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Clinical trial

Olfactory identification associates with cognitive function and the third ventricle width in patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Background: Olfactory dysfunction is a known clinical feature of multiple sclerosis (MS). Some studies have shown that odor identification impairment is an essential feature associated with cognitive function in MS. This study investigates the relationship between olfactory identification and the disease state, including cognitive function and central brain volume, to evaluate the utility of olfactory identification in the clinical assessment of relapsing-remitting (RR) MS.

Methods: Forty patients with RRMS and 40 healthy controls (HCs) were included. Their olfactory identification was measured using the Odor Stick Identification Test for the Japanese (OSIT-J). Cognitive function was evaluated by the Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), and depressive mood was evaluated by the Center for Epidemiologic Studies Depression Scale. Magnetic resonance imaging was used to measure the third ventricle width (3rd VW) as a marker of central brain atrophy.

Results: RRMS patients had a significantly lower OSIT-J score than HCs. The OSIT-J score was significantly lower in RRMS patients with low processing speed (PS) and working memory (WM) scores than RRMS patients with normal PS or WM scores. The OSIT-J score was significantly related to the PS, WM, and the 3rd VW. The OSIT-J score also showed a mild correlation with the expanded disability status scale and disease duration, but not with the number of clinical attacks or patient's age.

Conclusions: Our results suggest that olfactory identification impairment occurs in association with cognitive dysfunction and central brain atrophy. Thus, olfactory identification is a possible disease marker of RRMS as with cognitive impairment, especially PS, reflecting the diffuse neurodegeneration in RRMS.

1. Introduction

Olfactory dysfunction is a key feature in certain neurological disorders, such as Alzheimer disease and Parkinson disease, and can be used as an early marker for diagnosis (Doty, 2017). About 30–70% of patients with multiple sclerosis (MS) also exhibit olfactory dysfunction in their disease course (Joseph and DeLuca, 2016). Previous studies have shown olfactory dysfunction is associated not only with disease duration and the clinical disability of the patients with MS, but also the volume and number of lesions visible via brain magnetic resonance imaging (MRI) (Joseph and DeLuca, 2016; Lucassen et al., 2016). In addition, olfactory dysfunction is more evident in patients with a progressive form of MS than in patients with early relapsing-remitting (RR) MS (Silva et al., 2012; Carotenuto et al., 2019; Schmidt et al., 2017). These results suggest that olfactory dysfunction represents an aspect of fundamental symptoms, including disability and cognitive dysfunction, in MS. Therefore, an assessment of olfactory function could be a practical approach to evaluate MS patients.

Olfactory stimuli are transmitted through the olfactory bulb and tract into specialized cerebral regions, known as olfactory cortices, that are distributed widely over the frontal and temporal lobes and connect different cerebral regions (Joseph and DeLuca, 2016; Courtiol and Wilson, 2017). In MS, inflammatory demyelinating insults occur in both the gray and white matter of the central nervous system (CNS), including the olfactory network consisting of the olfactory bulb, tract olfactory, and olfactory cortices (Lassmann, 2019). Olfactory function has been investigated in patients with MS using different tools that measure the 3 components of olfactory function: threshold, discrimination, and identification (Joseph and DeLuca, 2016; Lucassen et al., 2016). Previous studies using these tools suggest that the

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olfactory threshold is associated with acute relapses reflecting inflammatory pathophysiology, and both discrimination and identification are associated with the neurodegenerative process (Bsteh et al., 2018a, 2018b, 2019a, 2019b). Moreover, recent studies have reported an association between olfactory dysfunction and cognitive impairment in patients with MS, especially its progressive form (Carotenuto et al., 2019; Bsteh et al., 2018b, 2019a; Batur Caglayan et al., 2016). Therefore, evaluating olfactory function discrimination and identification, in addition to expanded disability status scale (EDSS) and cognitive tests, are possible supplementary clinical markers of disease progression reflecting neurodegenerative changes in MS.

Hence, this study evaluates the relationship between olfactory identification ability and clinical status, including cognitive function, in Japanese patients with RRMS to elucidate the usefulness of olfactory identification as disease progression marker in MS. We adopted the olfactory identification test, which has been shown to be associated with neurodegenerative processes of MS, but not the olfactory threshold test, which has been shown to fluctuate depending on inflammatory processes including both clinical and subclinical acute aggravation (Bsteh et al., 2018a, 2018b, 2019a, 2019b). Also, the relationship between olfactory identification ability and central brain atrophy using the third ventricle width (VW) in an MRI is examined as well.

2. Patients and methods

2.1. Participants

We recruited 40 Japanese patients with RRMS, who were diagnosed according to the 2010 McDonald diagnostic criteria, between September 2015 and March 2018 at the outpatient clinic of the Department of Neurology at the University of Occupational and Environmental Health (Polman et al., 2011). Healthy controls (HCs) were recruited from the patients' families and the hospital staff. Patients with RRMS were evaluated during a remission period without corticosteroid treatment for at least 30 days. Exclusion criteria included people aged below 18 or above 65 years, those who had a clinical relapse within 3 months before testing or ongoing corticosteroid treatment, those who had a history or comorbidity of chronic otorhinolaryngeal diseases (such as chronic rhinitis, nasal polyposis, or sinus disease), those who had head trauma, those who had undergone nasal and/or oral surgery, those with nasal obstruction symptoms, those with mood disorders such as depression and other neurological diseases such as Parkinson disease and Alzheimer disease, or those who had other medical conditions associated with olfactory disturbances. No patients showed nasal abnormalities via MRI. The study was approved by the ethics committee of the University of Occupational and Environmental Health and all participants provided written informed consent and completed in accordance with the Helsinki Declaration.

2.2. Assessment of cognitive and olfactory identification

The Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) (Japanese WAIS-III Publication Committee, 2006) was used to assess cognitive function and the Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive moods (Vilagut et al., 2016). The WAIS-III evaluates full scale intelligence quotient (FIQ), verbal IQ (VIQ), and the performance IQ (PIQ) scores as well as the index scores of processing speed (PS), working memory (WM), perceptive orientation (PO), and verbal capacity (VC); these values are produced from 14 subtests according to the standardized instructions of the manual (Japanese WAIS-III Publication Committee). These 4 index scores (PS, WM, PO, VC) represent major components of intelligence and are susceptible to neural damage in MS (DeLuca et al., 2004). We also previously confirmed that WAIS-III well evaluated cognitive function of patients with MS (Okada et al., 2017). According to the manual, an IQ score and index $<$ 80 points were defined as borderline or abnormal [15]. Depression was defined as having a CES-D score $>$ 16, as previously recommended (Vilagut et al., 2016).

Olfactory identification was evaluated using the Odor Stick Identification Test for the Japanese (OSIT-J, Daiichi Yakuhin Sangyo, Tokyo, Japan) following the manufacturer's protocol (Saito et al., 2006). This test includes 12 odorants familiar to the Japanese population (perfume, rose, condensed milk, Japanese orange, curry, roasted garlic, fermented beans/sweaty socks, gas for a cooker, menthol, India ink, wood, and Japanese cypress) that have been selected from essential oils, pure chemicals, or mixed odorants produced by the Takasago International Corporation (Tokyo) (Saito et al., 2006; Iijima et al., 2008), similar to the Cross-Cultural Smell Identification Test (CC-SIT) (Doty et al., 1996). In the OSIT-J, each odorant was enclosed in microcapsules made of melamine resin and mixed into an odorless solid cream to be shaped into a lipstick-like structure. After the examiner applied each odor stick on a paraffin paper and rubbed it to grind the microcapsules, the participant opened the paraffin paper and sniffed the contents. Finally, the participant was asked to select an option on a card showing 4 names of odors and 2 other answers: "detectable but not recognizable" and "no smell detected." The total number of correct answers for the 12 odorants was recorded as the OSIT-J score. Hyposmia was defined as having an OSIT-J score $\leq$ 8 (Saito et al., 2006). The participants were directed to avoid eating and smoking 30 min prior to the evaluation.

2.3. MRI data acquisition and third ventricle width measurements

All MRI studies were performed with a Signa Excite 3T scanner (GE Healthcare, Milwaukee, Wisconsin) using a dedicated 8-channel phased array coil (USA Instruments, Aurora, Ohio). The imaging parameters for fluid-attenuated inversion recovery (FLAIR) imaging were repetition time: 12,000 msec, echo time: 140 msec, inversion time: 2600 msec, number of excitations (NEX): 1, echo spacing: 9.1, imaging time: 2 min 36 s, and echo train length: 21. The FLAIR images were acquired at a section thickness of 5 mm, an intersection gap of 1 mm, a field of view (FOV) of 22 cm, and a matrix of 320 $\times$ 224. According to a previous method (Benedict et al., 2004), the third VW measurement was performed in consensus by a neurologist and neuroradiologist with 28 and 25 years of experience, respectively, in the analysis of the brain MRI scans.

2.4. Statistical analysis

The Mann-Whitney U test was used for the comparison of the 2 groups. Correlations between the 2 groups were analyzed using the Spearman's rank correlation coefficient. SPSS 24.0 software (IBM corp, Chicago, IL, USA) was used to perform all statistical analyses. A p -value $<$ 0.05 was considered statistically significant.

3. Results

The characteristics of patients with RRMS and HCs are described in Table 1. Age and sex were matched between the 2 groups. Although CES-D scores were significantly higher in the RRMS group than the HC group, there were no patients with RRMS that had a score $>$ 16 points that would have indicated depression. Since the patient group showed a mild disability, a low frequency of clinical attacks, and a relatively short disease duration, patients chiefly exhibited mild and early RRMS symptoms. OSIT-J scores were significantly lower in the RRMS group (median 11, range 8–12) than the HC group (median 12, range 10–12, $p = 0.0471$) (Fig. 1). Six patients with RRMS had hyposmia, which was defined as an OSIT-J score $\leq$ 8 points, and the prevalence of hyposmia was 15%. All participants in the HC group had an OSIT-J score $\geq$ 10.

The WAIS-III results for patients with RRMS are shown in Table 2. The proportion of patients with a score below the normal value was equally high in PS and WM among the WAIS-III items. The patients with either low PS or low WM scores had a lower OSIT-J score than the

Table 1
Patients characteristics.

	RRMS	HC
Number	40	40
Sex	M: F = 8: 32	M: F = 8: 32
Age, years	38.5 (19–64)	35(24–61)
Age at onset, years	33 (13–48)	–
Duration, years	3.5 (1–24)	–
Total number of attacks	3 (2–6)	–
EDSS (median, range)	1.0 (0–3.0)	–
Smoking	n = 4 (M:F = 3:1)	n = 3
OCB positivity	n = 37 (92.5%)	–
CES-D (median, range)	10 (2–12)*	2(1–4)
Patients on DMT	n = 36 (90%)	–
IFN-βla	n = 8 (22.2%)	
IFN-βlb	n = 3 (8.3%)	
Glatiramer acetate	n = 2 (5.6%)	
Dimethyl fumarate	n = 14 (38.9%)	
Fingol imod	n = 8 (22.2%)	
Natalizumab	n = 1 (2.8%)	

Values shown are median (range). EDSS: OCB: oligoclonal band; CES-D: center for epidemiologic studies depression scale; DMT: disease modifying therapy; IFN: interferon. *$p < 0.05$.

Table 2
WAIS-III and third ventricular width of patients with RRMS.

WAIS-III	Score	Proportion of patients with the score below normal value (%)
FSIQ	87.5 (60–128)	17.9
VIQ	88 (64–123)	28.2
PIQ	91 (62–128)	23.1
PO	92.5 (55–123)	25.6
VC	88 (68–122)	25.6
WM	83 (65–115)	30.7
PS	92 (60–127)	30.7
3rd VW (mm)	3.87 (2.15–9.15)	

Values shown are median (range), 3rd VW; third ventricular width, FSIQ: full scale IQ; VIQ: verbal IQ; PIQ: performance IQ; PO: perceptive orientation; VC: verbal capacity; WM: working memory; PS: processing speed. . Normal value of WAIS-III scores are ≧ 80.

patients with a normal score (PS: median 9, range 8–11 vs median 11, range 9–12, p = 0.0078; WM: median 9, range 8–11 vs median 11, range 9–12, p = 0.0089).

When evaluating the relationship between the OSIT-J score and each item of the WAIS-III as a cognitive function test, the OSIT-J score had a relatively strong correlation with both PS and WM and a mild correlation with IQ (FIQ, VIQ, PIQ), VC, and PO (Fig. 2, Table 3). The OSIT-J score also had a mild correlation with EDSS and disease duration, but not with age or the number of clinical attacks (Table 3).

Specifically, there was a strong correlation between the OSIT-J score and the 3rd VW (Table 3, Fig. 2). Furthermore, the 3rd VW showed a significant correlation with PS, WM, EDSS, disease duration, and age of evaluation (Table 3, Fig. 3).

4. Discussion

Patients with RRMS had decreased olfactory identification abilities compared to HCs. Olfactory identification ability was especially decreased in patients with low WM or PS scores compared to patients with normal score. In addition, olfactory identification was significantly correlated with cognitive function in patients with RRMS, a finding consistent with that of a previous study (Carotenuto et al., 2019). Particularly, PS strongly correlated with olfactory identification among the cognitive function tests in the present study. Correspondingly, a previous study using the University of Pennsylvania Smell Identification Test reported that olfactory identification score was lower in the patients with RRMS and secondary progressive MS (SPMS) with cognitive impairments than those without any cognitive impairments, and was positively correlated with a variety of cognitive functions such as executive function, attention, information processing speed, spatial memory, and verbal fluency (Carotenuto et al., 2019). They showed that 28.57% of the patients with RRMS had an olfactory impairment, which is higher than the olfactory impairment prevalence in the present study (15%); moreover, they show a significant correlation between a variety of cognitive functions and olfactory identification (Carotenuto et al., 2019).

Including patients with SPMS seems to have increased the prevalence of impairments and may have also included the impairment of a wider range of cognitive functions compared to the present study, especially since SPMS has a more devastating inflammatory and degenerative change accompanied by a wider range of cognitive impairments than RRMS (Lassmann, 2019; Brochet and Ruet, 2019; DeLuca et al., 2015). On the other hand, olfactory identification was not correlated with disease duration or clinical attacks. Although a relatively short disease duration and low frequency of clinical attacks possibly affected the results, the present findings suggest that olfactory identification is affected by the imbalance of a diffuse neural network, more so than acute focal brain damage, and starts to deteriorate earlier than the apparent clinical onset. Hence, olfactory identification may be an early biomarker for the diffuse neural damage that occurs with RRMS.

Reduced PS is an important feature of cognitive impairment in MS and is known to occur frequently in patients with MS (Feinstein et al., 2013; Benedict et al., 2017; DeLuca et al., 2004). In the present study, 30.7% of the patients with RRMS had a PS score below the normal value in spite of their relatively short disease duration and mild disability (Table 1). This result is in line with recent reports demonstrating

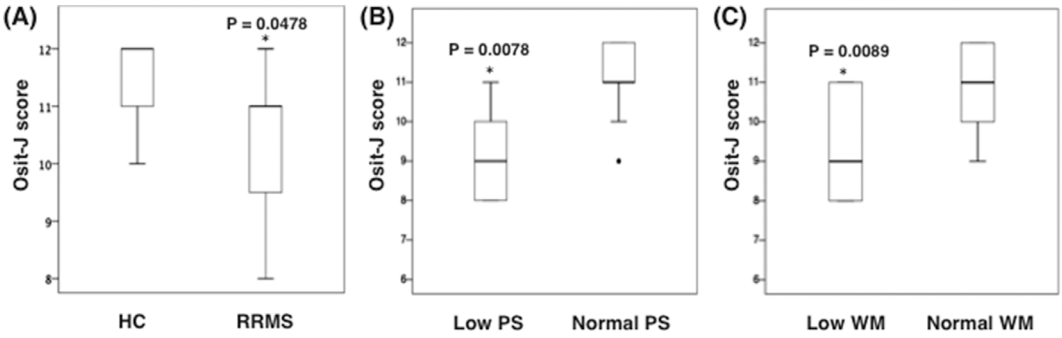

Fig. 1. Olfactory identification ability. (A) A comparison of OSIT-J scores between patients with RRMS and HCs. (B) A comparison of OSIT-J scores between patients with RRMS with a low PS and those with a normal PS. (C) A comparison of OSIT-J scores between patients with RRMS and low a WM and those with a normal WM. OSIT-J: Odor Stick Identification Test for the Japanese; RRMS: relapsing remitting multiple sclerosis; HC: healthy controls; PS: processing speed; WM: working memory.

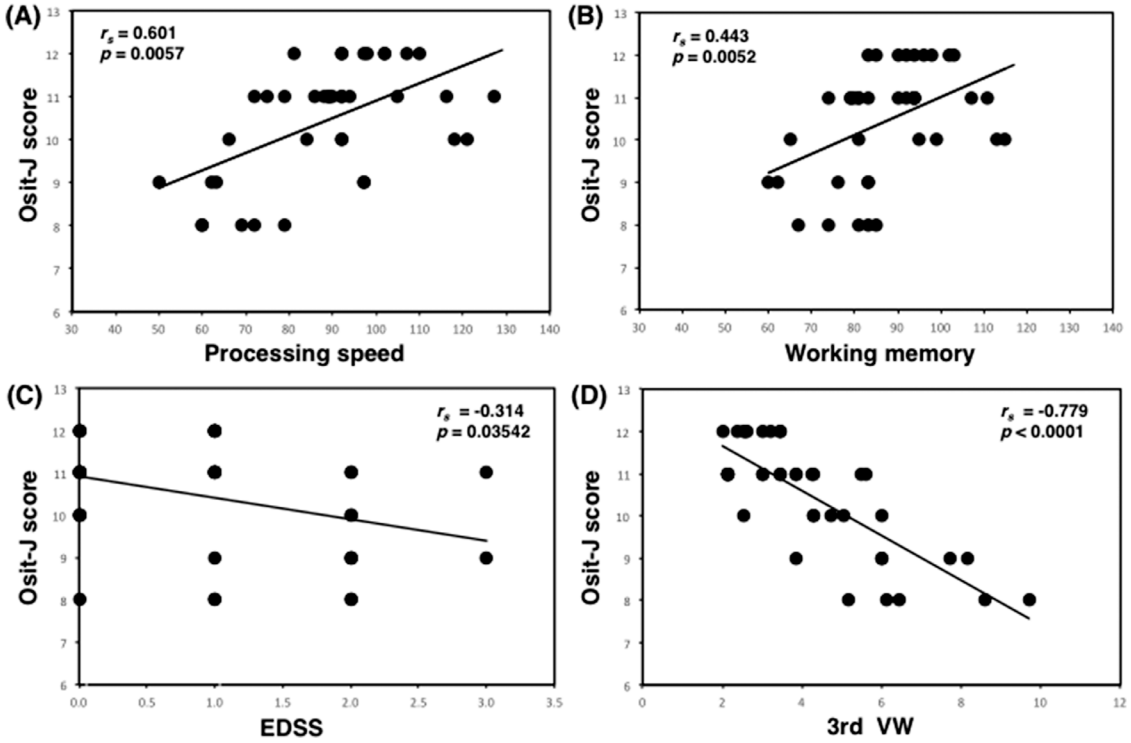

Fig. 2. Scatter plots of the correlation between olfactory identification ability (OSIT-J score) versus (A) PS, (B) WM, (C) EDSS, and (D) 3rd VW in patients with relapsing remitting multiple sclerosis. OSIT-J: Odor Stick Identification Test for the Japanese; PS: processing speed; WM: working memory; EDSS: expanded disability status scale; 3rd VW: third ventricle width. r_s: spearman's rank correlation efficient.

that PS is impaired early after RRMS onset (Van Schependom et al., 2015). Also, the relatively strong correlation between olfactory identification and PS in the present study suggests that olfactory identification and PS simultaneously develop soon after disease onset and share a common neuroanatomical background. Although neuroanatomical domains concerning PS are complicated and not yet fully elucidated, it has been suggested that a decrease in PS performance correlates with altered functional connectivity in the frontal areas and the fronto-thalamic connection in RRMS (Manca et al., 2018).

Moreover, a previous study using diffusion tensor imaging showed that patients with RRMS who performed worse in the Symbol Digit Modalities Test, which is associated with PS, had reduced fractional anisotropy in the uncinate fasciculus connecting the frontal area with the medial temporal area (Silva et al., 2019). These results indicate that the neural network distributed in the frontal and temporal areas in the brain has an important role in normal PS performance. However, olfactory identification, a higher brain function, requires an integrated interaction of both the temporal and frontal lobes including the orbitofrontal, entorhinal, and piriform cortices (Courtiol and Wilson, 2017; Fagundo et al., 2015). Furthermore, a previous study using diffusion tensor imaging reported that decreased olfactory identification correlated inversely with the fractional anisotropy value of lesions in the olfactory network, encompassing the medial temporal and inferior frontal cortices with underlying white matter, and highlights the contribution of the pathological changes in the olfactory cortices to olfactory identification impairments in patients with RRMS (Erb et al., 2012). Therefore, proper integrated network function in the frontal and temporal area of the brain is essential for the performance of both olfactory identification and PS.

The present study also demonstrated a strong correlation between the 3rd VW and olfactory identification in patients who had relatively mild disability. Third ventricle width, a simple marker of central atrophy, correlates with cognitive functions including PS, attention, and executive function; it also reflects diffuse brain atrophy, especially the volume loss of contiguous brain regions such as deep gray matter in MS (Doty et al., 1996; Benedict et al., 2006). Among the deep gray matter, thalamic volume loss also correlates significantly with cognitive impairments in MS (Papathanasiou et al., 2015; Minagar et al., 2013;

Table 3
Spearman's rank correlation coefficient.

vs OSIT-I score											
3rd VW	FIQ	VIQ	PIQ	PO	VC	WM	PS	EDSS	duration	attack	age
-0.779*	0.355**	0.335**	0.340**	0.333**	0.303**	0.443*	0.601*	-0.314**	-0.211	-0.225	-0.224
Vs 3rd VW											
FIQ	VIQ	PIQ	PO	VC	WM	PS	EDSS	duration	attack	age	
-0.262	-0.178	-0.242	-0.299	-0.150	-0.416**	-0.525**	0.403*	0.261*	0.198*	0.451**	

OSIT-J: Odor Stick Identification Test for the Japanese; EDSS: expanded disability status scale; 3rd VW; third ventricular width, FSIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; PO: perceptive orientation; VC: verbal capacity; WM: working memory; PS: processing speed. *p < 0.01, **p <0 0.05.

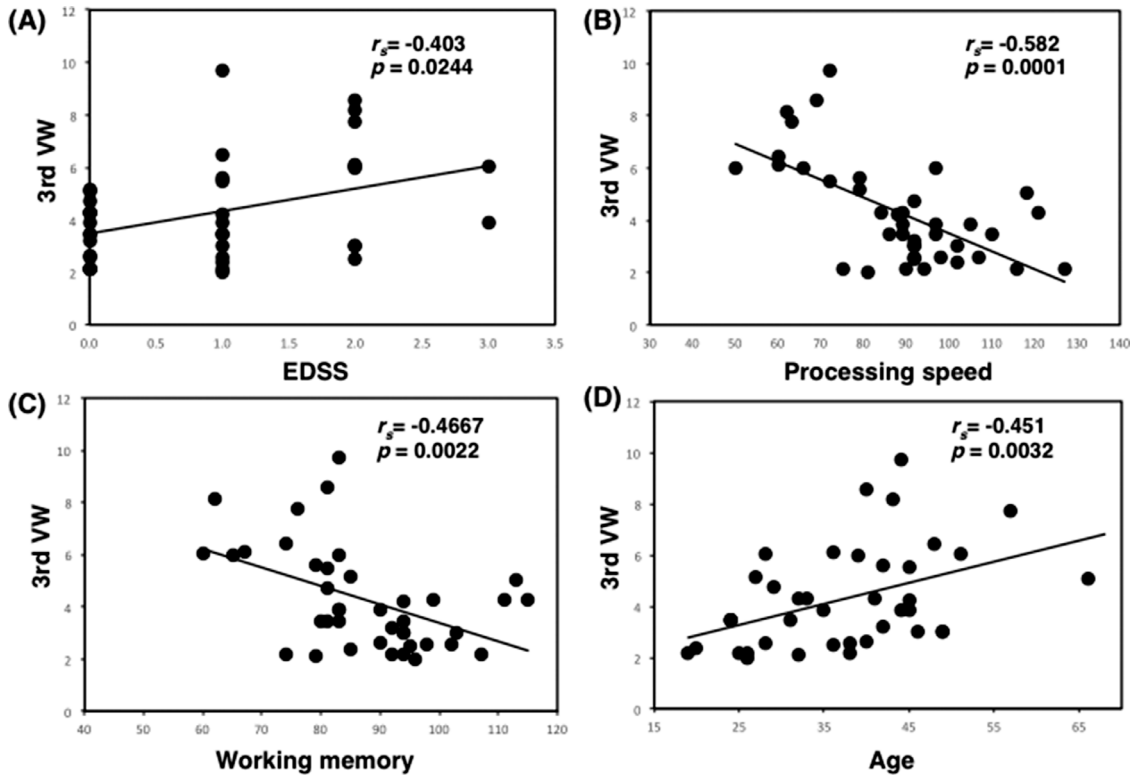

Fig. 3. Scatter plots of the correlation between the 3rd VW versus (A) EDSS, (B) PS, (C) WM, and (D) age of examination in patients with relapsing-remitting multiple sclerosis. 3rd VW: third ventricle width; PS: processing speed; WM: working memory. rs: spearman's rank correlation efficient.

Houtchens et al., 2007); in particular, the performance of PS is related to thalamic volume (Minagar et al., 2013; Bisecco et al., 2018). Previous studies have shown that thalamic volume loss occurs early in MS onset, even in clinically isolated syndromes (Azevedo et al., 2018). Some pathological and imaging studies also have uncovered the pathophysiology of thalamic atrophy, indicating that it includes inflammatory demyelination and oxidative insult in the thalamus, secondary neurodegeneration in the axonal transection of the thalamocortical tract in white matter, and inflammatory degeneration in cortical gray matter connecting the thalamus (Minagar et al., 2013; Azevedo et al., 2018). Thus, 3rd VW enlargement may reflect neurodegenerative changes in the diffuse area of the brain including the thalamus.

Recent studies have shown that olfactory identification impairment along with olfactory discrimination reflects neurodegenerative changes, but not the inflammatory phenomenon in MS; these findings are in line with the results of the present study that there was no correlation between olfactory identification ability and clinical attack frequency (Bsteh et al., 2018b, 2019a). In addition, previous studies have shown that impairments in the identification and discrimination of smell are associated with gray matter atrophy of the olfactory cortices, including the frontal and medial temporal areas in RRMS (Bsteh et al., 2019b). Therefore, olfactory identification is a possible surrogate marker of diffuse neurodegenerative changes of MS regarding cognitive impairment, especially PS.

This study has some limitations. For instance, the design of the study is cross-sectional and includes a small number of participants with varying disease durations. Longitudinal evaluation of olfactory identification along with clinical disability progression and cognitive function decrement soon after disease onset may elucidate the clinical utility of olfactory identification as a simple marker of early neurodegenerative changes in RRMS. Moreover, it is unknown whether olfactory identification and PS share a common module of a neural network from the present results. There is a possibility that a strong correlation between olfactory identification and PS may merely reflect a diffuse neurodegenerative change in MS. Using a high-quality non-conventional MRI technique to analyze the functional connectivity or perform a volumetric analysis of cortices and deep gray matter of the brain may help characterize the pathophysiology of olfactory identification impairment in MS and uncover pathological and functional relationships between olfactory identification and PS.

5. Conclusions

Impaired olfactory identification in patients with RRMS, even in an early stage, positively correlates with cognitive dysfunction and clinical disability. Notably, olfactory identification is strongly correlated with information PS and central brain atrophy in our study. These results suggest that olfactory identification is a specialized higher brain function and may share common neural modules with other higher cognitive functions, especially information PS. In addition, our results support the concept that neural damage starts considerably earlier than clinical onset and insidiously progresses in MS (Azevedo et al., 2015; Menascu et al., 2019). Consequently, olfactory identification may be a possible marker of cognitive impairment and neurodegeneration in MS.

Future studies with longitudinal observations are needed to evaluate the usefulness of an olfactory identification test as a tool to assess disease progression, reflecting neurodegeneration in MS. Also, it is important to elucidate whether olfactory identification and cognitive impairments begin early in RRMS and clinically isolated syndrome.

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Declaration of Competing Interest

The authors declare they have no competing interests.

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