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【 ORIGINAL ARTICLE 】

Prospective Memory Deficits in Multiple Sclerosis: Voxel-based Morphometry and Double Inversion Recovery Analysis

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Abstract:

Objective Prospective memory (PM) is an important social cognitive function in everyday life. PM is one of the most affected cognitive domains in multiple sclerosis (MS) patients. Gray matter (GM) atrophy and plaques have been attracting attention for various cognitive impairments in MS patients. This study aimed to clarify the atrophic GM regions associated with PM deficits and investigate the relationship between the atrophic GM regions and GM plaques.

Methods Twenty-one MS patients and 10 healthy controls (HCs) underwent neuropsychological tests and MRI. PM was assessed using subtests of the Rivermead Behavioural Memory Test. A lesion symptom analysis was performed using voxel-based morphometry (VBM). We then evaluated GM plaques in the corresponding areas using double inversion recovery (DIR).

Results MS patients showed lower PM scores than HCs (p=0.0064). The GM volume of MS patients tended to be lower than those of HCs. VBM analyses revealed correlations of the PM score with the orbital part of the left inferior frontal gyrus, the left hippocampus, and the right parahippocampus. There was no GM plaque in the orbital part of the left inferior frontal gyrus and the right parahippocampus. Only one patient (4.8%) had GM plaque in the left hippocampus.

Conclusion The left inferior frontal gyrus, the left hippocampus, and the right parahippocampus were associated with PM in MS, whereas these atrophic GM regions were not associated with GM plaque. Regardless of the location of plaques on DIR, both PM deficit and GM atrophy should be detected using neuropsychological tests and VBM in MS patients.

Key words: multiple sclerosis, prospective memory, voxel-based morphometry analysis, double inversion recovery

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Introduction

Prospective memory (PM) is the ability to remember to execute an intended action at the appropriate time in future (e.g., remembering to buy a book on the way home from work or remembering to take medication after dinner) (1, 2). PM is distinguished from retrospective memory, which is the ability to recall past events, semantic memory, or memory for word lists (3). There are two subtypes of PM, event-based PM and time-based PM. Event-based PM involves remembering to carry out an intention when a certain external

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event occurs (e.g., relaying a message to someone when he or she turns up for lunch). This type of task can be described as environmentally cued. Time-based PM involves remembering to perform some action after a period of time has elapsed or at a certain time (e.g., telephoning someone at 3:00 P.M. while at work). This type of task can be described as self-cued (1-3). Since PM is related to many real-world tasks, it is an important social cognitive function for daily life, employment, or attending school. Cognitive impairment is recognized as a core symptom of all phases and all subtypes of multiple sclerosis (MS) (4). Previous studies reported that general intelligence is preserved in MS, and PM in everyday life is one of the most affected cognitive domains in MS (5-7). Although MS is traditionally considered to be a demyelinating disease affecting the white matter (WM), gray matter (GM) atrophy and plaques in GM have been deemed crucial in cognitive disability of MS (8-10).

A relationship between regional GM atrophy and memory impairment in MS has been reported previously: hippocampal and episodic memory encoding/retrieval (11); the left frontal lobe and auditory/verbal memory; right frontal lobe and visual episodic memory (12); cerebellum and working memory (13). However, no association between regional GM atrophy and PM has been suggested previously. Clarifying the association between GM atrophy and PM deficits is crucial for detecting and reconsidering disease-modifying therapy (DMT) at an early stage of MS.

Meanwhile, MS plaques have been shown in the GM, particularly in the cerebral cortex, by pathological studies. Conventional MRI could not detect cortical plaques. However, the development of the double inversion recovery (DIR) technique enabled detection of cortical lesions in the MS brain (14). Although the pathophysiology of diffuse GM atrophy has been assumed to be the neurodegenerative mechanism of this disease (8), it is unclear if these plaques in GM lead to regional GM atrophy in the corresponding areas.

The purpose of this study was to elucidate the association between the atrophic GM regions and PM deficits in patients with MS, using voxel-based morphometry (VBM). Furthermore, we investigated the association of atrophic GM regions with GM plaques on DIR.

Materials and Methods

Participants

We recruited 21 relapsing-remitting MS (RRMS) patients (4 males, 17 females), who all met the revised McDonald's criteria (15). All patients were in remission and patients who relapsed within 3 months, and/or were affected with other central nervous system diseases, were excluded. To confirm the absence of recurrence radiographically, we assessed both three-dimensional fluid-attenuated inversion-recovery (3D-FLAIR) images and gadolinium (Gd) enhanced 3D-T1-weighted images.

For the healthy control (HC) group, we recruited 10 participants (2 males, 8 females). They were matched to the MS group for age and sex, and were confirmed to have no medical history of disease of the central nervous system.

This study was approved by ethics committee of Hiroshima University Hospital. Written informed consent was obtained from all the participants before enrolment.

Neuropsychological assessments

To evaluate attention, memory and executive functions, we performed neuropsychological tests: The Mini-Mental State Examination (MMSE) (16), Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (17), and Rivermead Behavioural Memory Test (RBMT) (18).

MMSE is the major instrument for screening dementia, and the most common cutoff scores are 23 and 24 (19). BRB-N consists of tests of verbal learning and memory (the Selective Reminding Test, SRT), visuospatial memory and learning (the 10/36 spatial recall test, SPART), the Symbol Digit Modalities Test (SDMT), attention, information processing, and working memory (the Paced Auditory Serial Addition Test, PASAT), and verbal fluency (the Word List Generation test, WLG) (17). The RBMT has characteristics that reflect everyday memory and prospective memory. It simulates daily life in which memory function is required. The scores are converted into standardized profile scores (SPS, range 0-24 points) and screening scores (SS, range 0-12 points). The cut-off scores of RBMT were 19 points (SPS)/7 points (SS) for participants under 39 years old, and 16 points (SPS)/7 points (SS) for participants 40-59 years old.

PM assessment

We used the RBMT to evaluate the PM function. We selected the following four sub-tests to evaluate PM: belonging (range 0-4 points), appointment (range 0-2 points), route (range 0-10 points), and message (range 0-6 points). The PM score ranges from 0 to 22 points using the raw scores of each subtest. The belonging sub-test is a remembering task in which the examiner asks to return the patient's belonging that was hidden somewhere at the beginning of the test. The appointment sub-test requires asking about a future appointment when an alarm rings. The route sub-test involves remembering the route that the examiner had shown. The message sub-test requires the participant to take an envelope and put it in the same place where the examiner had put it when demonstrating the route sub-test. Route and message sub-tests are composed of immediate and delayed recall, and we use both components.

MRI acquisition protocol

We used a 3.0-T clinical MRI unit (Ingenia 3.0 T; Philips Healthcare, Best, the Netherlands) at Hiroshima University Hospital. The imaging protocol included sagittal 3D-TI-weighted imaging [repetition time (TR)=6.2 ms, echo time (TE)=2.8 ms, inversion time (TI)=879 ms, sagittal 0.9-mm slices, slice gap=0.9 mm, field-of-view (FOV)=240 mm],

3D-DIR (TR=5,500 ms, TE=289 ms, TI: IR-1=2,550 mm, IR-2=450 mm, sagittal 1.4 mm slices, slice gap=0.7 mm, FOV=240 mm), 3D-FLAIR (TR=4,500 ms, TE=336 ms, TI=1,600 ms, sagittal 1.4-mm slices, slice gap=0.7 mm, FOV=240 mm), and Gd-enhanced 3D-T1-weighted imaging.

Image analyses

Plaque location

Two neuroradiologists (M.T., T.O.), who were blinded to the clinical information of the patients, independently detected GM and juxtacortical plaques, using DIR images. Cortical lesions were defined as lesions confined to the cortical ribbon and not involving the underlying subcortical white matter (Fig. 1A). Juxtacortical lesions were defined as lesions touching the cortex (Fig. 1B). The GM and juxtacortical plaques were determined by consensus. The kappa coefficient for the inter-rater agreement for the plaque was 0.73. Thereafter, the locations were confirmed using the atlas (20).

VBM analyses

We preprocessed and analyzed 3D-T1-weighted images using statistical parametric mapping version 12 (SPM12, the Welcome Trust Center for Neuroimaging, Institute of Neurology, University College of London) running under MATLAB R2019a (The MathWorks, Natick, USA). Three-dimensional-T1-weighted images were segmented into GM, WM, and cerebrospinal fluid (CSF). Using high-dimensional Diffeomorphic Anatomical Registration through Exponential Lie Algebra (DARTEL) normalization, registration to the stereotactic space of the Montreal Neurological Institute (MNI) consisted of linear affine transformation and nonlinear deformation. By applying nonlinear deformation, normalized images were modulated. Nonlinear deformation allows for a comparison of absolute amounts of tissue. Finally, GM images that were bias-corrected, modulated, and warped were smoothed with an 8-mm full-width at half-maximum Gaussian kernel. The voxel resolution of smoothed images was 1.5×1.5×1.5 mm. After these procedures, we calculated GM volume (GMV), WM volume (WMV), CSF volume, total intracranial volume (TIV), GMV/TIV ratio, and WMV/TIV ratio using segmented images.

Statistical analyses

Demographic and clinical variables and brain tissue volumes were statistically analyzed. Comparisons of baseline characteristics between two groups were assessed using χ^2 tests for categorical variables, and Student's *t*-tests or Mann-Whitney U tests for continuous variables. Correlations between the brain tissue volumes and the clinical variables [duration, recurrence, and expanded disability status scale (EDSS)], and between the PM score and subtests of the BRB-N score were assessed using the Spearman's correlation, respectively. Values of $p<0.05$ were considered to be significant. The JMP 14 software program (SAS Institute, Cary, USA) was used for the statistical analysis.

For neuroimaging data, we performed group comparisons between the HC and MS groups, employing the two-sample *t*-test model in SPM12. Age and sex were treated as covariates and TIV was treated as a global value. We also performed a correlation analysis to identify the brain regions associated with the BRB-N score and PM score by a general linear model, using a multiple regression analysis. The significance level was set at $p<0.05$ family-wise error (FWE)-corrected for multiple comparisons. Thereafter, an analysis of each dimension was reported to be significant if the cluster size exceeded 14.6; we set the extent threshold to 15. The anatomic location of each resulting cluster was determined using a software program (BioImage Suite Web: http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Then, we assessed the location of each cluster visually, and confirmed the adequacy of its anatomical location by using the human brain atlas (20). For global calculation, we used the TIV, and statistical significance was set at $p<0.05$ using FWE-correction for multiple comparisons at the cluster level.

Results

The baseline characteristics are shown in Table 1. Among the 21 MS patients, the expanded disability status scale (EDSS) scores were less than 3 points in 14 patients. Almost half of all the MS patients were treated with fingolimod (48%), while interferon β was used in 31%, and only one patient was treated with dimethyl fumarate. The MMSE scores of MS patients were almost maximal. The RBMT scores (SPS and SS scores) also exceeded the cut-off score in 19 of 21 MS patients. The PM score of the MS group was significantly lower than that in the control group ($p=0.006$). Among the sub-tests of BRB-N, the SDMT, PASAT3, and PASAT2 showed a significantly positive correlation with the PM score (Supplementary material 1).

The WMV and WMV/TIV were significantly lower in the MS than in the HC group ($p=0.028$ and $p=0.027$, respectively). Although GMV and GMV/TIV showed no significant difference between the HC and MS groups, the GMV/TIV tended to be lower in MS than in HC group (Fig. 2). The GMV/TIV was negatively correlated with the duration ($\rho=-0.59$, $p=0.005$). Significant negative correlations were found between recurrence and WMV ($\rho=-0.59$, $p=0.005$), and between EDSS and white matter ($\rho=-0.54$, $p=0.011$ for WMV; $\rho=-0.43$, $p=0.049$ for WMV/TIV) (Supplementary material 2). No significant atrophic GM regions were detected by two-sample t-tests between the HC and MS groups. The region that correlated with the SDMT score was the opercular part of the right inferior frontal gyrus (MNI coordinates: x, 57: y, 9: z, 13.5; cluster size, 24; Z score, 5.36; $p=0.003$) (Supplementary material 3). Other subtests of the BRB-N showed no regional correlation. The regions that correlated with the PM score were the orbital part of the left inferior frontal gyrus (MNI coordinates: x, -43.5: y, 19.5: z, -6; cluster size, 30; Z score, 5.35; $p=0.003$), left hippocampus (MNI coordinates: x, -315: y, -15: z, -18; clus-

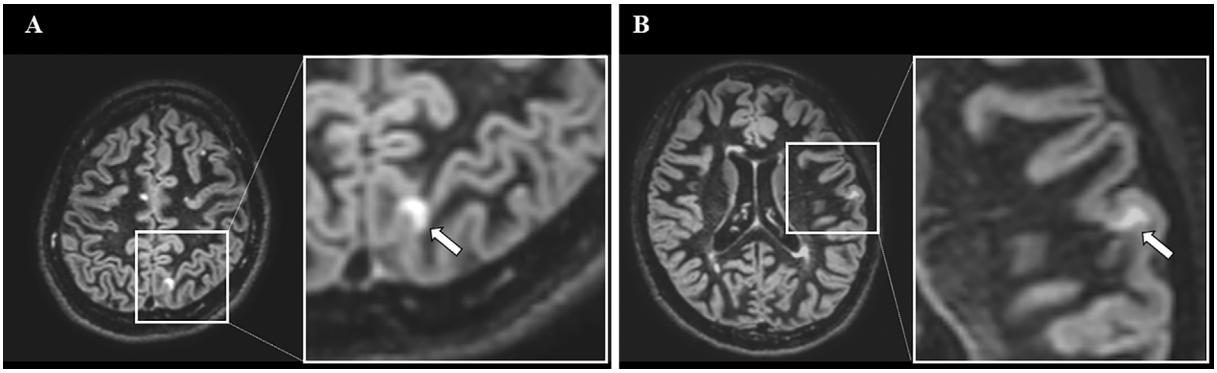

Figure 1. Representative images on double inversion recovery. Classification of cerebral cortical/ subcortical plaque lesions. Representative double inversion recovery. A: A cortical lesion in the left precuneus (case 7). B: A juxtacortical lesion in the left middle frontal gyrus (case 20).

Table 1. Baseline Characteristics and Results of Neuropsychological Tests of Patients and Controls.

	MS (n=21)	control (n=10)	p value
Age (years)	42±10.37	42.8±10.4	0.92
Sex (female/male)	17/4	8/2	0.95
Female/total (%)	81	80	-
Age at onset (years)	33.4±9.6	-	-
Disease duration (years)	8.9±5.6	-	-
Number of recurrences (times)	3.4±3.9	-	-
EDSS score	2.0 (0-8)	-	-
0-3; n (%)	14 (66.7)		
>3; n (%)	7 (33.3)		
Treatment, n, (%) IFN-β	8 (31)	-	-
FTY	10 (48)	-	-
DMF	1 (0.5)	-	-
MMSE score (0-30)	30 (26-30)	-	-
above cut off; n, (%)	21 (100)		
BRB-N score SRT-LTS (0-72)	47 (40.25-51.75)	-	-
SRT-CTLR (0-72)	36 (23.25-41)	-	-
10/36 SPART (0-30)	18 (13.5-23.5)	-	-
SDMT (0-110)	44.5 (33.25-51.75)	-	-
PASAT3 (0-60)	40.5 (32.75-51.75)	-	-
PASAT2 (0-60)	34 (23.25-39.75)	-	-
SRT-D (0-12)	10 (8.25-11.75)	-	-
SPART-D (0-10)	6 (5-9)	-	-
WLG	23 (21.25-26.5)	-	-
RBMT score SPS (0-24)	22 (20.5-23)	24 (23-24)	0.009
above cut off; n, (%)	19 (90.5)		
SS (0-12)	11 (9-11)	12 (11-12)	0.012
above cut off; n, (%)	19 (90.5)		
PM (0-22)	21 (20-22)	22 (22-22)	0.0064

For age, onset, duration, and recurrence, data are expressed as mean±standard deviation. For EDSS, data are expressed as the median value with the range. Data are shown as the median value of the total score for each person, with the 25th-75th interquartile range for MMSE, BRB-N, and RBMT scores. p values for comparisons between the two groups were obtained by using Student's *t*-test or the Mann-Whitney U test for continuous variables and Pearson's test for qualitative variables. -: not done, MS: Multiple sclerosis, IFN-β: interferon β, FTY: fingolimod, DMF: dimethyl fumarate, RBMT: The Rivermead Behavioral Test, MMSE: Mini-Mental State Examination, SS: screening score, SPS: standardized profile score, PM: prospective memory, BRB-N: Brief Repeatable Battery of Neuropsychological Tests, SRT: Selective Reminding Test, LTS: long-term storage, CTLR: consistent long-term retrieval, SPART: spatial recall test, SDMT: symbol digit modalities test, PASAT: Paced Auditory Serial Addition Test, D: delayed, WLG: Word List Generation Test

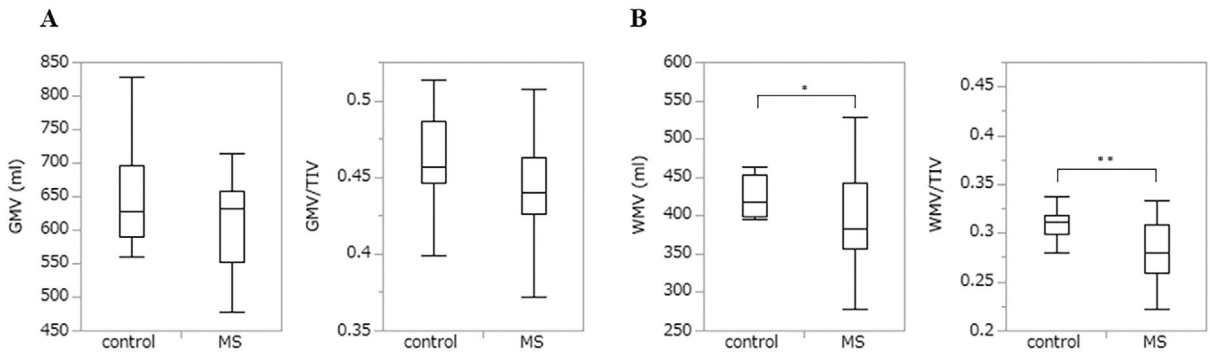

Figure 2. **Segmental brain volume comparison. The gray matter volume tended to be lower in the MS than in the HC group (A). The white matter volume was significantly lower in the MS than in the HC group (B). Differences between the two groups were evaluated with the Mann-Whitney U test. * p=0.028, **p=0.027. GMV: gray matter volume, WMV: white matter volume, TIV: total intracranial volume, MS: multiple sclerosis**

ter size, 97; Z score, 5.21; p=0.006), and right parahippocampus (MNI coordinates: x, 25.5: y, -15: z, -22.5; cluster size, 16; Z score, 4.85; p=0.025) (Fig. 3 and Table 2). Of the 21 patients, one (4.8%, Case 23) had cortical plaque and two (9.5%, Cases 6, 7) had juxtacortical plaques in the opercular part of the right inferior frontal gyrus. There was no plaque in the orbital part of the left inferior frontal gyrus. Of the 21 patients, one (4.8%, Case 22) had a cortical plaque while another (4.8%, Case 3) had a juxtacortical plaque in the left hippocampus. Of the 21 patients, one (4.8%, Case 3) had a juxtacortical plaque in the right parahippocampus. There was no plaque in the thalamus and the basal ganglia. The locations of the plaques are shown in detail in Supplementary material 4.

Discussion

In patients with MS, the PM score was lower than that in HCs, and was associated with GM atrophy in the orbital part of the left inferior frontal gyrus, left hippocampus, and right parahippocampus. In addition, there were few cortical and juxtacortical plaques in the atrophic GM regions related to PM deficits.

The interaction of the prefrontal cortex and the hippocampus has been reported to play an important role in PM. The prefrontal cortex is essential for representation and maintaining contextual information, and the hippocampus is responsible for the rapid encoding of novel associations and for using these to activate corresponding representations within the association cortex (21). PM is divided into three phases: the encoding of intention, the maintenance of intention, and the retrieval of intention. According to functional neuroimaging studies in healthy persons, the inferior frontal gyrus orbital region has been demonstrated to be one of the important areas involved in the retrieval phase of PM (22). Several studies have performed a lesion analysis to clarify the neuronal basis of PM, using diffusion tensor imaging (DTI) in traumatic brain injury. These studies have shown that injuries in the orbitofrontal WM and the left parahippocampal gyrus were associated with PM deficits (23, 24). Additionally, PM deficits were shown to be associated with hippocampal atrophy, based on a VBM study in adults with spina bifida myelomeningocele (25). Some studies have shown that PM in patients with MS was impaired (7, 26-28). However, few studies have investigated the relationships between PM deficits and brain regions in patients with MS. Pardini et al. reported that PM deficits were related to the reduced fractional anisotropy in the left uncinate fasciculus, using DTI (29). To the best of our knowledge, there are no previous reports which evaluated the associations between PM deficits and GM atrophy in MS patients. Our VBM analysis demonstrated that MS patients with PM deficits had GM atrophy in the left inferior frontal gyrus, the left hippocampus, and the right parahippocampus; this result was supported by the previous findings.

In no evidence of disease activity-4 (NEDA-4) (30), the criterion of no volume loss was added to NEDA-3, which includes no relapses and no progression of EDSS. Our study showed that GMV inversely correlated with the disease duration, but not with the times of recurrence and EDSS score. This result might not reflect the atrophy from MS purely, because we did not exclude the influence of age. However, the previous studies investigating brain atrophy and clinical status of MS revealed that GM atrophy associated with disease duration was independent of the effect of aging (31, 32). These results may reflect the fact that GM atrophy has a different mechanism from that of WM lesions in MS, and support clinical validity of NEDA-4.

In the present study, the GMV tended to be lower in patients with MS than in the HC group, but there were few detectable plaques on DIR in the atrophic regions that correlated with PM and the SDMT scores. Several likely explanations for this result were considered. First, the DIR technique could not visualize all the cortical plaques. Compared to conventional MRI, DIR enabled about a five-fold increase

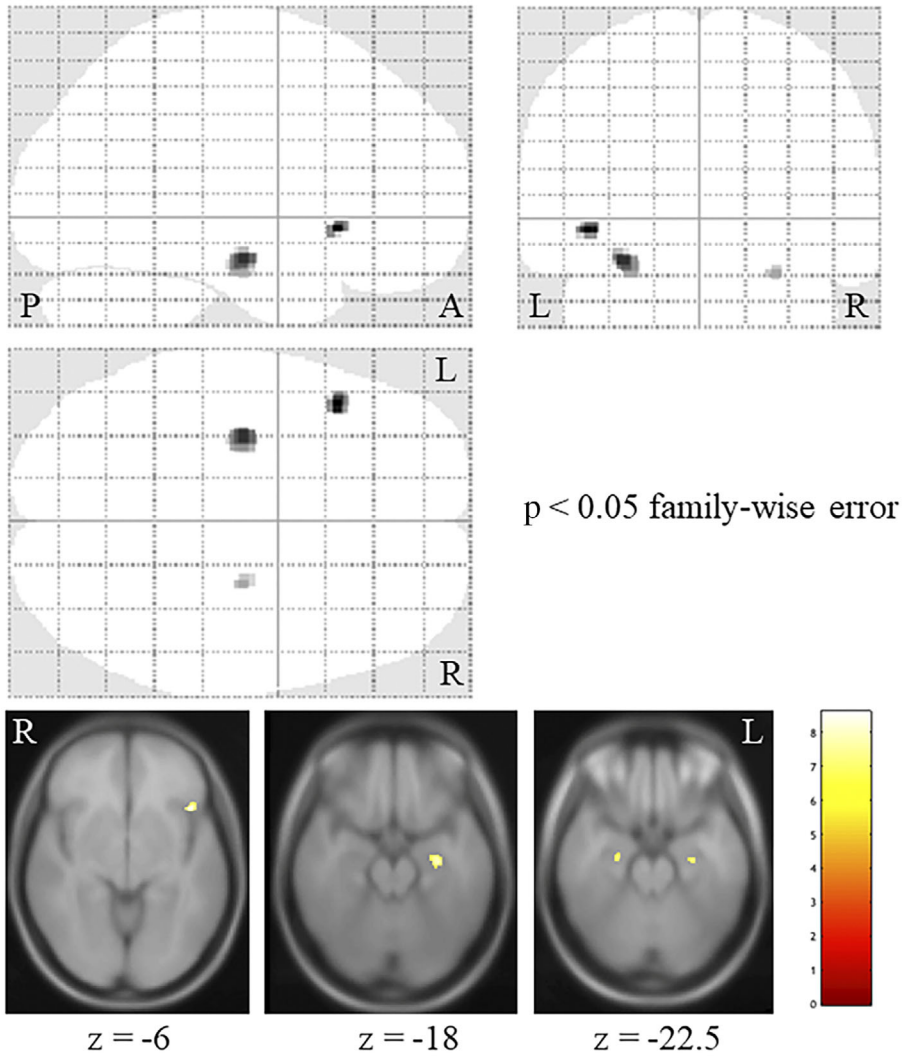

Figure 3. **The regions correlating with the prospective memory score. A voxel-based morphometry analysis showing that the prospective memory score correlated with several clusters, including the inferior frontal gyrus orbital part, the left hippocampus, and the right parahippocampus.**

Table 2. **Result of Correlation Analysis.**

Brain region	MNI coordinates			Z score	T value	p value (FWE- corrected)	Cluster size
	x	y	z				
Left inferior frontal gyrus orbital part	-43.5	19.5	-6	5.35	8.6	0.003	30
Left hippocampus	-31.5	-15	-18	5.21	8.14	0.006	97
Right parahippocampus	25.5	-15	-22.5	4.85	7.12	0.025	16

MNI: Montreal Neurological Institute

in the detection of cortical lesions. However, a postmortem study revealed that gray matter lesions were not fully detected on DIR (14). By using higher field MRI or combining phase-sensitive inversion recovery imaging (33), the relationship between cortical atrophy and cortical lesions can be further clarified. Second, GM lesions and regional GM atrophy seemed to reflect different mechanisms. Several hypotheses have been suggested to clarify this. GM atrophy was considered to occur by degeneration, caused by the dysregulation of copper homeostasis (34), mitochondrial dysfunction in axons (35), and combination of neurite transection and decreased synapses and glia (36), whereas cortical lesions were considered to be the result of demyelination caused by inflammation of the meninges (37).

There are some limitations associated with our study. First, most MS patients in this study had mild disabilities. An analysis of a larger population including severe MS patients may show a significant difference in the GM volume

between MS patients and HCs, and/or the association of GM plaques with regional GM atrophies. Second, our study population was small. In the future, an analysis stratified by severity, disease duration, and DMTs with more patients is required.

Conclusion

Atrophy of the GM in the left inferior frontal gyrus, the left hippocampus, and the right parahippocampus was associated with PM deficits in MS patients, and there was no association between these regions and plaques in the corresponding region. It is important not only to detect plaques by conventional MRI, but also to detect such regional atrophy, using VBM, and social cognitive deficits, using neuropsychological examination, including a PM battery.

This study was approved by the ethics committee of Hiroshima University Hospital. Written informed consent was obtained from all the participants for publication of this study and any accompanying data.

The authors state that they have no Conflict of Interest (COI).

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