Research Article

Effects of Tonic Muscle Activation on Amplitude-Modulated Cervical Vestibular Evoked Myogenic Potentials (AMcVEMPs) in Young Females: Preliminary Findings

CHRISTOPHER G. CLINARD,¹ ANDREW P. THORNE,¹ AND ERIN G. PIKER¹

¹*Department of Communication Sciences and Disorders, James Madison University, 235 Martin Luther King Jr. Way, MSC 4304, Harrisonburg, VA 22807, USA*

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ABSTRACT

Cervical vestibular evoked myogenic potentials (cVEMPs) are usually elicited by transient tonebursts, but when elicited by amplitude-modulated (AM) tones, they can provide new information about cVEMPs. Previous reports of cVEMPs elicited by AM tones, or AMcVEMPs, have not systematically examined the effects of tonic EMG activation on their response properties. Fourteen young, healthy female adults (ages 20–24) with clinically normal audiograms participated in this study. AMcVEMPs were elicited with bone-conducted 500 Hz tones amplitude modulated at a rate of 37 Hz and recorded for five different EMG targets ranging from 0 to 90 μ V. Amplitude increased linearly as tonic EMG activation increased. Signal-to-noise ratio (SNR) was minimal at 0 μ V, but robust and with equivalent values from 30 to 90 μ V; phase coherence and EMG-corrected amplitude had findings similar to SNR across EMG target levels. Interaural asymmetry ratios for SNR and phase coherence were substantially lower than those for raw or corrected amplitude. AMcVEMP amplitude scaled with tonic EMG activation similar to transient cVEMPs. Signal-to-noise ratio, phase coherence, and EMG-corrected amplitude plateaued across a range of EMG values, suggesting that these properties of the response reach their maximum values at relatively low

levels of EMG activation and that higher levels of EMG activation are not necessary to record robust AMcVEMPs.

Keywords: cVEMP, VEMP, otolith, steady state Portions of these data were presented at the 2019 American Auditory Society Meeting.

INTRODUCTION

Otolith organs respond to linear acceleration of the head and gravity. They can also be excited by acoustic or vibratory stimulation (for a review, see Curthoys 2010). When the resulting response is recorded over the sternocleidomastoid muscle it is referred to as the cervical vestibular evoked myogenic potential (cVEMP) and reflects the integrity of the saccule and vestibulocollic reflex pathway (Colebatch and Halmagyi 1992). Traditional cVEMPs reflect inhibitory onset responses; are typically elicited by brief, transient stimuli; and consist of positive and negative peaks occurring at approximately 13 and 23 ms, respectively (Colebatch et al. 1994); cVEMP amplitude is directly proportional to the level of tonic EMG activity (Akin et al. 2004; Lim et al. 1995). Later components, the n34 and p44, are sometimes present and are purported to be of cochlear origin (Colebatch et al. 1994). There are few reports of cVEMPs elicited by long-duration amplitude-modulated tones, analogous to auditory steady-state responses (ASSRs) (Bell et al. 2010; de Oliveira et al. 2014), and this alternate approach to eliciting cVEMPs may be used to investigate basic vestibular function or develop new clinical applications. However, the role of

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Correspondence to: Christopher G. Clinard · Department of Communication Sciences and Disorders · James Madison University · 235 Martin Luther King Jr. Way, MSC 4304, Harrisonburg, VA 22807, USA. email: clinarcg@jmu.edu

EMG activation has not been systematically examined in cVEMPs elicited by amplitude-modulated (AM) tones, leaving a basic property of these responses uninvestigated.

Higher stimulus levels elicit larger cVEMP amplitudes (e.g., Colebatch et al. 1994). In addition, the amount of tonic EMG activation of the sternocleidomastoid muscle is directly proportional to the amplitude of traditional cVEMPs (Akin et al. 2004; Colebatch and Halmagyi 1992; Lim et al. 1995; Noij et al. 2017). Because both factors, stimulus level and EMG activation, have profound effects on cVEMP amplitude, both factors must be accounted for in cVEMP interpretation. Common practice in cVEMP literature is to correct p1–n1 amplitude by dividing it by the rectified mean of the prestimulus baseline for each sweep as a measure of tonic EMG activation (Bogle et al. 2013; Colebatch et al. 1994; Rosengren et al. 2010). Practices vary for whether the participant monitors a type of biofeedback to keep EMG activation within a given range or not (Papathanasiou et al. 2014).

Several previous studies have used AM tones to elicit cVEMPs, and these studies have demonstrated that cVEMPs elicited by AM tones share some basic characteristics of conventional, transient cVEMPs. First, these responses were present in deaf individuals (de Oliveira et al. 2014). Second, response amplitude appears to be affected by EMG activation. Bell et al. (2010) reported that amplitudes were larger when the head was turned compared to when the head was not turned. de Oliveira et al. (2014) stated, qualitatively, that AMcVEMP amplitude increased with EMG activation. A fixed EMG activation range of 60–80 μ V was used in one study (de Oliveira et al. 2014), and other studies instructed participants to turn their head as far as was comfortable without reporting the amount of EMG activation or its relation to AMcVEMP amplitude (Bell et al. 2010; Caruba et al. 2013; Jurado and Marquardt 2019). Existing AMcVEMP literature has not reported a systematic evaluation of the effects of EMG activation on AMcVEMP properties. In addition, interaural asymmetry ratios (IARs) are a widely used clinical measure to detect vestibular pathologies, but have not been reported from AMcVEMPs.

Analysis of transient cVEMP waveforms has focused almost solely on peak latencies and amplitudes. An advantage of using a steady-state-evoked response approach to elicit cVEMPs is that a range of analyses may be applied to the data (for reviews, see Picton et al. 2003; Ross 2013). Bell et al. (2010) reported divergent trends in amplitude and signal-to-noise ratio (SNR) for 500 Hz AMcVEMPs across a range of modulation frequencies, indicating that these two aspects of the response may behave differently across stimulus conditions. Analyses that describe the quality

of phase locking, such as phase coherence (Clinard et al. 2017; Dobie and Wilson 1996; Ross 2013) may also be applied to steady-state responses to further explore response characteristics. AMcVEMP amplitude, SNR, and phase coherence may be affected differently by varying levels of tonic EMG activation, and different analyses may target different physiological processes. In auditory steady-state responses, half-wave rectification in sensory hair cells of the cochlea results in harmonic distortion products occurring at harmonics of the modulation frequency (Cohen et al. 1991; John et al. 1998). Otolith hair cells also act as rectifiers (e.g., Holt and Eatock 1995), and similar harmonic distortion products in AMcVEMPs do not appear to have been investigated. Recent modeling work by Lutkenhoner (2019) described cVEMPs elicited by temporal envelope fluctuations of a narrowband noise stimulus and focused on linear aspects of the response; the model used a half-wave rectified version of the stimulus to accurately describe physiological data. Here, nonlinearities expected to result from the half-wave rectification of otolith hair cells are examined in AMcVEMP recordings.

The present study presents preliminary findings on the effects of tonic EMG activation on basic characteristics of amplitude-modulated cVEMPs (AMcVEMPs). If alternate approaches to eliciting cVEMPs were further developed, then new diagnostic tests may be developed. The purposes of this experiment included examining the effect of tonic EMG activation on: (1) AMcVEMP amplitude, SNR, and phase coherence; (2) AMcVEMP interaural asymmetry ratios; and (3) harmonic distortion products present in AMcVEMP recordings.

METHODS

Participants

Fourteen young adults participated in this experiment (14 female). The average participant age was 21.7 (std. err = 1.6, range 20–24). All participants had normal audiometric thresholds at octave frequencies from 250 to 8000 Hz and normal tympanometric measures. All participants had negative histories for neurological and balance disorders. The initial ear of testing, left or right, was randomly ordered. All methods and procedures used in this study were approved and in accordance with the Institutional Review Board at James Madison University.

Stimulus

The stimulus was a sinusoidally amplitude-modulated tone. Its carrier frequency was 500 Hz, and its amplitude modulation frequency was 37.10938 Hz.

Carrier and modulation frequencies were precisely specified using coherent sampling to limit the response to one FFT bin (John et al. 1998). Maximal amplitudes using AMcVEMPs have been reported with AM rates of 37–43 Hz (Bell et al. 2010), and 37 Hz avoids overlapping frequencies between harmonics of 37 Hz and harmonics of 60 Hz electrical noise. Tone duration was 1024 ms and sampling rate was 44.1 kHz. Stimuli were presented in alternating polarity using a Neuroscan Stim2 system. Figure 1 illustrates the 500-Hz AM stimulus. Stimuli were delivered at 65 dB HL (123 dB force level re: 1 μ N) via a B81 bone vibrator (RadioEar) with its standard metal headband. Stimulus level was calibrated in dB HL, consistent with auditory steady-state literature (e.g., Small and Stapells 2004) and used a Larson Davis AMC493B artificial mastoid with a Larson Davis 824 sound level meter, a 6-cc coupler (AEC 100), and a 4–5-N weight.

Recording

Recordings were obtained using a Neuroscan RT system with Curry acquisition software. Disposable snap electrodes were used for two-channel recordings (Ambu Neuroline 720). Electrode positions were at the midpoint of the sternocleidomastoid muscle (noninverting for both channels), the sternoclavicular junction (inverting for response waveform channel), and on the sternocleidomastoid muscle just below the midpoint electrode (inverting for EMG monitoring channel); the ground electrode was at Fpz. The distance between the centers of the midpoint and inverting electrodes for the EMG monitoring channel was approximately 2.5 cm. Bandpass filters were 5–5000 Hz. Artifact rejection was not used. These acquisition settings follow conventional cVEMP methodology (Piker et al. 2013). Interstimulus interval was 43 ms, corresponding to a rate of 0.937/s. Each recording had 128 sweeps collected and lasted approximately 2.3 min. Analog-to-digital sampling rate was 20 kHz; this high A/D rate minimized the risk of carrier frequency stimulus artifact being aliased to the modulation frequency, which has been reported in the auditory steady-state response literature (Picton and John 2004; Small and Stapells 2004).

Procedure

Five EMG target levels were tested: 0, 30, 50, 70, and 90 μ V. During the 0 μ V EMG target condition, it was difficult for some participants to maintain single-digit EMG levels; therefore, 256 sweeps were collected for the 0 μ V condition and the 128 sweeps with the lowest EMG levels were analyzed. Each ear was tested separately. The order of ear testing and EMG target level were randomized. The B81 bone vibrator was

placed 3 cm posterior and 2 cm superior to the external auditory meatus to obtain maximum cVEMP amplitudes (Rosengren et al. 2005). For each participant, a spring scale (Ohaus 8003-PN) was used to verify that the headband applied 5.4 (+0.5) N of force (ANSI 2004). Data collection was performed in one 3 h session.

EMG monitoring was performed throughout each recording. Participants viewed a live, real-time bar graph that displayed the full-wave rectified average EMG of their sternocleidomastoid muscle activation (Akin et al. 2004; Rosengren et al. 2010). In a sitting position, participants turned their head to activate their sternocleidomastoid muscle until their rectified EMG reached the target line of activation. EMG data were passed from Curry acquisition software to Matlab to enable this monitoring. Prior to beginning the first recording, participants practiced reaching the EMG target to become familiar with activating and maintaining their sternocleidomastoid muscle a sufficient amount.

AMcVEMP Analysis

AMcVEMP analysis followed established analysis practices for ASSR analysis (Dobie and Wilson 1989; John et al. 1998) and included amplitude-based and phase coherence analyses performed in Matlab (R2017B). To calculate amplitude, fast Fourier transforms (FFTs) were performed on average waveforms from each recording. Amplitude values were obtained from the FFT bin of the modulation frequency. A noise estimate was obtained by averaging the amplitudes of the FFT bins surrounding the modulation frequency, ± 5 Hz over 10 bins (0.97 Hz bin width). Signal-to-noise ratios were calculated using these amplitude and noise estimates. Objective response detection was calculated by using the SNR as an *F*-ratio with 2, 10 degrees of freedom (Dobie and Wilson 1996; Zurek 1992). If the SNR was greater than 6.13 dB SNR, then the corresponding *p* value was less than 0.05 and indicated a present response. SNRs were also evaluated at the second, third, and fourth harmonics of the modulation frequency. Individual data in Fig. 2 demonstrate this analysis approach.

Phase coherence indicated the degree of phase locking to the modulation frequency and it is independent of response amplitude; it is calculated from the nonaveraged sweeps. This analysis is similar to the vector strength metric used in single-unit studies of phase locking (Dobie and Wilson 1989). FFTs were performed on each individual sweeps. Phase information from the modulation frequency FFT bin, across sweeps of a given recording, was analyzed using the Rayleigh test to assess circular uniformity (Fisher 1993); response presence was

FIG. 1. Time domain waveform (left panel) and corresponding FFT (right panel) for a 500-Hz carrier frequency amplitude modulated at 37 Hz. Stimulus energy is present at 500 Hz and ± 37 Hz

indicated by a p value < 0.05 . A phase coherence of 1 indicates perfect phase locking, or identical phase angle across sweeps, and a value of 0 indicates random phase, or an absent response. Example polar histograms and their corresponding phase coherence values, from an individual participant, are shown in Fig. 2.

Statistical Approach

Statistical analyses were performed in SPSS (version 26) and Matlab (2017B). Statistical analyses for AMcVEMP data across EMG targets (five levels) were performed separately for each side and used a one-way, repeated-measures analysis of variance (ANOVA);

FIG. 2. Individual AMcVEMP data from a 24-year-old participant across EMG targets. Responses were elicited by a 65-dB HL 500-Hz tone with a 37-Hz AM rate. EMG conditions are organized in rows. Left column, AMcVEMP waveforms. Middle column, FFTs of the waveforms in the left column; filled triangles represent present responses and open triangles represent absent responses. Amplitude

scales vary across the different EMG conditions. The SNR at the modulation frequency is shown in each panel. Right column, polar histograms of phase angles from the modulation frequency. Phase coherence and corresponding p value are shown with each polar histogram

Bonferroni corrections were used for post hoc p values. ANOVA results are reported separately for each side. Effects of side (left vs. right) were tested using a one-way repeated-measures ANOVA. Greenhouse–Geisser corrections were used when appropriate. Effect size is reported using partial-eta squared (Cohen 1988).

RESULTS

EMG Activation

To confirm that participants reached the target EMG levels for each condition, linear regression analyses were used to evaluate the relationship between EMG activation and target EMG levels. Participants accurately reached the EMG target (Fig. 3a), with values clustered around the line of equality. A simple linear regression was performed using EMG data from both left and right sides. EMG target was the independent variable and actual EMG activation was the dependent variable. The regression analysis revealed a significantly predictive relationship between the EMG target and the actual EMG activation of the two sides [$R^2 = 0.97$, $t_{(139)} = 70.145$, $p < 0.001$; $y = 0.865x + 5.3$]. Activation for the 0- μ V target averaged 5.75 μ V ($\pm$ std dev 2.66) for the left side and 6.30 μ V ($\pm$ 2.93) for the right side; these were the lowest EMG values reached when participants were in a reclined chair with their neck supported.

Participants achieved symmetrical sternocleidomastoid muscle activation between the left and right sides (Fig. 3b). A simple linear regression (independent variable left-side EMG activation, dependent variable right-side EMG activation)

Fig. 3. Bivariate scatterplots of EMG data. **a** EMG activation from left (blue) and right (red) sides as a function of EMG target; the filled, black symbols represent the combined average of the left and right sides. The diagonal gray line represents the line of equality, and the diagonal black line represents the best linear fit. **b** EMG activation from the left and right sides (circles, 0 μ V; downward triangles, 30 μ V; squares, 50 μ V; plus signs, 70 μ V; upward triangles, 90 μ V). Participants were able to accurately reach the EMG targets; EMG activation was more variable at the 90- μ V EMG target. Activation from the left and right sides was symmetrical

revealed a significantly predictive relationship between the left side and right side [$R^2 = 0.98$, $t_{(69)} = 57.773$, $p < 0.001$, $y = 0.983x + 0.352$]. A one-way repeated-measures ANOVA revealed that there was not a significant difference between the EMG activation of the left and right sides [$F_{(1.00, 69.00)} = 6.862$, $p = 0.347$]. These data confirm that participants were able to reach the EMG targets when activating the left and right sides and that EMG activation was symmetrical for both sides.

AMcVEMP Amplitude

Raw AMcVEMP amplitude was expected to linearly increase with EMG activation, consistent with transient cVEMP literature (Akin et al. 2004). Raw amplitude increased as a function of EMG target (Fig. 4a, b). One-way repeated-measures ANOVAs with a factor of EMG target (5 levels) revealed a significant main effect of EMG target for each side [left: $F_{(1.545, 20.085)} = 74.302$, $p < 0.001$, partial $\eta^2 = 0.851$; right: $F_{(1.730, 22.485)} = 57.651$, $p < 0.001$, partial $\eta^2 = 0.816$]. Post hoc comparisons for each side revealed that amplitude at each EMG target was significantly different from every other EMG target ($p < 0.001$), with the exception of 70 versus 90 μ V in the right side ($p = 0.239$). A one-way repeated-measures ANOVA revealed that AMcVEMP amplitude was significantly different across sides [$F_{(1.00, 69.00)} = 13.650$, $p < 0.001$, partial $\eta^2 = 0.165$]; post hoc, two-tailed t tests revealed a significant difference between the sides, left-side amplitude larger than the right side, only for the 90- μ V target condition ($p = 0.015$). In addition, average amplitude data for each side fall along the line of equality with amplitude approximating the EMG target for each condition (Fig. 4a). These results indicate that raw AMcVEMP amplitude is directly proportional to tonic EMG activation, as expected.

Corrected AMcVEMP amplitude was expected to be equivalent across the 30- to 90- μ V EMG targets, based on previous transient cVEMP literature (e.g., McCaslin et al. 2014). One-way repeated-measures ANOVAs with a factor of EMG target (5 levels) revealed a significant main effect of EMG target for each side [left: $F_{(4, 52)} = 54.326$, $p < 0.001$, partial $\eta^2 = 0.807$; right: $F_{(4, 52)} = 43.118$, $p < 0.001$, partial $\eta^2 = 0.768$]. Post hoc comparisons, performed separately for each side, showed that corrected AMcVEMP amplitude at EMG targets 30, 50, 70, and 90 μ V was significantly greater than corrected amplitude at the 0- μ V EMG target ($p < 0.001$) and that corrected amplitudes at 30, 50, 70, and 90 μ V were not significantly different from each other ($p = 0.557$ – 1.0) (Fig. 4c, d). Average corrected amplitude reached a value of approximately 1.0 at the 30- μ V EMG target and had roughly equivalent values through the 90- μ V

Fig. 4. AMcVEMP amplitude across EMG targets. **a** Error bar plot of raw AMcVEMP amplitude (solid lines) and noise (dashed lines) for left (blue) and right (red) ears. **b** Individual raw amplitude data for each ear. The thin gray line represents the line of equality. **c** Error bar plot of EMG-corrected AMcVEMP amplitude for left (blue) and right (red) ears. **d** Individual EMG-corrected amplitude data for each ear. Error bars represent one standard error

EMG target. A one-way repeated-measures ANOVA revealed that corrected amplitude was significantly different across sides [$F_{(1.00, 69.00)} = 10.020$, $p = 0.002$, partial $\eta^2 = 0.127$]; similar to raw amplitude, post hoc, two-tailed t tests revealed a significant difference between the sides at only the 90- μ V target condition ($p = 0.013$) where the left-side amplitude was larger than right side.

To better understand why AMcVEMP amplitude approximated the EMG targets (Fig. 4a), average waveforms of the full-wave rectified sweeps were examined. The cVEMP is an inhibitory reflex, and it does not represent the addition of energy as excitatory responses do. Instead, cVEMPs can be described as a response that modulates the underlying noise, or tonic EMG activation (Lutkenhoner and Basel 2011; Lutkenhoner et al. 2011; Prakash et al. 2015). The finding of AMcVEMP amplitudes approximating the EMG targets was likely related to the magnitude of tonic EMG activity required for cVEMPs. In addition, the average corrected amplitudes of approximately 1.0 (Fig. 4c, d) are consistent with the amplitude of the response equaling that of the mean, rectified EMG within a recording. The periodic and relatively long duration stimulus in the present study would be expected to elicit EMG activity that oscillates around the average tonic EMG activation for a given record-

ing. Transient click-evoked cVEMPs have been reported to show this behavior when the average waveform of the full-wave rectified sweeps is calculated (Colebatch et al. 1994; Rosengren et al. 2010). Plotting the average waveform of the full-wave rectified sweeps from an individual participant reveals instantaneous EMG amplitudes that oscillate around the tonic EMG level with the periodicity of the stimulus modulation frequency (Fig. 5). These rectified waveforms are consistent with the inhibitory cVEMP modulating the instantaneous amplitude of the tonic EMG activity with the periodicity of the amplitude-modulation frequency. Comparing the left and middle columns of Fig. 5 shows a close relationship between the tonic EMG activation and the FFT-based amplitude within the same recording.

Signal-to-Noise Ratio

Cervical VEMPs represent an inhibition of tonic EMG activation (Colebatch and Rothwell 2004). Response amplitude (signal) scales in proportion to the amount of EMG activation (noise) and an equivalent SNR across EMG targets would be expected because the signal-averaged noise from tonic EMG activity would also increase with EMG activation. The expected SNR plateau was observed in these data (Fig. 6). SNR was lowest at the 0- μ V condition and reached an approximately constant value across the EMG targets of 30, 50, 70, and 90 μ V. One-way repeated-measures ANOVAs with a factor of EMG target (5 levels) revealed significant main effects of EMG target for each side [left: $F_{(1.409, 18.303)} = 126.863$, $p < 0.001$, partial $\eta^2 = 0.907$; right: $F_{(1.604, 20.846)} = 82.146$, $p < 0.001$, partial $\eta^2 = 0.863$]. Post hoc comparisons revealed that, for each side, SNR at the 0- μ V EMG target was significantly different from that of each higher EMG target ($p < 0.001$), and the SNRs from 30 to 90 μ V were not significantly different from each other ($p = 0.325$ – 1.0). AMcVEMP SNR was not significantly different across sides [$F_{(1.00, 69.00)} = 0.132$, $p = 0.717$]. These findings were consistent across the group and individual data (Figs. 2, 5, and 6). At the 0- μ V EMG target, the actual EMG activation ranged from 2.61 to 12.775 μ V (average = 6.026 μ V; std. err = 0.737); minor EMG activation at this target was associated with small-amplitude AMcVEMPs, some of which met the SNR criterion for a present response (Fig. 6b).

In order to better understand the relationship between amplitude (signal) and noise over the range of EMG targets, these data were plotted on a log-linear axis (Fig. 7a). Amplitude and noise both increased as a function of EMG target. Although noise was of smaller magnitude than AMcVEMP amplitude, it also scaled linearly with EMG activation

FIG. 5. Individual AMcVEMP data from a 21-year-old participant across EMG targets. Responses were elicited by a 65-dB HL 500-Hz tone with an AM frequency of 37 Hz. EMG conditions are organized in rows. Left column, AMcVEMP waveforms calculated by averaging the full-wave rectified sweeps. The horizontal, gray line represents the tonic EMG activation for the recording. Middle column, FFTs of the nonrectified, alternating current waveforms; filled triangles

represent present responses and open triangles represent absent responses. Amplitude scales vary across the different EMG conditions. The SNR from the modulation frequency is shown in each panel. Right column, polar histograms of phase angles from the modulation frequency for each sweep. Phase coherence and corresponding p value are shown with each polar histogram

(dashed lines, Fig. 7a); this was expected because the noise represents the signal-averaged magnitude of tonic EMG activation (noise) over the number of sweeps. When these data are plotted on a linear axis, the increase in noise is difficult to visualize (Fig. 4a).

Simple linear regression was used to examine the rate at which amplitude and noise values changed as EMG target increased, as well as whether amplitude and noise had parallel growth over a range of EMG targets. Individual data were log transformed and separate simple linear regression analyses were performed on both amplitude and noise over the 30-, 50-, 70-, and 90- μV target data to analyze the rate at which amplitude and noise increased with EMG activation (Fig. 7b). EMG target was significantly predictive of AMcVEMP amplitude [both sides: $t(55)=7.713$, $p<0.001$, $R^2=.524$ ($y=0.018917x+2.763$)] and noise [both sides: $t(55)=11.489$, $p<0.001$, $R^2=.710$ ($y=$

$0.021081x+0.805$)]. The slopes of each regression analysis are very similar (Fig. 7b), consistent with SNR being approximately constant from 30 to 90 μV EMG targets (Fig. 6). In addition, a two-sided t test showed that these two regression slopes were not significantly different [both sides: $t(108)=0.011$, $p=0.991$], confirming that the two variables increased at comparable rates. Parallel slopes in the growth of amplitude and noise would be expected to result in approximately equal SNRs across the 30-, 50-, 70-, and 90- μV EMG target conditions, consistent with our results (Figs. 2, 5, and 6).

Phase Coherence

Phase-locking activity of single-unit otolith afferents has been previously reported from animal models (Curthoys et al. 2019; McCue and Guinan Jr 1994).

Fig. 6. AMcVEMP SNR across EMG targets. **a** Error bar plot of AMcVEMP SNR for left (blue) and right (red) ears. **b** Individual SNR data for each ear. The dotted gray line represents the SNR criterion for response detection. Error bars represent one standard error

However, there do not appear to be published reports of phase-based synchrony measures from human VEMP data. Phase coherence was lowest at the 0- μ V condition, which still contained some minor EMG activity (Fig. 3), and it reached an approximately constant value, almost at ceiling, across the EMG targets of 30, 50, 70, and 90 μ V (Fig. 8). One-way repeated-measures ANOVAs with a factor of EMG target (5 levels) revealed significant main effects of EMG target for each side [left: $F_{(1.394, 18.120)} = 105.657$, $p < 0.001$, partial $\eta^2 = 0.890$; right: $F_{(1.945, 25.286)} = 194.105$, $p < 0.001$, partial $\eta^2 = 0.937$]. Phase coherence was not significantly different across ears [$F_{(1.00, 69.00)} = 0.122$, $p = 0.728$]. Post hoc comparisons for each side revealed that phase coherence at the 0- μ V EMG target was significantly different from that of the 30-, 50-, 70-, and 90- μ V EMG targets ($p < 0.001$); phase coherence from 30 to 90 μ V were not significantly different from each other ($p = 0.616$ – 1.000). Similar to

the findings for SNR, the small amounts of EMG activity at the 0- μ V EMG target condition were associated with phase coherence values high enough to be considered present responses (Fig. 8).

Relationships Between Measurements

In auditory-evoked potentials, SNR and phase coherence have been reported to be highly correlated, at least in young, normal-hearing adults (Clinard et al. 2017; Wianda and Ross 2016). However, this relationship has not been previously reported for AMcVEMPs. AMcVEMP amplitude linearly increased as EMG activation increased (Fig. 4a), but SNR and phase coherence had equivalent values over the 30- to 90- μ V EMG targets (Figs. 6 and 8). The lowest amplitude data, corresponding to the 0- μ V condition, show that as amplitude increased so did SNR (Fig. 9a) and phase coherence (Fig. 9b). Phase coherence and SNR demonstrated a nonlinear relationship.

AMcVEMP Distortion Products

Harmonic distortion products of the modulation frequency would be expected to occur in AMcVEMPs due to the nonlinear, rectification processes in otolith hair cells (Holt and Eatock 1995). Data from the modulation frequency as well as its second, third, and fourth harmonics are plotted as a function of EMG target (Fig. 10) or harmonic number (Fig. 11) to show amplitude, SNR, and phase coherence data at these harmonics. Amplitude is most robust at the modulation frequency across all EMG targets (Figs. 10a and 11a). Second harmonic amplitude is approximately an

FIG. 7. AMcVEMP amplitude and noise across EMG targets. **a** Log-linear error bar plots of AMcVEMP amplitude (solid lines) and noise (dashed lines) for left (blue) and right (red) ears. The thin, solid gray line represents the line of equality; the thin, dashed gray line represents linear increase of the noise. Error bars represent one standard error. **b** Bivariate scatterplot of EMG target and log-

transformed AMcVEMP amplitude and noise; mean data points are shown separately for the left and right ears. The solid line represents the linear best fit to individual amplitude data; the dashed line represents the linear best fit to individual noise data. Regression formulae for amplitude (black) and noise (gray) are displayed in the panel

FIG. 8. AMcVEMP phase coherence across EMG targets. **a** Error bar plots of phase coherence for the left (blue) and right (red) ears. **b** Individual phase coherence data for each ear. The dashed gray line represents the criterion for response presence. Error bars represent one standard error

order of magnitude smaller than amplitude at the modulation frequency (Fig. 10a). On average, the second harmonic had present responses at each of the EMG targets; SNR (Figs. 10b and 11b) and phase coherence (Figs. 10c and 11c) are lower than at the modulation frequency. The average second harmonic SNR at 0 μV is greater than the modulation frequency SNR at 0 μV (Figs. 10b and 11b). A similar finding was present for phase coherence (Figs. 10c and 11c) and may be related to the spectrum of the underlying noise having less energy at the frequency of the second harmonic; individual data (Figs. 2 and 5; 0 μV FFT panels) show less noise in the vicinity of the second harmonic relative to the modulation frequency and could result in a larger SNR. The third and fourth harmonics, on average, have low SNRs and low phase coherence, consistent with weak-to-absent responses. Present AMcVEMPs were observed at harmonics of the modulation frequency, as expected, and this finding is consistent with rectification processes that are known to exist in otolith hair cells.

Interaural Asymmetry Ratios

IARs were compared across different response analyses (raw amplitude, EMG-corrected amplitude, SNR, and phase coherence) and EMG targets to assess their variability and the upper limit of the normal range (Fig. 12). At the 0- μV EMG target, the ranges of IARs were comparable across different metrics, although SNR has several participants with larger asymmetries (Fig. 12a). At 30, 50, 70, and 90 μV , the ranges of IARs are consistent for a given metric (e.g., raw amplitude) (Fig. 12b–e). Across these EMG targets, raw and EMG-corrected amplitude have comparable ranges of IARs, and the ranges of IARs for SNR and phase coherence are notably lower than for either amplitude measure. A common cutoff value for the normative upper limit of IARs is the mean plus two standard deviations (Papathanasiou et al. 2014). Cutoff values for the upper range of normal were calculated for the

present data set using this convention (Fig. 12f) for the 30- to 90- μV EMG target data. Across this range of EMG target values, the upper cutoff values were consistently lower for SNR and phase coherence when compared to those of the amplitude values. These data indicate that SNR and phase coherence may be inherently more symmetrical than amplitude-based measurements, or less susceptible to extra-vestibular factors that contribute to amplitude asymmetry (e.g., electrode placement, placement of transducer, SCM size and/or length, SCM fatigue, etc.) (Rosengren et al. 2019).

DISCUSSION

Effects of EMG Activation on AMcVEMP Amplitude

Previous literature reporting cVEMPs elicited by AM tones included minimal information regarding the effects of EMG activation levels. Bell et al. (2010) reported that amplitude from cVEMPs elicited by AM tones was larger when the head was turned instead of not turned; de Oliveira et al. (2014) qualitatively reported that preliminary data demonstrated proportional relationships between tonic EMG activation and response amplitude. Results from the present study demonstrate that AMcVEMP amplitude increases with increasing levels of tonic EMG activation, similar to previous findings for transient cVEMPs (Akin et al. 2004, 2011). These findings confirm that AMcVEMP amplitude demonstrates a key feature of transient cVEMPs—a dependence on tonic EMG activation.

Previous AMcVEMP studies reported average amplitudes of approximately 19 μV (de Oliveira et al. 2014) and 3 μV (Bell et al. 2010); amplitudes from the present study had averaged amplitude that approximated the EMG target, up to 90 μV (Fig. 4a). The use of air-conducted stimuli in the previous studies, the effectiveness of bone conduction stimulation (Curthoys 2010; McNerney and Burkard 2011;

FIG. 9. Bivariate scatterplots of AMcVEMP amplitude, SNR, and phase coherence across EMG targets for the left (blue) and right (red) ears. **a** Amplitude and SNR. **b** Amplitude and phase coherence. Log-scaled amplitude data are shown in **a** and **b**. **c** Phase coherence and

SNR. Gray, dotted lines represent the criteria for SNR and phase coherence. SNR and phase coherence increase as amplitude increases, even at the smallest amplitudes that correspond to data from the 0- μ V EMG target condition

Welgampola et al. 2003), and noise-exposure considerations of air conduction stimulus level (Bell et al. 2010; de Oliveira et al. 2014; Portnuff et al. 2017) may have influenced these amplitude differences between studies, in addition to EMG activation differences. Although the present study reported a significant amplitude difference across ears, this was driven by amplitude values at the 90- μ V EMG target; some participants reported difficulty maintaining 90 μ V of activation throughout the $\sim$ 2.5 min of the recording. Previous literature has not addressed the harmonics of AMcVEMPs, but our results indicate that their amplitude also scales with EMG activation (Figs. 10a and 11a).

The present study used bone conduction to deliver stimuli. Previous AMcVEMP literature used air conduction. One advantage of bone-conducted cVEMPs is that their thresholds are lower than air-conducted cVEMPs when quantifying stimulus level with units relative to the auditory perceptual detection thresholds of the eliciting stimulus, or dB nHL (McNerney and Burkard 2011; Welgampola et al. 2003). Additional advantages of bone-conducted cVEMPs include less risk of noise-induced damage (Portnuff et al. 2017), they are less affected by conductive hearing loss than air-conducted cVEMPs (Mahdi et al. 2013), and

bone conduction may be an inherently more efficient otolith stimulus (Clinard et al. 2019; Curthoys 2010). Bone-conducted cVEMPs recorded from the SCM are believed to reflect primarily saccular activity, even though the utricle is also stimulated; animal and human-lesion reports indicate that cervical VEMPs represent primarily saccular activity, innervated by the inferior vestibular nerve, and ocular VEMPs reflect primarily utricular activity, innervated by the superior vestibular nerve (Curthoys 2010; Curthoys et al. 2014; Iwasaki et al. 2009; Manzari et al. 2010). In the recordings of the present study, oscillator placement was controlled for using the methods of Rosengren et al. (2005), a spring scale was used to ensure an appropriate amount of force was being applied by the bone-vibrator headband, and oscillator placement was checked between recordings; although there may have been individual differences in bone conductance, these procedures help to minimize intersubject variability. Air conduction is used more often in cVEMP literature. However, the effective level of an air-conducted stimulus that reaches the otolith organs may also be affected by individual differences in ear canal volume (Thomas et al. 2017), ear canal resonance, the acoustic reflex, the middle-ear transfer function, and audiometric air-bone gaps.

FIG. 10. Error bar plots of AMcVEMP amplitude (**a**), SNR (**b**), and phase coherence (**c**) at Fo and harmonic distortion products as a function of EMG target. Error bars represent one standard error

FIG. 11. Error bar plots of AMcVEMP amplitude (a), SNR (b), and phase coherence (c) at Fo and harmonic distortion products as a function of harmonic number. Error bars represent one standard error

Independence from Tonic EMG Activation

On average, amplitude and noise had parallel, linear growth as EMG target increased (Fig. 7a, b). The primary source of noise in cVEMP recordings is tonic EMG activation that consists of stochastic motor unit action potentials, having peak spectral energy at approximately 40 Hz (Lutkenhoner and Basel 2012;

Wit and Kingma 2006). Noise estimates in the present study came from FFT bins ± 5 Hz from the modulation frequency, 37 Hz. The frequency range from which the noise estimate was obtained most likely contains energy from motor unit action potentials, and energy at those frequencies would be expected to increase with additional tonic EMG activation. The

FIG. 12. a–e Boxplots of interaural asymmetry ratios from each EMG target. The bottom and top of the box represent the 25th and 75th percentiles, respectively. The red horizontal line represents the median. Whiskers extend to the 1st and 99th percentiles. Data points beyond the 99th percentile are plotted as individual symbols.

Individual data are shown by thin, gray lines. f The upper limit of normal, defined as the mean + two standard deviations, is plotted for each metric and each EMG target. Asymmetry ratios for SNR and phase coherence were lower than raw and corrected amplitude IARs at the 30-, 50-, 70-, and 90- μ V EMG targets

parallel increases in amplitude and noise across EMG targets (Fig. 7) were likely a contributing factor to the plateau observed in the SNR and corrected amplitude data from 30 to 90 μ V. Previous cVEMP studies have also reported a plateauing trend in EMG-corrected cVEMP amplitude across EMG targets ranging from 50 to 400 μ V (Lutkenhoner et al. 2010; McCaslin et al. 2014; Rosengren 2015; van Tilburg et al. 2014). In addition, the spectrum of the noise may explain the finding that, at the 0- μ V target, the second harmonic SNR was higher than that of the modulation frequency; the amplitude of EMG noise would be less at 74 Hz than at 37 Hz and could result in a higher SNR (Figs. 2 and 5; 0 μ V FFT panels, Figs. 10b and 11b). Overall, the results indicate that corrected amplitude, SNR, and phase coherence were somewhat independent of EMG activation once 30 μ V activation was achieved (Figs. 4, 6, and 8).

The equivalent SNRs across a range of EMG activation may indicate that the proportion of inhibition is comparable across a range of EMG activations. This finding is consistent with literature that has focused on quantifying the depth of inhibition in transient cVEMPs (Noij et al. 2018; Prakash et al. 2015), as well as the nature of the cVEMP representing the modulation of tonic EMG activation, or underlying noise. The present study reported SNRs of approximately 15 dB, consistent with the average SNR of 15.2 dB reported by Bell et al. (2010) with a modulation frequency of 39 Hz for air-conducted 500 Hz AM tones. High correlations between phase coherence and SNR have been reported in auditory-evoked potentials (Clinard et al. 2017; Wianda and Ross 2016). The present study also found close relationships between these two measures for AMcVEMPs in young, healthy adults (Fig. 9).

Phase coherence values across the 30-, 50-, 70-, and 90- μ V EMG targets averaged 0.9160 (std dev = 0.0861) (Fig. 8). These phase coherence values are similar to the phase-locking data reported from otolith afferent fibers of animal models (Curthoys et al. 2019; McCue and Guinan Jr 1994). Curthoys et al. (2019) recorded from guinea pig utricular afferents stimulated with bone-conducted 500 Hz tones and reported a mean vector strength of 0.92 (std dev = 0.05). Bone-conducted cVEMPs, as in the present study, reflect primarily saccular activity with some utricular activity contributing (Curthoys 2017; Govender et al. 2015), while Curthoys et al. (2019) recorded from afferent fibers of the utricle. Although Curthoys and colleagues measured phase locking to the carrier frequency and the present study measured phase locking to the envelope frequency of a 500-Hz carrier, both studies indicate a high degree of neural synchrony resulting from the stimulation of otolith organs. An important distinction between the present study and previous animal studies is that the present study

recorded cVEMPs at the end of a reflex pathway; previous animal studies of otolith afferent phase locking were recorded from primary afferent fibers (Curthoys et al. 2019; McCue and Guinan Jr 1994). The authors are not aware of studies that have examined phase-locking analyses from animal cVEMPs. Data from the present study may indicate that precise phase locking at otolith afferents is preserved through the vestibulospinal tract to the sternocleidomastoid muscle. Once 30 μ V of EMG activation was achieved, corrected amplitude, SNR, and phase coherence maintained stable values.

Present Responses with Minimal EMG Activation

The present study included a 0- μ V EMG target condition, during which participants were reclined and relaxed their SCMs as much as they were able to. Participants had difficulty reaching and maintaining 0 μ V even when reclined with their neck supported; the actual EMG activation for this condition, across both ears, averaged 6.03 μ V (std dev = 2.76). This small level of activity is consistent with that reported by Akin et al. (2004) from a 0- μ V EMG target condition. Some participants had present AMcVEMPs even at these low levels of EMG activation (Figs. 6 and 8), and typically those individuals with absent responses at the 0- μ V target also had the lowest amplitudes (Fig. 9a, b). It appears that even single-digit levels of EMG activation, when the SCM is not intentionally activated, may be sufficient to detect AMcVEMPs, and this may be related to the linear scaling of amplitude and noise with EMG activation. Few studies have systematically examined transient cVEMPs at EMG targets below 30 μ V. Akin et al. (2011) included a 10- μ V EMG target and reported individual amplitudes as high as 100 μ V (mean = 31 μ V, std dev = 24); cVEMPs were present in 22 of 24 participants at the 10- μ V target. Other studies have reported present cVEMPs with EMG activation at or below approximately 25 μ V, although specific targets were not utilized which complicates calculating averages across participants (Bogle et al. 2013; Lim et al. 1995; Rosengren 2015). Akin et al. (2004) reported no present transient cVEMPs at a 0- μ V EMG target, while the present study did detect some AMcVEMPs at the 0- μ V target. The nature of the elicited responses and their respective methods of detection may contribute to this difference between the studies.

Transient cVEMPs, in clinical and research environments, commonly rely on subjective visual detection to determine response presence. In contrast, AMcVEMPs have spectral content that is focused in a single FFT bin at the modulation frequency of the stimulus envelope (individual data Figs. 2 and 5), and signal processing strategies used in AMcVEMPs, as

well as ASSRs, lend themselves to the application of statistical, objective detection algorithms (Dobie and Wilson 1996; Picton et al. 2003) that remove subjective visual detection from response detection and analysis. These signal processing strategies allow small-amplitude responses to be detected, in part because of the narrow bandwidth of the response (i.e., 1 Hz).

It is unlikely that stimulus artifact is responsible for the small-magnitude responses present with minimal EMG activation. The stimulus has no energy at the modulation frequency, at which the response occurs (Fig. 1). In ASSR literature, artifactual responses have been detected by carrier frequency stimulus artifact being aliased to the modulation frequency during analog-to-digital conversion when using sampling rates in the range of 1000 Hz where the Nyquist limit is violated (Picton and John 2004; Small and Stapells 2004); the high sampling frequency and the use of alternating polarity stimuli in the present study minimized the risk of artifactual responses from occurring.

Clinical Implications

Clinical applications of AMcVEMPs are currently untested, but may have future applications for more sensitive interaural asymmetry ratios, threshold measurement, automated screening applications, or measuring frequency tuning. Unilateral pathologies may be detected using IARs (Rosengren et al. 2019). IARs over a critical threshold of asymmetry are the most used VEMP clinical metrics to identify vestibular involvement (Papathanasiou et al. 2014). cVEMP amplitude measures vary widely between individuals. This is common with vestibular testing (e.g., caloric testing) where interindividual variability limits the clinical utility of absolute amplitude measures. Individual measures are not ignored, but interpretation is complemented by IAR calculations. IARs will not identify all disorders, but traditional VEMPs are a site of lesion test and not a test of a specific disorder, and multiple metrics are used (IARs, amplitudes, thresholds, etc.) in clinical interpretation. Clinically, VEMPs have proven useful in identifying the presence of vestibular damage in many disorders including vestibular neuritis (e.g., Halmagyi et al. 2002), vestibular migraine (Makowiec et al. 2018), Meniere's disease (Taylor et al. 2011), superior semicircular canal dehiscence (Zuniga et al. 2013), and benign paroxysmal positional vertigo (Murofushi 2016).

In the present study, amplitude-based IARs are consistent with the published literature (Li et al. 2015; McCaslin et al. 2014; van Tilburg et al. 2014; Welgampola and Colebatch 2001); the upper cutoff of the normal range (95th percentile) was approximately 45 % for both raw and corrected amplitude across the 30-, 50-, 70-, and 90- μ V EMG target

conditions (Fig. 12f). Interaural asymmetry ratios for SNR and phase coherence were substantially lower and less variable than amplitude-based IARs (Fig. 12); their upper cutoff values across the same EMG targets were approximately 15 % (Fig. 12f). Reducing the variance of IARs as well as the upper limit of the normal range of IARs may improve the sensitivity and specificity of IAR as a clinical tool to detect unilateral otolith-related pathologies. The present study included only young, healthy participants, so the diagnostic utility of AMcVEMP IAR is not yet known. Future studies would need to include individuals with known pathologies to better understand the clinical utility of AMcVEMP SNR and phase coherence IARs and whether the low IARs observed in young, healthy adults would generalize to improve the sensitivity and specificity in diagnostic applications.

Recommendations for EMG targets in clinical applications of transient cVEMPs range from 50 to 200 μ V (Akin et al. 2011; Papathanasiou et al. 2014; Rosengren 2015). Some older adults have difficulty reaching and maintaining even 50 μ V EMG activation in a sitting position (Akin et al. 2011). Results from the present study showed that EMG activation as low as 30 μ V resulted in the same corrected AMcVEMP amplitude, SNR, and phase coherence as were observed at 50, 70, and 90 μ V EMG targets. These findings indicate that maximal EMG activation may not be necessary to detect cVEMPs, consistent with recent literature on transient cVEMPs (Noij et al. 2017; Rosengren 2015). In potential clinical applications, AMcVEMPs may have an advantage of not using visual detection or manual peak picking and may have future applications where statistical detection algorithms could be useful to shorten test time (e.g., screenings). AMcVEMPs may be informative regarding normal and pathological populations, and the frequency specificity of AM tones may be especially useful in pathological and nonpathological populations where frequency tuning of cVEMPs is of interest (Kim-Lee et al. 2009; Piker et al. 2013). The longer duration stimuli of AMcVEMPs can have greater frequency specificity than transient tone bursts, allowing a finer examination of cVEMP tuning. In addition, AMcVEMPs may allow investigations into new aspects of human vestibular physiology and may be useful for comparative physiology studies.

The present study focused on how the AMcVEMP behaved across a range of EMG activations while stimulus level was constant. Establishing an AMcVEMP threshold could easily be performed by keeping EMG activation constant and changing stimulus level, just as with transient cVEMPs. Superior semicircular canal dehiscence has been associated with transient cVEMP thresholds that are lower (better) than nonpathological individuals (Govender et al. 2016). Latencies of transient cVEMPs have been associated with pathologies of the central nervous system, such as

multiple sclerosis (Di Stadio et al. 2019). Although peak latencies were not reported in the present study, there are p1 and n1 peaks present throughout the time domain waveforms (Figs. 2 and 5) and their latencies could be analyzed in future studies.

Limitations of the Current Study

The electrode montage used to monitor EMG activation in the present study may indicate less activation than other electrode montages. Interelectrode distance and electrode dimensions can have effects on the quantified value of EMG activation, as well as a range of physiological parameters (De Luca et al. 2012; Merletti et al. 2001). EMG monitoring methods in the present study approximated those of Akin et al. (2004, 2011) who used closely spaced electrodes on the belly of the SCM to systematically examine the effects of varied EMG activation on the cVEMP. Other labs have used montages with one electrode of a bipolar montage on the belly of the SCM paired with an electrode on either the forehead (Smith et al. 2019), midpoint of the upper sternum (Colebatch et al. 1994), the sternoclavicular junction (Bogle et al. 2013), or the midpoint of the clavicle (Rosengren 2015); these reference electrode locations are also unlikely to be electrically neutral considering their proximity to the SCM or neural generators. While there are several reports of cVEMP p1n1 amplitudes with different electrode montages (Bogle et al. 2013; Colebatch 2012; Rosengren et al. 2016; Smith et al. 2019), the effect of electrode location on quantifying rectified EMG activity in cVEMP conditions appears to have received little attention (Colebatch 2012). Electrode locations for cVEMPs have not been standardized across laboratories. In the present study, it is possible that the closely spaced electrodes used to quantify EMG activation may have reflected a smaller-amplitude value than if the electrodes were spaced further apart. In the condition with the least amount of EMG activation, it is possible that cVEMP activity may have been recorded from neck muscles other than the SCM; in the lowest EMG condition, the distribution of phase angles was sometimes random (Fig. 2), but sometimes shifted to a different average phase angle in some individuals (Fig. 5). Regardless, SNR and phase coherence were robust and consistent across all but the lowest EMG activation conditions.

The initial p1 and n1 peaks of the inhibitory transient cVEMP are sometimes followed by peaks at 34 and 44 ms, n34 and p44, that are purported to be of cochlear origin (Colebatch et al. 1994). These later components have poorer reliability than the earlier p13–n23 peaks, even in normal-hearing individuals (Eleftheriadou et al. 2009; Huang et al. 2004; Wang and Young 2004). In addition, these later components have thresholds equivalent to those of the earlier p13 and n23 components (Wang and Young 2004), and the later components can be present in deaf individuals (Wu and Young 2002), consistent with vestibular

origins. However, they may also be present in individuals that have undergone vestibular nerve resection (Colebatch et al. 1994), consistent with cochlear origins. Investigations into the mechanisms of n34–p44 origins have not been conclusive. Earlier and later cVEMP components may have a common vestibular origin but different neural pathways. Mathematical modeling has accurately described transient cVEMPs using only the earlier p13–n23 components (Lutkenhoner et al. 2010; Wit and Kingma 2006). It is possible that the later components may be present in some of the waveforms of the current study, and it is possible that muscle afferents may have been activated by the bone-conducted stimulus. The present study had all female participants, but previous transient cVEMP research has not found sex differences (Basta et al. 2005).

CONCLUSIONS

AMcVEMP amplitude increases linearly with increasing EMG activation, similar to transient cVEMPs. However, AMcVEMP-corrected amplitude, signal-to-noise ratio, and phase coherence reach their nominal levels with EMG activation as low as 30 μ V and are relatively constant from 30 up to 90 μ V of EMG activation. This plateau is likely related to the finding that both amplitude and noise increase with EMG activation. Harmonic distortion products of the amplitude modulation frequency are consistent with AMcVEMPs reflecting nonlinear processing of otolith hair cells.

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AUTHOR CONTRIBUTIONS

All authors designed and performed the research. All authors analyzed the data and wrote the paper.

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COMPLIANCE WITH ETHICAL STANDARDS

All methods and procedures used in this study were approved and in accordance with the Institutional Review

Board at James Madison University.

Conflict of Interest The authors declare that they have no conflict of interest.

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