Olfactory dysfunction in patients with primary progressive MS

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ABSTRACT

Objective: We tested the hypothesis that olfactory function is more impaired in patients with primary progressive MS (PPMS) than that in relapsing-remitting MS (RRMS).

Methods: Standardized olfactory testing was performed in 32 patients with PPMS, 32 patients with RRMS, and 32 healthy controls (HCs). Patients with olfactory dysfunction due to an alternative primary etiology were excluded. The validated olfactory testing method yielded individual scores for olfactory threshold, odor discrimination, and odor identification, along with a composite Threshold Discrimination Identification (TDI) score.

Results: Olfactory dysfunction was identified in 27 (84%) patients with PPMS, 10 (31%) patients with RRMS, and 1 (3%) HC. While age and sex were similar between PPMS and HCs, the TDI score and all olfactory subscores were significantly worse in patients with PPMS compared with HCs (all $p < 0.001$). After adjustment for differences in age, sex, Expanded Disability Status Scale (EDSS), and disease duration, odor discrimination, odor identification, and the composite TDI score were worse in patients with PPMS vs RRMS ($p = 0.03$, 0.04, and 0.02, respectively). Neither age, sex, EDSS, nor disease duration was significantly associated with the composite TDI score.

Conclusions: Olfactory dysfunction was more frequent and severe in PPMS compared with RRMS, independent of disease duration and overall disability status. Further research on cellular level differences in olfactory neural pathways may lead to new insights about disease pathogenesis in MS.

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GLOSSARY

EDSS = Expanded Disability Status Scale; **HC** = healthy control; **PPMS** = primary progressive MS; **RRMS** = relapsing-remitting MS; **TDI** = Threshold Discrimination Identification.

MS is a chronic inflammatory demyelinating disease of the CNS, which typically follows a relapsing-remitting disease course (relapsing-remitting MS [RRMS]). However, approximately 15% of all patients with MS initially present with a primary progressive disease course (primary progressive MS [PPMS]) characterized by steadily increasing neurologic disability without recovery.[1] Some evidence suggests that—albeit part of the same underlying pathobiology—PPMS presents a less inflammatory course of MS.[2]

Different studies have reported olfactory dysfunction in patients with MS at rates of 20%–40% in cohorts comprised mostly of RRMS.[3] The underlying pathophysiologic distinctives leading to PPMS vs RRMS are not well understood. Differences in the pattern of disease symptomatology may identify opportunities to better understand disease pathophysiology. Exploring for differences in olfactory dysfunction between PPMS and RRMS has been

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identified by other experts as a gap in the literature and potential area for future research.[3] As such, we sought to test the hypothesis that olfactory sense impairment is present in patients with PPMS, and that olfactory dysfunction is more severe in PPMS than in RRMS.

METHODS **Subjects.** Standardized olfactory function testing was performed in patients diagnosed with PPMS and RRMS according to the 2010 McDonald criteria[4] and in age-matched healthy controls (HCs). Predefined exclusion criteria were as follows: age younger than 18 or older than 70 years, pregnancy, olfactory disorders with a known different etiology (posttraumatic, postinfectious, sinonasal, infections of the upper respiratory tract, allergies, tumors treated with chemotherapy or radiation, depression, and Parkinson or Alzheimer disease), and patients taking medications that could cause olfactory dysfunction (e.g., amitriptyline, methotrexate, and doxycycline), including patients who had received corticosteroid treatment within the last 3 months since corticosteroids can also affect the olfactory function.[5] We used the Expanded Disability Status Scale (EDSS) to measure physical disability.

Olfactory testing. The Threshold Discrimination Identification (TDI) Test was used for orthonasal olfactory testing.[6] The olfactory threshold (T) was measured using 48 Sniffin' Sticks with a 16-stage dilution series of n-butanol. The discrimination test (D) was performed with 48 Sniffin' Sticks of different smell qualities to test the distinction of smells. Everyday odors were identified with the identification test, which consisted of 16 Sniffin' Sticks. A TDI value of less than 16 points was defined as anosmia, up to 31 points as hyposmia, and a value above 31 points as normosmia.[6]

Data analysis. Olfactory function measures in patients with PPMS were compared with HCs and patients with RRMS using the Fisher exact test for categorical variables and the Student *t* test for continuous variables after confirming normality. There were no differences in age or sex between the PPMS and HC cohorts, although differences were identified between the PPMS and RRMS cohorts. To isolate the effect of PPMS vs RRMS pathology, we created linear regression models for each olfactory measure that included terms for MS subtype (PPMS vs RRMS), age, sex, EDSS, and disease duration. Statistical analyses were performed using SPSS 23.0 (IBM SPSS Statistics, Armonk, NY).

The study was approved by the medical ethics committee of Charité–Universitätsmedizin Berlin and was conducted in accordance with the Declaration of Helsinki and its currently applicable version and applicable German laws. All participants provided written informed consent to participate in the study.

RESULTS We studied 96 subjects, 32 with PPMS, 32 with RRMS, and 32 HCs. The demographics and clinical characteristics of study participants are shown in table 1. In the PPMS cohort, 26 (81%) were hyposmic and 4 (13%) anosmic, whereas 13 (41%) patients with RRMS were hyposmic and none were anosmic. Olfactory test results of the 3 cohorts and univariate differences in those characteristics are summarized in table 1 and presented in the figure. Of 16 possible points, the observed range of olfactory function scores was 0–12 for odor threshold, 5–16 for odor discrimination, and 1–16 for odor identification.

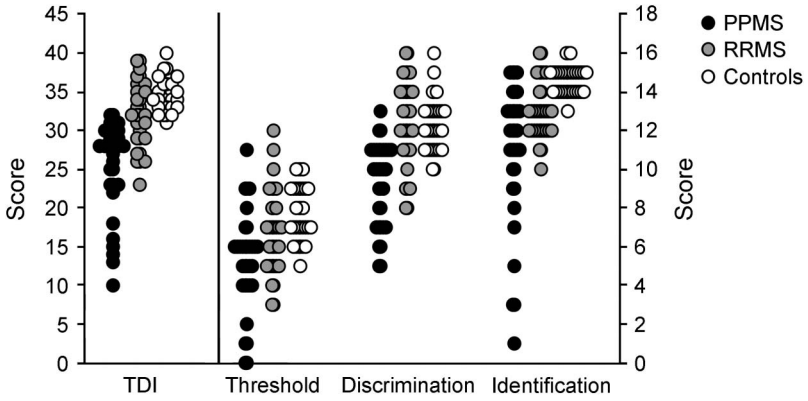
There were no significant differences in age or sex between the PPMS and HC groups. Patients with PPMS were found to have diminished odor threshold, odor discrimination, and odor identification, resulting in a lower composite olfactory function score compared with HCs. Univariate analysis also showed

Table 1 Patient characteristics

Diagnosis	PPMS	RRMS	Controls	*p* Value (PPMS vs RRMS)	*p* Value (PPMS vs controls)	*p* Value (RRMS vs controls)
No. of cases	32	32	32			
Age, y	53.4 ± 9.3	35.5 ± 9.3	51.9 ± 17.6	<0.001	0.68	<0.001
Sex (female)	13 (40.6)	22 (68.8)	17 (53.1)	0.044	0.45	0.31
Odor threshold	5.3 ± 2.6	6.8 ± 2.2	7.8 ± 1.4	0.016	<0.001	0.034
Odor discrimination	9.3 ± 2.2	12.4 ± 2.3	12.3 ± 1.4	<0.001	<0.001	0.84
Odor identification	10.9 ± 3.7	13.0 ± 1.5	14.6 ± 0.7	0.004	<0.001	<0.001
Composite (TDI)	25.4 ± 6.1	32.2 ± 4.2	34.8 ± 2.1	<0.001	<0.001	
Qualitative olfactory status						
Normal	2 (6)	19 (59)	31 (97)	<0.001	<0.001	<0.001
Hyposmic	26 (81)	13 (41)	1 (3)			
Anosmic	4 (13)	0 (0)	0 (0)			
EDSS	4.9 ± 2.1	2.6 ± 1.8	NA	<0.001	NA	NA
Disease duration, y	11.3 ± 8.4	5.6 ± 5.9	NA	0.002	NA	NA

Abbreviations: EDSS = Expanded Disability Status Scale; NA = not applicable; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; TDI = Threshold Discrimination Identification.
All values are presented in mean ± SD or n (%) unless otherwise specified.

Figure **Olfactory function test results: differences of Threshold Discrimination Identification composite score and all individual olfactory subscores between 3 cohorts**



Results are displayed with mean and SDs. Controls = healthy controls; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; TDI = Threshold Discrimination Identification.

that patients with PPMS had lower odor threshold, discrimination, identification, and composite TDI score compared with patients with RRMS, although patients with PPMS also had worse EDSS and longer disease duration as well as differences in age and sex. Multivariate models that adjusted for age, sex, EDSS, and disease duration found that PPMS diagnosis was still associated with worse odor discrimination, identification, and composite TDI score compared with RRMS after adjustment for covariates, although no difference in odor threshold. There were no associations between any other patient characteristics and olfactory function measures except that higher EDSS was associated with diminished odor discrimination (table 2).

DISCUSSION This study shows that patients with PPMS have significantly decreased olfactory function compared with HCs. Moreover, in comparison with a cohort of patients with RRMS, PPMS diagnosis was an independent predictor of worse olfactory function after adjustment for important covariates, whereas a standardized measure of disease disability (EDSS) and disease duration did not emerge as significant contributor to olfactory function.

Previous studies investigating olfactory function in patients with MS primarily included patients with RRMS. A decreased odor threshold was found in patients with clinically isolated syndrome and early disease stages of RRMS, whereas odor discrimination and odor identification were more often affected in later disease stages.[3] A single study has reported olfactory assessments in patients with PPMS by testing odor identification alone and found mild impairment (13% affected).[7] We have now demonstrated a significantly worse olfactory function in PPMS as compared to RRMS and further provide a model that adjusts for the significant baseline differences in disease duration and EDSS to show that the differences are not merely reflective of general disease burden but seem to be particular to disease subtype.[7] It is important that we also found a much higher rate of olfactory impairment than in the prior cited study, suggesting that our testing method may be more sensitive.

The reasons for olfactory dysfunction in patients with MS are not well understood.[3] A human autopsy cohort reported demyelination in parts of the olfactory pathway in 71% of pathologically confirmed MS cases.[8] Decreased olfactory bulb volume is correlated with increased MS lesion load in the olfactory brain, both of which are linked to impaired olfactory function.[3,9] Olfactory dysfunction is sometimes recognized in the context of acute relapses as well, implicating inflammatory damage.[10] Observed differences between PPMS and RRMS, independent of other disease severity measures, suggest that PPMS may uniquely affect the olfactory brain tissue more than RRMS.

Although the olfactory testing techniques used here were robust, we did not use MRI to measure the lesion load and atrophy of the olfactory pathway

Table 2 **Linear regression models for olfactory function measures**

Olfactory measure	Threshold	Discrimination	Identification	Composite (TDI)
PPMS diagnosis (vs RRMS)	−0.86 (−2.71 to 0.99), $p = 0.36$	−1.87 (−3.54 to −0.20), $p = 0.03$[a]	−2.32 (−4.55 to −0.10), $p = 0.04$[a]	−5.00 (−9.05 to −0.95), $p = 0.02$[a]
Age, y	−0.04 (−0.11 to 0.04), $p = 0.31$	−0.04 (−0.10 to 0.03), $p = 0.28$	0.02 (−0.07 to 0.11), $p = 0.61$	−0.06 (−0.22 to 0.11), $p = 0.49$
Female sex	−0.41 (−1.76 to 0.94), $p = 0.54$	0.25 (−0.97 to 1.47), $p = 0.68$	−0.06 (−1.68 to 1.56), $p = 0.94$	−0.19 (−3.14 to 2.77), $p = 0.90$
EDSS	−0.19 (−0.54 to 0.16), $p = 0.28$	−0.35 (−0.67 to −0.03), $p = 0.03$[a]	−0.1 (−0.52 to 0.33), $p = 0.66$	−0.64 (−1.42 to 0.14), $p = 0.10$
Disease duration, y	0.07 (−0.03 to 0.17), $p = 0.16$	0.04 (−0.04 to 0.13), $p = 0.32$	0.00 (−0.12 to 0.11), $p = 0.94$	0.11 (−0.10 to 0.33), $p = 0.30$

Abbreviations: EDSS = Expanded Disability Status Scale; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; TDI = Threshold Discrimination Identification.
[a] Significant.

and compare it with other regions of the brain, which may have helped clarify the etiology of the differences we observed between the PPMS and RRMS groups. At this time, techniques to accurately measure lesion burden in the small structures comprising the olfactory system are not well established or anatomically-pathologically validated. Finally, although we constructed a multivariate model to control for important disease covariates such as age and overall disability, the size of our cohort is relatively small, and we cannot exclude the possibility that the relationship between the MS subgroup and olfactory dysfunction is mediated or confounded by a variable we did not measure, or incompletely adjusted for age, sex, EDSS, and disease duration.

We conclude that olfactory dysfunction is a frequent symptom in patients with PPMS, leading to severe olfactory impairment, and is uniquely more severe in PPMS compared with RRMS. The findings suggest that olfactory dysfunction might be a surrogate of neurodegeneration in these patients. Studies correlating olfactory function with radiologic and clinical markers of disease progression would be of interest.

AUTHOR CONTRIBUTIONS

Felix Schmidt: study concept and design, acquisition of data, draft of the manuscript and figures, and study supervision. Matthew Maas: analysis and interpretation of data and critical revision of manuscript for intellectual content. Rohat Geran and Charlotte Schmidt: acquisition of data and critical revision of manuscript for intellectual content. Hagen Kunte, Klemens Ruprecht, Friedemann Paul, and Önder Göktas: critical revision of manuscript for intellectual content. Lutz Harms: study concept and design and critical revision of manuscript for intellectual content.

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