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Auditory middle latency responses in individuals with debilitating tinnitus

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Abstract

Many researchers have investigated the possibility of using auditory evoked potentials (AEPs) to objectively diagnose tinnitus. Published AEP studies suggest differences in neural activity in individuals with tinnitus compared to control groups, but the results are not consistent. There is a great deal of variability seen in auditory evoked- and event-related potentials in the tinnitus population, which reflects AEP variability in general. At the present time, there is not a specific AEP measure able to objectively diagnose tinnitus. The auditory middle latency response (AMLR) has not been extensively examined to determine its potential as an objective measure of tinnitus; therefore, this study examined the AMLR in fourteen individuals with and without severe tinnitus to determine its potential as a diagnostic measure of tinnitus. The data from this study revealed similar AMLR results between groups. This outcome suggests that this AMLR protocol may not be specific enough to detect neurophysiological changes associated with tinnitus.

Keywords: auditory, auditory perception, evoked potentials, tinnitus.

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INTRODUCTION

A reliable physiological measure capable of diagnosing tinnitus would be a valuable addition to the assessment and management of tinnitus patients. There have been many attempts to develop objective measures of tinnitus, but to date, none have been successful. Researchers have investigated utilizing auditory evoked potentials (AEPs) to detect changes in neural activity associated with tinnitus (Maurizi et al., 1985; Ikner & Hassen, 1990; Lemaire & Beutter, 1995; Rosenhall & Axelsson, 1995; Colding-Jorgensen et al., 1992; Hoke et al., 1989; Jacobson et al., 1991; Jacobson et al., 1996; Kadner et al., 2002; Weisz et al., 2004; Norena et al., 1999; Attias et al., 1993; Gerken et al., 2001). Results from these studies vary, and although group differences between individuals with tinnitus compared to those without tinnitus are sometimes reported in the literature, the findings often are not replicable.

AEPs are non-invasive measurements evoked by sound that evaluate the integrity of central auditory pathways and are classified according to their latency: short latency (i.e., occur 1-10 ms following a stimulus), middle latency (i.e., occur 15-70 ms following a stimulus), and late latency (i.e., occur 75 ms or later following a stimulus). The generators of the early AEP responses are associated with the auditory nerve and brainstem, whereas the middle and late responses correspond to neural activity higher in the central auditory pathway such as the midbrain and cortex (Hall, 1992).

Auditory electrophysiological measures have been extensively studied in individuals with tinnitus to determine whether AEP results offer insight into the mechanisms of tinnitus perception. Tinnitus by definition involves the perception of sound in the absence of acoustic stimulation and is theorized to manifest in the central auditory system (Eggermont, 2003; Cacace, 2003). Variability seen in AEP results in individuals with tinnitus may be explained by the various neurophysiological models of tinnitus perception including: tonotopic reorganization of the auditory cortex (Eggermont, 2006; Mühlnickel et al., 1998), increased spontaneous firing rate of auditory neurons (Kaltenbach, 2000), and increased neural synchrony (Norena & Eggermont, 2003), all of which results in altered neural processing. Another possibility is that variability in AEPs is not related to tinnitus, but to something strongly correlated with tinnitus (e.g., hearing loss, aging). The current study attempted to control for confounding variables through the statistical model employed. Of the many studies that utilized electrophysiological measures in individuals with tinnitus, limited information has been published on the auditory middle latency response (AMLR) in this population. Gerken, Hesse, and Wiorkowski (2001) published one of the few studies to evaluate the AMLR in individuals with problem-tinnitus. Gerken et al. grouped their participants into four categories: problem-tinnitus (9 individuals, mean age 45.7 years); normal hearing without tinnitus (11 individuals, mean age 28 years); hearing loss without tinnitus (8 individuals, mean age 40.9 years); and elderly without tinnitus (7 individuals, mean age 63.6 years). No significant differences in the AMLR results were found between groups. Gerken et al. then performed further analysis on the AMLR data and reported that 5 of the 9 individuals in the problem-tinnitus group had enhanced AMLR amplitudes defined by 3 standard deviations or more compared to the normal hearing group.

As a result of these analyses, Gerken et al. suggested that tinnitus subtypes might exist in the general population and account for the enhanced AMLR amplitudes found in certain individuals within this group. This view is consistent with the general finding that tinnitus sufferers display a high degree of variability on auditory electrophysiological measures.

OBJECTIVES

To further evaluate AMLR as a possible physiological measure of tinnitus, this study investigated whether increased AMLR amplitude is characteristic of individuals with severe tinnitus and hearing loss opposed to individuals who report no tinnitus, but have hearing loss.

The current study's hypothesis was that individuals with severe tinnitus would reveal a pattern of enhanced AMLR amplitudes compared to a control group, consistent with the findings from Gerken et al. If results reveal this pattern of AMLR activity, a clinical application could be developed using AMLR to monitor tinnitus management.

MATERIALS AND METHODS

Participants

Fourteen individuals with severe tinnitus (20 to 61 years; mean age of 50.3 years; standard deviation of 12.7 years; 4 females) and fourteen individuals without tinnitus (25 to 62 years; mean age of 40.5 years; standard deviation of 13.2 years; 8 females) participated in this study. Eligibility criteria for the tinnitus group were: constant, severe tinnitus described as disabling (interfering with daily activities), no history of neurological disease, no significant hearing loss from .25 to 3 kHz (pure tone hearing thresholds $\leq$ 25 dB HL from .25 to 2 kHz and $\leq$ 30 dB HL at 3 kHz), and no middle ear pathology. Individuals undergoing treatment for their tinnitus or who had tried tinnitus treatments in the past were not excluded. The non-tinnitus individuals served as a control group and the eligibility criteria were the same as above except adults needed to report no history of constant tinnitus.

Informed consent was obtained prior to any measurements being performed. All research procedures were approved by the University of Illinois at Urbana-Champaign and Oregon Health & Science University Institutional Review Boards (IRB# 05356 & 2047 respectively).

Tinnitus severity was quantified using the Tinnitus Handicap Inventory Questionnaire (THI) developed by Newman, Jacobson, and Spitzer (1996). The THI is a 25-item questionnaire scaled from 1 to 100. The higher the score, the more the individual feels handicapped by his/her tinnitus. THI scores for participants in the tinnitus group ranged from 44 to 98. Reported duration of the tinnitus ranged from 1 year to greater than 32 years (mean=9.7 years; standard deviation=9.2 years).

In cases where the tinnitus was more severe in one ear (i.e., perceived to be louder in one ear) or localized to one ear, that ear was designated as the test ear. In cases where the tinnitus was equally severe bilaterally, the test ear was chosen randomly. Each participant in the non-tinnitus control group was matched to a participant in the tinnitus group in regards to the test ear.

AMLR Measurements

Data were recorded using a Bio-logic (Natus Medical Inc., San Carlos, CA) Navigator Pro or Explorer measurement system installed on a desktop computer. The eliciting stimulus was an acoustic click, 100 μs in duration, rarefaction polarity, presented through Bio-logic insert earphones using E.A.R. 3A foam ear-tips (Aearo Company Auditory Systems, Indianapolis, IN). A slow click rate of 1.1/sec was used to optimize the recording of Pb (Nelson, Hall III, & Jacobson, 1997). The stimulus level was 70 dB nHL. Silver disk electrodes were applied according to the International 10/20 System with placements at Cz-A1 or Cz-A2 relative to the ear receiving the stimulus (i.e., test ear). Inter-electrode impedance was maintained below 5 kΩ. Evoked responses were amplified with a gain of 75 K and band-pass filtered from .003 to 1.5 kHz over a 106.6 ms time window. Click stimuli were presented and averaged in trials of 500 sweeps. Recordings were performed until two waveforms with good replication were collected. Displayed in Figures 1 and 2 are sample AMLR waveforms from a non-tinnitus participant and tinnitus participant respectively. Single trials that were contaminated with the post-auricular sonomotor reflex or had a greater than 50% rejection rate were discarded.

Absolute latencies of AMLR components were designated as the negative most amplitude point or highest positive amplitude point within the time domain of 16-25 ms for Na, 25-35 ms for Pa, 35-45 ms for Nb, and 50-80 ms for Pb (Jerger et al., 1988). If the waveform had multiple peaks or a broad plateau shape, the highest point in the middle of the plateau was marked. The relative peak to peak amplitude of the Na-Pa complex and Nb-Pb complex were computed from the voltage measured at the absolute latency of the AMLR components Na, Pa, Nb, and Pb.

The goal of the analysis was to determine if tinnitus affects AMLR latency and amplitude, after adjusting for known effects such as age, hearing ability, and gender. The observed AMLR latencies and relative amplitudes define a 6-dimensional response vector measured on each subject. The AMLR mean vector denotes the vector of the means of these six elements (Na, Pa, Nb, and Pb latencies and Na-Pa and Nb-Pb relative amplitudes) indexed by tinnitus status. To achieve our goal of testing the effects of tinnitus on mean AMLR responses, we developed a multivariate response regression model of the AMLR mean vector as a function of gender, hearing ability, and age as well as tinnitus status. This approach is a natural extension of standard multiple analysis of variance (MANOVA) models to include continuous and categorical predictors, with the exception that we use restricted maximum likelihood estimation, as opposed to the method of moments, for inferences (Littell et al., 2000).

The AMLR mean vector was modeled using the multivariate response regression model, with an unstructured correlation among AMLR latencies and amplitudes measured on the same subject. The model included age, mean pure tone thresholds between .25 and 3 kHz, mean pure tone thresholds between 4 and 8 kHz as continuous covariates, and gender and tinnitus as categorical predictors. We tested the null hypothesis of no tinnitus effects on the AMLR mean vector using an F-Test with 6 numerator and 28 denominator degrees of freedom.

RESULTS

AMLR waveforms were recorded for all participants in both groups. Absolute latencies (ms) of AMLR components Na, Pa, Nb, Pb and the relative amplitude (μV) of Na-Pa and Nb-Pb were analyzed to determine if group differences existed. Wave V of the auditory brainstem response was present in the recordings and was within the normal range for all subjects, suggestive of normal function in the neural auditory pathway preceding the AMLR. The mean values for AMLR latencies and relative amplitudes are displayed in Figures 3 and 4 respectively.

A multivariate response regression model was fit to the AMLR data, including tinnitus status, age, gender, and hearing ability as predictors. The tinnitus effect was not statistically significant ($F_{6,28} = 1.59$, $p=0.19$), indicating that the results showed insufficient evidence to conclude that tinnitus affects mean AMLR latency or amplitude at the 0.05 test level, after adjusting for important covariates.

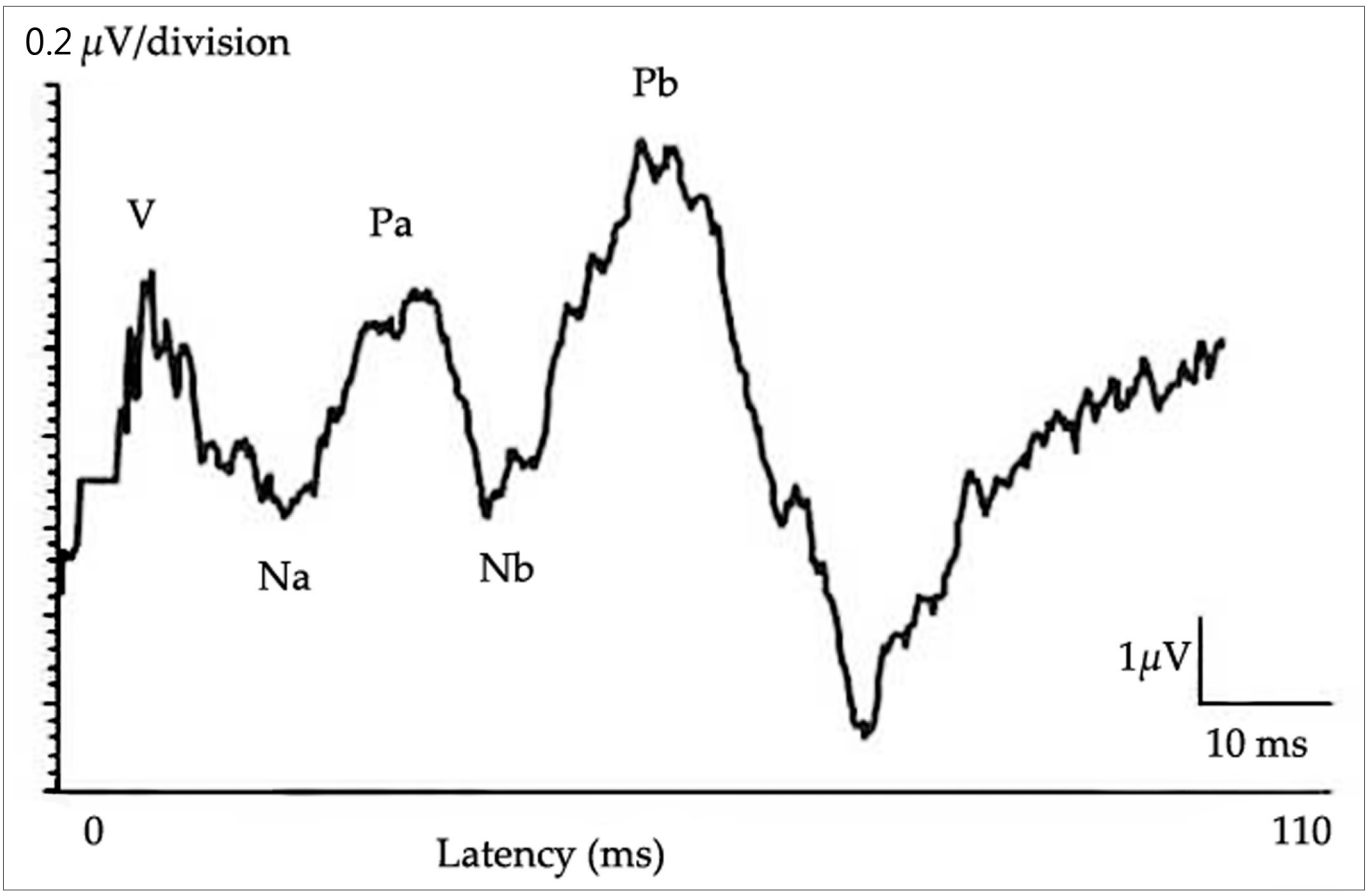

Figure 1. AMLR Waveform: Non-Tinnitus - Sample AMLR waveform recorded from a non-tinnitus participant. ABR wave V and AMLR components Na, Pa, Nb, and Pb are labeled.

A summary of the sample characteristics for both groups is shown in Table 1. In regards to gender, most of the tinnitus participants (n=10; 71.4%) were male, while most non-tinnitus participants were female (n = 8; 57.1%). Although the age ranges were similar between groups (20 to 62 years old for the entire sample), tinnitus participants were slightly older than non-tinnitus participants with a mean age of 50.3 versus 40.5 years, respectively. Average pure tone hearing thresholds from .25 to 3 kHz were slightly higher among tinnitus participants (11.6 dB HL) than among non-tinnitus participants (6.1 dB HL). Average pure tone thresholds between 4 and 8 kHz were markedly different between the tinnitus and non-tinnitus group (36.4 versus 11.3 dB HL, respectively). There is relatively little overlap in average pure tone thresholds for these frequencies in this sample, with only one non-tinnitus participant above the mean threshold observed for tinnitus participants.

CONCLUSION

The hypothesis that the AMLR would be sensitive to detect neurophysiological changes in the central auditory system secondary to tinnitus was not supported by data collected in the current study. Although participants with tinnitus in the current study were older and had more hearing loss than non-tinnitus control participants, AMLRs recorded from both groups were statistically similar.

The purpose of the current study was to follow-up on the results from Gerken et al. focusing on patients with severely debilitating tinnitus in order to see if a group of patients with the most severe tinnitus symptoms would be more likely to show larger AMLR amplitudes. Enhanced AMLR amplitudes did not characterize the tinnitus group in the current study. This finding, although not supporting the Gerken et al. results, does not negate their findings, but reinforces the fact that severe tinnitus alone does not comprise a homogeneous group of individuals with tinnitus. It is important to consider the diversity of etiologies associated with tinnitus. In the current study, self-reported etiology included noise exposure, side-effect of medication, head injury, and sudden onset not associated with any event (see Table 2).

Many factors contribute to the generation of AEP waveforms, such as neuronal firing rate and neural

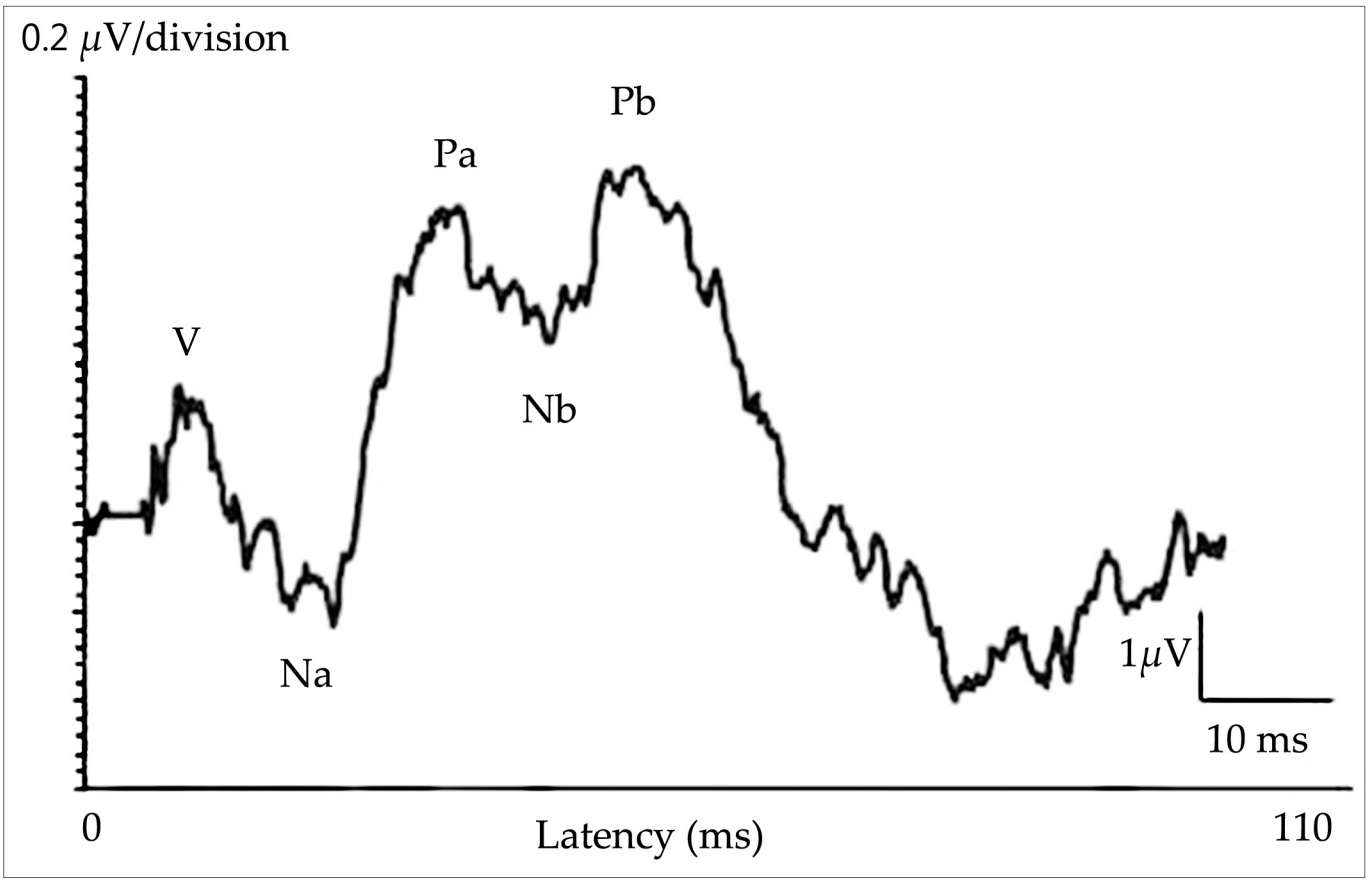

Figure 2. AMLR Waveform: Tinnitus Participant - Sample AMLR waveform from a tinnitus participant. ABR wave V and AMLR components Na, Pa, Nb, and Pb are labeled.

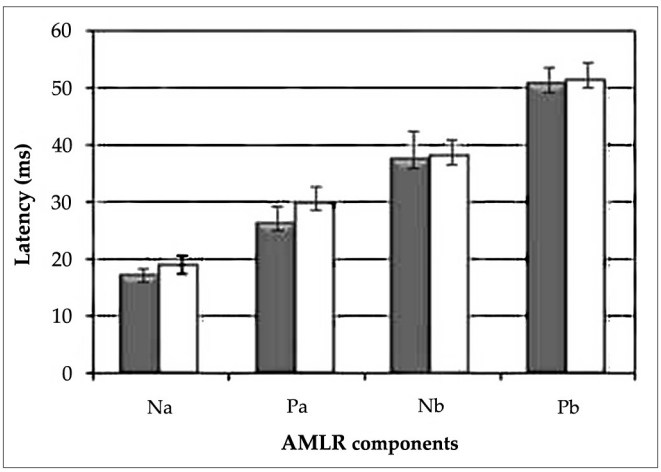

Figure 3. Latency - Mean AMLR latencies (ms) are represented by black bars for the non-tinnitus group and by white bars for the tinnitus group. Standard deviations are also included.

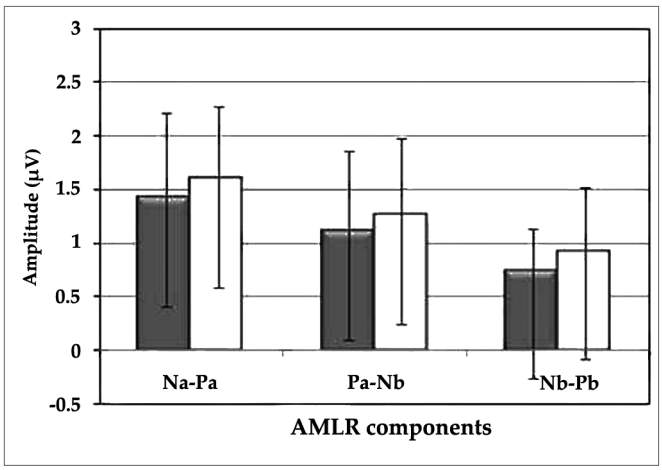

Figure 4. Amplitude - Relative AMLR amplitudes (μV) are represented by black bars for the non-tinnitus group and by white bars for the tinnitus group. Standard deviations are also included.

synchrony of AEP components (Eggermont, 2007). In addition, age and hearing loss affect AMLR amplitude and latency in a well documented way, for example, Pa latency becomes delayed and amplitude sometimes enhanced with advancing age (Woods & Clayworth, 1986; Chambers & Griffiths, 1991; Chambers, 1992). The current study attempted to control for hearing loss by restricting enrollment to individuals with hearing within the clinically accepted normal range at frequencies .25 to 3 kHz and to control for age by having the two groups be

Table 1. Summary Characteristics.

		Tinnitus		All
		Tinnitus	No tinnitus	
N		14	14	28
Gender				
Female	N	4	8	12
	%	28.6	57.1	42.9
Male	N	10	6	16
	%	71.4	42.9	57.1
Age (years)	Mean	50.3	40.5	45.4
	Min	20.0	25.0	20.0
	Max	61.0	62.0	62.0
Mean PTT. 25-3 kHz	Mean	11.6	6.1	8.8
	Min	5.0	0.0	0.0
	Max	20.0	12.0	20.0
Mean PTT 4-8 kHz	Mean	36.4	11.3	23.9
	Min	3.3	0.0	0.0
	Max	76.7	58.3	76.7

Summary of sample tinnitus characteristics.
Mean PTT = Average pure tone threshold in dB HL.

Table 2. Self-Reported Tinnitus Etiology.

Accident
Skiing accident
Work-related accident (left-sided pain)
Noise Exposure
Work related (used impact tools, mechanic)
Shooting off firecrackers
Rock concert
Doctor's Appointment
Dental visit for jaw pain (pain resolved, tinnitus persisted)
Cerumen impaction (tinnitus persisted after cerumen removed)
Side-effect of medication
Associated with medication (Celexa)
Miscellaneous
Associated with move to the West Coast
Associated with vacation to Oregon coast, but not a particular event
Sudden onset, not associated with illness, accident, or event

within the same approximate age range. The sampling strategy of balancing on age and hearing loss helped to reduce confounding on these important effects. Furthermore, we fit a regression model to statistically adjust for these confounders. The results from the current study did not reveal tinnitus to have a large enough effect to demonstrate differences in any portion of the AMLR.

Published studies utilizing electrophysiological measures to evaluate tinnitus usually report differences in neural activity in individuals with tinnitus, but it is not possible to know to what degree concomitant factors contributed to the results. The AMLR protocol used in the current study elicited patterns of neuronal activation that were similar for subjects with or without tinnitus.

In summary, previous studies of auditory electrophysiology in individuals with tinnitus have shown prolonged latencies and enhanced amplitudes of AEP components. However, without better replication of these results, to date no AEP measure offers consistent diagnostic capabilities for tinnitus. Rather than attempting to use AEPs to objectively diagnose tinnitus, other physiological measures (e.g., neural imaging) may offer more promise to identify a biological marker of tinnitus.

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