JARO (2013)
DOI: 10.1007/s10162-013-0416-x

JARO
Journal of the Association for Research in Otolaryngology

Clinical Testing of Otolith Function: Perceptual Thresholds and Myogenic Potentials

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Received: 30 October 2012; Accepted: 26 August 2013

ABSTRACT

Cervical and ocular vestibular-evoked myogenic potential (cVEMP/oVEMP) tests are widely used clinical tests of otolith function. However, VEMP testing may not be the ideal measure of otolith function given the significant inter-individual variability in responses and given that the stimuli used to elicit VEMPs are not physiological. We therefore evaluated linear motion perceptual threshold testing compared with cVEMP and oVEMP testing as measures of saccular and utricular function, respectively. A multi-axis motion platform was used to measure horizontal (along the inter-aural and naso-occipital axes) and vertical motion perceptual thresholds. These findings were compared with the vibration-evoked oVEMP as a measure of utricular function and sound-evoked cVEMP as a measure of saccular function. We also considered how perceptual threshold and cVEMP/oVEMP testing are each associated with Dizziness Handicap Inventory (DHI) scores. We enrolled 33 patients with bilateral vestibulopathy of different severities and 42 controls to have sufficient variability in otolith function. Subjects with abnormal oVEMP amplitudes had significantly higher (poorer) perceptual thresholds in the inter-aural and naso-occipital axes in age-adjusted analyses; no significant associations were observed for vertical perceptual thresholds and cVEMP amplitudes. Both oVEMP amplitudes and naso-occipital axis perceptual thresholds were significantly associated with DHI scores. These data suggest that horizontal perceptual thresholds and oVEMPs may estimate the same underlying physiological construct: utricular function.

Keywords: DHI score, motion perception threshold testing, otolith function, vestibular-evoked myogenic potential

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Published online: 27 September 2013

The vestibular system is integral to balance control. The paired vestibular organs, housed within the temporal bone, consist of three orthogonal semicircular canals (superior, posterior, and horizontal) and two otolith organs (the utricle and saccule). The semicircular canals detect angular head rotation in each of the canal planes, whereas the saccule and the utricle sense linear translations of the head in the vertical and horizontal planes, respectively (Minor 1998). Information from the vestibular end organs and their central pathways allows for the maintenance of gaze stability via the vestibulo-ocular reflex (VOR) and postural stability via the vestibulo-spinal reflexes.

Physiological assessment of the vestibular system chiefly consists of tests of semicircular canal function, including caloric irrigation, rotatory chair testing, and head-impulse test (HIT) which measure the function of the horizontal VOR Proctor et al. (1975). In recent years, vestibular tests have been developed that also probe the function of the otolith organs. Vestibular-

evoked myogenic potential (VEMP) tests are among the most widely used clinical tests of otolith function. The sound-evoked cervical vestibular-evoked myogenic potential (cVEMP) is perhaps the most widely accepted test of saccular function (Welgampola and Colebatch 2005). The vibration-evoked ocular vestibular-evoked myogenic potential (oVEMP) is the best-characterized measure of utricular function (Welgampola et al. 2009).

VEMP testing has significantly broadened the scope of the vestibular test battery and has particular clinical validity for the diagnosis of superior canal dehiscence syndrome and in localizing superior vs. inferior vestibular nerve pathology (Streubel et al. 2001; Halmagyi et al. 2003; Iwasaki et al. 2009). However, the clinical utility of VEMP testing as a measure of otolith function remains subject to certain limitations. There is significant inter-individual variability in VEMP responses, perhaps because the amplitude and latency of the evoked myogenic potentials reflect not only otolith function but also extra-vestibular factors such as the status of the outer and middle ear (for air-conducted sound stimuli), skull thickness (for bone-conducted vibration stimuli), and the extent of muscle activation during electromyographic recording (Clarke et al. 2003; Iwasaki et al. 2008). Moreover, the air-conducted sounds and bone-conducted vibrations that are used to elicit VEMPs do not resemble the physiological stimuli to which the otoliths have evolved to respond (Welgampola and Carey 2010).

Alternative methods of testing otolith function are being investigated and validated, including assays based on linear motion perceptual thresholds similar to auditory threshold testing (Kingma 2005; MacNeilage et al. 2010a; Merfeld 2011; Roditi and Crane 2012; Valko et al. 2012). Motion perceptual threshold testing is a promising vestibular testing modality given that the stimuli (head translations or rotations) are physiological and thus test performance may better correlate with symptoms and functional status relative to VEMP testing (Merfeld et al. 2010). Here, we evaluated a multi-axis motion platform that can deliver linear translations of precise amplitudes and frequencies in a horizontal plane (along the inter-aural and naso-occipital axes) and in a vertical plane (along the head-vertical axis). We correlated linear motion perceptual thresholds with oVEMP/cVEMP testing. We also evaluated how both perceptual threshold and VEMP testing are associated with the Dizziness Handicap Inventory (DHI), a measure of functional impairment. We anticipate that these analyses will aid in the identification of a clinical otolith function test that is of diagnostic and therapeutic value.

METHODS

Subjects

Study subjects were recruited from an outpatient neurology clinic in a tertiary care academic medical center (German Center for Vertigo and Balance Disorders in Munich). We recruited normal controls from the Center staff and their family members who had no prior history of dizziness, neurologic or neurotologic disease. We also recruited patients with bilateral vestibulopathy (BV) to have sufficient variability in otolith function for correlation analyses. BV resulted from different etiologies, including aminoglycoside toxicity, bilateral Menière's disease, immune mediated, and idiopathic. A diagnosis of BV was made based on the following criteria: (1) bilaterally diminished (defined as a mean peak slow-phase velocity (SPV) of <5 °/s on both sides) or absent caloric responses on video-oculography, and/or (2) bilaterally pathologic HIT (Halmagyi and Curthoys 1988; Jorns-Haderli et al. 2007; Zingler et al. 2007). Patients with BV were administered the DHI as a measure of their functional impairment (Jacobson and Newman 1990). Control subjects were assigned a DHI score of zero. This study was approved by the Ludwig-Maximilians University institutional review board and all participants gave their informed consent prior to their inclusion in the study.

Laboratory vestibular testing

Linear motion perception threshold testing. Experiments were conducted using a Moog (6DOF2000E) 6-degree-of-freedom motion platform. Subjects were seated in a padded racing seat and held in place with a 5-point harness. The subject's head rested against a form-fitted vacuum pillow and was held firmly in place with a forehead strap. Subjects wore noise cancellation headphones, and white noise was played throughout the experiment to cancel and mask sounds associated with platform movement. Subjects also wore blackout goggles to eliminate visual cues to movement. Responses were collected using a wireless numeric keypad.

For each trial, subjects experienced a 2-s linear movement in one of two opposite directions and they had to indicate in which direction they had moved, a two-alternative-forced-choice task. The axis of testing was specified for each block of trials, so only the direction of movement was unknown. The velocity followed a raised cosine profile with frequency 0.5 Hz. In the three conditions, movements were either (1) left or right along the inter-aural (IA) axis, (2) forward or backward along the naso-occipital (NO) axis, or (3) up or down along the head-vertical (HV) axis. These conditions were run in separate blocks, and the order

was randomized across subjects: 26 subjects completed the NO axis first, 26 completed the IA axis first, and 23 completed the HV axis first.

Within each block, movement direction (e.g., left or right) was randomized such that on average the same number of trials was presented in each direction. Movement magnitude was modified from trial to trial according to a staircase procedure. The largest displacement was 15 cm (peak acceleration, 23.6 cm/s^2), and this displacement was reduced by one third with each step down on the staircase (15, 10, 6.66 cm, etc.). Displacement, velocity, and acceleration scaled together because duration was fixed. The block began with the largest displacement (15 cm). While we did not measure the acceleration at the head for each subject on each trial, we have previously used an accelerometer mounted on the platform to verify that the platform reproduces the desired trajectories very accurately (MacNeilage et al. 2010b).

The staircase always started with a 1-up-1-down stepping rule. This means that stimulus magnitude was decreased one step after each correct answer and increased one step after each incorrect answer. In this way, stimulus magnitude converged as quickly as possible to smaller magnitudes where performance for the subject was approximately at chance level. After four reversals (i.e., a step down followed by a step up or a step up followed by a step down), the stepping rule changed to either a 2-down-1-up (2D1U) or 3-down-1-up (3D1U); the same rule (either 2D1U or 3D1U) was used during all blocks for a given subject. Stimulus magnitude was decreased one step after either 2 (2D1U) or 3 (3D1U) consecutive correct answers, and increased one step after each incorrect answer. The first 30 subjects were tested with 3D1U, and the remaining subjects were tested with 2D1U. The 2D1U procedure converges to the threshold level more quickly, but simulations (not shown) indicate that the choice of rule has very little impact on the final estimated threshold values.

Example staircase histories for these two procedures are illustrated in Figure 1A (2D1U) and C (3D1U) for two different subjects in two different conditions. These rules converge to stimulus magnitudes where performance is at ~70 and ~80 % correct, respectively (Leek 2001). The block continued until at least ten total staircase reversals were completed (Fig. 1C) or until 50 trials were completed (Fig. 1A). The procedure required ~8 min/axis. Each axis was tested only once. These methods resemble those of several prior studies of vestibular perception (Benson et al. 1986; Grabherr et al. 2008; MacNeilage et al. 2010a; Mallery et al. 2010; Roditi and Crane 2012; Valko et al. 2012).

Data from each block were fit with a psychometric function (Fig. 1B, D) to determine the stimulus magnitude required for 84 % correct performance, i.e., one standard deviation from chance (50 %) performance. This quantifies the standard deviation of the noise on the perceptual self-motion estimate (MacNeilage et al. 2010a; Merfeld 2011). Stimulus magnitude was plotted on the *x*-axis on a log scale and percent correct for each magnitude was plotted on the *y*-axis; responses for oppositely directed movements were pooled. The function was fit using a maximum likelihood method (Wichmann and Hill 2001a; Wichmann and Hill 2001b), and the stimulus magnitude corresponding to 84 % correct was recorded as the threshold for that subject and condition. It should be noted that because of the limited range of motion of the platform, there was an upper limit on thresholds that could be reliably measured. In cases where performance was <84 % correct at the largest stimulus, threshold was conservatively assigned as equal to the largest stimulus magnitude (23.5 cm/s^2).

Cervical VEMP testing. Participants were positioned supine with their upper bodies elevated at a 30° angle from horizontal. The neck was actively flexed by the participant during cVEMP stimulation and recording to provide tonic background muscle activity. Air-conducted 500-Hz, 125-dB SPL tone bursts with a linear envelope (1 ms rise/fall time, 2 ms plateau), at a repetition rate of 5 per second were delivered monaurally via intra-auricular speakers. Cervical VEMPs were recorded from an electrode montage consisting of a non-inverting electrode placed at the midpoint of the ipsilateral sternocleidomastoid muscle belly, an inverting electrode placed on the manubrium sterni, and a ground electrode placed on the forehead. Recording was only initiated if baseline rectified electromyographic (EMG) activity, monitored in real time by the experimenter, was approximately 30 μV, to ensure sufficient tonic muscle contraction as well as adequate electrode impedance. EMG activity was recorded (Nicolet Biomedical Inc, Madison WI, USA), amplified and bandpass filtered, and the responses to 50–100 stimuli were averaged. The first positive and negative peaks that occurred between 13 and 23 ms after stimulus onset were designated p13 and n23, respectively. The raw peak-to-peak amplitude was calculated as the sum of the p13 and the n23 amplitudes. The corrected peak-to-peak amplitude was calculated by dividing the raw peak-to-peak amplitude by the rectified background EMG activity recorded during the 10-ms interval before stimulus onset. The corrected peak-to-peak amplitude was evaluated given prior data demonstrating a high inter-rater reliability of this measure (Nguyen et al. 2010).

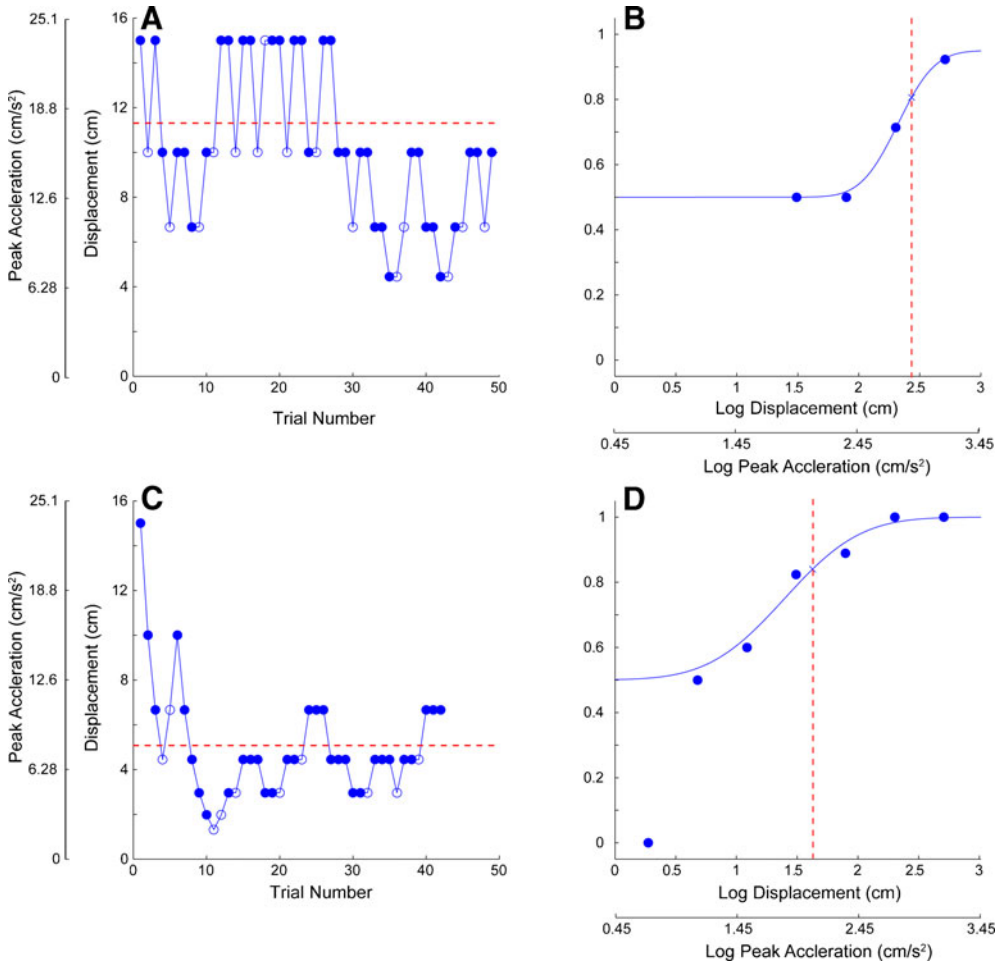

FIG. 1. Individual staircase history and psychometric fits for two different subjects in two different conditions. **A** Staircase history for 2D1U staircase terminated after 50 trials. *Filled and unfilled points* show correct and incorrect responses, respectively. **B** Cumulative Gaussian fit to data from (**A**). Proportion of correct responses is plotted as a function of the log of the stimulus magnitude. Threshold is the stimulus value corresponding to 84 % correct shown by *red dashed lines* in (**A**) and (**B**). **C** Staircase history same as in (**A**) except a 3D1U stepping rule was used and the staircase terminated after ten total reversals. **D** Cumulative Gaussian fit to data from (**C**).

Ocular VEMP testing. Participants were positioned supine with their upper bodies elevated at a 30 ° angle from horizontal. Maximum upgaze was maintained during oVEMP stimulation and recording. "Mini taps," as described by Iwasaki et al. (Iwasaki et al. 2008), were delivered with a Bruel and Kjaer Mini-Shaker Type 4810 (1-ms clicks of positive polarity, with a repetition rate of 5/s) at the Fz cranial site (in the midline at the hairline, 30 % of the distance between the inion and nasion). Fz taps have been shown to provide an acceleration wave that propagates through the cranium to the mastoid on either side, predominantly causing an outward linear acceleration of the utricles bilaterally (Curthoys 2010). Ocular VEMPs were recorded from an electrode montage consisting of a non-inverting electrode placed over the contralateral inferior oblique muscle approximately 3 mm below the eye and centered beneath the pupil, an inverting electrode on the chin, and a ground electrode placed under the chin. The responses to 50–100 stimuli were averaged. The first negative and positive peaks of the oVEMP response that occurred between 10 and 20 ms after stimulus onset were designated n1 and p1, respectively. The oVEMP n1 amplitude was evaluated, given that this is the portion of the response that is most clearly vestibular and previous data demonstrating a high inter-rater reliability of this measure (Smulders et al. 2009; Nguyen et al. 2010). Sample ocular and cervical VEMP traces are provided in Figure 2.

Statistical analysis

Mean linear motion perceptual thresholds and mean VEMP amplitudes were compared between BV patients and controls using non-parametric Wilcoxon

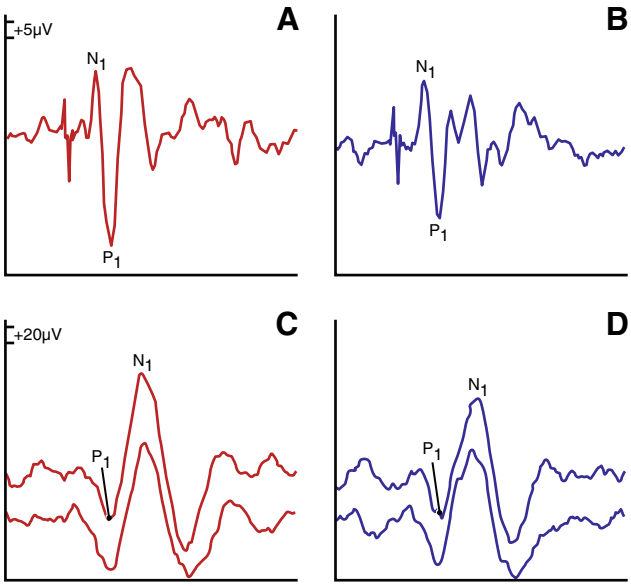

FIG. 2. Sample right (**A**) and left (**B**) ocular VEMP traces from a control subject. N1 and P1 peaks are marked. Sample right (**C**) and left (**D**) cervical VEMP traces from a control subject; two separate trials are depicted for each side. P1 (P13) and N1 (N23) peaks are marked. N1 amplitudes were used in oVEMP analyses, and peak-to-peak amplitudes were used in cVEMP analyses, as specified in the text.

two-sample tests. Spearman's rank correlation coefficients were computed to compare vestibular physiological test measures and age in controls. Given the significant inter-individual variability in VEMP amplitudes, clinical laboratories typically establish cutoff values for normal vs. abnormal results based on a reference control population tested in that laboratory. Accordingly, we classified subjects into normal and abnormal oVEMP and cVEMP categories, with an abnormal VEMP defined as an amplitude less than the 5th percentile of the control group (5.2 μV oVEMP n1 amplitude and 0.29-μV corrected cVEMP peak-to-peak amplitude). Mean thresholds were compared between normal and abnormal VEMP groups in analysis of covariance (ANCOVA) analyses controlling for age. Additionally, we regressed DHI scores on both perceptual threshold and VEMP tests to determine how performance on the otolith function tests was associated with functional impairment using multiple linear regression analyses controlling for age. We performed a power calculation as follows: assuming an alpha level of 0.05, a sample size of N=18–20 individuals with abnormal VEMPs, and 2-to-1 matching of individuals with normal-to-abnormal VEMPs, we would have a 0.76 power to find a significant difference in motion perceptual thresholds by normal vs. abnormal VEMP category (set at threshold difference of 5≈1 SD). SAS 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

We enrolled 75 subjects (41 females) with a mean age (SD) of 48.2 (21.2 years), age range 15–83 years. Of these subjects, 33 were patients with BV (mean age (SD) of 64.7 (14.4) years; age range, 24–83; 17 females), and 42 were normal controls (mean age (SD) of 35.4 (16.3) years; age range, 15–72; 24 females). Patients had significantly higher mean linear motion perceptual thresholds in the IA, NO and HV axes compared with control subjects based on the Wilcoxon two-sample test (p=0.0004, p< 0.0001, and p=0.0002 respectively; Table 1). Patients also had significantly lower mean oVEMP n1 amplitudes and lower mean peak-to-peak cVEMP amplitudes relative to control subjects using the Wilcoxon two-sample test (p<0.0001 and p<0.0001; Table 1). All control subjects had present oVEMP and cVEMP responses, whereas 18 % of patients had absent oVEMP responses and 42 % had absent cVEMP responses. We evaluated the percentage of controls and BV patients with maximum linear perceptual thresholds (23.5 cm/s^2) and absent VEMP responses in Chi-square analyses. As expected, we observed significantly higher percentages of patients compared with controls with maximum IA thresholds (55.6 vs. 16.7 %, χ^2=7.39, p=0.0066), NO thresholds (66.7 vs. 11.9 %, χ^2=19.7, p<0.0001), and HV thresholds (88.9 vs. 40.5 %, χ^2= 13.0, p=0.0003). We also observed significantly higher percentages of patients compared with controls with absent oVEMP responses (18.2 vs. 0 %, χ^2=8.43, p=0.0037) and absent cVEMP responses (53.9 vs. 0 %, χ^2=20.5, p<0.0001).

We evaluated linear motion perceptual thresholds in the IA, NO, and HV axes as a function of age in the control group using Spearman's rank correlation analyses. We observed that perceptual thresholds in the NO and HV axes were significantly positively correlated with age (Fig. 3), consistent with previous studies (Roditi and Crane 2012). We also found that thresholds in the HV axis were significantly higher than in the IA and NO axes (p<0.0001 for both comparisons, Wilcoxon signed rank sum test data not shown), again in line with prior work (Benson et al. 1986; MacNeilage et al. 2010a; Roditi and Crane 2012). We did not observe any significant differences in perceptual thresholds by gender. We also correlated oVEMP n1 amplitudes and cVEMP peak-to-peak amplitudes as a function of age in the control group using Spearman rank correlation analyses (Fig. 3). We

TABLE 1

Linear motion perceptual thresholds, ocular and corrected cervical VEMP amplitudes in BV patients and control subjects

Subjects	*Number*	*Sigma[a] IA* *Mean (SD)*	*Sigma NO* *Mean (SD)*	*Sigma HV* *Mean (SD)*	*oVEMP (μV)* *Mean (SD)*	*cVEMP (μV)* *Mean (SD)*
Control	42	10.3 (7.7)	8.2 (7.4)	16.7 (7.1)	12.8 (6.6)	0.83 (0.41)
BV patients	33	17.4 (7.5)	20.0 (5.7)	22.0 (3.9)	6.7 (6.6)	0.23 (0.27)
Z statistic[b]		3.55	5.62	3.71	−4.48	−5.61
p value[c]		0.0004	<0.0001	0.0002	<0.0001	<0.0001

BV bilateral vestibulopathy, *VEMP* vestibular-evoked myogenic potential, *IA* inter-aural, *NO* naso-occipital, *HV* dorso-ventral, *SD* standard deviation

[a]Sigma refers to the stimulus magnitude (in centimeters per second) corresponding to 84 % correct responses

[b]*Z* test statistic of Wilcoxon two-sample test

[c]*p* value of Wilcoxon two-sample test

observed significant decreases in cVEMP peak-to-peak amplitudes but not oVEMP n1 amplitudes with increasing age, as has been reported previously (Agrawal et al. 2012).

To determine whether these significant associations are due to confounding by age, we evaluated associations between motion perceptual thresholds and VEMP amplitudes in age-adjusted analyses. We compared mean perceptual threshold values between subjects with normal and abnormal oVEMPs/cVEMPs in ANCOVA analyses controlling for age. For oVEMPs, 5 % of control subjects (N=2) and 55 % of BV patients (N=18) were classified as having abnormal oVEMPs. For cVEMPs, 5 % of control subjects (N=2) and 50 % of BV patients (N=16) were classified as having abnormal cVEMPs, where abnormal VEMPs were defined as having an amplitude less than the 5th percentile of the control group (see "METHODS"). We observed that subjects with abnormal oVEMP amplitudes had significantly higher (poorer) IA and NO axis perceptual thresholds in age-adjusted ANCOVA analyses (p=0.0093 and p=0.0285 respectively; Table 2). We did not observe any significant associations between normal vs. abnormal oVEMPs and HV axis perceptual thresholds, nor between normal vs. abnormal cVEMP corrected peak-to-peak amplitudes and perceptual threshold along any axis (Table 2). Given histologic data suggesting an accelerated decline in hair cell counts beginning at age 60 (Rosenhall 1973; Rauch et al. 2001), we repeated the ANCOVA analyses excluding subjects age >60 years. We did not observe any differences in the pattern of significant responses. Additionally, given the heterogeneity of BV etiologies and potential confounds associated with this, we repeated the ANCOVA analyses including only control subjects and BV patients with a history of aminoglycoside toxicity (N=9). Again, the pattern of significant responses was the same, with the exception of the difference in NO axis thresholds by oVEMP category which was no longer significant (mean (SD) threshold for normal oVEMP, 8.1 (7.2); mean (SD) threshold for abnormal oVEMP, 16.8 (8.5); p=0.1274).

Furthermore, we evaluated how each type of otolith function test was associated with functional impairment as represented by the DHI, using multiple linear regression analyses controlling for age. We observed that perceptual thresholds along the NO axis, and both oVEMP and corrected cVEMP amplitudes were significantly associated with DHI scores (β=0.93, p=0.0430; β= −0.99, p=0.0071; and β= −17.2, p=0.0359 respectively; Table 3). As expected, higher NO axis perceptual thresholds were associated with higher DHI scores (indicating greater functional impairment), whereas lower oVEMP and cVEMP amplitudes (indicating poorer utricular and saccular function respectively) were associated with higher DHI scores. The association between IA axis perceptual thresholds and DHI scores was borderline statistically significant (β=0.63, p=0.0771; Table 3). We did not observe any significant associations between HV axis perceptual thresholds and DHI scores.

DISCUSSION

In this study, we compared VEMP testing and linear motion perceptual thresholds as measures of otolith function. We found that subjects with abnormal oVEMPs had significantly higher (poorer) IA and NO perceptual thresholds in age-adjusted analyses. oVEMPs in response to bone-conducted vibration are thought to represent a reflex mediated by the utricle, whose horizontally-oriented macula make the organ responsive to horizontal linear head translations. Indeed, we found that oVEMP amplitudes were significantly associated with perceptual thresholds along the IA and NO axes, both of which are in the horizontal plane, and that oVEMP amplitudes were not associated with vertical HV axis perceptual thresholds. These findings suggest that

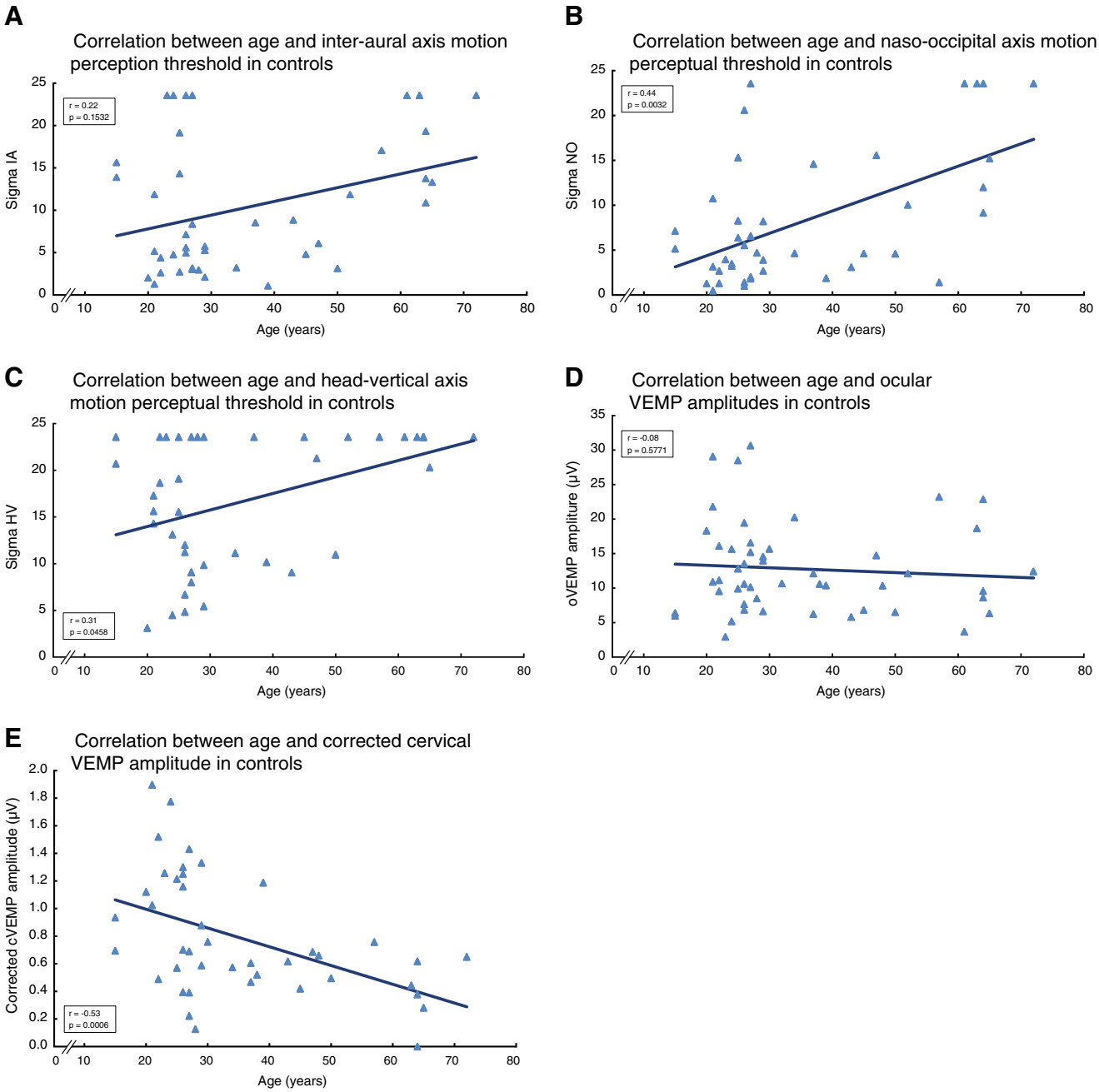

FIG. 3. Spearman's rank correlations between linear motion perceptual thresholds and VEMP amplitudes and age in controls. **A** Correlation between IA axis threshold and age (r=0.22, p=0.1532). **B** Correlation between HV axis threshold and age (r=0.31, p=0.0458). **C** Correlation between corrected cVEMP peak-to-peak amplitude and age (r=−0.53, p=0.0006). **D** Correlation between NO axis threshold and age (r=0.44, p=0.0032). **E** Correlation between oVEMP n1 amplitude and age (r=−0.08, p=0.5771).

the oVEMP and IA/NO perceptual threshold tests measure the same underlying physiological process: the function of the utricle. A recent study by Todd et al., which varied the stimulus frequency of whole-body vibration along the NO axis, also observed that the oVEMP may represent a high-frequency manifestation of the linear VOR (Todd et al. 2012). Interestingly, neither oVEMP amplitudes nor IA perceptual thresholds were significantly correlated with age, perhaps in further support of a common physiological origin.

We did not observe any significant associations between cVEMP amplitudes and perceptual thresholds along the vertical or horizontal axes. The perceptual thresholds along the HV axis were significantly higher than along the IA or NO axes, and among subjects with abnormal cVEMP or oVEMP

TABLE 2

Mean (SD) linear motion perceptual thresholds by normal and abnormal VEMPs in age-adjusted ANCOVA analyses in total study group (*N*=75)

	oVEMP				*cVEMP*			
Perceptual threshold	*Normal*[a] *(mean (SD))*	*Abnormal*[a] *(mean (SD))*	*F statistic*[b]	*p value*[c]	*Normal*[a] *(mean (SD))*	*Abnormal*[a] *(mean (SD))*	*F statistic*[b]	*p value*[c]
Sigma IA	*11.3 (7.9)*	*19.4 (6.9)*	*7.15*	*0.0093*	10.8 (8.1)	19.1 (6.4)	3.27	0.0758
Sigma NO	*11.1 (8.5)*	*19.7 (6.6)*	*5.00*	*0.0285*	10.7 (8.6)	19.9 (6.2)	1.73	0.1938
Sigma HV	17.8 (6.8)	22.4 (3.4)	1.67	0.2000	17.4 (7.0)	22.5 (3.8)	0.57	0.4542

Significant comparisons are set in italics

SD standard deviation, *VEMP* vestibular-evoked myogenic potential, *ANCOVA* analysis of covariance, *IA* inter-aural, *NO* naso-occipital, *HV* dorso-ventral

[a]Normal and abnormal VEMPs based on 5th percentile of amplitudes in normal controls

[b]*F* statistic of ANCOVA test

[c]*p* value of ANCOVA test

amplitudes, mean HV axis thresholds were at or near the maximum stimulus that could be delivered by the motion platform at 0.5 Hz frequency (23.5 cm/s^2). It is therefore possible that an association between cVEMP (and oVEMP) amplitudes and HV axis thresholds could not be identified due to this ceiling effect. Additionally, recent data suggest that the saccule responds most vigorously to stimuli around 500 Hz, whereas the best frequency of the utricle is near 100 Hz (regardless of the stimulus type) (Zhang et al. 2011, 2012). The VEMP stimuli used in this study were designed to stimulate each otolith organ around its best frequency. There is a greater discrepancy between the 0.5 Hz perceptual threshold stimulation frequency used in this experiment and the 500 Hz sound stimulus used to evoke the cVEMP compared with the 80–100 Hz vibration stimulus used to evoke the oVEMP, which may account for the lack of significant association between cVEMP amplitudes and perceptual thresholds. Moreover, the air-conducted sound stimulus used to evoke the cVEMP does not result in head acceleration unlike a bone-conducted vibration stimulus. Although we selected the sound-evoked cVEMP given that it is perhaps the most widely accepted measure of saccular function, additional studies evaluating the association between bone-conducted vibration evoked cVEMPs and perceptual thresholds may be worthwhile.

We observed that oVEMP, cVEMP, and NO perceptual threshold measures were significantly correlated with functional impairment based on the DHI, suggesting that loss of utricular and perhaps saccular function confer clinically significant disability. Interestingly, HV axis perceptual thresholds were not significantly associated with DHI scores. HV thresholds in general were higher than IA or NO thresholds, consistent with previous observations (Benson et al. 1986; MacNeilage et al. 2010a; Roditi and Crane

TABLE 3

Association between dizziness handicap inventory and linear motion perceptual thresholds and VEMPs in age-adjusted analyses in total study group (*N*=75)

Predictor variable	*β*[a]	*t statistic*[b]	*p value*[c]
Sigma IA	0.63	1.80	0.0771
Age	0.62		<0.0001
Sigma NO	0.93	2.07	0.043
Age	0.45		0.0213
Sigma HV	0.09	0.19	0.8485
Age	0.73		<0.0001
oVEMP (μV)	−0.99	−2.77	0.0071
Age	0.56		<0.0001
cVEMP (μV)	−0.06	−2.15	0.1887
Age	0.60		0.0003

VEMP vestibular-evoked myogenic potential, *IA* inter-aural, *NO* naso-occipital, *HV* dorso-ventral

[a]β coefficient interpreted as change in DHI score associated with each unit change in threshold or VEMP variable

[b]Partial *t* test statistic in multiple linear regression model

[c]*p* value of partial *t* test

2012). HV thresholds have been postulated to be higher to reduce sensitivity to the predominantly vertical oscillations associated with normal locomotion. It is possible that further decreases in HV axis sensitivity may not confer significant functional impairment. Alternatively, the DHI may not capture the deficits associated with loss of HV axis motion sensitivity.

Other tests of otolith function have been developed but each is also characterized by certain limitations. The subjective visual vertical (SVV), ocular counter roll, and horizontal linear head thrust test (to compute a translational VOR) are all measures of utricular function, although are typically abnormal only in acute, uncompensated cases of unilateral peripheral hypofunction (Clarke et al. 2003). Unilateral centrifugation, which exposes the eccentric labyrinth to a force along the IA axis, coupled with SVV estimation has been employed as a measure of utricular function; however, saccular function cannot be tested by this paradigm, and the equipment required for off-axis rotation is not readily accessible in most clinical settings (Clarke 2001).

Several limitations of the current study should be noted. Perceptual thresholds can be measured at a variety of frequencies, thereby allowing characterization of sensitivity as a function of frequency, similar to an audiogram (Merfeld et al. 2010; Valko et al. 2012). In the present study, we chose a frequency of 0.5 Hz because we suspected that contributions of other sensory modalities (e.g., somatosensory and proprioceptive) may increase at higher frequencies. However, assuming responses continue to reflect vestibular rather than somatosensory function, thresholds measured for higher frequency motions may be better correlated particularly with cVEMP measurements. In addition, the use of higher frequency stimuli would allow presentation of larger accelerations without exceeding the positional limits of the motion platform, thus allowing better threshold measurements even in less sensitive subjects. It remains to be determined which frequencies of motion are most important to use for diagnostic purposes.

Moreover, with respect to VEMP testing, limitations include the current lack of complete specificity of VEMP stimuli and responses for particular otolith organs. Significant evidence suggests that the sound-evoked cervical VEMP is the best-characterized VEMP measure of saccular function, and that the vibration-evoked ocular VEMP is the best-characterized VEMP measure of utricular function (Colebatch 2010; Curthoys 2010; Curthoys 2012). However, recent studies suggest that the physiological basis of VEMP testing may be more complex. Laterally directed head impulsive translations which stimulate the utricle can evoke both cVEMPs and oVEMPs, suggesting the presence of both utriculo-collic and utriculo-ocular projections (Brantberg et al. 2008; Brantberg et al. 2009). Both sound and vibration can stimulate both otoliths; the responses appear to be driven by the frequency of the stimulus matching the intrinsic best frequency of each otolith organ (Zhang et al. 2011; Zhang et al. 2012). A study looking specifically at frequency tuning of tone-burst evoked cVEMP responses observed two peaks at 300 and 1,000 Hz possibly suggesting the presence of two response generators for the sound-evoked cVEMP (Wei et al. 2013). Indeed, sound has been shown to stimulate not just the saccule but also the utricle and semicircular canals to a lesser degree (Zhu et al. 2011). Thus, the specificity of VEMP testing paradigms for measuring specific vestibular end-organ function requires further investigation. Additionally, we did not measure VEMP thresholds in this study; future investigations will need to consider the association between VEMP thresholds and linear perceptual thresholds. With respect to the subjects tested, we enrolled BV patients to have sufficient variability in otolith function for correlation analyses (such that not all values were clustered around normal levels). The BV patients were significantly older than control subjects, and the etiology of BV was heterogeneous. However, it should be noted that in this study correlating two measurement techniques, each subject served as their own basis for comparison, i.e., testing results were correlated within each single subject. Moreover, when subjects over the age of 60 were excluded from analyses, as well as when only BV patients with aminoglycoside toxicity (N=9) and controls were included in analyses, the pattern of statistically significant findings did not change. We did not collect DHI data from our control subjects and assigned a value of 0 (indicating no handicap) given that to serve as a control in our study, subjects had to report no history of dizziness. Although all DHI questions further relate to a dizziness "problem," it is possible that there may have been some non-zero DHI scores among the controls which may have introduced some error in the DHI analysis. Additionally, the DHI scores were not normally distributed (based on a Shapiro–Wilk test with p value<0.05), thereby violating one of the assumptions of multiple linear regression. Log-transformation of the DHI score did not improve normality; therefore, we performed our analyses with untransformed values. We evaluated quantile–quantile plots of the multiple linear regression residuals vs. quantiles from a normal distribution and observed reasonable concordance with a normal distribution. However, we acknowledge that some of the statistical inferences in the multiple linear regression analyses relating to DHI may be biased, particularly the standard errors of the β-coefficients.

VEMP testing currently predominates as a clinical otolith function test. We have found in this study that linear motion perceptual threshold testing correlates well with VEMPs, particularly in the horizontal plane. The limitations of VEMP testing have been discussed previously, specifically with respect to the specificity of end-organ testing and the significant inter-individual variability associated with VEMP responses. Motion perceptual threshold testing offers the advantage of delivering a head translation stimulus, which is a physiological input to the otolith organs. Moreover, the method of threshold determination is more analogous to other sensory modality testing (e.g., auditory and visual), and is not prone to anatomical sources of inter-individual variability that influence VEMPs. Disadvantages at present of applying perceptual threshold testing in the clinical setting include the need for a platform or sled capable of multi-axis linear translations, as well as the time needed to perform the test (~8 min/axis.) As the technology and methods are progressively refined, and we learn more about the stimulus frequencies that are most clinically relevant, vestibular threshold testing may become a more feasible clinical test of otolith function.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Thomas Brandt for his valuable contributions and the peer reviewers for their thoughtful comments.

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