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PURE-TONE AUDITORY THRESHOLDS ARE NOT CHRONICALLY ELEVATED IN MULTIPLE SCLEROSIS

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Abstract

Despite the fact that acute cases of MS-related pure-tone hearing loss have been reported in the literature, consensus is lacking as to the chronic influences of MS on pure-tone thresholds. Most studies examining such influences have been limited by small sample sizes, lack of statistical comparisons between patients and controls, and confounding of the hearing measure with influences from sex and age. To date, associations between pure-tone thresholds and central MS-related brain lesions have not been assessed. In this study, pure-tone thresholds ranging from 0.5 kHz to 8 kHz were measured in 73 MS patients and 73 individually age- and gender-matched normal controls. In 63 MS patients, correlations were computed between the threshold values and MRI-determined lesion activity in 26 central brain regions. Although thresholds were strongly influenced by sex, age, and tonal frequency, no meaningful influences of MS were discerned. Moreover, no significant association between the threshold values and central MS-related lesion activity was evident in any brain region evaluated. This study, the largest on this topic to employ carefully matched control subjects and the sole study to assess relationships between auditory thresholds and central MS-related lesions, strongly suggests that (a) MS is not chronically associated with pure-tone hearing loss and (b) pure-tone thresholds are unrelated to MS lesion activity in higher brain regions. These findings, along with general reports from the literature, support the concept that when MS-related hearing threshold deficits are found, they are episodic and primarily dependent upon lesions within the eighth nerve or brainstem.

Keywords

multiple sclerosis; hearing; audition; pure-tone thresholds; psychophysics; magnetic resonance imaging

Multiple sclerosis (MS) is a debilitating autoimmune disease of the central nervous system (CNS). MS-related lesions involving the eighth cranial nerve, as well as the cochlear nucleus and pontine trapezoid body of the brainstem, are known to *acutely* influence pure-tone

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thresholds, the most widely used measure of hearing acuity (e.g., Robinson & Rudge, 1977; Arnold & Bender, 1983; Furman, Durrant, & Hirsch, 1989; Drulovic, Ribaric-Jankes, Kostic, & Sternic, 1993; Fischer, Mauguiere, Ibanez, Confavreux, & Chazot, 1985; Hellmann, Steiner, & Mosberg-Galili, 2011). Consensus is lacking, however, as to the *chronic* influences of MS on pure-tone thresholds, with some studies reporting no such influences (Citron, Dix, Hallpike, & Hood, 1963; LeZak & Selhub, 1966) and others reporting losses mainly at low frequencies (Simpkins, 1961), high frequencies (Djupesland, Tvete, Stein, & Bachen, 1981; Musiek, Gollegly, Kibbe, & Reeves, 1989), or all frequencies, with the higher frequencies predominating (Dayal & Swisher, 1967; Noffsinger, Olsen, Carhart, Hart, & Sahgal, 1972; Luxon, 1980; Lewis et al., 2010). Unfortunately statistical comparisons of thresholds between MS patients and matched controls are seldom made and confounding of the hearing measure with age and sex is common. It is rarely appreciated, for example, that nearly 18% of the American population between the ages of 40 and 49 years – an age range when MS is frequently detected – exhibit hearing loss (i.e., pure tone thresholds > 25 dB in at least one ear) (Cheng et al., 2009).

Six published studies have evaluated pure-tone thresholds in both MS patients and controls. As with MS studies in general, the results have been conflicting and the quality of data suspect. Half of these studies have claimed that MS chronically and adversely influences auditory sensitivity (Simpkins, 1961; Dayal & Swisher, 1967; Lewis et al., 2010), whereas half have found no meaningful adverse influences of MS on such sensitivity (Cohen & Rudge, 1984; Coelho, Ceranic, Prasher, Miller, & Luxon, 2007; Zeigelboim et al., 2007).

In the first of the three studies reporting chronic influences of MS on pure-tone thresholds, Simpkins (1961) tested 78 MS patients and 83 controls. Elevated thresholds occurred more often at lower than at higher frequencies in the MS patients, a finding that others have been unable to replicate (LeZak & Selhub, 1966; Dayal & Swisher, 1967). No statistical analyses were performed and the controls, while being aged-matched by decade, were not sex-matched, a critical issue since women, on average, have lower pure-tone thresholds than men (Nash et al., 2011). In the second of these three studies, Dayal & Swisher (1967) found greater average MS-related threshold losses for the right, but not left, ear of 13 women. The thresholds of nine men did not differ from those of controls and, as with the Simpkins study, no statistical analyses were performed. In the third study, Lewis et al. (2010) reported that 47 MS patients had pure-tone thresholds that were, on average, 5–10 dB higher than those of 49 controls at both low (0.25, 0.50 & 0.75 kHz) and high (3.0, 4.0 & 6.0 kHz) frequencies. Although analysis of variance was employed, the controls differed from the MS cohort in ways that would bias the findings in the direction of the results (e.g., more women and fewer army veterans).

In contrast to the aforementioned studies, Coelho et al. (2007) found normal thresholds (i.e., ≤ 20 dB HL) in 30 patients presenting with MS and in 22 age- and sex-matched controls. Ten of the MS patients had identifiable brain stem lesions and 20 had lesions elsewhere in the brain, particularly in the periventricular area. Similarly, Cohen & Rudge (1984), in a study of 44 MS patients and 44 matched controls, observed normal audiometric thresholds at all frequencies save 0.5 and 1.0 KHz, where bilateral and left-ear decrements, respectively, were noted. No statistical analyses were employed to determine if these latter alterations were statistically significant. While Zeigelboim et al. (2007) found that the pure-tone thresholds of 6–9 women with MS did not differ from controls at 10.0, 11.2, and 12.5 kHz, they were paradoxically *lower* than those of controls in at least one ear to other ultrahigh frequencies (9.0, 14.0 & 16.0 kHz). Age matching was made within three decade intervals (30–40 yrs; 40–50 yrs; 50–60 yrs). No men were evaluated.

In light of the above-mentioned discrepancies and methodological issues, the present study sought to definitively establish, in 73 MS patients and 73 controls individually matched on the basis of age, sex, and ethnic background, the influences of MS on pure-tone thresholds ranging from 0.5 kHz to 8 kHz. Additionally, it sought to determine, for the first time, whether such thresholds are correlated with MS-related lesion activity within each of 26 brain regions, as measured by a well-validated MRI segmentation algorithm. If, in fact, correlations are present between central lesions and auditory threshold values, the general belief that such thresholds primarily reflect peripheral auditory function in humans would be thrown into question. Central lesions in some other sensory systems, most notably olfaction, can influence human detection threshold measures (Doty, Reyes and Gregor, 1987).

Materials and Methods

Subjects

The demographics of the primary study group are presented in Table 1. Approximately half came from within the University of Pennsylvania Health Care 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. Expanded Disability Status Scale (EDSS) scores were available from 29 patients whose physicians were at the University of Pennsylvania, but were generally unavailable from patients referred by other sources [mean (SD) = 4.54 (1.80) for 12 men and 3.36 (1.60) for 17 women]. Persons with EDSS scores of 3.5 – 4.5 are fully ambulatory despite relatively severe disability and are able to walk without aid from 300 to 500 meters (for details, see Kurtzke, 1983).

Usable magnetic resonance images (MRI) were available for 63 of the patients and were employed to quantify the lesion numbers and volumes in specific brain regions. A subgroup of 7 female and 3 male MS patients [mean age (SD) = 49.20 (10.89) yrs] and 7 female and 3 male matched controls [mean age (SD) = 49.90 (13.10) yrs] was tested on two occasions separated from one another by a mean (SD) of 2.07 (1.20) years to assess test-retest reliability of the auditory measures and the stability of the MRI lesion activity in brain regions exhibiting significant lesion activity. All subjects were paid $20 per hour for their participation and were reimbursed for travel and food expenses. 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 (2000).

This study was a component of a comprehensive program that evaluated auditory, olfactory, gustatory, vestibular, and neuropsychological function of the same set of MS patients. The non-auditory findings will be published elsewhere. Individuals were excluded from consideration if they had a positive medical history for non-MS disorders that could confound not only the auditory, but 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.

Hearing Measurement

An otoscopic examination was initially performed to ensure cerumen was not occluding the external auditory meatus and no abnormalities of the tympanic membrane were evident. If

cerumen was present, it was removed before the hearing tests were administered. The test stimuli were presented using a Grason-Stadler 61 clinical audiometer in a Model S-122 Eckoustic Noise Control Booth. The pure-tone thresholds were determined using the modified Hughson-Westlake method; ISO 8253-1) for the left and right ears at 0.25, 0.50, 1.0, 2.0, 4.0 and 8.0 kHz) (Carhart & Jerger, 1959). In this procedure, the air conduction thresholds are determined by a descending method of limits. The hearing level was calculated in dB according to the ANSI S3.6 (1996). In addition to assessing absolute hearing values, clinical function was categorized as follows: < 20dB HL = normal hearing; 20–40dB HL = mild hearing loss; 40–60dB HL = moderate hearing loss; 60–70dB HL = moderately severe hearing loss; 70–90dB HL = severe hearing loss; > 90dB HL = profound hearing loss.

Imaging Protocol

All MS patients underwent, usually on the same day as the psychophysical testing, thin section magnetic resonance imaging (MRI) of the brain with gadolinium enhancement using a General Electric (Milwaukee, WI) 1.5-T signal scanner employing a standard head coil. All MRI evaluations included T1-weighted sagittal sections 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 (Goldszal et al., 1998; Bazin et al., 2007). Lesions were then defined semi-automatically by first using a fuzzy segmentation algorithm applied to the multichannel brain extracted images (Pham & Prince, 1999; Pham, 2001). This algorithm was modified to model lesion intensities as outliers, similar to the approach described by Van Leemput, Maes, Vandermeulen, Colchester, & Suetens (2001). The resulting segmentation was inclusive of all lesions but included false-positives that were manually removed by a trained operator. The intra-rater reliability intraclass correlation coefficient for this 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 (Van Leemput et al., 2001; Shen & Davatzikos, 2002). A total of 26 brain regions were defined for each side of the brain (i.e., 52 total brain structures; see results section).

Statistical Analyses

All statistical analyses were made using modules from SYSTAT (Wilkinson, 1990). For initial analyses, the categorical clinical thresholds were assessed using χ^2 analysis. Non-categorical data were evaluated using analysis of variance (ANOVA) or covariance (ANCOVA). Given that the MS and control subjects were matched on the basis of age, sex, and ethnicity, the MS and control threshold values were treated as within group measures. The main factors were group (MS, control), sex (M, F), ear side (L, R) and stimulus frequency (0.25, 0.5, 1.0, 2.0, 4.0 & 8.0 kHz). Age was entered as a covariate. Analyses were performed on square root transformed threshold data to provide more normally distributed underlying frequency distributions (Irvine, Martin, Klimkeit, & Smith, 2000). Similar analyses were performed within subgroups of the data, such as among subjects who exhibited plaque loads in the pons and brainstem and controls matched to these individuals on sex and age. To simplify the presentation of results, F values and degrees of freedom are not reported in the text; η^2_p values, which reflect effect sizes, are reported only when significant p values are present. In the subgroup of 10 MS patients who were evaluated longitudinally, estimates of test-retest reliability and lesion stability within brain regions

exhibiting significant plaque activity were established using Pearson product moment correlations.

To address whether systematic associations existed among the auditory threshold measures and lesions within brain regions represented by a least 30 subjects, two principal component (PC) analyses were performed, one employing lesion volumes and the other lesion numbers. In essence, PC analyses extract independent clusters of variables that correlate with one another but are generally independent, i.e., not correlated, with other clusters of intercorrelated variables. The intercorrelation matrices of the brain region lesion values, age, and pure-tone threshold values (0.25, 0.5, 1.0, 2.0, 4.0 & 8.0 kHz) were subjected to analysis. All measures except age were square root transformed. The lesion data from the following brain regions were employed: anterior cingulate gyrus, cerebral cortex, hippocampus, inferior frontal lobe, insular white matter, insular gray matter, medial frontal lobe, medial temporal area (i.e., hippocampus, amygdala, and immediate parahippocampal area), orbitofrontal cortex, superior frontal lobe, temporal lobe (which includes the medial temporal lobe), and thalamus. Note that while most of the regions are mutually exclusive, in some cases overlap was present (e.g., the frontal lobe subsumes inferior, medial, and superior frontal lobe sectors; the temporal lobe subsumes the medial temporal area). Since preliminary analyses found no left:right differences in either the threshold or the lesion measures, the data were averaged across the left and right sides of the brain to stabilize the measures and minimize the number of variables in the model. We followed the convention of analyzing principal components with eigenvalues >1 (Wilkinson, 1990). In our case, the lowest of these eigenvalues fell immediately above the directional break of the scree plot. Varimax rotations were employed to better define the principal components. We focused on component loadings ≥ 0.40 in light of the relatively small sample sizes and the fact that this resulted in logically interpretable factors. To establish the stability of the component structures, each analysis was run 20 times using a bootstrap procedure that randomly omitted a single subject from each iteration.

Results

The percent of the MS and control subjects falling into each of the pure-tone threshold clinical function/dysfunction categories is presented in Table 2 for each stimulus frequency and side of ear tested. No significant differences in the overall distributions of the MS and control groups were present, as indicated by χ^2 analyses performed at each stimulus frequency for each ear side, with those cells containing <5 cases combined with mild or moderate hearing loss categories to ensure adequate cell sizes for valid analysis (all ps > 0.20).

Statistical Evaluation of Threshold Measures from MS and Control Subjects

The mean (SD) threshold values for the men and women of the MS and control groups are shown in Table 3. No statistically significant influence of MS on the threshold measures was evident, as indicated by a non-significant subject group (MS vs. control) main effect in the ANCOVA ($p = 0.19$). The side of ear tested was also not significant ($p = 0.59$). Frequency was statistically significant ($p < 0.001$, $\eta^2_p = 0.23$), reflecting the increase in threshold values at higher frequencies in the entire group of 146 subjects. A significant age effect was also present ($p < 0.001$, $\eta^2_p = 0.40$), as was a significant age by frequency interaction ($p < 0.001$, $\eta^2_p = 0.22$). These effects reflect the well known age-related decrement in hearing sensitivity which is more marked at higher frequencies. Also as expected from the literature, women exhibited lower average thresholds than did men ($p < 0.001$, $\eta^2_p = 0.14$). A subject group by gender interaction was significant at the 0.08 alpha level, reflecting the tendency for the male:female difference to be smaller in the MS than in the control group. Subject group did not interact with any other variable (all ps > 0.20).

Relationship of Auditory Threshold Measures to Lesion Activity within the Pons and Brainstem

The average number of lesions, lesion volumes, and volumes of the left- and right-side brain areas are shown in Table 4 for those brain regions that contained lesions. Brain regions not containing lesions are shown in Table 5. It is apparent from these tables that only a few lesions were located in brain regions specifically associated with auditory function (e.g., pons, brainstem, and inferior colliculus), although larger brain regions associated with hearing in some manner, such as the temporal cortex, exhibited considerable lesion activity.

To probe whether the left or right hearing thresholds of those nine patients with MS who had lesions in the brain stem differed from those of nine age- and sex-matched MS patients who had no such lesions, an ANCOVA was performed using the within subject factors of hearing threshold frequency and ear side and the between subject factor of lesion group (lesion left/lesion right/no lesion). Age served as a covariate. No significant influences of lesion group or its interaction with the other factors were present (all ps > 0.30), although significant effects were noted for age ($p = 0.003$; $\eta^2_p = 0.14$), hearing threshold frequency ($p < 0.001$, $\eta^2_p = 0.11$), and age by hearing threshold frequency ($p < 0.001$; $\eta^2_p = 0.17$). A similar analysis performed for age- and sex-matched MS patients with and without lesions within the pons (n = 8/group) revealed no significant influences of lesion group or its interaction with the other factors (ps > 0.20). Significant effects were again present, however, for age ($p = 0.003$; $\eta^2_p = 0.14$), hearing threshold frequency ($p < 0.001$, $\eta^2_p = 0.10$), and the age by hearing threshold frequency interaction ($p < 0.001$; $\eta^2_p = 0.15$).

To explore this issue relative to controls, we compared the left and right thresholds of the nine patients with brainstem lesions to those of nine age- and gender-matched controls using an ANOVA. No main effects of group (patients, controls) ($p = 0.52$) or ear side ($p = 0.21$) were present. No significant interactions between group and frequency ($p = 0.28$), frequency and ear side ($p = 0.88$), or group by ear side by frequency ($p = 0.47$) were observed. Frequency was highly significant ($p < 0.001$, $\eta^2_p = 0.25$). The same analysis performed for the eight patients with pontine lesions vs. eight matched normal controls found similar results; i.e., no significant main effects of group ($p = 0.32$) or ear side ($p = 0.25$) or interactions between group and frequency ($p = 0.23$), frequency and ear side ($p = 0.87$), or group by ear side by frequency ($p = 0.61$). However, frequency was again highly significant ($p < 0.001$, $\eta^2_p = 0.30$).

Relationship of Auditory Threshold Measures to Lesion Activity throughout the Brain

The principal component analyses performed on the intercorrelation matrices among the variables of age, sex, auditory threshold values, and the two lesion measures (volume, number) found no evidence of associations between the threshold measures and the lesion measures. The first principal components analysis was performed on the threshold measures and *lesion volumes* from brain regions for which a minimum of 30 MS patients exhibited lesion activity. In this analysis, thirteen of the 20 iterations resulted in a five principal component (hereafter termed factor) solution with eigenvalues > 1 and seven iterations with a 6 factor solution. The percent of total variance accounted for in these iterations ranged from 74.87 to 83.98. The first factor of note, which we termed the **general auditory threshold factor**, loaded solely with auditory threshold values. In all 20 iterations the 0.25, 0.5, 1.0 and 2.0 kHz frequencies loaded ≥ 0.40 in on this factor. In 16 of these iterations, the 4 kHz frequency also exhibited loadings ≥ 0.40, whereas in 11 the 8 kHz frequency was also represented. No meaningful loadings from other variables were present. The second factor, termed the **age and high frequency threshold factor**, loaded with age and both the 4 and 8 kHz threshold values on 19 of the 20 iterations. Meaningful loadings from other factors were not present, save five iterations when the orbitofrontal cortex was represented. A third

factor, termed a **limbic/paralimbic lesion volume factor**, was comprised of loadings ≥ 0.40 for plaque volumes from the hippocampus (17 iterations), inferior frontal lobe (20 iterations), medial frontal lobe (20 iterations), anterior cingulate gyrus (16 iterations), orbitofrontal cortex (11 iterations), and thalamus (12 iterations). No other meaningful loadings were evident. A fourth factor, which we termed **the global cortical lesion volume factor**, was comprised of loadings ≥ 0.40 of plaque volumes from the whole cortex (20 iterations), superior frontal lobe (20 iterations), medial frontal lobe (20 iterations), temporal lobe (18 iterations), and hippocampus (8 iterations). A fifth factor, perhaps best termed an **insular white and gray matter lesion volume factor**, consistently loaded with lesion volumes from both insular white and gray matter, with loadings ≥ .40 occurring for 18 and 19, respectively, of the iterations (the other loadings from these structures were > 0.30). This factor was accompanied by lesion volume loadings ≥ .40 for the anterior cingulate gyrus on 14 iterations, orbitofrontal cortex on 11 iterations, and the inferior frontal lobe on 12 iterations. No other meaningful loadings were present. The sixth factor that appeared in seven iterations was heterogeneous in terms of factor loadings ≥ .40, with each iteration loading with one to three sets of lesion volumes from various structures.

The second principal components analysis was performed on the auditory threshold measures and the *lesion numbers* for the aforementioned brain regions. Fifteen of the 20 iterations resulted in a five factor solution and five in a 4 factor solution with eigen values > 1. The percent of total variance accounted for by these iterations ranged from 74.55 to 81.98. As with lesion volumes, one factor that emerged was a **general auditory threshold factor** that uniquely loaded with the six auditory threshold values. The 1 kHz frequency loaded on this factor ≥ .40 on all 20 iterations, whereas the 0.25 and 0.5 kHz frequencies did so on 19 of the iterations. The 2 kHz frequency was represented on 16 of the iterations, the 4 kHz on 12 of the iterations, and the 8 kHz frequency on 9 of the iterations. No other variables meaningfully loaded on this factor. Also in accord with lesion volumes was an **age and high frequency threshold factor** that loaded with age and both the 4.0 and 8.0 Hz threshold values on 15 of the 20 iterations. No consistent meaningful loadings from other measures were present on this factor. In a similar manner to lesion volumes, an **insular white and gray matter lesion number factor** received lesion number loadings ≥ 0.40 from both of these brain regions on all 20 iterations, from the orbitofrontal cortex on 17 iterations, and from the inferior frontal lobe on 15 iterations. The anterior cingulate gyrus was similarly represented on 14 iterations. No other measures were regularly represented on this factor. The factor that accounted for most of the variance in the lesion numbers was a **global lesion number factor**, which had some pattern similarities with the global cortical lesion factor observed for lesion volumes, such as positive loadings ≥ 0.40 from the whole cortex (20 iterations), the temporal lobe (20 iterations), the medial frontal lobe (12 iterations) and, less frequently, the superior frontal lobe (7 iterations). Unlike the global cortical lesion volume factor, however, loadings ≥ 0.40 occurred from lesion numbers of the thalamus (20 iterations), hippocampus (17 iterations in the positive direction), inferior frontal lobe (17 iterations), orbitofrontal cortex (14 iterations), medial temporal lobe (18 iterations), and anterior cinculate gyrus (11 iterations). No other meaningful loadings were present on this factor. The fifth most common factor shared some common loadings with the global cortical lesion volume factor; namely, whole cortex (10 iterations), superior frontal lobe (12 iterations), and medial frontal lobe (10 iterations). The other loadings were infrequent ones from the orbitofrontal cortex (4 iterations), anterior cingulate gyrus (3 iterations), inferior frontal lobe (2 iterations), and thalamus (2 iterations). The lesion numbers within the hippocampus were represented on only one iteration.

Test-Retest Reliability of Pure-Tone Thresholds in MS Patients and Matched Controls

The Pearson correlation coefficients computed for the left and right transformed threshold values obtained on the repeated test occasions of the 10 MS and 10 matched control subjects are presented in Table 6. No meaningful differences between the correlation coefficients of the MS and control subjects emerged. Of the 12 comparisons of coefficients between the MS and controls, 6 were nominally larger in the MS patients and 6 were nominally larger in the controls, but a statistically significant difference was never observed at any frequency. The measures were suggestive of high reliability, particularly in light of the relatively small samples. The slight tendency for the coefficients to be larger at higher than at lower frequencies conceivably reflects the greater range of individual threshold values commonly present at higher frequencies.

Changes in Relative Lesion Activity Across the Test-Retest Periods

The Pearson correlations computed for both lesion volumes and lesion numbers across the test-retest periods for the aforementioned 10 MS patients are presented in Table 7. Only those brain regions in which at least half of the subjects exhibited lesion activity were assessed. It is apparent that considerable stability in the lesion numbers and volumes was present across the test-retest periods, despite the fact that the mean test-retest intervals was ~ two years. The mean number or volume of the MS-related lesions obtained on two test occasions did not differ significantly (two-tailed t-tests; all ps > 0.15).

DISCUSSION

The present study – the most extensive study on this topic ever performed – found no evidence that pure-tone auditory thresholds are chronically influenced by MS. Indeed, the percentage of individuals with hearing loss in both the control and MS groups was essentially equivalent (Table 2) and, in fact, somewhat lower than that expected in the general population, as determined from the National Health and Nutritional Examination Survey (NHANES) (Agrawal, Platz, & Niparko, 2008). In NHANES, for example, 43% of 'normal' persons between the ages of 40 and 59 exhibited either unilateral or bilateral *high frequency* thresholds > 25 dB. In our study, where the cut-off for abnormality was 20 dB, the percent of MS patients and controls with decreased hearing at 4 kHz and 8 kHz ranged from 26% to 28%.

The lack of an effect of MS on the pure-tone thresholds was evident not only from the assessment of the number of patients exhibiting abnormal thresholds, but from statistical comparisons of hearing threshold scores of the MS and control subjects. Moreover, principal components analysis suggested the threshold measures were independent of MS-related lesions within a large number of brain regions. Importantly, those brain regions that are most closely associated with audition contained no or few lesions. These findings imply that when MS-related hearing losses occur, they are rare, typically acute, and most commonly involve the peripheral auditory system or brainstem, in accord with numerous case reports.(Jabbari, Marsh, & Gunderson, 1982; Daugherty, Lederman, Nodar, & Conomy, 1983; Drulovic et al., 1993; Shea, III & Brackmann, 1987; Franklin, Coker, & Jenkins, 1989; Bergamaschi, Romani, Zappoli, Versino, & Cosi, 1997; Oh, Oh, Jeong, Koo, & Kim, 2008) In one study of 705 MS patients, only 1.7% exhibited hearing loss during a period of symptom exacerbation (Fischer et al., 1985). In all but one of these cases the loss was unilateral. In another study of 253 patients evaluated at a MS clinic over a six-year period, 4.35% (i.e., 11 cases) had sudden hearing loss early in the course of the disease (Hellmann et al., 2011). In seven of these cases, the hearing loss was the presenting complaint. In all cases, the loss resolved with a residual deficit in only two cases.

While our auditory findings are in general accord with a number of case-control studies (e.g., Cohen & Rudge, 1984; Coelho et al., 2007), they contrast with those of several others (Simpkins, 1961; Dayal & Swisher, 1967; Lewis et al., 2010). With rare exception (e.g., Dayal & Swisher, 1967), one-to-one matching of the MS subjects to controls on the basis of sex and age was not performed in these studies, and most employed relatively small samples. Among the larger case-control studies was that of Lewis et al. (2010). As noted in the introduction, these investigators reported that the pure-tone thresholds of 47 MS patients – mostly veterans – were, on average, higher than those of 49 controls, with a greater deficit occurring in patients with secondary progressive MS (SP) than in normal controls or in patients with relapsing-remitting MS (RR). Unfortunately, while the groups were matched on age, they were not matched on sex, a factor that, as the present study confirms, clearly influences pure-tone thresholds. Thus, their SP group was 71.4% male (15/21), their RR group 42.3% male (11/26), and their control group 49% male (24/25). Based on sex alone, one would predict that their SP group would underperform the two other groups. Importantly, an unspecified number of their controls were from a different general population than their MS subjects, being non-veterans who had participated in other auditory-related studies. Veterans within the age range of 48–59 years have significantly higher average pure tone thresholds at high frequencies than non-veterans, although the magnitude of the average effect is reportedly small (< 3 dB) (Wilson, Noe, Cruickshanks, Wiley, & Nondahl, 2010).

The present research represents the first time associations have been sought between pure-tone threshold values and MS-related lesion activity in a large number of relatively specific brain regions. While meaningful relationships were not noted, it should be pointed out that inferring associations between specific brain regions and MS-related behavioral, sensory, and cognitive deficits is challenging, since lesions generally occur at multiple sites and can develop or regress at different rates. It is noteworthy that lesion activity measured in this study was relatively stable in the 10 MS patients tested longitudinally, as indicated by the strong test-retest correlations shown in Table 6 and the lack of significant differences in the mean numbers and volumes of lesions between the two test periods. These effects reflect, in part, between-subject differences in baseline lesions and relatively subtle changes in total lesion activity over the time course of the measurements. Although the small sample size may have lacked enough power to observe meaningful changes in lesion activity over this time period, other investigators have reported, in small samples, general stability of chronic lesions in serial MRI scans of patients with both relapsing/remitting and chronic progressive MS over periods extending from six months to a year (e.g., Harris et al., 1991; Willoughby et al., 1989). When new lesions develop, they tend to reach a maximum size in about a month before remitting and largely disappearing by six months (Harris et al., 1991). In many cases, a small residual abnormality is left that is indistinguishable from the chronic MS lesions. This observation led Willoughby et al. (1989) to suggest (p. 43) that "… the expanding and contracting new lesions are the basic or primary lesion in MS, that the characteristic demyelinated plaque is represented by the small residual area that these lesions shrink down to, and that the typical collection of scatted white matter lesions in chronic MS may represent the accumulated resida of dozens or more of these active lesions occurring over many years."

There are multiple mutually non-exclusive explanations for why associations between MS-related lesion activity and pure-tone threshold values were not found in this study. First and foremost, if no threshold deficits were present then one would not expect to see meaningful associations between threshold values and lesion activity. Second, compensatory mechanisms may overcome compromises induced by slowly developing lesions, a well-known phenomenon in several modalities (Helmchen et al., 2011). Third, central lesions, while they may alter conduction times, may not be severe enough to completely block the

conduction of activity from simple tones, reflecting so-called 'silent' lesions. As one ascends the auditory pathway from the receptor level into the brain, pathways become more distributed, likely limiting the influences of small punctuate lesions within the involved structures. In accord with this concept is the finding that the magnitude of pure-tone deficits resulting from pontine lesions, when present, is less than that resulting from auditory nerve fiber lesions (Parker, Decker, & Richards, 1968). Fourth, the lesions observed in this study may simply not have involved brain regions critical for auditory processing. The MS-related lesions were only rarely detected in brain regions known specifically to be related to hearing, such as the brainstem, pons, and the inferior colliculus. Most case reports of MS-related hearing loss – losses which are typically unilateral -- suggest the lesions are usually located peripheral to the level of the cochlear nucleus (Luxon, 1980; Daugherty et al., 1983; Franklin et al., 1989; Furman et al., 1989; Drulovic et al., 1993). Unilateral loss would not be expected from lesions above the cochlear nucleus, given the bilateral division of the upper auditory pathways. According to Dix (1965), "perfectly normal" audiograms have been observed in patients subjected to hemispherectomy. Finally, pure-tone thresholds may not challenge the auditory system strongly enough to detect underlying dysfunction, such as that detected by stimuli varying in the temporal domain (Levine et al., 1994). Measures that require rapid temporal responding or that recruit more cortical resources, such as speech perception, are reported to be influenced by MS even in the absence of pure-tone deficits. For example, in one study 62 patients with MS were administered an auditory test battery consisting of measures of the acoustic reflex (AR), the auditory brainstem evoked potential (BAEP), masking level differences (MLD), and speech audiometry (SA) (Jerger, Oliver, Chmiel, & Rivera, 1986). Seventy-one percent of the patients exhibited abnormalities in the AR, 55% in the SA, 52% in the BAEP, and 45% in the MLD. The combination of an abnormality on the AR, BAEP, or SA yielded a 90% rate of identifying MS. Interestingly, the combination of AR or SA or MLD yielded an 87% identification rate without any contribution from BAEP. Of 26 MS patients with normal pure tone thresholds assessed by Musiek et al. (1989), nearly two-thirds (16/26) exhibited abnormalities on at least one element of the BAEP. Of these 16 patients, 11 (69%) had bilateral abnormalities.

In conclusion, the present data strongly suggest that pure-tone auditory thresholds are not chronically influenced by MS. Moreover, this study supports the concept that MS-related lesions within the lower auditory pathways are rare and that lesions in higher brain regions are generally unrelated to pure-tone threshold deficits. This research affirms the need to adequately control for such basic variables as sex and age before inferences regarding causal associations of hearing deficits in MS can be made.

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Table 1

Basic demographics of the MS and matched control subjects.

Subject Group	No.	Mean Age (SD)	Ethnicity (W/B)	Mean Yrs Education (SD)	Mean (SD) Disease Duration	Disease Classification*
MS - Males	21	45.24 (11.41)	(17/4)	15.10 (2.74)	7.36 (3.96)	RR: 15; PP: 2; SP: 2; U: 2
MS - Females	52	45.60 (8.61)	(38/14)	14.52 (2.20)	7.84 (6.61)	RR: 42; PP: 1; SP: 4; U: 5
C - Males	21	45.43 (10.78)	(17/4)	15.10 (3.23)	----	----
C - Females	52	46.60 (9.35)	(38/14)	15.51 (2.36)	----	----

*RR = relapsing remitting; PP = primary progressive; SP = secondary progressive; U = undefined

Table 2

Percent of MS and control subjects falling into five hearing ability categories as a function of ear side and tonal frequency, as defined by ANSI S3.6 (1996). See text for details.

MS GROUP	.25 kHz		.50 kHz		1.0 kHz		2.0 kHz		4.0 kHz		8.0 kHz		Mean
Ear Side:	L	R*	L	R	L	R	L	R	L*	R	L	R	
≤20dB (normal)	92	82	92	84	92	88	84	81	74	75	74	75	82.75
21–40dB (mild)	8	16	8	15	8	12	16	19	21	21	14	16	14.50
41–60dB (moderate)		1		1					6	3	9	6	4.33
61–70dB (moderately severe)										1			1.00
71–90dB (severe)											3	3	3.00

CONTROL GROUP	.25 kHz		.50 kHz		1.0 kHz		2.0 kHz		4.0 kHz		8.0 kHz		Mean
Ear Side:	L	R	L	R	L	R	L	R	L*	R	L*	R	
≤20dB (normal)	93	89	96	83	90	92	87	83	73	73	70	73	83.50
21–40dB (mild)	7	7	4	14	10	7	13	16	20	17	21	14	12.50
41–60dB (moderate)		1				1		1	6	7	7	7	4.28
61–70dB (moderately severe)		3		3						3		3	3.00
71–90dB (severe)											1	3	2.00

*Columns not adding to 100% reflect rounding errors.

Table 3

Mean (SD) pure-tone threshold values for MS and control men and women for each of six frequencies.

MALE MS PATIENTS (N = 21)						
	0.25 kHz	**0.50 kHz**	**1.0 kHz**	**2.0 kHz**	**4.0 kHz**	**8.0 kHz**
Mean (SD)	15.87 (5.39)	14.05 (5.94)	12.52 (7.43)	12.79 (8.97)	20.03 (11.71)	17.02 (17.26)
Median	17.50	12.50	12.50	12.50	17.50	15.00
95% CI	13.52–18.42	11.47–16.88	9.36–16.14	9.03–17.20	15.06–25.73	10.07–25.79
MALE CONTROLS (N = 21)						
Mean (SD)	14.35 (8.24)	15.90 (8.68)	15.53 (8.58)	17.74 (8.93)	22.77 (16.08)	20.23 (22.49)
Median	12.50	15.00	15.00	17.50	22.50	22.50
95% CI	10.84–18.34	12.19–20.09	12.69–18.66	13.91–22.03	16.04–30.68	11.29–31.77

FEMALE MS PATIENTS (N = 52)						
	0.25 kHz	**0.50 kHz**	**1.0 kHz**	**2.0 kHz**	**4.0 kHz**	**8.0 kHz**
Mean (SD)	12.85 (6.88)	12.49 (6.50)	12.05 (6.59)	14.62 (7.19)	15.65 (8.97)	13.28 (12.38)
Median	12.50	11.25	12.50	15.00	15.00	12.50
95% CI	11.00–14.83	10.74–14.36	10.28–13.97	12.68–16.69	13.25–18.25	10.06–16.95
FEMALE CONTROLS (N = 52)						
Mean (SD)	11.28 (7.77)	12.52 (7.60)	10.45 (6.82)	11.62 (8.17)	13.92 (8.79)	12.65 (12.60)
Median	10.00	12.50	10.00	10.00	12.50	12.50
95% CI	9.22–13.54	10.50–14.73	8.63–12.43	9.46–14.00	11.58–16.48	9.36–16.43

Table 4

Brain regions containing MS-related lesions.

Brain Region	No. with Lesions	Median (Range) Lesions	Mean (SD) Lesions	Median (Range) Lesion Volumes (mm^3)	Mean (SD) Lesion Volume (mm^3)	Median (Range) Region Volume (mm^3)	Mean (SD) Region Volume (mm^3)	% Volume& No. Lesions/Mean Region Volume
Cerebral Cortex Left	63	26 (6–119)	32.52 (22.75)	5102.47 (748.89–18726.05)	6537.50 (5283.93)	364954.16 (285698.56–525370.75)	372977.06 (47800.37)	1.75 & .00
Cerebral Cortex Right	63	27 (6–97)	31.64 (20.25)	448.88 (19.94–18757.07)	6396.37 (5106.45)	374941.94 (289699.88–521832.44)	380037.92 (47377.99)	1.68 & .00
Medial Frontal Lobe Left	63	12 (2–74)	14.44 (10.59)	1167.61 (90.84–6336.55)	1503.67 (1511.21)	95958.82 (76663.37–148421.45)	99267.06 (14813.33)	1.51 & .01
Medial Frontal Lobe Right	63	13 (1–41)	13.00 (6.99)	926.11 (2.22–7222.78)	1526.88(1623.76)	100844.17 (77777.80–149932.47)	103422.50 (15002.34)	1.48 & .01
Temporal Lobe Left	63	10 (1–37)	12.86 (8.30)	704.55 (24.37–6041.88)	1170.74 (1200.34)	112783.91 (85505.73–141699.39)	112548.18 (13785.93)	1.04 & .01
Temporal Lobe Right	61	12 (0–34)	15.03 (9.02)	746.65 (0–5448.10)	1121.33 (1202.92)	117857.58 (89059.52–164145.39)	119117.01 (14855.76)	.94 & .02
Medial Temporal Area Left	58	4 (0–15)	5.27 (4.29)	28.80 (0–356.71)	55.39 (65.70)	5764.93 (4515.34–7349.07)	5741.75 (715.49)	.96 & .09
Medial Temporal Area Right	57	6 (0–20)	6.94 (5.22)	44.31 (0–352.28)	80.82 (86.00)	6214.69 (4630.55–9048.41)	6381.95 (875.38)	1.27 & .11
Superior Frontal Lobe Left	60	5 (0–25)	6.16 (4.97)	197.19 (0–4076.66)	525.02 (832.79)	68826.88 (55050.42–93497.31)	70159.46 (8843.42)	.75 & .00
Superior Frontal Lobe Right	54	4 (0–28)	4.71 (5.01)	170.60 (0–3296.78)	401.37 (621.85)	65288.60 (50896.22–88217.59)	66075.80 (8208.68)	.61 & .01
Hippocampus Left	48	3 (1–13)	3.42 (3.20)	15.51 (0–314.61)	40.27 (56.35)	2767.26 (1632.88–3717.74)	2715.59 (399.95)	1.48 & .13
Hippocampus Right	47	3 (0–11)	3.44 (3.24)	17.73 (0–288.03)	37.14 (53.42)	2222.22 (1440.12–3013.18)	2207.70 (343.99)	1.68 & .16
Inferior Frontal Lobe Left	46	2 (0–25)	3.87 (5.11)	28.80 (0–908.39)	88.73 (159.65)	24639.42 (18947.61–33630.23)	25081.41 (3414.52)	.35 & .02
Inferior Frontal Lobe Right	48	1 (0–20)	5.16 (5.37)	17.73 (0–762.16)	78.00 (143.33)	26216.91 (20988.15–36492.76)	26880.43 (3627.71)	.29 & .02
Insular White Matter Left	39	1 (0–19)	2.02 (3.50)	4.43 (0–194.97)	17.58 (35.81)	2038.33 (1328.48–2818.21)	2030.24 (335.06)	.87 & .10
Insular White Matter Right	42	1 (0–11)	2.09 (2.60)	4.43 (0–139.58)	16.18 (26.16)	1741.44 (1304.97–2895.76)	1799.54 (330.77)	.90 & .12
Insular Gray Matter Left	36	1 (0–17)	1.95 (3.35)	2.22 (0–383.30)	23.32 (66.48)	4887.56 (3015.40–7151.88)	5012.94 (330.77)	.46 & .04
Insular Gray Matter Right	39	1 (0–12)	1.98 (2.64)	4.43 (0–168.38)	21.03 (66.48)	5574.39 (3949.16–8000.45)	5576.32 (883.16)	.38 & .04
Anterior Cingulate Gyrus Left	37	1 (0–11)	1.25 (1.81)	2.21 (0–141.80)	11.64 (22.99)	6150.44 (4590.67–8875.60)	6286.86 (1036.49)	.19 & .02
Anterior Cingulate Gyrus Right	36	1 (1–10)	1.51 (1.98)	4.43(0–602.64)	25.36 (81.84)	8040.33 (6172.60–13734.36)	8181.42 (1448.92)	.31& .02
Orbitofrontal Cortex Left	38	1 (0–9)	1.79 (2.03)	6.65 (0–190.54)	27.33 (45.65)	11000.34 (8197.63–16009.75)	11378.36 (1740.91)	.24 & .02
Orbitofrontal Cortex Right	36	1 (0–10)	1.83 (2.55)	2.22 (0–248.15)	23.77 (47.58)	10523.99 (7585.83–14119.87)	10567.77 (1515.99)	.22 & .02
Thalamus Left	30	0 (0–9)	1.40 (2.15)	0 (0–268.09)	16.28 (39.78)	6314.39 (4211.81–9103.80)	6358.35 (959.02)	.26 & .02
Thalamus Right	32	1 (0–13)	1.48 (2.30)	2.22 (0–303.53)	13.65 (43.49)	5691.82 (3298.99–7479.79)	5743.72 (844.77)	.24 & .03
Parietal Operculum Left	29	0 (0–4)	.70 (.94)	0 (0–146.23)	12.59 (29.28)	1761.38 (901.74–2951.15)	1780.41 (427.23)	.71 & .04
Parietal Operculum Right	21	0 (0–5)	.60 (1.13)	0 (0–223.77)	14.03 (37.83)	1214.14 (613.71–2321.92)	1251.13 (353.97)	1.12 & .05

Brain Region	No. with Lesions	Median (Range) Lesions	Mean (SD) Lesions	Median (Range) Lesion Volumes (mm^3)	Mean (SD) Lesion Volume (mm^3)	Median (Range) Region Volume (mm^3)	Mean (SD) Region Volume (mm^3)	% Volume& No. Lesions/Mean Region Volume
Amygdala Left	7	0 (0–4)	.18 (.55)	0 (0–24.37)	.74 (3.31)	514.01 (248.15–837.49)	517.78 (119.24)	.14 & .03
Amygdala Right	5	0 (0–2)	.13 (.46)	0 (0–141.80)	.88 (4.41)	469.70 (241.50–952.70)	492.31 (145.41)	.18 & .03
Brainstem Left	5	0 (0–1)	.08 (.27)	0 (0–26.59)	1.09 (4.71)	11190.88 (7796.61–14895.32)	11415.70 (1535.31)	.01 & .00
Brainstem Right	4	0 (0–2)	.08 (.33)	0 (0–90.84)	2.74 (14.92)	10260.33 (7016.73–14042.32)	10489.84 (1439.51)	.03 & .00
Pons Left	4	0 (0–1)	.06 (.25)	0 (0–24.37)	0.53 (3.13)	6850.56 (4570.73–9438.35)	6875.53 (1005.03)	.01 & .00
Pons Right	4	0 (0–4)	.11 (.54)	0 (0–48.74)	1.13 (6.50)	6234.63 (4249.48–8826.86)	6346.82 (924.35)	.02 & .00
Cerebellum Left	2	0 (0–1)	.03 (0–1)	0 (0–62.04)	1.09 (7.85)	56293.36 (47495.31–78384.87)	57195.03 (599.59)	.00 & .00
Cerebellum Right	1	0 (0–1)	.02 (0–1)	0 (0–2.22)	.04 (.28)	59494.87 (43500.62–77206.19)	59252.67 (6598.92)	.00 &.00
Medial Lemniscus Left	0	0 (0)	0 (0)	0 (0)	0 (0)	571.62 (350.06–839.70)	577.18 (103.34)	--
Medial Lemniscus Right	2	0 (0–2)	.05 (.28)	0 (0–6.65)	.18 (1.00)	562.76 (383.30–786.53)	567.43 (85.04)	.03 & .00
Superior Colliculus Left	0	0 (0)	0 (0)	0 (0)	0 (0)	307.97 (175.03–509.58)	314.79 (73.67)	--
Superior Colliculus Right	1	0 (0–1)	.12 (.13)	0 (0–4.43)	0.07 (.58)	316.83 (197.19–595.99)	335.04 (88.31)	.02 & .04

Listing is in order of the number of subjects exhibiting lesions within the given brain regions and the % volume of the brain region involved. Dark gray indicates brain regions most closely associated with hearing. N = 63.

Table 5

Brain regions containing no MRI-determined lesions.

Brain Region	No. of 63 Subjects with Lesions	Median (Range) Volume (mm^3) of Brain Region	Mean (SD) Volume (mm^3) of Brain Region
Medulla Left	0	3158.98 (2372.88–4251.69)	3202.74 (484.72)
Medulla Right	0	3352.17 (2257.67–4661.57)	3374.04 (484.72)
Inferior Colliculus Left	0	274.73 (146.23–469.70)	278.78 (68.98)
Inferior Colliculus Right	0	241.50 (159.52–489.64)	256.90 (60.73)
Central Tegmental Tract Left	0	225.99 (161.74–401.02)	236.82 (46.91)
Central Tegmental Tract Right	0	206.05 (139.58–347.85)	212.66 (139.58–347.85)
Pontine Parabrachial Nucleus Left	0	77.55 (44.31–135.15)	78.99 (22.60)
Pontine Parabrachial Nucleus Right	0	66.47 (35.45–106.35)	68.89 (16.43)
Medial Geniculate Body Left	0	73.11 (31.02–130.72)	78.18 (24.18)
Medial Geniculate Body Right	0	55.39 (11.08–106.35)	57.78 (18.93)
Solitary Nucleus Left	0	57.61 (22.16–110.78)	57.32 (16.42)
Solitary Nucleus Right	0	48.74 (17.73–88.62)	48.04 (14.29)
Brachia Inferior Colliculus Left	0	35.45 (6.65–11.08)	36.79 (13.06)
Brachia Inferior Colliculus Right	0	31.02 (11.08–55.39)	31.19 (9.55)

Listing is in order of the relative size of each brain region. Dark gray denotes brain regions most closely associated with auditory function. N = 63.

Table 6

Test-retest reliability coefficients for pure-tone threshold measures computed between two longitudinal test sessions for Multiple Sclerosis (MS) and control subjects.

	LEFT EAR			RIGHT EAR		
	Controls	**MS**	**P†**	**Controls**	**MS**	**P†**
250 Hz	0.82	0.49	0.16	0.73	0.55	0.24
500 Hz	0.74	0.79	0.42	0.79	0.91*	0.24
1000 Hz	0.73	0.78	0.43	0.72	0.75	0.46
2000 Hz	0.91*	0.79	0.25	0.72	0.94*	0.20
4000 Hz	0.88*	0.86*	0.45	0.87*	0.95*	0.22
8000 Hz	0.94*	0.85*	0.22	0.78	0.74	0.43

N = 10 MS and 10 controls. P values in column for test of differences between control and MS coefficients.

*$p \leq 0.05$ after Bonferroni alpha correction.

†Calculated according to Preacher (2002).

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Table 7

Pearson correlations computed between measures of MRI-determined lesions from the first and second test occasions of 10 MS patients who received repeated tests. Correlations computed only on structures for which lesion activity was detected in a least half of the 10 subjects.

Brain Region	Lesion Numbers	Lesion Volumes
Cerebral Cortex	0.96	0.97
Hippocampus	0.84	0.91
Inferior Frontal Lobe	0.88	0.90
Insular White Matter	0.87	0.87
Insular Gray Matter	0.94	0.82
Medial Frontal Lobe	0.83	0.99
Medial Temporal Area	0.99	0.82
Orbitofrontal Cortex	0.76†	0.63†
Superior Frontal Lobe	0.70†	0.92
Temporal Lobe	0.82	0.89

Values represent left and right sides of the brain combined. All correlations are significant at $p \leq 0.05$ following Bonferroni correction for inflated alpha except for those signified by †.