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Unilateral olfactory sensitivity in multiple sclerosis

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HIGHLIGHTS

- Most extensive study of its type performed on olfactory function and multiple sclerosis
- MS-related deficits in odor detection and identification are present to the same degree on the two sides of the nose
- Olfactory test scores and MRI-determined lesion volumes are correlated in some cortical regions

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ABSTRACT

It is not known whether lateralized olfactory sensitivity deficits are present in MS. Since projections from the olfactory bulb to the olfactory cortex are largely ipsilateral, and since both functional imaging and psychophysical studies suggest that the right side of the brain may be more involved in olfactory processing than the left, we addressed this issue by administering well-validated tests of odor detection, along with tests of odor identification, to each side of the nose of 73 MS patients and 73 age-, gender-, and race-matched normal controls. We also determined, in 63 of the MS patients, whether correlations were present between the olfactory test measures and MRI-determined lesions in brain regions ipsilateral and contralateral to the nose side that was tested. No significant left:right differences in either olfactory sensitivity or identification were present, although in both cases mean performance was lower in the MS than in the control subjects ($ps < 0.0001$). Scores on the two sides of the nose were positively correlated with one another (threshold $r = 0.56$, $p < 0.0001$; Identification $r = 0.71$, $p < 0.0001$). The percent of MS patients whose bilateral test scores fell below the 10th percentile of controls did not differ between the odor identification and detection threshold tests. Both left and right odor identification and detection test scores were weakly correlated with lesion volumes in temporal and frontal lobe brain regions (r's < 0.40). Our findings demonstrate that MS does not differentially influence odor perception on left and right sides of the nose, regardless of whether sensitivity or identification is being measured. They also indicate that tests of odor identification and detection are similarly influenced by MS and that such influences are associated with central brain lesions.

1. Introduction

Multiple sclerosis (MS), the most common cause of neurologic disability in the young adult, is characterized pathologically by central nervous system (CNS) demyelination. This disorder afflicts millions of people worldwide [1] and is known to alter the function of a number of sensory systems [2–5]. However, the influence of MS on the ability to smell has been a subject of controversy for at least two reasons. First, in contrast to the myelinated optic nerves, the axons of the olfactory nerve, i.e., Cranial Nerve I, are unmyelinated, leading some to view the olfactory system as largely unmyelinated and, thus, unaffected by MS [6,7]. Second, published psychophysical studies on this topic are conflicting, with some reporting no MS-related influences on either threshold [8] or suprathreshold measures [9], whereas others reporting identification or threshold deficits in 10% to 80% of the evaluated

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patients [10–22]. While it is true that the olfactory receptor neurons themselves are unmyelinated, the centripetal projections from the mitral and tufted cells of the olfactory bulb are myelinated, as are multiple regions of the brain associated with olfactory transduction [23], essentially negating the notion that olfactory function should be spared from the influences of MS. It is noteworthy that authoritative MS textbooks fail to mention impaired olfaction as a possible pathognomonic sign (e.g., [24–26]).

There is evidence from functional imaging and psychophysical studies that the right hemisphere may be more involved in olfactory processing than the left [27–29]. In the case of MS, an impaired cortical network has been found whose nexus is within the right hemisphere [30]. Moreover, greater right-side damage to the locus coeruleus has been noted in MS which could differentially influence right hemisphere attentional processes [31]. Since the olfactory projections from the bulb to cortical regions are largely ipsilateral, it is conceivable that patients with MS may be less sensitive to smells on the right than on the left side of the nose. Although tests of odor identification have failed to show laterality effects in MS [32], some investigators have argued that threshold tests may be more sensitive than identification tests to MS-related olfactory deficits [33], particularly in regards to peripheral segments of the olfactory system, conceivably making thresholds more sensitive to lateralized deficits [34]. Regardless of whether laterality is present, however, an understanding of the relationship between olfactory threshold scores and lesions within olfactory eloquent brain structures remains to be determined.

The present study had three primary goals: first, to confirm that olfactory thresholds, as measured by a well-validated forced-choice test, are influenced by MS; second, to ascertain whether asymmetry, i.e., left-right nostril differences, occur in such scores; and third, to determine whether the threshold and identification test scores are correlated with the number and volume of MS-related lesions in central brain regions, most notably those ipsilateral to the side of the nose being tested. This study also sought to establish the degree of correlation between the two test measures and whether the left- and right-side test scores correlate with one another.

2. Materials and methods

2.1. Subjects

Seventy three MS patients and 73 healthy controls matched on age, gender, and ethnicity participated in this study (see Table 1 for subject demographics). Although the proportion of smokers within each group did not differ significantly, the male MS patients had the highest cumulative levels of smoking (as measured by pack-years), whereas female control subjects had the lowest cumulative levels [$F_{(3,24)} = 4.6$, $p < 0.02$; Tukey's HSD $p < 0.02$]. All other groups did not differ from one another on this measure. No differences were present between male and female MS patients on duration of illness or on the Expanded Disability Status Scale (EDSS) score.

Participants were excluded from consideration if they had a medical history positive for a disorder in addition to MS that might influence olfaction. These included Bell's palsy, chronic rhinosinusitis, chronic lung infection, nasal polyposis, epilepsy, emphysema, liver disease, stroke, seizure disorder, neurodegenerative disease, schizophrenia, psychosis, bipolar disorder, dementia, amnesia, depression requiring medication or hospitalization, chronic alcoholism or drug abuse, brain surgery, or facial injuries or head trauma leading to loss of consciousness, among others. Approximately half came from within the University of Pennsylvania Medical System, whereas the remainder came from outside this system. Most patients learned of the study through their physician, MS support group, or a local MS newsletter. Controls learned of the study either through their participant MS spouses or through advertisements placed in newspapers or fliers posted in the Hospital of the University of Pennsylvania or around the University's campus. Each subject was compensated for participation, provided with a free lunch, and reimbursed for parking or transportation costs to and from the testing site. The study was approved by the University's Office of Regulatory Affairs and all subjects provided informed written consent.

2.2. Testing protocol

The 146 subjects underwent a comprehensive battery of olfactory, gustatory, auditory, vestibular, imaging, and neuropsychological tests that required, in total, ~8 h for completion. The olfactory tests were the first, and the MRI imaging scans the last, of the procedures administered on a test day. Findings from non-olfactory components of this program have been published, or are being published, elsewhere (e.g., [5, 35]). In rare cases, the test sessions were distributed across two days, depending upon a subject's availability, health, and tolerance for the testing procedures. Appropriate rest periods were provided between tests. Additionally, the test day was broken up by an hour-long lunch break.

Two olfactory tests were administered to each side of the nose separately, with the non-tested side being occluded by a small piece of Microfoam™ tape (3M Corp. Minneapolis MN). The side of nose that was tested first was counterbalanced across subjects. *Olfactory sensitivity* was measured using an odor detection threshold test that employed the rose-like odorant phenyl ethyl alcohol (PEA), as described in detail elsewhere [36–40]. A single staircase procedure was used, with the staircase beginning at the −6.00 log concentration step of a half-log step (vol/vol) dilution series that extended from −10.00 log concentration to −2.00 log concentration. The odorant concentration was increased in full log steps until correct detection occurred on five sets of consecutive trials at a given concentration. If an incorrect response was given on any trial, the staircase was moved upward one full log step. When correct responses were made on all five trials, the staircase was reversed and subsequently moved up or down in 0.50 log increments or decrements, depending upon the subject's performance on two pairs of trials at each concentration step. If the subject missed the first of these two trials, the second was not administered, and the next higher 0.50 log concentration was presented. The average of last four of seven staircase reversals served as the threshold measure. *Odor identification ability* was tested using the University of Pennsylvania Smell Identification Test (UPSIT) [22]. In this test, the subject's task is to

Table 1
Basic demographics of the MS and matched control subjects.

Subject group	Sample size	Mean age (SD)	Ethnicity W/B (% W)	Mean yrs education (SD)	Number of smokers/ non-smokers (% smokers)	Mean (SD) disease duration	Mean EDSS score (SD)	Disease classification
MS - males	21	45.24 (11.42)	17/4 (81.0)	15.10 (2.74)	5/16 (23.8%)	7.36(4.0)	4.54 (1.80)	RR: 15; PP: 2; SP: 2; U: 2
MS - females	52	45.60 (8.61)	38/14 (73.1%)	14.51 (2.20)	12/40 (23.1%)	8.84(6.6)	3.32 (1.66)	RR: 42; PP: 1; SP: 4; U: 5
C – males	21	45.43 (10.78)	17/4 (81.0)	15.10 (3.22)	4/17 (19.0%)	–	–	–
C – females	52	46.0 (9.35)	38/14 (73.1%)	15.51 (2.36)	5/47 (9.6%)	–	–	–

Abbreviations: w/b = white/black; MS = multiple sclerosis; C = control; RR = relapsing remitting; PP = Primary progressive; SP = secondary progressive; U = Unknown. EDSS = Expanded Disability Status Score based on 22 patients. No significant differences are present between any of the means or frequencies across the MS and control groups or between the males and females.