J Neurol (2016) 263:677–688
DOI 10.1007/s00415-016-8030-6

ORIGINAL COMMUNICATION

Taste dysfunction in multiple sclerosis

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Received: 28 October 2015 / Revised: 9 January 2016 / Accepted: 11 January 2016 / Published online: 25 January 2016

Abstract Empirical studies of taste function in multiple sclerosis (MS) are rare. Moreover, a detailed assessment of whether quantitative measures of taste function correlate with the punctate and patchy myelin-related lesions found throughout the CNS of MS patients has not been made. We administered a 96-trial test of sweet (sucrose), sour (citric acid), bitter (caffeine) and salty (NaCl) taste perception to the left and right anterior (CN VII) and posterior (CN IX) tongue regions of 73 MS patients and 73 matched controls. The number and volume of lesions were assessed using quantitative MRI in 52 brain regions of 63 of the MS patients. Taste identification scores were significantly lower in the MS patients for sucrose ($p = 0.0002$), citric acid ($p = 0.0001$), caffeine ($p = 0.0372$) and NaCl ($p = 0.0004$) and were present in both anterior and posterior tongue regions. The percent of MS patients with identification scores falling below the 5th percentile of controls was 15.07 % for caffeine, 21.9 % for citric acid, 24.66 % for sucrose, and 31.50 % for NaCl. Such scores were inversely correlated with lesion *volumes* in the temporal, medial frontal, and superior frontal lobes, and with the *number* of lesions in the left and right superior frontal lobes, right anterior cingulate gyrus, and left parietal operculum. Regardless of the subject group, women outperformed men on the taste measures. These findings indicate that a sizable number of MS patients exhibit taste deficits that are associated with MS-related lesions throughout the brain.

Keywords Multiple sclerosis · Magnetic resonance imaging · Taste · Chemosensory transduction · Taste disorders · Sex differences

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Introduction

The influence of multiple sclerosis (MS), the most common neurologic disease of young adulthood, on taste perception has received scant attention, despite the fact that 10–15 % of community dwelling patients with MS suffer from malnutrition [1]. Based on self-report or cursory sensory testing, MS-related taste disorders have been assumed to be rare, often being <5 % [2–7]. However, people reporting taste deficits typically have olfactory, not taste, dysfunction [7], and are generally inaccurate in recognizing true taste dysfunction when present [8]. Studies employing

electrogustometry and other quantitative taste tests typically observe somewhat higher prevalence rates. For example, Rollin [9] reported that 9 of 75 MS patients exhibited elevated electrogustometric thresholds (12 %), although specific details of the testing were lacking. Three relatively recent whole-mouth taste studies have reported levels of disturbance in approximately 20 % of MS patients, although distinctions among taste qualities and tongue regions were not made [10–12]. In the sole study to examine possible associations between taste test scores and MS-related lesions, the identification scores of 25 subjects, combined across taste qualities, were inversely correlated with lesion numbers ($r = -0.49$) and lesion volumes ($r = -0.52$) within the "olfactory brain", i.e., the piriform and entorhinal cortices, frontal agranular regions of the insular lobe up to the anterior commissure, and the orbitofrontal cortex [12].

In this study, we administered a sensitive and well-validated 96-trial taste test to a relatively large number of MS patients and matched controls to more definitively assess the influences of MS on taste function. The study had four main objectives: first, to establish the frequency and magnitude of taste deficits in the MS patients; second, to determine whether such dysfunction, when present, is uniform across disparate tongue regions; third, to determine whether the MS-related taste deficits differ among sweet, sour, bitter and salty tasting stimuli; and fourth, to evaluate whether taste test scores are associated with the number and volume of MS-related lesions in 26 brain regions within each side of the brain (i.e., 52 total brain structures).

Materials and methods

Subjects

The subjects were 73 patients with well-documented MS and 73 healthy controls matched to the patients on the basis of age, sex, ethnicity, and education (Table 1). Approximately half came from within the University of Pennsylvania Health System, whereas the remainder came from outside this system. Most were recruited through their physician, MS support group, or a local MS newsletter. Controls were obtained through advertisements placed in newspapers or fliers posted in the Hospital of the University of Pennsylvania or around the University's campus. Individuals were excluded from consideration if they had a positive medical history for non-MS disorders that could confound not only the gustatory, but also the other sensory tests performed in the program. These included Bell's palsy, chronic rhinosinusitis, chronic lung infection, epilepsy, emphysema, liver disease, stroke, seizure disorder, neurodegenerative disease other than MS, 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.

This research was a component of a comprehensive program that evaluated auditory, olfactory, gustatory, vestibular, and neuropsychological function of the same set of MS patients. Findings from the other elements of the program have been published [13] or are in preparation for publication. The study was approved by the University's Office of Regulatory Affairs and all subjects provided informed written consent. The research was performed in accordance with the ethical principles of the Declaration of Helsinki (1964) and its later amendments. Each subject was paid $20 per hour for participation and was reimbursed for travel and food expenses.

Taste test protocol

The standardized taste test that was employed is described elsewhere [14, 15]. Briefly, 15 μL of single concentrations of sucrose (0.49 M), sodium chloride (0.31 M), citric acid (0.015 M), and caffeine (0.04 M), equated for viscosity by the addition of cellulose to minimize stimulus migration, were presented via an Eppendorf pipette to the left and right sides of the tongue tip and on or near the left and right lateral circumvallate papillae. Each subject indicated whether a given stimulus tasted sweet, sour, bitter or salty by pointing to names on a chart before retracting the tongue and orally rinsing with purified water. A total of 96 stimulus trials and accompanying rinses was employed (4 tastants × 6 trials × 4 tongue regions). Additionally, perceived intensity was rated on a visually graded category scale with anchors of "very weak" and "very strong" and a logarithmic visual density background denoting non-linear increasing sensation magnitudes [16].

Imaging protocol

All MS patients underwent, usually on the same day as the sensory testing, thin section magnetic resonance imaging (MRI) of the brain with gadolinium enhancement using a General Electric (Milwaukee, WI) 1.5-T Signa scanner employing a standard head coil. Usable images were available for 63 of the patients and were employed to quantify the number of lesions and volumes in multiple brain regions. The MRI evaluations included fluid-attenuated inversion recovery (FLAIR) and double-echo long-TR axial scans with 3-mm thick slices through the entire brain. The matrix was 256 × 192 pixels and the field of view was

240 mm^2, allowing for detailed assessment of MS-related lesion intensity within selected brain regions. Brain volumes were extracted semi-automatically using a combination of thresholding, morphological operators, and region growing, followed by manual refinement [17, 18]. Lesions were then defined semi-automatically by first using a fuzzy segmentation algorithm applied to the multichannel brain extracted images [19, 20]. This algorithm was modified to model lesion intensities as outliers, similar to the approach described by Van Leemput et al. [21]. The resulting segmentation was inclusive of all lesions but included false-positives that were manually removed by a trained operator. If a lesion fell into two regions, it was counted as a lesion in both of the regions. However, its volume was parceled between the two regions into which it fell. The intra-rater reliability intraclass correlation coefficient for our approach based upon 10 cases repeated twice by the same operator was above 0.99. Regions of interest were defined automatically by applying a high-dimensional, non-linear registration of a manually parcellated atlas image to each subject (Figs. 1, 2) [22, 23]. The atlas was based on a T1-weighted MRI from a healthy subject. Thus, the regions of interest were defined by manually labeling a template MRI brain and deforming this image into each subject's brain image using the HAMMER algorithm. The labels were transferred with this deformation. A total of 26 brain regions were defined for each side of the brain (i.e., 52 total brain structures; Table 2). These regions were chosen to incorporate well-established brain structures applicable to a range of sensory studies that are being performed on the data set.

Statistical analyses

All statistical analyses were made using modules from SYSTAT [24]. Initially we determined the number of MS

Table 1 Basic demographics of the MS and matched control subjects

Subject group	Sample size	Mean age (SD)	Ethnicity W/B (% W)	Mean years 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 (3.96)	4.54 (1.80)	RR: 15; PP: 2; SP: 2; U: 2
MS—Females	52	45.60 (8.61)	38/14 (73 %)	14.52 (2.20)	12/40 (23.1 %)	7.84 (6.61)	3.36 (1.60)	RR: 42; PP: 1; SP: 4; U: 5
C—Males	21	45.43 (10.78)	17/4 (81.0)	15.10 (3.23)	4/17 (19.0 %)	–	–	–
C—Females	52	46.60 (9.35)	38/14 (73.1 %)	15.51 (2.36)	5/47 (9.6 %)	–	–	–

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 29 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

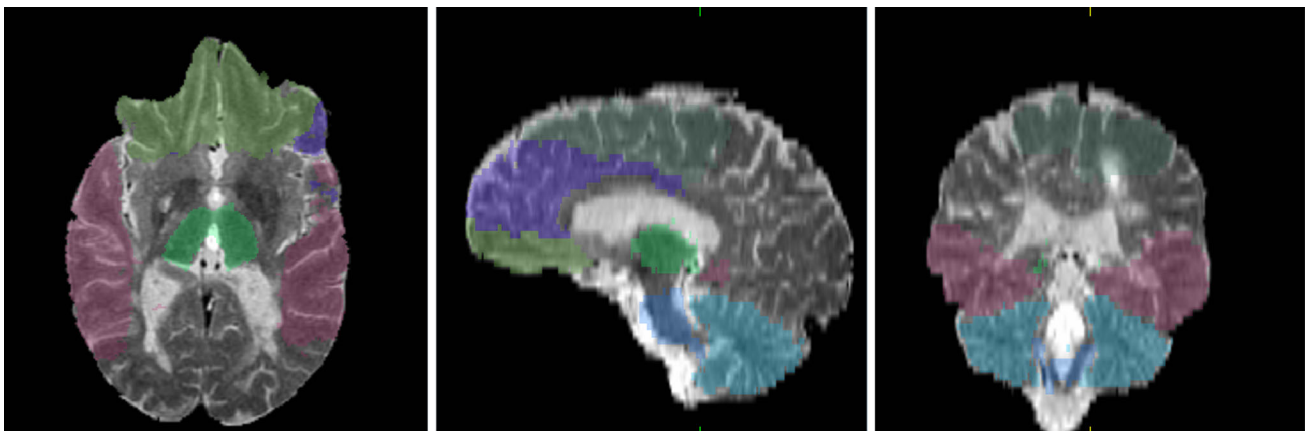

Fig. 1 Triplanar view of registration-based parcellation of the brain into superior, medial, and inferior frontal lobes, temporal lobes, cerebellum, thalamus, and brainstem. Other labels denoted in the text are not shown because several regions overlap. See text for details

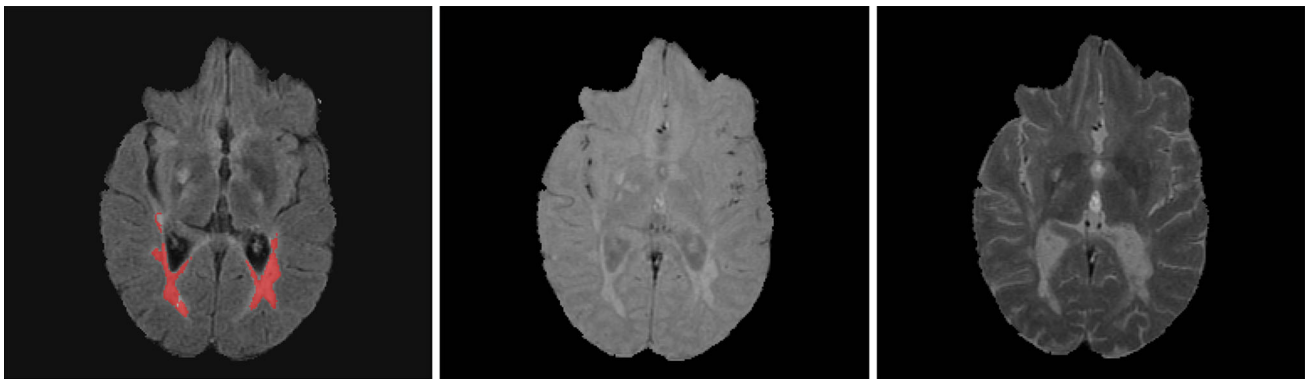

Fig. 2 *Left* axial slice of the FLAIR image with semi-automatic lesion segmentation highlighted in *red*. *Middle* proton density weighted image. *Right* T2-weighted image. See text for details

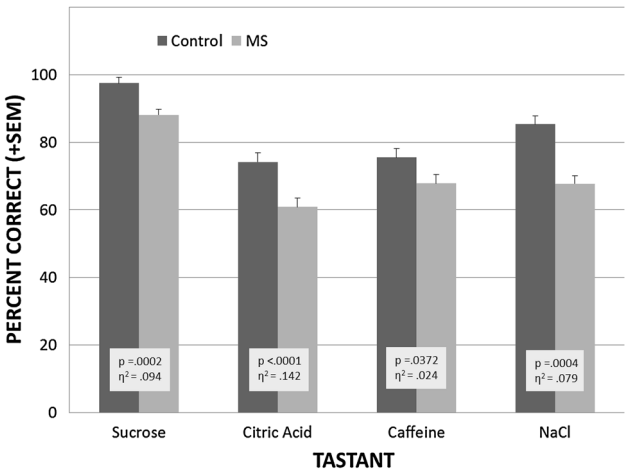

Fig. 3 Mean (±SEM) percent correct taste identifications for sweet (sucrose), sour (citric acid), bitter (caffeine) and salty (sodium chloride) tasting stimuli for the 146 subjects of the study (73 multiple sclerosis patients and 73 matched controls). The dependent measure reflects the percent of correct responses from a total of 24 trials for each stimulus (6 trials × 4 tongue regions). Copyright © 2015 Richard L Doty. See text for details

subjects who performed more poorly than the control subjects, as determined by taste identification test scores falling below the 5th percentile of those of the controls. Preliminary analyses were performed on each test measure and taste stimulus to explore the influences of key variables on the dependent measures. Smoking behavior, disease duration, and handedness did not meaningfully contribute to any of the analyses and were dropped from subsequent models. Since tongue side was not significant, the data from the two sides of the tongue were combined for subsequent analyses, resulting in anterior (CN VII) and posterior (CN IX) measures. The final model, performed on the data for each tastant separately, was an analysis of covariance (ANCOVA) with the between group factors of patient group (MS, control) and sex (M,F), and the within group factor of tongue region (anterior, posterior). Age served as a covariate. To simplify the presentation of results, F values and degrees of freedom are not reported in the text; η^2 values, which reflect effect sizes, are reported only when significant p values are present.

Because the lesion frequency distributions were strongly skewed to the right, non-parametric Spearman correlations were computed to determine whether meaningful associations were present among the taste measures and the two lesion measures (lesion number, volume) within the target brain regions. p values were unadjusted for multiple comparisons to avoid type II errors and associated problems [25, 26]; however, the number of computations was limited to subgroups with lesion activity. In these analyses, the lesion data from the left and right sides of the brain were retained as separate entities in light of possible lateralized associations with lesions in some brain regions [27, 28].

Results

Taste quality identification

The percent of MS patients whose overall taste identification test scores fell below the 5th percentile of control subjects was 15.07 % for caffeine (bitter), 21.9 % for citric acid (sour), 24.66 % for sucrose (sweet), and 31.50 % for NaCl (salty). The patients with MS identified, on average, fewer stimuli than did the control subjects for each taste quality, as demonstrated by a significant main effect of subject group (MS/control) in all analyses (Fig. 3; p and η^2 values shown in figure). Irrespective of subject group, women outperformed men in identifying the taste qualities [caffeine: respective means (SEMs) = 82.38 (1.97) and 60.95 (3.10); $p < 0.001$, $\eta^2 = 0.186$), sodium chloride: 80.72 (1.87) and 72.31

Table 2 Brain regions and MS-related lesions

Brain region	Number of subjects with lesions	Mean (SD) number of lesions	Mean (SD) volume of lesions (mm^3)	Mean (SD) region volume (mm^3)	% Lesion volume/ mean region volume
Cortex + Cerebral White Matter L	63	32.52 (22.75)	6537.50 (5283.93)	372977.06 (47800.37)	1.75
Cortex + Cerebral White Matter R	63	31.64 (20.25)	6396.37 (5106.45)	380037.92 (47377.99)	1.68
Med Frontal Lobe L	63	14.44 (10.59)	1503.67 (1511.21)	99267.06 (14813.33)	1.51
Med Frontal Lobe R	63	13.00 (6.99)	1526.88 (1623.76)	103422.50 (15002.34)	1.48
Temporal Lobe L	63	12.86 (8.30)	1170.74 (1200.34)	112548.18 (13785.93)	1.04
Temporal Lobe R	61	15.03 (9.02)	1121.33 (1202.92)	119117.01 (14855.76)	0.94
Med Temp Lobe L	58	5.27 (4.29)	55.39 (65.70)	5741.75 (715.49)	0.96
Med Temp Lobe R	57	6.94 (5.22)	80.82 (86.00)	6381.95 (875.38)	1.27
Sup Frontal Lobe L	60	6.16 (4.97)	525.02 (832.79)	70159.46 (8843.42)	0.75
Sup Frontal Lobe R	54	4.71 (5.01)	401.37 (621.85)	66075.80 (8208.68)	0.61
Hippocampus L	48	3.42 (3.20)	40.27 (56.35)	2715.59 (399.95)	1.48
Hippocampus R	47	3.44 (3.24)	37.14 (53.42)	2207.70 (343.99)	1.68
Inf Frontal Lobe L	46	3.87 (5.11)	88.73 (159.65)	25081.41 (3414.52)	0.35
Inf Frontal Lobe R	48	4.16 (5.37)	78.00 (143.33)	26880.43 (3627.71)	0.29
Insular WM L	39	2.02 (3.50)	17.58 (35.81)	2030.24 (335.06)	0.87
Insular WM R	42	2.07 (2.52)	16.18 (26.16)	1799.54 (330.77)	0.90
Insular GM L	36	1.95 (3.35)	23.32 (66.48)	5012.94 (330.77)	0.46
Insular GM R	39	1.95 (2.61)	21.03 (66.48)	5576.32 (883.16)	0.38
Ant Cing Gyr L	37	1.25 (1.81)	11.64 (22.99)	6286.86 (1036.49)	0.19
Ant Cing Gyr R	36	1.51 (1.98)	25.36 (81.84)	8181.42 (1448.92)	0.31
Orb Front Cortex L	38	1.79 (2.03)	27.33 (45.65)	11378.36 (1740.91)	0.24
Orb Front Cortex R	36	1.83 (2.55)	23.77 (47.58)	10567.77 (1515.99)	0.22
Thalamus L	30	1.40 (2.15)	16.28 (39.78)	6358.35 (959.02)	0.26
Thalamus R	32	1.48 (2.30)	13.65 (43.49)	5743.72 (844.77)	0.24
Parietal Opercul L	29	0.70 (0.94)	12.59 (29.28)	1780.41 (427.23)	0.71
Parietal Opercul R	21	0.60 (1.13)	14.03 (37.83)	1251.13 (353.97)	1.12
Amygdala L	5	0.13 (0.55)	0.63 (3.31)	517.78 (119.24)	0.14
Amygdala R	5	0.13 (0.46)	0.88 (4.41)	492.31 (145.41)	0.18
Brainstem L	5	0.08 (0.27)	1.09 (4.71)	11415.70 (1535.31)	0.01
Brainstem R	4	0.08 (0.33)	2.74 (14.92)	10489.84 (1439.51)	0.03
Pons L	4	0.06 (0.25)	0.53 (3.13)	6875.53 (1005.03)	0.01
Pons R	4	0.11 (0.54)	1.13 (6.50)	6346.82 (924.35)	0.02
Cerebellum L	2	0.03 (0–1)	1.09 (7.85)	57195.03 (5996.59)	0.00
Cerebellum R	1	0.02 (0–1)	0.04 (0.28)	59252.67 (6598.92)	0.00
Med Lemniscus L	0	0 (0)	0 (0)	577.18 (103.34)	–
Med Lemniscus R	2	0.05 (0.28)	0.18 (1.00)	567.43 (85.04)	0.03
Sup Colliculus L	0	0 (0)	0 (0)	314.79 (73.67)	–
Sup Colliculus R	1	0.02 (0.13)	0.07(0.58)	335.04 (88.31)	0.02
Medulla L	0	0	0	3202.74 (484.72)	0.00
Medulla R	0	0	0	3374.04 (484.72)	0.00
Inferior Colliculus L	0	0	0	278.78 (68.98)	0.00
Inferior Colliculus R	0	0	0	256.90 (60.73)	0.00
Central Teg. Tract L	0	0	0	236.82 (46.91)	0.00
Central Teg. Tract R	0	0	0	212.66 (49.85)	0.00
Pont. Parabrach. N. L	0	0	0	78.99 (22.60)	0.00
Pont. Parabrach. N. R	0	0	0	68.89 (16.43)	0.00

Table 2 continued

Brain region	Number of subjects with lesions	Mean (SD) number of lesions	Mean (SD) volume of lesions (mm^3)	Mean (SD) region volume (mm^3)	% Lesion volume/ mean region volume
Med. Gen. Body L	0	0	0	78.18 (24.18)	0.00
Med. Gen. Body R	0	0	0	57.78 (18.93)	0.00
Solitary Nucleus L	0	0	0	57.32 (16.42)	0.00
Solitary Nucleus R	0	0	0	48.04 (14.29)	0.00
Bracial Inf. Collicul. L	0	0	0	36.79 (13.06)	0.00
Bracial Inf. Collicul. R	0	0	0	31.19 (9.55)	0.00

Listing is in order of the number of subjects exhibiting lesions within the given brain regions and the % volume of the brain region involved. The cortex subsumes all lobes excepting the temporal lobes. $N = 63$

(2.95); $p = 0.017$, $\eta^2 = 0.032$), citric acid: 73.12 (2.00) and 61.91 (3.13); $p = 0.003$, $\eta^2 = 0.056$), sucrose: 95.06 (1.30) and 90.60 (2.04); $p = 0.062$, $\eta^2 = 0.022$)]. The age covariate was significant only for sodium chloride ($p = 0.014$, $\eta^2 = 0.034$; all other $ps \geq 0.10$], reflecting an overall age-related decline in performance for this stimulus.

In general, the MS-related influences on taste function were found on both the front and the back of the tongue, as no interactions were evident between tongue region and subject group (all $ps > 0.20$). However, a significant subject group by tongue region by sex interaction was present for caffeine ($p = 0.003$). This reflected the fact that women with MS significantly underperformed their female controls in identifying the bitter taste of caffeine on the front, but not the back, of the tongue [respective MS and control anterior values: 74.59 (2.89) and 86.63 (2.89); $p = 0.004$, $\eta^2 = 0.079$, respective posterior values: 82.14 (2.67) and 85.97 (2.67); $p = 0.311$, $\eta^2 = 0.010$], whereas a non-significant trend in the opposite direction was present for the men [respective anterior MS and control values: 60.23 (6.28) and 60.41 (6.28), $p = 0.984$, $\eta^2 < 0.001$; respective posterior MS and control values: 54.70 (5.73) and 69.12 (5.73), $p = 0.083$, $\eta^2 = 0.070$].

Intensity ratings

The mean intensity rating of the MS patients was significantly lower than that of the controls for caffeine [respective means (SEMs) = 4.95 (0.22) and 4.41 (0.22), $p < 0.05$, $\eta^2 = 0.086$), but not for any other tastant ($ps > 0.20$). Significant main effects of sex were present for all tastants, reflecting larger intensity ratings given by women than by men [respective female and male means (SEMs) for sucrose, citric acid, caffeine and sodium chloride: 5.77 (0.15) and 4.90 (0.23), $p = 0.002$, $\eta^2 = 0.067$; 5.06 (0.14) and 4.10 (0.23), $p < 0.0001$, $\eta^2 = 0.086$; 5.33 (0.15) and 4.03 (0.24), $p < 0.0001$, $\eta^2 = 0.133$; 5.29 (0.15) and 4.64 (0.24), $p = 0.023$, $\eta^2 = 0.037$)].

Relationship of taste test measures to brain lesions within the MS group

Because lesions were absent or sparse in a number of the targeted brain structures and a range of lesion values was needed to establish meaningful correlation coefficients with the taste measures, we focused our correlation analyses on brain structures in which lesions were present in at least 21 of the 63 MS patients (Table 2). The Spearman correlations between lesion volumes in the primary brain regions and the taste identification test scores for the left and right sides of the tongue are presented in Table 3. It is apparent that the taste identification scores were correlated, albeit weakly, with lesion volumes within the larger brain structures—structures in which typically more than 1 % of their volume was comprised of lesions (Table 2). No systematic associations between the side of the lesions and the side of the tongue that was tested were observed. Only four significant negative correlations were found between the number of lesions and the taste identification test scores, in contrast to the 40 significant negative coefficients shown in Table 3 for lesion volumes. Two were between the left side sour identification scores and the number of lesions in the left and right superior frontal lobes (both $rs = -0.26$, $ps < 0.025$), one was between the left side bitter scores and the number of lesions in the right superior frontal lobe ($r = -0.24$, $p < 0.05$) and one was between the left side sweet identification test score and the number of lesions in the right anterior cingulate gyrus ($r = -0.29$, $p < 0.05$).

As would be expected from our finding of fewer significant differences in the taste intensity ratings between

Table 3 Spearman correlation coefficients between taste identification test scores and MS-related lesion volumes

Brain region	Number of subjects with lesions	Mean (SD) number of lesions	Mean (SD) volume of lesions	Sucrose L	Sucrose R	Citric acid L	Citric acid R	Caffeine L	Caffeine R	NaCl L	NaCl R	% Negative r's
Cortex + White Matter L	63	32.52 (22.75)	6537.50 (5283.93)	−0.35[d]	−0.22[a]	−0.17	−0.25[b]	−0.18	−0.06	−0.15	−0.07	100
Cortex + White Matter R	63	31.64 (20.25)	6396.37 (5106.45)	−0.45 [g]	−0.35[d]	−0.30[c]	−0.36[e]	−0.32[d]	−0.20[a]	−0.20[a]	−0.16	100
L_Medial Frontal Lobe	63	14.44 (10.59)	1503.67 (1511.21)	−0.34[d]	−0.23[a]	−0.21[a]	−0.32[d]	−0.27[b]	−0.11	−0.23[a]	−0.14	100
R_Medial Frontal Lobe	63	13.00 (6.99)	1526.88 (1623.76)	−0.29[c]	−0.24[a]	−0.18	−0.33[d]	−0.31[c]	−0.17	−0.17	−0.09	100
L_Temporal Lobe	63	12.86 (8.30)	1170.74 (1200.34)	−0.34[d]	−0.32[d]	−0.31[c]	−0.29[c]	−0.19	−0.11	−0.19	−0.07	100
R_Temporal Lobe	61	15.03 (9.02)	1121.33 (1202.92)	−0.40[f]	−0.33[d]	−0.35[e]	−0.39[f]	−0.21[a]	−0.14	−0.23[a]	−0.13	100
L_Superior Frontal Lobe	60	6.16 (4.97)	525.02 (832.79)	−0.18	−0.15	−0.11	−0.16	−0.21[a]	−0.10	−0.16	−0.17	100
R_Superior Frontal Lobe	54	4.71 (5.01)	401.37 (621.85)	−0.28[b]	−0.28[b]	−0.23[a]	−0.27[b]	−0.31[c]	−0.20	−0.13	−0.18	100
L_Medial Temporal Lobe	58	5.27 (4.29)	55.39 (65.70)	0.07	−0.13	0.03	0.18	−0.26[b]	−0.23[a]	0.16	0.12	38
R_Medial Temporal Lobe	57	6.94 (5.22)	80.82 (86.00)	0.04	−0.05	−0.04	0.08	0.18	−0.23[a]	0.19	0.14	13
L_Inferior Frontal Lobe	46	3.87 (5.11)	88.73 (159.65)	−0.09	−0.19	0.03	0.03	0.12	0.08	0.01	0.10	25
R_Inferior Frontal Lobe	48	4.16 (5.37)	78.00 (143.33)	−0.12	−0.26[a]	−0.18	0.00	0.07	0.07	0.03	0.01	38
L_Hippocampus	48	3.42 (3.20)	40.27 (56.35)	−0.01	−0.07	−0.09	0.07	0.21	0.11	0.02	−0.03	50
R_Hippocampus	47	3.44 (3.24)	37.14 (53.42)	0.06	−0.03	0.00	0.06	0.05	0.03	0.19	0.11	0
L_Insular _WM	39	2.02 (3.50)	17.58 (35.81)	−0.11	−0.16	−0.19	−0.10	0.07	0.02	0.10	0.15	50
R_Insular_WM	42	2.07 (2.52)	16.18 (26.16)	−0.05	−0.14	0.12	−0.07	0.10	0.03	−0.05	0.04	50
L_Insular_GM	36	1.95 (3.35)	23.32 (66.48)	−0.16	−0.12	−0.14	−0.15	0.05	−0.04	0.02	0.10	63
R_Insular_GM	39	1.95 (2.61)	21.03 (66.48)	−0.03	−0.11	0.21	0.02	0.06	0.04	0.00	0.11	25
L_Orbital Frontal Cortex	38	1.79 (2.03)	27.33 (45.65)	0.11	0.00	0.17	0.07	0.11	0.02	0.14	0.23	0
R_Orbital Frontal Cortex	36	1.83 (2.55)	23.77 (47.58)	−0.07	−0.12	−0.13	−0.04	0.04	−0.02	0.00	0.00	50
L_Anterior Cingulate	37	1.25 (1.81)	11.64 (22.99)	−0.12	0.13	0.04	0.10	0.09	0.10	0.24	0.19	0
R_Anterior Cingulate	36	1.51 (1.98)	25.36 (81.84)	−0.23	−0.22	−0.16	−0.23	−0.04	−0.14	−0.02	−0.03	100
L_Thalamus	30	1.40 (2.15)	16.28 (39.78)	0.29	0.16	0.13	0.22	0.10	−0.03	0.12	0.06	13

Table 3 continued

Brain region	Number of subjects with lesions	Mean (SD) number of lesions	Mean (SD) volume of lesions	Sucrose L	Sucrose R	Citric acid L	Citric acid R	Caffeine L	Caffeine R	NaCl L	NaCl R	% Negative r's
R_Thalamus	32	1.48 (2.30)	13.65 (43.49)	0.00	−0.09	−0.07	0.09	0.05	−0.07	0.01	−0.03	50
L_Parietal Operculum	29	0.70 (0.94)	12.59 (29.28)	−0.22	−0.08	−0.14	−0.06	−0.16	−0.14	−0.17	−0.08	100
R_Parietal Operculum	21	0.60 (1.13)	14.03 (37.83)	−0.04	−0.02	−0.12	−0.16	−0.04	0.03	−0.01	−0.09	88

The cerebral cortex subsumes all lobes excepting the temporal lobes. Italics signify coefficients with p values ranging from 0.05 to 0.0005

[a] $p < 0.05$; [b] $p < 0.025$; [c] $p < 0.01$; [d] $p < 0.005$; [e] $p < 0.0025$; [f] $p < 0.001$; [g] $p < 0.0005$

the MS patients and the controls, i.e., an association only for caffeine, we found few correlations among lesion volumes and the intensity ratings, with only 8 of 216 coefficients being significant, albeit all in the negative direction. Interestingly, none of these correlations reached the nominal 0.05 alpha level for caffeine, the only stimulus for which a significant difference appeared in the mean intensity ratings between the MS patients and the controls. Five of the correlations were related to lesions in the right superior frontal lobe, one in the right cortex, and two in the left cortex (Table 4). Correlations between the number of lesions and intensity ratings were similarly sparse. Thus, only two significant negative correlations were observed: sour intensity ratings on the left side of the tongue with lesion numbers in the left and right frontal lobes (both $rs = -0.28$, $ps < 0.025$). All coefficients computed between the lesion numbers in these two brain structures and the 8 taste test measures were in the expected negative direction (16/16; 100 %).

A small subset, i.e., 4–5, of the patients had lesions within the brainstem and/or pons that were lateralized to one side or the other. Since an initial segment of the taste pathway passes through these structures, it was conceivable that taste function might be more compromised on the side of the tongue ipsilateral to the location of the lesions. However, the average taste scores on the side of the tongue ipsilateral to the side of the brainstem lesions did not differ from that of the average taste scores on the tongue contralateral to the lesion side, providing no support for the concept that, in MS, unilateral lesion activity within the brainstem differentially altered taste function on the left or the right sides of the tongue.

Discussion

This research represents the most comprehensive study performed to date on the influences of MS on the ability to taste. It determined whether associations are present between taste function and quantitative measures of brain lesions in MS and whether MS differentially influences various taste qualities and taste function mediated by CN VII (anterior 2/3rds of the tongue) and CN IX (posterior third of the tongue) afferents. MS significantly influenced the ability to identify tastants for all four classic taste qualities on both anterior and posterior regions of the tongue. Additionally, MS altered intensity ratings for the tastant caffeine. Taste identification test scores were correlated with the lesion volumes in the frontal and temporal lobes and a sizable proportion of the MS patients exhibited scores falling below the 5th percentile of those of matched controls. No lateralized taste deficits relative to lateralized lesions within the pons, brainstem, or elsewhere were

apparent. The fifth taste quality that is generally recognized today, umami, was not tested in this study, although presumably it would also be influenced by MS since deficits in umami taste have been found to be related to deficits in other taste qualities in clinical studies (e.g., [29]). In accord with earlier taste research in normal subjects [30], women generally outperformed men on all of our tests in both the MS and control groups, conceivably reflecting the fact that women possess a larger number of taste papillae and taste buds than do men [31].

Although the 15–32 % prevalence rate for taste dysfunction relative to controls was about half of that generally found for optic neuritis, a hallmark in the diagnosis of MS [32], it is nonetheless a substantial number. This suggests that altered taste function, albeit modest in magnitude and less noticeable than changes in vision, is a relatively common feature of MS. In general, most of our prevalence estimates of MS-related taste dysfunction (caffeine, 15.07 %; citric acid, 21.9 %; sucrose, 24.66 %; NaCl, 31.50 %) are higher than the 8 to ∼22 % prevalence estimates noted by other investigators who have performed quantitative or semi-quantitative taste testing of MS patients [5, 7, 10–12, 33]. Presumably this reflects differences in the criteria for defining dysfunction, the types of tastants and test procedures employed, sample sizes, and other factors. The low prevalence of taste dysfunction reported in numerous surveys presumably reflects the fact that most persons are unaware of less-than-total or near-total taste loss [8]. Such lack of awareness also is evident in the general population, as well as in Alzheimer's disease and Parkinson's disease. However, lack of awareness does not avert clinical significance, since such losses can be harbingers for nutritional deficits [34] and higher subsequent mortality [35, 36].

An important finding of the present study is that MS influenced the ability to identify all four classic taste qualities (Fig. 1). Most previous MS studies have not distinguished between taste qualities [5, 10, 11] or have reported that the deficits were limited to only a few such qualities. For example, Catalanotto et al. [37] noted adverse influences for taste quality identification and suprathreshold intensity perception only for NaCl (salty) and quinine hydrochloride (bitter); sweet (sucrose) and sour (citric acid) perception was not similarly affected. Our research suggests that the influence of MS is more widespread, although it is of interest that the only stimulus for which we observed an MS-related intensity deficit was for the bitter tasting agent caffeine, in accord with one of the observations of Catalanotto et al.

Our finding that MS impacted taste identification ability more than intensity perception conceivably reflects several factors. First, higher brain regions—regions with the most MS-related lesion activity—may influence taste quality more than perceived strength. For example, one functional imaging

Table 4 Spearman correlation coefficients between taste intensity ratings and MS-related lesion volumes and associated *p* values

Brain region	Number of subjects with lesions	Mean (SD) number of lesions	Mean (SD) lesion volumes	Sucrose L	Sucrose R	Citric acid L	Citric acid R	Caffeine L	Caffeine R	NaCl L	NaCl R	% Negative r's
Cortex + White Matter L	63	32.52 (22.75)	6537.50 (5283.93)	*−0.21*[a]	−0.16	*−0.28*[b]	−0.18	−0.18	−0.19	−0.14	−0.02	100
Cortex + White Matter R	63	31.64 (20.25)	6396.37 (5106.45)	−0.19	0.14	*−0.26*[b]	−0.14	−0.17	−0.14	−0.09	−0.08	88
R_Superior Frontal Lobe	54	4.71 (5.01)	401.37 (621.85)	*−0.27*[b]	*−0.24*[a]	*−0.32*[c]	−0.18	−0.21[†]	−0.21[†]	*−0.22*[a]	*−0.23*[a]	100

Italics signify coefficients with p values ranging from 0.05 to 0.005. The cerebral cortex subsumes all lobes excepting the temporal lobes

[a] $p < 0.05$; [b] $p < 0.025$; [c] $p < 0.005$

[†] Although these correlations were of the same magnitude as one of those for sucrose, they were not statistically significant at the 0.05 level because of the smaller sample size

study found the anterior insula/operculum and caudolateral orbitofrontal cortex to be less sensitive to stimulus intensity than the amygdala, pons, and middle insula [38]. Second, our intensity measure, based upon a single concentration for each of four tastants, may have lacked the sensitivity to detect a broader range of MS-related intensity deficits. However, it should be noted that both threshold and identification tests appear to be more sensitive to chemosensory deficits than suprathreshold scaling procedures. A classic example is a magnitude estimation study that completely missed the well-established age-related deficit observed using tests of odor identification and threshold sensitivity [39]. A recent meta-analysis of studies of taste function in older persons found taste threshold deficits in 94 % of the studies evaluated (17/18), whereas suprathreshold intensity deficits were observed in only 64 % of the evaluated studies (16/25) [40]. Nevertheless, the question remains as to what degree the smaller decrements observed in suprathreshold intensity measures represent methodological or physiological processes.

Although we observed very few lesions within the pons and brainstem, those that were observed were lateralized. Our finding that this lateralization was not mirrored by lateralized taste function may reflect the fact that such lesions are not independent of bilateral lesions found elsewhere in the brain. Under the assumption that the latter lesions influence the ability to taste, any unilateral influences at the level of the brainstem would likely be swamped. Had lesions other than the brainstem and pons lesions not been present, disproportionate unilateral dysfunction would have been expected. Thus, Onoda and Ikeda noted, in a review of 15 non-MS clinical cases of taste function, that unilateral gustatory impairment occurred with unilateral injury to any one of several brain structures, namely the pons (8 cases), thalamus (5 cases), midbrain (one case), and internal capsule (one case) [41]. These authors surmised, based on the side of the lesions and their effect on either unilateral or contralateral gustatory function, that the gustatory pathways ascend homolaterally from the medulla, cross in their course from the pons to the midbrain, and synapse within the contralateral thalamus. Bilaterally diminished taste responses have been observed in patients with unilateral midbrain and unilateral paramedian thalamic infarcts [42, 43].

Another important finding of our study is that the taste identification scores were negatively correlated with lesion volumes in the cortex, frontal lobe, and temporal lobes. Similar associations were less evident in other brain structures or for taste intensity ratings. Although the correlation coefficients are moderate, they are similar in magnitude to those reported by others between MS lesions and cognitive measures [44, 45]. Like some other studies (e.g., [46]), we found lesion volumes to be more strongly correlated with the dependent measures than lesion numbers, conceivably reflecting the fact that lesions can vary in size, with some spanning larger sectors of neural tissue than others [47].

It is of significance that a number of brain structures intimately associated with taste function had no or few MS-related lesions, implying that the adverse influence of MS on taste largely involves higher brain structures. Nevertheless, lesions made up <2 % of the volume of the large brain regions with the most lesion activity, suggesting that only a minority of such lesions impact neural pathways related to taste function, potentially explaining why normal taste function is present in most MS patients. Other explanations of weak associations between taste test scores and MS-related lesions include the potential redundancy and plasticity of neural circuits in higher brain regions [48] and the underestimation of disease burden due to generalized changes in normally appearing CNS white matter [49, 50]. Importantly, one cannot rule out the possibility that much of the influence of MS on taste function is not directly related to observable lesion activity but is due to more subtle damage to membrane channels. At the receptor level, taste perception depends upon movement of Na^+ and H^+ ions through specialized membrane channels, either directly as in the case of salty and sour tastants (e.g., the amiloride-sensitive Na^+ channel and ENaC-like channels) [51] or indirectly, as in the case of sweet- and bitter-tasting stimuli that activate G-protein coupled receptors [52–54]. MS is known to influence both ionotropic and metabotropic forms of neural transmission and could conceivably exert some of its effects at the level of the cell membrane [55, 56].

Among the strongest influences on taste function observed in this study was that of sex. Women generally outperformed men on all of our tests in both the MS and control groups. This is in accord with sex differences noted in other taste studies [30], as well as the fact that women typically outperform men on a wide range of sensory tasks, including ones involving hearing, olfaction, and touch [57]. Women have been found to possess a larger number of taste papillae and taste buds than men [31] and, after correcting for cranial volume, have larger frontal and medial paralimbic cortices. Men, on the other hand, have larger relative volumes of the hypothalamus, frontomedial cortex, and amygdala [58]. To what degree such factors dictate the sex differences observed in taste function is unknown, although being a female may afford some degree of protection from adverse influences on the taste system.

The present study has both strengths and weaknesses. Among its strengths are its relatively large sample size, sophisticated regional taste testing of both sexes, and assessments of associations between the taste test scores and the MS-related lesions, as measured by MRI. Multiple tongue regions and stimuli were evaluated, allowing for a determination of regional deficits in taste function and their associations with MS-related CNS brain lesions. Among its weaknesses are (a) its focus on only the four classic taste qualities, despite the plethora

of available taste stimuli, including numerous sodium and potassium salts, (b) its evaluation of only suprathreshold taste perception, which may be less sensitive than taste threshold measures, and (c) the calculation of a relatively large number of correlations between the taste measures and the brain lesion activity, potentially inflating the type I error rate. That being said, the observed correlations were logically consistent and were in the expected negative direction. As noted above, it is of interest that in our patient population lesions were sparse in brain structures generally associated with the primary taste projections, namely the brainstem, pons, and medulla, yet clear-cut associations between lesion volumes and taste function were evident throughout higher brain structures.

In summary, the present study clearly demonstrates that MS is commonly associated with decrements in the ability to identify all four classic taste qualities within both anterior and posterior regions of the tongue. Female MS patients, like women in general, identified tastants more accurately and rated their perception as more intense than did male MS patients. Our study demonstrates that lesion volumes within large sectors of the frontal and temporal lobes are correlated with functional measures of taste. In light of the discovery of taste receptor proteins within the alimentary tract [51], future research may be of value in determining whether MS-related changes in oral taste function are associated with gastric motility, changes in microbiota, and other MS-related alterations in which extraoral taste receptors may play a role [59].

Acknowledgments We are indebted to the subjects who participated in this study. We thank Nancy A. Lee, M.D., Andre S. Souza, M.D., and Hussam Tallab, M.D., for their contributions to this work, and Greg Smutzer, Ph.D., for comments on an earlier version of the manuscript. Special thanks goes out to Inna Chung, who played a significant role in preparing the manuscript for journal submission. This research was supported by the U.S. National Institutes of Health Grants RO1 DC 02974 (Doty), R01 NS 37172 (Doty), and R01 NS070906 (Pham).

Compliance with ethical standards

Conflicts of interest None of the authors of this study declare any conflicts of interest.

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