



Differential Olfactory Dysfunction Indicates Inflammation and Network Degeneration in Multiple Sclerosis

Multipl Sklerozda Koku İşlev Bozukluğu Paternleri: Enflamasyon ve Nöral Ağ Dejenerasyonu ile İlişkisi

Aslı Aksoy Gündoğdu¹, Dilcan Kotan², Ayşe Öznur Akidil³, Gürkan Kayabaşoğlu⁴, Aytuğ Altundağ⁵

¹Department of Neurology, Tekirdağ Namık Kemal University, Faculty of Medicine, Tekirdağ, Türkiye

²Department of Neurology, Sakarya University, Faculty of Medicine, Sakarya, Türkiye

³Department of Otorhinolaryngology, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Türkiye

⁴Alle Clinic, İstanbul, Türkiye

⁵Department of Otorhinolaryngology, Biruni University, Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Multiple sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative disease of the central nervous system. Although olfactory dysfunction in MS has been investigated for decades, systematic assessment remains limited. This study aimed to evaluate olfactory function in people with MS (PwMS) in relation to clinical parameters and magnetic resonance imaging (MRI) plaque distribution, using the Sniffin' Sticks test.

Methods: Twenty-eight patients with MS, one participant with clinically isolated syndrome (22 women, 75.9%), and 27 healthy controls were included. Participants with primary olfactory disorders were excluded. Clinical disability was assessed using the Expanded Disability Status Scale (EDSS). Plaque locations on brain MRI scans were recorded. The Sniffin' Sticks test was performed, and threshold, discrimination, identification, and total threshold + discrimination + identification (TDI) scores were obtained for each participant.

Results: Threshold, identification, and TDI scores were significantly lower in PwMS than in controls ($p = 0.021$, 0.004 , and 0.005 , respectively). Discrimination, identification, and TDI scores were significantly correlated with age ($p = 0.001$, 0.048 , and 0.004 , respectively) and with disease duration ($p = 0.001$, 0.028 , and 0.001 , respectively). Olfactory performance was unrelated to sex, smoking, clinical classification, EDSS, or MRI plaque distribution (all $p > 0.05$). A progressive disease course did not influence olfactory measures ($p > 0.05$).

ÖZ

Amaç: Multipl skleroz (MS), merkezi sinir sisteminin enflamatuvar, demiyelinizan ve nörodejeneratif bir hastalıdır. MS'te koku işlev bozukluğu uzun yıllardır araştırılmasına rağmen koku işlevini sistematik ve çok boyutlu biçimde değerlendiren çalışmaların sayısı halen sınırlıdır. Bu çalışmada, MS'li bireylerde koku işlevinin klinik parametreler ve manyetik rezonans görüntüleme (MRG) plak dağılımı ile olan ilişkisinin Sniffin' Sticks testi kullanılarak değerlendirilmesi amaçlandı.

Yöntemler: Çalışmaya ardışık 28 MS hastası, bir klinik izole sendrom katılımcısı (22 kadın, %75,9) ve 27 sağlıklı kontrol dahil edildi. Primer koku bozukluğuna yol açabilecek herhangi bir durumu bulunan katılımcılar çalışma dışında bırakıldı. Klinik dizabilite genişletilmiş engellilik durumu ölçeği (EDSS) ile değerlendirildi. Beyin MRG incelemelerinde saptanan demiyelinizan plakların anatomik lokalizasyonları ayrıntılı olarak kaydedildi. Sniffin' Sticks testi uygulanarak her katılımcının koku eşiği, ayırt etme, tanıma ve toplam eşik + ayırt etme + tanımlama (TDI) skorları ayrı ayrı elde edildi.

Bulgular: Eşik, tanıma ve TDI skorları hasta grubunda kontrollere göre anlamlı düzeyde düşüktü (sırasıyla $p = 0,021$, $0,004$ ve $0,005$). Ayırt etme, tanıma ve TDI skorları yaş (sırasıyla $p = 0,001$, $0,048$ ve $0,004$) ve hastalık süresiyle (sırasıyla $p = 0,001$, $0,028$ ve $0,001$) anlamlı düzeyde ilişkiliydi. Koku performansı cinsiyet, sigara kullanımı, klinik sınıflandırma, EDSS veya MRG plak dağılımı ile ilişkili değildi (tüm $p > 0,05$). Progresif hastalık seyri koku ölçümlerini etkilemedi ($p > 0,05$).

Cite this article as: Aksoy Gündoğdu A, Kotan D, Akidil AÖ, Kayabaşoğlu G, Altundağ A. Differential olfactory dysfunction indicates inflammation and network degeneration in multiple sclerosis. Gazi Med J. 2026;37(4):461-466

Address for Correspondence/Yazışma Adresi: Aslı Aksoy Gündoğdu, Department of Neurology, Tekirdağ Namık Kemal University, Faculty of Medicine, Tekirdağ, Türkiye

E-mail / E-posta: aagundogdu@nku.edu.tr

ORCID ID: orcid.org/0000-0002-6898-0469

Received/Geliş Tarihi: 18.11.2025

Accepted/Kabul Tarihi: 05.09.2026

Publication Date/Yayınlanma Tarihi: 15.10.2026



Copyright 2026 The Author(s). Published by Galenos Publishing House on behalf of Gazi University Faculty of Medicine. Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

Telif Hakkı 2026 Yazar(lar). Gazi Üniversitesi Tıp Fakültesi adına Galenos Yayınevi tarafından yayımlanmaktadır. Creative Commons Atıf-GayriTicari-Türetilemez 4.0 (CC BY-NC-ND) Uluslararası Lisansı ile lisanslanmaktadır.

ABSTRACT

Conclusion: Olfactory dysfunction can be observed across MS subtypes and becomes more pronounced with increasing age and longer disease duration. Threshold impairment may reflect inflammatory activity, whereas reductions in identification and TDI scores likely indicate cumulative neurodegeneration. Multidimensional olfactory testing is simple, accessible, and low-cost. Our findings support its use as a non-invasive complementary biomarker for monitoring long-term neurodegenerative processes in MS.

Keywords: Multiple sclerosis, olfactory dysfunction, Sniffin' Sticks test, threshold, discrimination, identification

Öz

Sonuç: Koku bozukluğu MS alt tiplerinde görülebilmekte ve artan yaş ve daha uzun hastalık süresiyle belirginleşmektedir. Eşik bozukluğu enflamatuvar aktiviteyi yansıtabilirken tanıma ve TDI skorlarındaki düşüşler muhtemelen kümülatif nörodejenerasyonu göstermektedir. Çok boyutlu koku değerlendirmesi basit, erişilebilir ve düşük maliyetlidir. Bulgularımız, bu yöntemin MS'de uzun dönemli nörodejeneratif süreçlerin izlenmesinde non-invaziv tamamlayıcı bir biyobelirteç olarak kullanımını desteklemektedir.

Anahtar Sözcükler: Multipl skleroz, koku işlev bozukluğu, Sniffin' Sticks testi, eşik, ayırım, tanıma

INTRODUCTION

Olfactory function is mediated by a neural network consisting of both peripheral and central pathways. Impaired olfactory function negatively affects daily functioning and quality of life (1,2). Olfactory dysfunction is observed in several neurological diseases such as Parkinson's disease, Alzheimer's disease, Huntington disease, motor neuron disease, multiple sclerosis (MS) and migraine (3-7).

MS is a chronic, immune-mediated disease characterized by inflammation, demyelination and neuroaxonal degeneration of the central nervous system (8). Although optic nerve, brainstem, and spinal cord symptoms are well recognized, olfactory dysfunction in MS remains frequently underdiagnosed (6,9). Histopathological evidence demonstrates demyelination and axonal degeneration in the olfactory bulb and tract in approximately 70% of MS brains (10).

The prevalence of olfactory dysfunction in MS ranges from 30% to 75% and has been associated with longer disease duration, higher Expanded Disability Status Scale (EDSS) scores and greater plaque load particularly within frontal and temporal regions (6,7,11,12). Recent studies show that olfactory impairment is more pronounced in progressive MS and correlates with clinical worsening and disability progression (6,7,13).

Emerging evidence indicates that olfactory impairment reflects central network-level neurodegeneration, particularly involving orbitofrontal, limbic and associative cortices (14,15). Longitudinal magnetic resonance imaging (MRI) studies have shown that a decline in olfactory performance parallels structural degeneration in these regions and that orbitofrontal cortex atrophy is strongly linked to impaired odor identification (16).

Various olfactory assessment tools have been used in MS, including the University of Pennsylvania smell identification test, the brief smell identification test, the Connecticut Chemosensory clinical research center test, and the Sniffin' Sticks test (12,17-19). The Sniffin' Sticks test provides a three-domain evaluation (threshold, discrimination, identification) and has been validated in the Turkish population (20).

Furthermore, recent clinical work supports the Sniffin' Sticks test as a practical clinical marker in MS monitoring (13,16). This study aimed to evaluate olfactory function in MS using the Sniffin' Sticks test and to determine relationships between olfactory function and disease duration, EDSS score, and MRI plaque distribution.

MATERIALS AND METHODS**Patient Selection**

This study included 29 patients aged 18-65 years, comprising 28 patients with MS and one participant with clinically isolated syndrome (CIS), classified according to the 2017 revised McDonald criteria (21) together with 27 healthy controls. Patients were recruited from the MS outpatient clinic of the Department of Neurology, and healthy controls from the Department of Otorhinolaryngology at patients were recruited from the MS outpatient clinic of the Department of Neurology, and healthy controls from the outpatient clinic of the Department of Otorhinolaryngology at Sakarya University Training and Research Hospital. The control group consisted of individuals without neurological disease or known olfactory dysfunction. The study was approved by the Institutional Ethics Committee of Sakarya University, Faculty of Medicine (ethical approval number: E-16214662-050.01.04-28539-97, date: 21.04.2021), and written informed consent was obtained from all participants.

Exclusion criteria included subjective olfactory complaints, nasal obstruction, history of nasal surgery, nasal polyps, rhinitis, paranasal sinusitis, recent upper respiratory tract infection, head trauma, toxic exposures, smoking >20 cigarettes/day, pregnancy, hormone replacement therapy, diabetes mellitus, hypertension, major neurological or psychiatric disorders, severe cognitive impairment, Alzheimer's disease, and Parkinson's disease. Patients who had experienced an MS relapse or received corticosteroid treatment within 30 days of olfactory testing were also excluded.

Demographic and clinical data, including age, sex, smoking status, relapse history, and medication use, were recorded. Disease-related variables included disease duration and clinical classification: CIS, relapsing-remitting MS (RRMS), primary progressive MS (PPMS), or secondary progressive MS (SPMS). Neurological examinations were performed by the same neurologist. Disability level was assessed using the EDSS.

Olfactory Assessment

Olfactory function was assessed using the Sniffin' Sticks test (Burghart Medical Technology, Wedel, Germany), a validated psychophysical battery that evaluates three domains: Odor threshold, odor discrimination and odor identification. The three subscores were summed to obtain the TDI composite score.

The test was performed in a well-ventilated, odor-free room, following standardized procedures. Participants were instructed to refrain from consuming food or beverages (other than water), smoking, or using scented products for at least 1 hour before testing. Odorants were presented in felt-tip dispensers. The pen cap was removed for a few seconds, and the tip was held approximately 1-2 cm in front of both nostrils.

Odor threshold was assessed using n-butanol in a 3-alternative forced-choice staircase paradigm. For each trial, one pen contained n-butanol at ascending dilutions (1:2 dilution steps), and two pens contained only solvent. Participants identified the pen with the odorant, and the threshold score was calculated after seven reversals based on the lowest correctly recognized concentration. Odor discrimination was evaluated using 16 triplets of pens, each consisting of two pens with identical odors and one pen with a different odor. Participants were asked to identify the pen with a different odor. Odor identification was assessed using 16 common odorants, each presented with four response options. A minimum 30-second interval was maintained between odor presentations to prevent olfactory desensitization. Each subtest had a maximum score of 16 points, and the total TDI score reflected global olfactory performance (range: 0-48), with higher scores indicating better function (Table 1).

Based on established normative criteria, TDI scores <16.5 were classified as anosmia, scores of 16.5-30.5 as hyposmia, and scores >30.5 as normosmia. Threshold, discrimination, and identification scores of <10, <12, and <11, respectively, were considered abnormal (Table 2).

MRI

MRI was performed using a 1.5 T scanner. MRI abnormalities were evaluated by an experienced neurologist blinded to the olfactory test results. T2-weighted and FLAIR sequences were used to assess hyperintense demyelinating plaques, while T1-weighted sequences were used to assess hypointense lesions. Post-contrast gadolinium-enhanced T1 images were reviewed to determine the presence of active lesions. Plaque localization was recorded across the following regions: Frontal, temporal, parietal, and occipital; brainstem; cerebellum; cervical spinal cord; and periventricular and/or juxtacortical areas.

Statistical Analysis

Statistical analyses were performed using the SPSS 24.0 software package (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as frequencies and percentages, and continuous variables as means and standard deviations or medians and interquartile ranges, as appropriate. Normality of the distribution was assessed

using the Kolmogorov-Smirnov test. Group comparisons were performed using the chi-squared test for categorical variables, and the independent t-test, Mann-Whitney U test, One-Way ANOVA, or Kruskal-Wallis test for continuous variables, depending on distributional assumptions. Correlations between olfactory measures and clinical variables were examined using Pearson's correlation analysis. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The patient group comprised 28 patients with MS and one patient with CIS; the control group included 27 healthy participants. There were no significant differences between the groups regarding age, sex distribution, or smoking status (all $p > 0.05$). Demographic and clinical characteristics are presented in Table 3.

Based on the TDI score, one participant in the patient group (3.4%) was classified as anosmic, and 17 (58.6%) were classified as hyposmic. Abnormal threshold, discrimination, and identification scores were observed in 16 (55.2%), 20 (69.0%), and 17 (58.6%) participants, respectively. In the control group, 5 (18.5%) participants were classified as hyposmic based on the TDI score, while abnormal threshold, discrimination, and identification scores were observed in 4 (14.8%), 19 (70.4%), and 8 (29.6%) participants, respectively. Compared with healthy controls, the patient group showed significantly lower odor threshold, identification, and total TDI scores ($p = 0.021, 0.004, 0.005$, respectively) (Table 3).

According to clinical classification, 13 patients (44.8%) had RRMS, 1 patient (3.4%) had CIS, 1 patient (3.4%) had PPMS, and 14 patients (48.3%) had SPMS. 15 patients (51.7%) had a progressive disease course. There were no significant differences in olfactory threshold, discrimination, identification, or total TDI scores across the clinical classifications (all $p > 0.05$). The presence of a progressive disease course did not influence olfactory performance (all $p > 0.05$).

MRI showed periventricular plaques in all 29 participants in the patient group (100%), followed by juxtacortical plaques in 18 (62.1%), frontal plaques in 16 (55.2%), cervical spinal cord plaques in 16 (55.2%), temporal plaques in 12 (41.4%), brainstem plaques in 12 (41.4%), and cerebellar plaques in 5 (17.2%) (Table 4). No significant associations were found between plaque distribution in any region and olfactory scores (all $p > 0.05$).

Correlation analysis showed that, in the patient group, odor discrimination, identification, and total TDI scores were significantly correlated with age ($r = -0.600, -0.370$ and -0.514 ; $p = 0.001, 0.048$ and 0.004 , respectively) and disease duration ($r = -0.592, -0.409$ and -0.579 ; $p = 0.001, 0.028$ and 0.001 , respectively) (Table 5). No

Table 2. Sniffin' Sticks subtest cut-off values and interpretation of abnormal scores.

Subtest	Cut-off score	Interpretation of scores below cut-off
Threshold (T)	<10	Reduced odor detection sensitivity
Discrimination (D)	<12	Impaired differentiation between odor qualities
Identification (I)	<11	Impaired odor recognition

Cut-off values based on validated normative data.

Table 1. Classification of olfactory function according to Sniffin' Sticks TDI criteria.

Classification	TDI score range	Interpretation
Anosmia	<16.5	Absence of functional olfaction
Hyposmia	16.5-30.5	Reduced olfactory function
Normosmia	>30.5	Normal olfactory function

TDI: Threshold + discrimination + identification scores (range 0-48).

Table 3. Demographic, clinical characteristics and Sniffin' Sticks test scores of the MS and control groups.

	Patient group (n = 29)	Control group (n=27)	p-value
Sex: n (% female)	22 (75.9%)	15 (55.6%)	0.109
Age: years $\pm$ SD (min.-max.)	38.86 $\pm$ 11.38 (23-65)	29.7 $\pm$ 5.94 (19-63)	0.057
Smoking: n (%)	8 (27.6%)	12 (44.4%)	0.188
Disease duration: mean $\pm$ SD (years)	11.45 $\pm$ 8.29	-	-
EDSS: mean $\pm$ SD (min.-max.)	3.5 $\pm$ 2.7 (0-8)	-	-
OTS: mean $\pm$ SD	9.81 $\pm$ 3.49	11.62 $\pm$ 1.93	0.021*
ODS: mean $\pm$ SD	10.21 $\pm$ 2.44	10.7 $\pm$ 1.93	0.405
OIS: mean $\pm$ SD	9.28 $\pm$ 3.2	11.3 $\pm$ 1.51	0.004*
TDI: mean $\pm$ SD	29.21 $\pm$ 6.64	33.51 $\pm$ 3.83	0.005*

MS: Multiple sclerosis, SD: Standard deviation, EDSS: Expanded disability status scale, OTS: Odor threshold score, ODS: Odor discrimination score, OIS: Odor identification score, TDI: Threshold, discrimination, and identification.

Table 4. Distribution of demyelinating plaques by anatomical region on MRI in the patient group (n = 29).

Region	n (%)
Periventricular	29 (100%)
Juxtacortical	18 (62.1%)
Frontal	16 (55.2%)
Temporal	12 (41.4%)
Cerebellar	5 (17.2%)
Brainstem	12 (41.4%)
Cervical spinal cord	16 (55.2%)

MRI: Magnetic resonance imaging.

significant correlation was observed between EDSS scores and any olfactory measure (all $p > 0.05$).

DISCUSSION

Olfactory function is increasingly recognized as a clinically relevant neurobiological marker in MS (6,13). In this study, we demonstrated impaired global olfactory performance in the patient group compared with healthy controls, consistent with previous studies reporting olfactory dysfunction in 30% to 75% of patients with MS (6,22). In our cohort, 58.6% of patients were classified as hyposmic and 3.4% as anosmic based on TDI scores, corresponding to an overall olfactory

dysfunction frequency of 62.1%. Odor threshold, identification, and total TDI scores were significantly lower than those of the control group. Odor discrimination did not differ significantly between the patient and control groups, supporting the notion that individual olfactory subdomains may reflect distinct underlying mechanisms.

Consistent with earlier findings, we observed that odor identification, discrimination, and TDI scores were lower with increasing age and longer disease duration (7). This observation supports the hypothesis that olfactory performance reflects cumulative neurodegenerative burden rather than acute inflammatory activity. In contrast, odor threshold impairment has been associated with short-term inflammatory processes, particularly during relapsing-remitting phases (23). Other studies suggest that threshold abnormalities may show sensitivity to inflammatory activity, whereas identification and discrimination deficits more strongly reflect neurodegenerative mechanisms (23-25). Our results align with this view, as abnormal threshold scores were observed in more than half of the patients, suggesting that threshold impairment may indicate ongoing inflammatory activity.

Importantly, we found no significant relationships between olfactory test performance and clinical MS subtype, EDSS score, or MRI plaque distribution. Previous studies have reported mixed results, with some indicating correlations between olfactory dysfunction, higher EDSS scores, and progressive disease course (13,26,27), while others found no such associations (6,17,28,29). Our findings suggest that EDSS scores and plaque counts obtained by conventional MRI may not adequately reflect the functional impact of MS on the olfactory network. Standard imaging techniques often lack the sensitivity to

Table 5. Correlations between age, disease duration, EDSS scores, and olfactory test scores for the patient group.

Sniffin' Sticks test results	Age		Disease duration		EDSS	
	r	p	r	p	r	p
OTS	-0.234	0.221	-0.330	0.080	-0.058	0.766
ODS	-0.600**	0.001	-0.592**	0.001	-0.268	0.160
OIS	-0.370*	0.048	-0.409*	0.028	-0.278	0.144
TDI	-0.514**	0.004	-0.579**	0.001	-0.276	0.148

EDSS: Expanded disability status scale, OTS: Odor threshold score, ODS: Odor discrimination score, OIS: Odor identification score, TDI: Threshold, discrimination, and identification, *: Correlation is significant at the 0.05 level, **: Correlation is significant at the 0.01 level.

detect subtle microstructural and network-level changes that likely contribute to olfactory impairment.

The network-based model of olfactory dysfunction provides an integrative framework for understanding the multisystem nature of olfactory impairment in MS. Consequently, plaque burden detected on conventional MRI may not adequately represent the physiologically relevant network-level damage underlying olfactory dysfunction. Advanced imaging studies have shown significant correlations between olfactory deficits and reduced olfactory bulb volume, frontotemporal cortical thinning, and reduced connectivity across olfactory network pathways (6,7,30-33). In our cohort, plaques were predominantly located in periventricular and juxtacortical regions; however, no significant associations were found between plaque topography and olfactory scores. This finding may be attributed to the limited spatial resolution of standard MRI rather than the absence of true structural involvement.

Taken together, these findings emphasize that olfactory impairment in MS arises from distributed inflammatory and neurodegenerative processes rather than from isolated focal lesions. This highlights the importance of comprehensive olfactory assessment as a clinically feasible and non-invasive approach for detecting subtle network-level alterations that may occur before measurable functional decline.

Among the olfactory subcomponents, threshold impairment appears to reflect ongoing inflammatory activity, whereas identification and discrimination deficits may correspond to cumulative neurodegenerative burden. This pattern has been observed in several recent studies demonstrating that odor threshold fluctuates with relapse-related inflammation, while identification and discrimination scores show progressive reduction with longer disease duration and greater cortical atrophy (13,23-25,34). Evaluating these subcomponents separately, rather than relying solely on the composite TDI score, may provide deeper insights into the transition from inflammation to neurodegeneration in MS and may support the development of olfactory testing as a complementary clinical biomarker.

From a clinical perspective, olfactory assessment represents a simple, inexpensive, and non-invasive tool that can be easily incorporated into routine neurological evaluations. By assessing threshold, discrimination, and identification separately, multidimensional olfactory testing may help distinguish inflammatory activity from cumulative neurodegeneration in people with MS. Integrating olfactory evaluation with neuroimaging and cognitive assessment may enhance early detection of disease progression and identify patients at higher risk for neurodegenerative decline (13). As recent studies have underscored the value of sensory biomarkers in neuroinflammatory disorders, olfactory measures could serve as complementary indicators reflecting both functional and structural aspects of central nervous system involvement (13,25,34). Further longitudinal studies are warranted to determine whether specific olfactory parameters can reliably predict clinical or radiological disease activity, thereby refining their role as complementary biomarkers in MS monitoring.

Study Limitations

This study has several limitations. First, the relatively small sample size and cross-sectional design limit the generalizability of our

findings and preclude causal inferences. The small number of patients within individual clinical categories also reduced the statistical power of subgroup comparisons. Therefore, the absence of significant subtype-related differences should be interpreted cautiously. Second, patients experiencing acute relapses or receiving corticosteroid treatment were excluded, limiting our ability to evaluate the direct effects of acute inflammation on olfactory function. Third, only conventional MRI techniques were used, which may not have been sufficiently sensitive to detect subtle microstructural or network-level alterations associated with olfactory impairment. Future longitudinal studies using advanced neuroimaging methods in larger and more diverse MS populations are needed to confirm and extend these findings.

CONCLUSION

Olfactory dysfunction was frequent in patients with MS. Lower discrimination, identification, and total TDI scores were associated with older age and longer disease duration. Threshold impairment may be related to inflammatory processes, whereas lower identification and discrimination scores may reflect cumulative neurodegenerative changes. Comprehensive olfactory assessment is a practical, non-invasive, and inexpensive approach that may complement clinical evaluation in MS. Longitudinal studies are needed to determine whether olfactory measures can be used to monitor neurodegenerative changes or disease progression.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Sakarya University, Faculty of Medicine (ethical approval number: E-16214662-050.01.04-28539-97, date: 21.04.2021).

Informed Consent: Written informed consent was obtained from all participants.

Acknowledgments

For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support text editing and language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Concept: A.A.G., D.K., G.K., Design: A.A.G., D.K., G.K., A.Ö.A., A.A., Data Collection or Processing: A.Ö.A., G.K., A.A., Analysis or Interpretation: A.A.G., D.K., Literature Search: A.A.G., D.K., A.Ö.A., Writing: A.A.G., A.Ö.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses*. 2014; 39: 185-94.

2. Han SA, Kim JK, Cho DY, Patel ZM, Rhee CS. The olfactory system: basic anatomy and physiology for general otorhinolaryngologists. *Clin Exp Otorhinolaryngol*. 2023; 16: 308-16.
3. Efendioglu MK, Orhan EK, Sen C, Sonmez S, Orhan KS, Baykan B. Olfactory function assessment of migraine patients by using the Sniffin' Sticks test: a clinical study. *Am J Otolaryngol*. 2024; 45: 104076.
4. Patino J, Karagas NE, Chandra S, Thakur N, Stimming EF. Olfactory dysfunction in Huntington's disease. *J Huntingtons Dis*. 2021; 10: 413-22.
5. Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA. Olfactory dysfunction in aging and neurodegenerative diseases. *Ageing Res Rev*. 2021; 70: 101416.
6. Lucassen EB, Turel A, Knehans A, Huang X, Eslinger P. Olfactory dysfunction in multiple sclerosis: a scoping review of the literature. *Mult Scler Relat Disord*. 2016; 6: 1-9.
7. Bsteh G, Berek K, Hegen H, Teuchner B, Auer M, Wurth S, et al. Smelling multiple sclerosis: different qualities of olfactory function reflect either inflammatory activity or neurodegeneration. *Mult Scler*. 2020; 26: 57-68.
8. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. *Nat Rev Dis Primers*. 2018; 4: 43.
9. Good KP, Tourbier IA, Moberg PJ, Cuzzocreo JL, Geckle RJ, Yousem DM, et al. Unilateral olfactory sensitivity in multiple sclerosis. *Physiol Behav*. 2017; 168: 24-30.
10. DeLuca GC, Joseph A, George J, Yates RL, Hamard M, Hofer M, et al. Olfactory pathology in central nervous system demyelinating diseases. *Brain Pathol*. 2015; 25: 543-51.
11. Schmidt FA, Maas MB, Geran R, Schmidt C, Kunte H, Ruprecht K, et al. Olfactory dysfunction in patients with primary progressive MS. *Neurol Neuroimmunol Neuroinflamm*. 2017; 4: e369.
12. Doty RL, Li C, Mannon LJ, Yousem DM. Olfactory dysfunction in multiple sclerosis: relation to longitudinal changes in plaque numbers in central olfactory structures. *Neurology*. 1999; 53: 880-2.
13. Printza A, Boziki M, Valsamidis C, Bakirtzis C, Constantinidis J, Grigoriadis N, et al. Smell as a disease marker in multiple sclerosis. *J Clin Med*. 2022; 11: 5215.
14. Kulason S, Ratnanather JT, Miller MI, Kamath V, Hua J, Yang K, et al. A comparative neuroimaging perspective of olfaction and higher-order olfactory processing: on health and disease. *Semin Cell Dev Biol*. 2022; 129: 22-30.
15. Almasi M, Sahraian MA, Akhouni FH, Ezzati HR, Rohani M. The factors associated with olfactory dysfunction in patients with multiple sclerosis. *Basic Clin Neurosci*. 2021; 12: 89-94.
16. Uecker FC, Olze H, Kunte H, Gerz C, Göktas O, Harms L, et al. Longitudinal testing of olfactory and gustatory function in patients with multiple sclerosis. *PLoS One*. 2017; 12: e0170492.
17. Batur Caglayan HZ, Irkeç C, Nazliel B, Akyol Gurses A, Capraz I. Olfactory functioning in early multiple sclerosis: Sniffin' Sticks test study. *Neuropsychiatr Dis Treat*. 2016; 12: 2143-7.
18. Kandemir S, Muluk NB, Melikoglu B, Dag E, Inal M, Sarin O. Smell functions in patients with multiple sclerosis: a prospective case-control study. *B-ENT*. 2016; 12: 323-31.
19. Atalar AC, Erdal Y, Tekin B, Yildiz M, Akdogan O, Emre U. Olfactory dysfunction in multiple sclerosis: relation with magnetic resonance imaging findings and disease parameters. *Mult Scler Relat Disord*. 2018; 21: 92-6.
20. Öñiz A, Erdoğan İ, İkiz AÖ, Evirgen N, Özgören M. The modified Sniffin' Sticks test in Turkish population based on odor familiarity survey. *J Neurol Sci Turk*. 2013; 30: 270-80.
21. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018; 17: 162-73.
22. Joseph A, DeLuca GC. Back on the scent: the olfactory system in CNS demyelinating diseases. *J Neurol Neurosurg Psychiatry*. 2016; 87: 1146-54.
23. Lutterotti A, Vedovello M, Reindl M, Ehling R, Di Pauli F, Kuenz B, et al. Olfactory threshold is impaired in early, active multiple sclerosis. *Mult Scler*. 2011; 17: 964-9.
24. Carotenuto A, Costabile T, Moccia M, Falco F, Scala MR, Russo CV, et al. Olfactory function and cognition in relapsing-remitting and secondary-progressive multiple sclerosis. *Mult Scler Relat Disord*. 2019; 27: 1-6.
25. Bsteh G, Hegen H, Ladstätter F, Berek K, Amprosi M, Wurth S, et al. Change of olfactory function as a marker of inflammatory activity and disability progression in MS. *Mult Scler*. 2019; 25: 267-74.
26. Mirmosayyeb O, Ebrahimi N, Barzegar M, Afshari-Safavi A, Bagherieh S, Shayannejad V. Olfactory dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis. *PLoS One*. 2022; 17: e0266492.
27. Zorzon M, Ukmar M, Bragadin LM, Zanier F, Antonello RM, Cazzato G, et al. Olfactory dysfunction and extent of white matter abnormalities in multiple sclerosis: a clinical and MR study. *Mult Scler*. 2000; 6: 386-90.
28. Jordy SS, Starzewski Junior A, Macedo FAB, Manica GR, Tilbery CP, Carabetta EG. Olfactory alterations in patients with multiple sclerosis. *Arq Neuropsiquiatr*. 2016; 74: 697-700.
29. Todd LL, Sivakumar R, Lynch SG, Diebolt JH, White J, Villwock JA. Longitudinal olfactory patterns in multiple sclerosis: a scoping review and implication for use in management of disease. *Int J MS Care*. 2023; 25: 131-6.
30. Goektas O, Schmidt F, Bohner G, Erb K, Lüdemann L, Dahlslett B, et al. Olfactory bulb volume and olfactory function in patients with multiple sclerosis. *Rhinology*. 2011; 49: 221-6.
31. Holinski F, Schmidt F, Dahlslett SB, Harms L, Bohner G, Olze H. MRI study: objective olfactory function and CNS pathologies in patients with multiple sclerosis. *Eur Neurol*. 2014; 72: 157-62.
32. Yaldizli Ö, Penner IK, Yonekawa T, Naegelin Y, Kuhle J, Pardini M, et al. The association between olfactory bulb volume, cognitive dysfunction, physical disability and depression in multiple sclerosis. *Eur J Neurol*. 2016; 23: 510-9.
33. Ciurleo R, De Salvo S, Caminiti F, Militi A, Bonanno L. Olfactory evoked potentials and brain MRI outcomes in multiple sclerosis patients: a cross-sectional study. *J Clin Med*. 2025; 14: 141.
34. Doty RL. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? *Lancet Neurol*. 2017; 16: 478-88.