD) unless indicated otherwise

Results in bold are statistically significant

CIS clinically isolated syndrome, *EDSS* Expanded Disability Status Scale, *MSNQ* Multiple Sclerosis Neuropsychological Questionnaire, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *RAVLT delayed* RAVLT delayed recall after 30 min, *BVMT-R* Brief Visuo-spatial Memory Test Revised, *BVMT-R delayed* BVMT-R delayed recall after 25 min, *SDMT* Symbol Digit Modalities Test, *PASAT* Paced Auditory Serial Addition Test, *TMT* Trail Making Test, *COWAT* Controlled Oral Word Association Test, *JLO* Judgement of Line Orientation, *CFT* Category Fluency Test, *nBP* normalized brain parenchymal volume, *nWM* normalized white matter volume, *nGM* normalized grey matter volume, *IQR* interquartile range

[a] Effect size reported using Cohen's d

[b] Effect size reported using Cramér's V

[c] Based on a sample restricted to those who underwent an experimental MRI protocol ($n = 30$)

[d] Based on a sample restricted to those who underwent an experimental MRI protocol ($n = 45$)

lower cognitive performance was present in verbal memory for 25.5% of CIS subjects, in nonverbal memory for 17.6% of CIS subjects, in information processing speed/attention/working memory for 25.5% of CIS subjects, in executive functions for 23.5% of CIS subjects, in visuo-spatial functions for 13.7% of CIS subjects, and in language functions for 0.0% of CIS subjects. Characteristics of the patients with CIS at high risk for MS with normal and lower cognitive performance (based on the overall cognitive performance using the criterion of 1.5 SDs) are presented in Table 3.

Volumetric measurements

The CIS group had reduced nBP ($p = 0.006$), nWM ($p = 0.029$) and nGM ($p = 0.027$) volume, and cortical volume in frontal and temporal regions and also in parietal, limbic, and occipital regions ($p \leq 0.019$). Volume was further reduced in the thalamus and also in the hippocampus and amygdala in the CIS group ($p < 0.001$). Next, the CIS group had a significant enlargement of lateral ventricles ($p < 0.001$) and reduced volume in ventral cerebellar area and the brain

Table 2 Correlational matrix of the group with clinically isolated syndrome at high risk for multiple sclerosis

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. EDSS	–												
2. Age	0.15	–											
3. Years of education	−0.18	−0.01	–										
4. Verbal memory	0.13	0.04	0.41**	–									
5. Nonverbal memory	−0.06	0.07	0.22	0.38**	–								
6. Information processing speed/attention/working memory	−0.08	−0.07	0.27	0.21	0.47***	–							
7. Executive functions	−0.13	0.07	0.24	0.49***	0.53***	0.51***	–						
8. Visuo-spatial functions	−0.02	0.24	0.17	0.08	0.21***	0.34*	0.12	–					
9. Language functions	−0.05	0.03	0.31*	0.34*	0.43**	0.20	0.57***	0.02	–				
10. CCS	0.00	0.12	0.40**	0.63***	0.84***	0.62***	0.76***	0.56***	0.62***	–			
11. nBP[a]	−0.38*	−0.35*	−0.21	−0.09	−0.02	−0.14	0.07	0.10	0.07	0.01	–		
12. nWM[a]	−0.28	0.04	−0.22	−0.15	0.11	−0.10	0.03	0.31*	0.06	0.08	0.72***	–	
13. nGM[a]	−0.27	−0.50***	−0.15	−0.02	−0.10	−0.13	0.08	−0.07	0.06	−0.04	0.89***	0.32*	–
14. Lesion Load[a]	0.26	−0.03	0.15	0.17	−0.01	0.10	0.06	−0.07	0.10	0.08	−0.39**	−0.43**	−0.24

EDSS Expanded Disability Status Scale, *CCS* cognitive composite score (representing overall cognitive performance), *nBP* normalized brain parenchymal volume, *nWM* normalized white matter volume, *nGM* normalized grey matter volume

* 0.05 level (2-tailed). ** 0.01 level (2-tailed). *** 0.001 level (2-tailed)

[a] Based on a sample restricted to those who underwent an experimental MRI protocol ($n = 45$)

Table 3 Characteristics of the patients with clinically isolated syndrome at high risk for multiple sclerosis with normal and lower cognitive performance

	CIS at high risk for MS with normal cognitive performance ($n = 35$)	CIS at high risk for MS with lower cognitive performance ($n = 16$)	p values	Effect sizes
Age (years)	32.26 (8.50)	30.19 (10.17)	0.452	0.23[a]
Women, n (%)	12 (60.0)	8 (50.0)	0.503	0.09[b]
Education (years)	15.57 (2.95)	14.13 (2.47)	0.095	0.52[a]
EDSS	1.51 (0.57)	1.69 (0.79)	0.384	0.28[a]
MSNQ (score)	9.43 (7.04)	16.94 (9.66)	**0.003**	**0.97**[a]
BDI (score)	5.23 (4.39)	7.88 (7.62)	0.123	0.48[a]
BAI (score)	6.14 (6.33)	9.73 (7.36)	0.086	0.55[a]
RAVLT 1–5 (score)	55.91 (9.34)	50.25 (8.27)	**0.043**	**0.64**[a]
RAVLT delayed (score)	11.71 (2.91)	9.75 (2.60)	**0.025**	**0.71**[a]
BVMT-R 1–3 (score)	28.57 (3.49)	23.25 (4.31)	**0.000**	**1.44**[a]
BVMT-R delayed (score)	10.89 (0.96)	9.00 (1.46)	**0.000**	**1.70**[a]
SDMT (score)	59.69 (9.43)	49.50 (6.51)	**0.000**	**1.20**[a]
PASAT (score)	49.17 (7.76)	37.88 (12.60)	**0.000**	**1.21**[a]
Digit span forward (score; digits)	9.03 (1.95)	9.13 (2.16)	0.875	0.05[a]
Digit span backward (score; digits)	7.34 (2.24)	6.44 (2.16)	0.181	0.41[a]
TMT A (time in s)	29.69 (7.44)	33.94 (7.24)	0.062	0.59[a]
TMT B (time in s)	60.29 (12.70)	98.81 (40.45)	**0.000**	**1.59**[a]
COWAT (score)	47.11 (13.49)	31.94 (10.67)	**0.000**	**1.22**[a]
JLO (score)	26.91 (3.11)	23.69 (5.77)	**0.012**	**0.80**[a]
CFT animals (score)	27.86 (5.77)	19.63 (3.30)	**0.000**	**1.63**[a]
CFT shopping (score)	28.43 (7.63)	21.75 (3.86)	**0.002**	**1.02**[a]
nBP (volume; cm^3)	1448.88 (85.36)[c]	1472.31 (64.20)[d]	0.354	0.30[a]
nWM (volume; cm^3)	679.20 (39.36)[c]	687.30 (37.40)[d]	0.512	0.21[a]
nGM (volume; cm^3)	769.68 (59.40)[c]	785.01 (55.21)[d]	0.408	0.28[a]
Lesion load (volume; cm^3)	2.82 (4.83)[c]	2.00 (2.86)[d]	0.551	0.20[a]
Lesion load, median (IQR) (volume; cm^3)	1.22 (1.72)[c]	0.91 (2.25)[d]	NA	NA

Demographic, neuropsychological, and MRI characteristics. The values represent mean (SD) unless indicated otherwise

Results in bold are statistically significant

CIS clinically isolated syndrome, *MS* multiple sclerosis, *EDSS* Expanded Disability Status Scale, MSNQ Multiple Sclerosis Neuropsychological Questionnaire, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *RAVLT delayed* RAVLT delayed recall after 30 min, *BVMT-R* Brief Visuo-spatial Memory Test Revised, *BVMT-R delayed* BVMT-R delayed recall after 25 min, *SDMT* Symbol Digit Modalities Test, *PASAT* Paced Auditory Serial Addition Test, *TMT* Trail Making Test, *COWAT* Controlled Oral Word Association Test, *JLO* Judgement of Line Orientation, *CFT* Category Fluency Test, *nBP* normalized brain parenchymal volume, *nWM* normalized white matter volume, *nGM* normalized grey matter volume, *IQR* interquartile range

[a] Effect size reported using Cohen's d

[b] Effect size reported using Cramér's V

[c] Based on a sample restricted to those who underwent an experimental MRI protocol ($n = 30$)

[d] Based on a sample restricted to those who underwent an experimental MRI protocol ($n = 15$)

stem ($p < 0.001$). In the CIS group, increased grey matter volume was detected in occipital region, putamen, dorsal cerebellar area, and the brain stem ($p \leq 0.021$). The FSL-VBM results are presented in Figs. 1 and 2 and Online Resource Tables 3 and 4. The average lesion load volume was 2750 mm^3, and the median was 1200 mm^3 (Table 1).

Associations between cognitive functions and volumetric measurements

Worse visuo-spatial performance (lower JLO score) was correlated with lower nWM volume ($r = 0.31$; $p = 0.037$) in the CIS group. In the regression analysis adjusted for age, gender, and education, this association remained

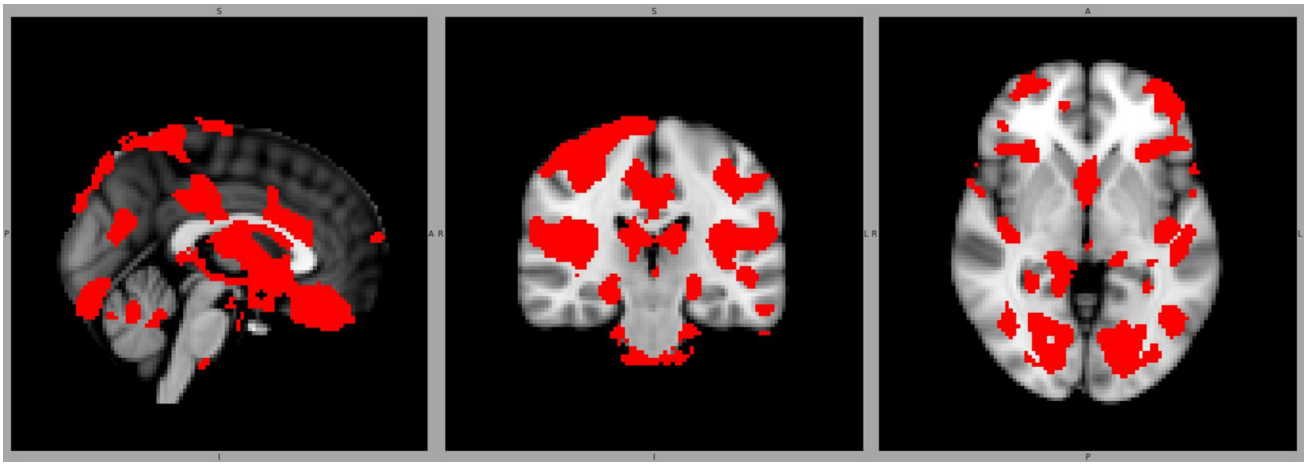

Fig. 1 Regional brain volumes reduced in the group with clinically isolated syndrome at high risk for multiple sclerosis compared to controls

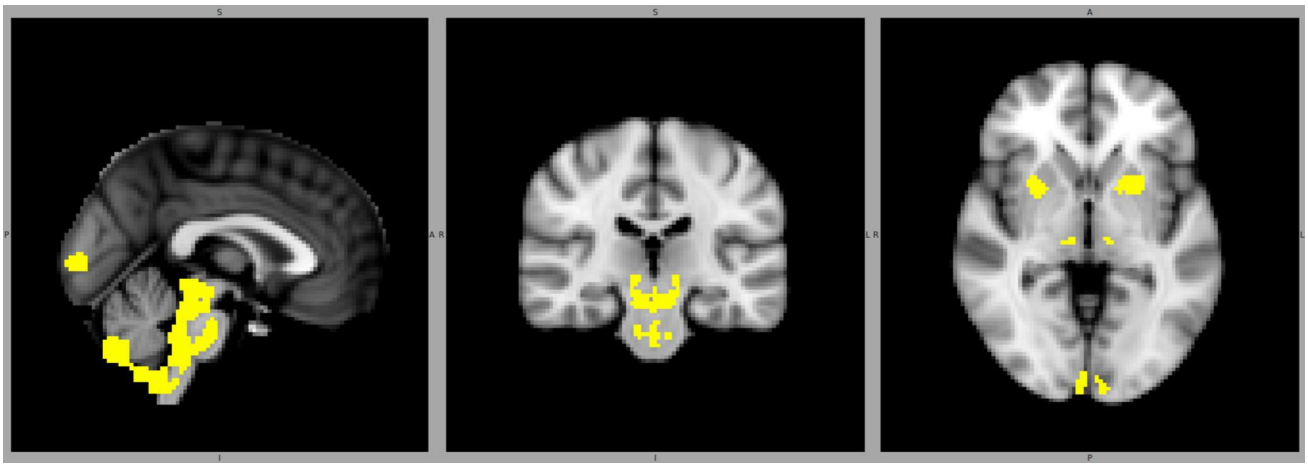

Fig. 2 Regional brain volumes increased in the group with clinically isolated syndrome at high risk for multiple sclerosis compared to controls

significant ($\beta = 0.29$; $p = 0.042$). Other correlations of cognitive functions, overall cognitive performance, and neuropsychological tests' scores with nBP, nWM, and nGM volume, lesion load (Table 2 and Online Resource Table 1), and volumes of cortical and subcortical regions (not reported) were not significant.

Discussion

Cognitive impairment is present in 43–72% of patients with MS, where all cognitive functions may be affected [1]. In patients with CIS, a few selected domains were found to be affected, predominantly information processing speed, attention, working memory, and verbal fluency [2, 24, 27]. However, patients with CIS may constitute a heterogeneous group comprising individuals after a first clinical episode and an objective clinical evidence of one lesion with no apparent brain lesions on MRI brain scan as well as those with an additional dissemination of brain lesions in space who may represent individuals at high risk for MS [21]. This heterogeneity is also reflected in studies showing a large variability of cognitive impairment in 12–57% of patients with CIS [2, 19]. We recruited a very homogeneous cohort of patients with CIS, who are at high risk of developing clinically definite MS [32, 51], and we characterized their cognitive profile using a comprehensive neuropsychological battery. Compared to demographically matched healthy controls, the patients with CIS at high risk for MS had lower cognitive performance in most of the neuropsychological tests encompassing verbal and non-verbal memory (in both learning and delayed recall), information processing speed/attention/working memory (especially in the tests with significant information processing speed demands—SDMT and PASAT), and executive and visuo-spatial functions. The pattern of lower cognitive performance more resembled findings in patients with MS than those in patients with CIS [2, 9]. This may be

explained by the inclusion criteria used in our study, which resulted in recruitment of a homogeneous cohort of patients with CIS at high risk for MS compared to heterogeneous cohorts of CIS patients in the previous studies [24, 26]. Next, we used a more comprehensive neuropsychological battery, which may be more reliable in detecting lower cognitive performance, compared to the previous studies in patients with CIS, where individual neuropsychological tests or the Brief Repeatable Battery of Neuropsychological Tests were used [2, 9, 23]. Although the differences between patients with CIS at high risk for MS and healthy controls were statistically significant with a moderate effect size in most of the neuropsychological tests, based on the applied criteria, only 18–37 and 14–26% of patients with CIS at high risk for MS had lower cognitive performance, which resembled the findings of the previous studies in patients with CIS [9, 22]. This was after application of a liberal definition of lower cognitive performance as impairment in at least one neuropsychological test for each cognitive domain using the criterion of scoring more than 1.5 and 2 SDs, respectively, below the mean of the control group. These findings indicate that although the pattern of cognitive impairment resembled the pattern found in patients with MS [29], the cognitive decline seemed to be mild and to be present in a subset of patients with CIS at high risk for MS. In addition, the differences in cognitive performance were influenced by years of education and disease duration, which mitigated the differences between the groups in visuo-spatial functions and nonverbal memory, respectively. Years of education and disease duration should, therefore, be taken into account when evaluating cognitive performance in patients with CIS at high risk for MS.

The previous studies demonstrated widespread cortical and subcortical atrophy in patients with MS [4, 7, 11–13] and regional cortical atrophy, especially in frontal and temporal lobes together with atrophy of the subcortical structures, especially of the thalamus, in patients with CIS [6, 23, 29]. In our study, patients with CIS at high risk for MS had widespread global and regional cortical atrophy, predominantly in frontal and temporal regions and further in parietal and limbic regions together with subcortical atrophy of the thalamus. Thus, they had a similar pattern of atrophy that was reported in patients with MS [6]. This more pronounced cortical brain atrophy in our current study compared to findings of the previous studies in patients with CIS may reflect the inclusion criteria leading to the recruitment of a very homogeneous cohort of patients with CIS, who are at high risk of developing clinically definite MS. Consistent with our findings, atrophy of the thalamus was found previously in patients with CIS [23, 29, 52] and some studies further reported atrophy of the hippocampus, amygdala, basal ganglia, cerebellum, and the brain stem [52, 53]. In our study, atrophy of the hippocampus and amygdala, unlike atrophy of the basal ganglia, was present in patients with CIS at high risk for MS. Next, some areas of the cerebellum and brain stem were also atrophied in patients with CIS at high risk for MS, while the other areas of the cerebellum and brainstem, together with some areas of the occipital region and the putamen, seemed to be "hypertrophic". This pseudo-hypertrophy may be related to tissue repair [54], which may be more likely in individuals with less disability (e.g., patients with CIS) who have more efficient repair processes. Further studies are required to resolve whether the basal ganglia, cerebellum, and the brain stem are atrophied as early as cortical regions and the thalamus in patients with CIS at high risk for MS. The average lesion load was 2750 mm^3 in this study, which is similar to results reported previously in patients with CIS [6, 27].

The previous studies in patients with MS found associations of cognitive impairment with cortical and subcortical atrophy and demyelinating lesions [4, 11–13]. Based on these findings, one would expect similar associations in patients with CIS. However, the studies, with one exception, did not find such associations in patients with CIS [23, 27, 29]. Similarly, in our current study, cognitive performance in neuropsychological tests and cognitive functions were not associated with structural brain changes with a single exception of the association between visuo-spatial functions and nWM volume in patients with CIS at high risk for MS. The discrepancy between the findings of cognitive impairment and lack of its structural brain correlates in patients with CIS was described earlier as cognitive-pathological dissociation [4]. This dissociation may be explained by variability of cognitive performance among patients with CIS, where a cognitive reserve and a positive effect of interferon-beta on cognition may play an important role [55, 56]. The association between visuo-spatial functions and atrophy of the interhemisferic white matter (corpus callosum) was reported previously in patients with early MS [14] but was not evaluated in patients with CIS. However, interhemisferic white matter is one of the first structures atrophied in patients with CIS [57] due to demyelination and axonal disruption [58], which may lead to less efficient interneuronal communication and consequently result in lower cognitive performance [59]. The possible association between visuo-spatial impairment and white matter atrophy in patients with CIS at high risk for MS thus needs further exploration. The EDSS score was correlated with lower nBP volume indicating that greater clinical disability may be related to more pronounced global brain atrophy in patients with CIS at high risk for MS. This is in line with the previous findings in early MS [60].

One of the strengths of this study is the fact that we used a very homogeneous sample of patients with CIS at high risk for MS and a comprehensive battery of neuropsychological tests covering major cognitive functions together with a detailed MRI brain volume measurement. In addition, cognitive performance and structural MRI findings were directly compared between patients with CIS and demographically matched healthy controls that underwent the same protocols. This study also has limitations. This was a cross-sectional study, which does not allow for evaluating the predictive value of cognitive performance and structural MRI findings for achieving clinical endpoints, such as conversion to MS, but longitudinal follow-up is ongoing. Because of the lack of normative data for the Czech population, we were unable to provide corrected *z*-scores for each neuropsychological score from normative values and to compare neuropsychological performance of patients with CIS at high risk for MS with a normative data set. In addition, because of the lack of scores for some of the cognitive domains, we used the liberal definition of lower cognitive performance as impairment in at least one neuropsychological test for each cognitive domain, which may influence our results. Next, our comprehensive neuropsychological battery did not include tests of conceptual reasoning, which may lead to underestimation of the severity and extent of executive dysfunction in our cohort of patients with CIS at high risk for MS. Furthermore, there is not a uniform approach how to assign the tests of verbal fluency into different cognitive functions. We built on the previous studies assigning the tests of letter fluency to executive functions and the tests of category fluency to language functions [43, 44]. However, both tests of verbal fluency may to some extent examine both cognitive functions and this may reduce generalizability of our findings for executive and language functions. Another possible limitation of this study may be the fact that we did not estimate premorbid intelligence. The National Adult Reading Test, which is widely used for this purpose, has not been validated for the Czech population. In addition, preliminary data suggest a weaker association of premorbid intelligence with the Czech version of the National Adult Reading Test than with level of education [61]. For this reason, we used years of education as a more appropriate criterion for matching the control group, which may, however, influence our results. Next, limitation is a small sample size. Because our small sample size increases the chances of bias towards the Type II error and because the use of a correction for the Type I error will further increase this bias, we did not correct our analyses for multiple comparisons. Furthermore, we did not limit analyses of neuropsychological variables to those patients with experimental MRI protocol, because reduction of our small sample size will further increase the chances of bias towards the Type II error. These steps may, however, influence our results. Finally, the median time between start of the treatment and experimental MRI brain scan was 6 months, so we cannot fully exclude that this may influence the results of volumetric measurements (e.g., pseudo-hypertrophy due to treatment-related brain tissue repair processes or time-related brain atrophy due to progression of the disease).

In conclusion, using a comprehensive neuropsychological battery, we demonstrated generally lower cognitive performance encompassing verbal and nonverbal memories, information processing speed/attention/working memory, and executive and visuo-spatial functions in patients with CIS at high risk for MS. Lower cognitive performance was present in 18–37 and 14–26%, respectively, of patients with CIS at high risk for MS with a similar profile to that found in patients with MS [6]. Patients with CIS at high risk for MS had widespread global and regional cortical and subcortical atrophy, which was most pronounced in fronto-temporal regions and in the thalamus, representing a similar pattern of atrophy to that found in patients with MS [10, 11]. However, there was a lack of consistent associations between structural brain changes and cognitive performance except for the association between white matter atrophy and lower visuo-spatial performance. Future studies are needed to evaluate predictive value of lower cognitive performance and abnormal structural MRI findings for conversion to MS among patients with CIS at high risk for MS.

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Compliance with ethical standards

Conflicts of interest On behalf of all author, the corresponding author states that there is no conflict of interest.

Ethical standards The study was approved by the institutional ethics committee of the Motol University Hospital. Written informed consent was obtained from all subjects participating in the study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsiniki.

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