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Smell functions in patients with multiple sclerosis: a prospective case-control study

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Abstract. *Smell functions in patients with multiple sclerosis: a prospective case-control study. Objectives:* The aim of this study is to evaluate the smell function in patients with multiple sclerosis (MS).
Methods: Twenty subjects (six males, 14 females) who were diagnosed as having MS, based on the 2010 Revised McDonald criteria, and 20 healthy individuals (six males, 14 females) were included in this study. In order to measure smell identification abilities, each subject completed the 12-item Brief Smell Identification Test (BSIT). Central and peripheral regions of smell were measured using cranial magnetic resonance (MR) images. The central regions of smell (the temporal lobe insular gyrus and the corpus amygdala) and the peripheral regions of smell (the olfactory bulb, tract and sulcus) were examined in the cranial MR images. Regions of smell were also evaluated for the presence of MS lesions (plaques).
Results: The total BSIT scores of the subjects in the MS group were found to be significantly lower than those of the control group ($p<0.05$). In the MS group, measurement values of the central regions of smell (right corpus amygdala diameter, right and left corpus amygdala) were significantly higher than those of the control group ($p<0.05$). There were no MS lesions in the peripheral regions of smell, but MS lesions were observed in the central regions: the right temporal lobe insular gyrus (four patients, 20.0%); the left temporal lobe insular gyrus (two patients, 10.0%); and the right corpus amygdala (one patient, 5.0%). While these results are not sufficient for statistical analysis, the total smell scores of these patients were found to be low.
Conclusion: There is a deterioration in the smell functions of patients with MS. Therefore, we highly recommend that ENT specialists use the easily accessible and reliable BSIT for the diagnosis of smell disorders.

Introduction

Multiple sclerosis (MS)[1] is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) characterized by the destruction of myelin sheaths and axonal loss.[2] Its diagnosis is made on the basis of neurological examinations, magnetic resonance imaging (MRI) of the CNS and the presence of oligoclonal bands or an elevated IgG index[3] in the cerebrospinal fluid (CSF), according to the McDonald criteria.[4] Olfactory disturbances are one of the most common early manifestations of certain CNS neurodegenerative diseases, such as Parkinson's disease.[5] A diminished sense of smell has also been reported in patients diagnosed with MS.[6-8]

One recently developed commercial test of olfactory function, the Brief Smell Identification Test (BSIT), comprising 12 items, is derived from the University of Pennsylvania Smell Identification Test (UPSIT, containing a total of 40 items) and was developed as a rapid and effective cross-cultural screening test to detect olfactory deficits.[9,10]

In the present study, we performed a prospective controlled clinical trial to determine the olfactory perception abilities of MS patients using the BSIT, compared the results with healthy controls and analysed correlations between cranial MR in terms of measurement values of the central and peripheral smell regions.

Materials and methods

This prospective study was carried out in the Ear, Nose and Throat (ENT), Neurology and Radiodiagnostics Departments of the Kırıkkale

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University Faculty of Medicine. The BSITs were assessed in the ENT Department. All the data in this study were derived from the expertise thesis of the first author (S.K.).[11]

Subjects

The study group included 20 patients (six males, 14 females; mean age: 34.2±7.1 years) with MS, diagnosed according to the 2010 Revised McDonald criteria.[4] The study group consisted of patients diagnosed with MS between four months and 12 years ago. In the study group, nine patients (45%) were determined to be in relapse, and 11 patients (55%) were determined to be in remission. The treatment usage conditions of the MS group were determined to be 10 patients (50%) using the drug Interferon beta-1a, seven patients (35%) using the drug Interferon beta-1b, and three patients (15%) not using any drugs.

Twenty healthy volunteers without MS (six males, 14 females; mean age: 34.2±9.5 years) were recruited into the study to serve as controls. Individuals in the control group were referred to the Neurology Department with nonspecific complaints; no pathologies were detected by physical examination and MRI results.

The inclusion criteria for the study and control groups were as follows:

(1) Between the ages of 18 and 80.

(2) No smell disorder that affects function other than MS.

(3) Absence of severe septum deviation.

(4) No detection of nasal polyposis during endoscopic examination.

(5) No detection of acute or chronic infections (acute or chronic rhinosinusitis) during nasal examination.

(6) No other organic or psychiatric diseases (Alzheimer's disease, epilepsy, Parkinson's disease).

The exclusion criteria for the study and control groups were as follows:

(1) MS patients with a duration of diagnosis shorter than four months.

(2) Women of childbearing potential using birth control.

(3) Pregnant women.

(4) Lactating women.

All subjects in the study and control groups provided their written and signed informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of the Research Hospital (Kırıkkale University Faculty of Medicine Ethics Committee, number: 08/01, date: 01.04.2013). The study was conducted in accordance with the basic principles of the Declaration of Helsinki and was funded by Kırıkkale University Scientific Research Projects Coordination Unit (No:2013/52, Date: 2013).

Methods

ENT and neurology examinations were performed on all subjects in the study and control groups. Initially, ENT and endoscopic examinations – including nasal endoscopic examination for the olfactory region, neurological examination and BSIT – were applied to all patients. Later, MR images, to be used for the routine follow-up of the patients with MS (taken in the last two years), were examined retrospectively. The Brinkman index (the number of cigarettes smoked per day times the number of years smoking) was also calculated for each patient.[12]

Evaluation of olfactory function

The ability to identify odours was tested using the BSIT (Sensonics Inc., Haddon Heights, NJ, USA), which is a self-administered 'scratch and sniff' test that incorporates 12 different items (Table 1).[9] The BSIT is a brief, easily administered

Table 1

Multiple choices for the 12-item BSIT test[9]*

1	Fruit, ***cinnamon***, wood, coconut
2	***Turpentine***, soap, dog, black pepper
3	Motor oil, garlic, rose, ***lemon***
4	Apple, grass, ***smoke,*** grape
5	lemon, ***chocolate,*** strawberry, black pepper
6	Mint, ***rose,*** lime, fruit
7	Watermelon, peanut, rose***, paint thinner***
8	***Banana,*** garlic, cherry, motor oil
9	Smoke, whisky, ***pineapple***, onion
10	Rose, lemon, apple, ***gasoline***
11	***Soap***, black pepper, chocolate, peanut
12	Chocolate, banana, ***onion,*** fruit

*Correct answers are indicated in italics and bold

Figure 1

A: Axial T1-weighted examination shows area measurements of bilateral amygdala in images in which they were monitored as maximum.
B: In coronal T2-weighted images, both olfactory bulb areas (inferior) and both olfactory sulcus areas (superior) are measured at the maximum section.

and convenient instrument derived from the 40-item UPSIT.[13] It is composed of 12 odorants embedded on microencapsulated scent strips from which an odour is released when scratched with a pencil tip. Examinees were asked to identify each item from a forced-choice list of four alternatives. The test scores ranged from zero to 12 and corresponded to the total number of correct choices.

Image evaluation

Conventional MRI examinations

Cranial MR images were acquired using a 1.5-Tesla Philips scanner (Philips Medical Solutions, Netherlands) and were evaluated by a single doctor (M.I.). Fluid-attenuated inversion recovery (FLAIR) images in the axial plane (TR msn/TE msn; 6000/120, field of view [FOV] 230 x 183 mm and matrix 256 x 173 mm); axial T1-weighted images (TR msn/TE msn; 596/15, FOV 230 x 183 mm and matrix 256 x 205 mm); axial T2-weighted images (TR msn/TE msn; 2200/120, FOV 230 x 185 mm and matrix 288 x 223 mm); sagittal T1-weighted images (TR msn/TE msn; 614/14, FOV 240 x 216 mm and matrix 240 x 192 mm); and fat-suppressed T2-weighted images in the coronal plane (TR msn/TE msn; 9012/70, FOV 220 x 175 mm and matrix 256 x 179 mm) were obtained using a 5 mm slice thickness and 1 mm intersection gap, such that 18-22 slices were obtained.

Diffusion-weighted images

An echo planar imaging (EPI) sequence (Philips Medical Systems) was used to obtain diffusion-weighted images. The parameters were as follows: 25 slices were obtained in the axial plane (TR msn/TE msn; 3469/92, deflection angle 90°, FOV 230 x 230 mm, matrix 112 x 89 mm, 5 mm slice thickness, 1 mm intersection gap). Initially, T2-weighted images were obtained without the application of a diffusion gradient (b = 0 mm^2/sn, later using the value of b = 1000 mm^2/sn), subsequently, diffusion-sensitive gradients were applied in three directions (x, y, z). Trace images were obtained with an average of three gradients, and apparent diffusion coefficient (ADC) mapping was reconstructed from these images.

Measurements in the MR images

The central regions of smell (the temporal lobe insular gyrus and the corpus amygdala) and the peripheral regions of smell (the olfactory bulb, tract and sulcus) were examined in the cranial MR images. Regions of smell were evaluated for the presence of MS lesions (plaques). The location, distribution and measurement of these MS lesions were noted.

The dimension and area of both the corpus amygdala and the olfactory bulb were measured in the sections in which they were observed as maximum (Figures 1A, 1B).[14,15] The dimension and area measurements of the insular lobes were performed on images in which the head of the caudate nucleus and the putamen were seen. The insular lobe was observed as maximum (Figure 2A). MS plaques were also evaluated, especially T2-weighted FLAIR sequences (Figure 2B).[14,15]

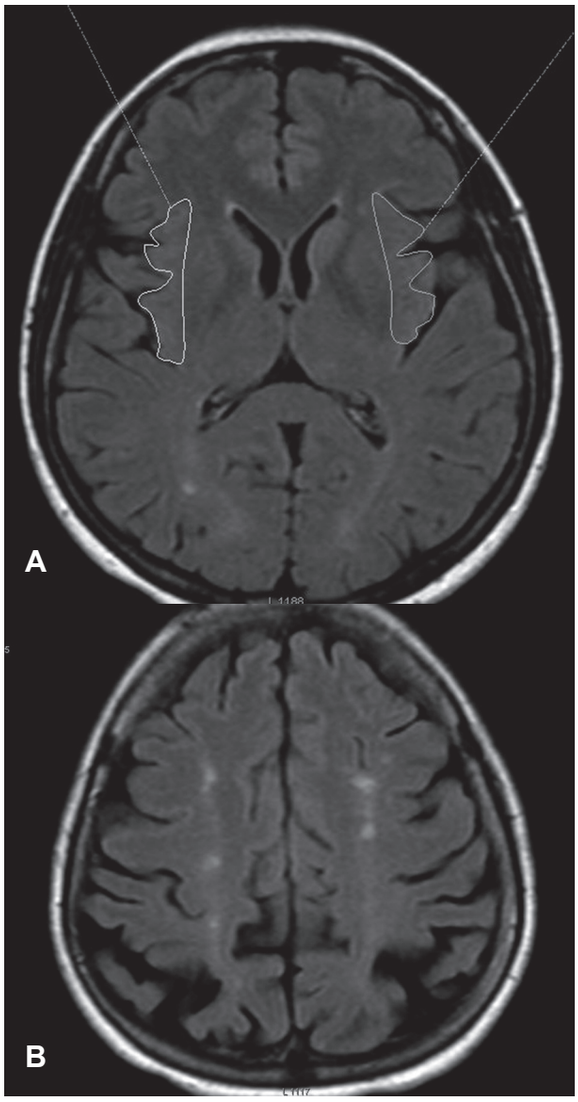

Figure 2

A:In axial T2-FLAIR sequences, bilateral insular lobe area measurements are performed in the sections in which the head of the caudate nucleus and the putamen are seen, and the insular lobe is observed as maximum.
B: In axial T2-FLAIR sequences, MS plaques are evaluated at the level of the centrum semiovale.

Statistical analysis

The statistical packet for SPSS (Version 20.0) was used for statistical evaluation. For the statistical analysis, the values were expressed as mean ± standard deviation (SD) whenever appropriate. Mann–Whitney U tests were used to compare the groups. Categorical variables were compared with chi-squared tests. Spearman's correlation rho efficient test was used for correlation tests.

A value of $p<0.05$ was considered to be statistically significant.

Results

MS and control groups did not significantly differ in terms of gender, age, education or smoking habits (Brinkman index) ($p>0.05$).

BSIT results

Participants identified three items with good identification scores (chocolate, soap and onions). All of the participants in both groups identified these odours. In the MS group, the least recognized smell (35.0%) was 'lemon', while, in the control group, the least recognized smell (45.0%) was 'roses'.

Total BSIT scores are presented in Table 2. The mean BSIT score of all participants (study and control group) was 9.5. The total smell scores of the patients in the MS group (mean: 8.95, median: 9.00) were significantly lower than those of the individuals in the control group (mean: 10.05, median: 10.00) ($p<0.05$). There was no significant difference between the total smell scores of the MS group patients in relapse (mean: 9.33, median: 9) and those in remission (mean: 8.64, median: 8) ($p>0.05$) (Table 2). There was no significant difference between the total smell scores of the patients in the MS group using Interferon beta-1a (mean: 8.90, median: 8.5) and Interferon beta-1b (mean: 8.86, median: 9) ($p>0.05$) (Table 2).

Spearman's correlation rho efficient test showed no significant relationship between total smell scores and age, gender or Brinkman index values ($p>0.05$). Furthermore, there was no statistically significant correlation between total smell scores and disease duration, remission or relapse condition, or the drugs used by the study group ($p>0.05$).

Measurement results of the central and peripheral smell regions

All the central and peripheral regions of smell measurement values are presented in Table 3. In the MS group, the measurement values of the central regions of smell (right corpus amygdala diameter, right and left corpus amygdala area) were significantly higher than those of the control group ($p<0.05$).

In the MS group, there was no statistically significant correlation between central and peripheral regions of smell measurement values and total smell scores ($p>0.05$) (Table 4).

In the control group, as total smell scores increased, one of the items of the central region of smell (the right temporal lobe insular gyrus diameter value) decreased ($p<0.05$) (Table 4). Similarly, as total smell scores increased, one of the items of the peripheral region of smell (the right olfactory bulb diameter value) decreased ($p<0.05$) (Table 4).

In all individuals of both groups, as total smell scores increased, the central regions of smell measurement values (right temporal lobe insular gyrus diameter and area) decreased (Table 4).

MS lesions (plaques)

There were no MS lesions in the peripheral regions of smell, but MS lesions were observed in the central regions of smell – right temporal lobe insular gyrus (four patients, 20.0%); left temporal lobe insular gyrus (two patients, 10.0%); and right corpus amygdala (one patient, 5.0%). While these results are not sufficient for statistical analysis, the total smell scores of these patients were found to be low.

Discussion

MS is an autoimmune inflammatory demyelinating disease of the CNS, and olfactory dysfunction in patients with MS can result either from a neurodegenerative process, as suggested by its observation in Parkinson's and Alzheimer's disease, or from brain inflammation.[16] Both processes – inflammation and neurodegeneration – are involved in the MS pathology[8] in which there are focal regions of inflammation, demyelination and gliosis, which influence sensory perception and decreased olfactory function.[17] Olfaction requires complex cognitive processing, such as discrimination and identification. It seems to worsen as MS progresses, which could reflect overall cognitive alteration.[18]

Zivadinov et al.[6] reported that 10% of the 40 MS patients they studied displayed 'borderline normal olfactory function' and 12.5% of patients showed 'abnormal olfactory function' in the 12-item Cross-Cultural Smell Identification Test (CC-SIT, now known as BSIT), whereas this function was normal in all controls (40 age-, sex- and smoking-habit-matched healthy controls.) ($p <0.02$). Similarly, in the present study, we found that patients with MS displayed lower olfactory function BSIT results than did the subjects of the control group.

Contrary to some contradictory studies performed in the past,[13,19] recent studies have shown that diminished smell identification ability is relatively frequently observed in MS patients.[17,20] Furthermore, the degree of MS-related olfactory loss appears to be directly and strongly associated with the number of plaques in the olfactory cortex, as determined by MRI.[17,20]

In our study, participants identified three items with good identification scores (chocolate, soap and onions). In the MS group, the least recognized

Table 2

Groups' smell test scores

		n	Mean	Median	Min	Max	SD	P*
Total smell test score	Study	20	8.95	9.00	6.00	11.00	1.43	**0.013**
	Control	20	10.05	10.00	7.00	12.00	1.05	
	Total	40	9.50	10.00	6.00	12.00	1.36	
Total smell test score**	Relapse	9	9.33	9	8	11	1.22	**0.290**
	Remission	11	8.64	8	6	11	1.57	
	Total	20	8.95	9	6	11	1.43	
Total smell test score***	Interferon beta-1a	10	8.90	8.5	7	11	1.29	**0.920**
	Interferon beta-1b	7	8.86	9	6	11	1.77	
	Total	17	8.88	9	6	11	1.45	

*p value shows the results of the Mann–Whitney U test
**The study group's values are presented
***The drug usage condition of the study group and their smell test scores are presented

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Table 3
Central and peripheral regions of smell measurement values*

REGIONS OF SMELL				STUDY GROUP (n=20)					CONTROL GROUP (n=20)					P**
				Mean	Median	Min	Max	SD	Mean	Median	Min	Max	SD	
CENTRAL	Insular Gyrus	Diameter (mm)	R	11.01	11.04	9.18	13.35	1.09	10.59	9.90	7.11	22.38	3.16	0.060
			L	10.31	9.90	8.44	14.08	1.55	11.13	10.82	7.32	19.86	2.48	0.081
		Area (mm^2)	R	386.77	367.40	276.43	506.69	57.84	369.91	351.33	217.97	568.80	93.81	0.330
			L	369.28	368.76	240.50	479.53	72.35	368.54	347.72	210.54	645.96	98.81	0.745
	Corpus Amygdala	Diameter (mm)	R	21.64	22.14	10.65	29.28	4.21	20.60	20.78	15.98	22.91	1.74	**0.036**
			L	22.46	23.00	11.72	28.06	4.27	21.40	20.99	18.62	25.32	2.04	0.079
		Area (mm^2)	R	251.38	253.97	148.69	312.43	42.81	206.03	200.52	139.33	291.58	34.58	**0.001**
			L	268.61	267.93	211.20	348.88	40.24	221.57	215.77	161.41	341.98	37.58	**0.000**
PERIPHERAL	Olfactory Bulb	Diameter (mm)	R	3.07	3.26	1.58	4.49	0.86	3.10	3.08	1.86	4.62	0.64	0.756
			L	3.05	3.17	0.76	4.45	0.83	3.17	3.20	1.98	4.41	0.62	0.695
		Area (mm^2)	R	6.08	5.85	2.40	12.72	2.55	6.34	6.31	1.68	12.05	2.39	0.588
			L	7.53	7.92	0.73	12.35	2.96	6.57	6.72	3.07	10.73	1.80	0.094
	Olfactory Sulcus	Diameter (mm)	R	2.29	2.28	1.28	3.50	0.64	2.11	2.02	1.18	3.29	0.62	0.358
			L	2.14	2.19	1.30	2.84	0.46	2.14	2.07	1.36	3.12	0.53	0.903
		Area (mm^2)	R	12.50	12.14	3.28	19.20	4.56	12.85	12.50	2.57	20.93	4.43	0.787
			L	13.22	14.73	4.38	24.29	4.87	13.25	13.62	7.13	21.69	3.92	0.818

*R: Right, L: Left
**p value shows the results of the Mann–Whitney U test

smell was lemon, while, in the control group, the least recognized smell was roses. It was reported that important differences were found in the psychometric performance of certain BSIT items. The lowest reliability coefficient was for turpentine and the highest coefficient was for onion.[21] These four items (paint thinner, gasoline, soap and onion) account for a majority of the information assessed by BSIT.[21]

In the MS group, neither relapse or remission condition nor drugs used (Interferon beta-1a or Interferon beta-1b) affected total smell scores. There is no statistically significant correlation between total smell scores and disease duration, remission or relapse condition, or the drugs used by the study group. It was concluded that these conditions did not affect total smell scores.

In several clinical and MR studies, neuropathology based on plaque numbers has been directly correlated with olfactory function.[7] As plaque numbers declined or increased in the inferior frontal and temporal lobes, olfactory function declined or improved in correlation.[20,22] There is thus proof of a clear inverse correlation between the number of plaques in the olfactory cortex and olfactory function in patients with MS.[7,20] In the present study, there were no MS lesions in the peripheral regions of smell (olfactory bulb, tract and sulcus), but MS lesions were observed in the central regions of smell: right temporal lobe insular gyrus (four patients, 20.0%); left temporal lobe insular gyrus (two patients, 10.0%); and right corpus amygdala (one patient, 5.0%). While these results are not sufficient for statistical analysis, the total smell scores of these patients were found to be low. These MS plaques may cause lower total smell scores in the MS group. Moreover, the neurodegenerative process of MS[16] and the focal regions of inflammation, demyelination and gliosis[17] may affect sensory perception and thereby also cause lower total smell scores in the MS group.

In the MS group, the measurement values of the central regions of smell (right corpus amygdala diameter, right and left corpus amygdala area) were significantly higher than those of the control group. No correlation was detected between central and peripheral regions of smell measurement values and total smell scores. In the control group, as

total smell score increased, one of the items of the central regions of smell (the right temporal lobe insular gyrus diameter value) decreased. Similarly, as total smell scores increased, one of the items of the peripheral regions of smell (the right olfactory bulb diameter value) decreased. Additionally, in all individuals from both groups, as total smell scores increased, the central regions of smell measurement values decreased.

A study by Hang et al.[23] investigated the correlation between olfactory bulb volumes and age, as well as olfactory bulb volumes and olfactory function in healthy adults. They found that olfactory bulb volumes were negatively correlated with the ages of the subjects. They also reported that the olfactory discrimination threshold was negatively correlated with olfactory bulb volumes in the subjects (r values were -0.624 and -0.587, respectively, both $p<0.01$).

A recent study by Goektas et al.[24] assessed the olfactory bulb volume of MS patients with MRI and compared this to the patients' olfactory functioning. They found that, in patients with a decreased olfactory bulb volume, there was a positive correlation between the volume of the olfactory bulb and olfactory function.[24] These findings show that the olfactory bulb may provide valuable information about olfactory dysfunction of MS patients. A diminished sense of smell in MS patients has also been reported in a recent study.[8] While, in our study, we could not find a difference between the olfactory bulb diameter and area of the MS and control groups, we did find the olfactory bulb and insular gyrus diameter values to be lower in control group subjects with higher smell scores.

Monahan and Lomvardas[25] reported that one's sense of smell collects vital information about the environment by detecting a multitude of chemical odorants. Breadth and sensitivity are provided by a huge number of chemosensory receptor proteins, including more than 1400 olfactory receptors (ORs). Organizing the sensory information generated by these receptors so that it can be processed and evaluated by the CNS is a major challenge. The single OR expressed by each olfactory sensory neuron determines the neuron's odour sensitivity and the axonal connections it will make to neurons downstream in the olfactory bulb. The expression

Table 4

The relationship between central and peripheral regions of smell measurement values with total smell test scores*

				Total score of smell					
				STUDY GROUP (n=20)		CONTROL GROUP (n=20)		TOTAL GROUP (n=40)	
				r	p**	r	p**	r	p**
CENTRAL	Insular Gyrus	Diameter (mm)	R	-0.041	0.863	-0.529	**0.016**	-0.333	**0.036**
			L	0.197	0.405	-0.123	0.607	0.181	0.263
		Area (mm^2)	R	-0.376	0.102	-0.258	0.272	-0.364	**0.021**
			L	-0.022	0.928	-0.170	0.472	-0.122	0.453
	Corpus Amygdala	Diameter (mm)	R	0.012	0.961	-0.030	0.900	-0.144	0.374
			L	-0.020	0.933	-0.162	0.496	-0.067	0.680
		Area (mm^2)	R	-0.297	0.203	0.069	0.773	-0.214	0.185
			L	-0.012	0.959	-0.019	0.938	-0.227	0.160
PERIPHERAL	Olfactory Bulb	Diameter (mm)	R	0.223	0.346	-0.486	**0.030**	-0.115	0.481
			L	0.396	0.084	0.022	0.927	0.232	0.150
		Area (mm^2)	R	0.315	0.176	-0.216	0.360	0.129	0.426
			L	0.328	0.158	0.212	0.370	0.128	0.432
	Olfactory Sulcus	Diameter (mm)	R	0.201	0.396	-0.132	0.578	0.035	0.831
			L	-0.083	0.728	0.045	0.852	-0.013	0.938
		Area (mm^2)	R	0.325	0.162	-0.307	0.188	0.069	0.674
			L	-0.186	0.432	-0.260	0.269	-0.186	0.251

* R: Right, L: Left

**p value shows the results of Spearman's correlation rho efficient test

of a single OR per neuron is accomplished by coupling a slow chromatin-mediated activation process to a fast negative-feedback signal that prevents the activation of additional ORs.[25]

We conclude that there is a deterioration in smell function in patients with multiple sclerosis, but it is not yet clear whether olfactory impairment is an early hallmark of the disease. However, evaluation of the functionality of the olfactory system may provide predictions of certain brain regions' involvement in MS. Therefore, every patient diagnosed with MS should be administered the smell test to evaluate olfactory functions. We highly recommend that ENT specialists use the easily accessible and reliable BSIT for the diagnosis of smell disorders. In the future, we plan to replicate this study with a larger participant pool.

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