# Age-Related Changes in Vestibular Evoked Myogenic Potentials and Dynamic Visual Acuity at Near and Far Distances

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## LIST OF ACRONYMS

| | |
|---|---|
| VEMP | Vestibular Evoked Mygenic Potentials |
| DVA | Dynamic Visual Acuity |
| VOR | Vestibulo-ocular Reflex |
| aVOR | Angular Vestibulo-ocular Reflex |
| lVOR | Linear Vestibulo-ocular Reflex |
| VNG | Visualnystagmography |
| EOG | Electro-oculography |
| VCR | Vistibulocollic Reflex |
| COR | Cervico-ocular Reflex |
| SCM | Sternocleidomastoid Muscle |
| EMG | Electromyography |
| BPM | Blood Pressure Manometer |
| MMSE | Mini Mental State Examination |
| KUMC | University of Kansas Medical Center |
| AEP | Auditory-Evoked Potential |
| Hz | Hertz |
| ms | Millisecond |
| m | Meter |
| dBnHL | Decibel Normal Hearing Level |
| mm Hg | Millimeters of Mercury |
| IAD | Interamplitude Difference |
| µV | Micro Volts |
| logMAR | Log of Minimal Angle of Resolution |
| SVA | Static Visual Acuity |
| Speed 1 | 0.75 meters per second |
| Speed 2 | 1.5 meters per second |
| Fixed | Head fixed to trunk |
| Free | Head free from trunk |
| Near | 0.5 meters |
| Far | 3.0 meters |
| GLM | General Linear Model |
| MANOVA | Multivariate Analysis of Variance |
| MD | Meniere's Disease |
| LVST | Lateral Vestibulo-spinal Tract |
| MVST | Medial Vestibulo-spinal Tract |
| VSR | Vestibulospinal Reflex |
| SCC | Semi Circular Canal |
| CDP | Computerized Dynamic Posturography |
| SCD | Superior Canal Dehiscence |
| BPPV | Benign Proximal Positional Vertigo |
| MRI | Magnetic Resonance Imaging |
| CNS | Central Nervous System |

## ABSTRACT

Morphological changes in the vestibular system associated with aging are well documented, but the ability to measure these changes clinically has been limited. Two such tests that have been useful for this purpose are Dynamic Visual Acuity (DVA) and Vestibular Evoked Myogenic Potentials (VEMP). DVA is reportedly sub served by the angular vestibulo-ocular reflex (aVOR) for “far” distances (>2 m) and the linear VOR (lVOR) at “near” distances (<1 m). The VEMP also has been shown to be sub served by the linear otolith system. The current study characterized age-related changes in DVA (distance, speed & neck condition) and VEMP in three groups of adults (20-30 yrs, 65-74 yrs, & 75-85 yrs) and analyzed the relationship between the VEMP and DVA. Strength of muscle contraction was monitored by having patients press their heads against a stabilized blood pressure cuff. A significant age-related decline was seen in VEMP amplitude and threshold in the older groups when compared to the younger group, while latency and interamplitude ratios of VEMP components remained consistent across age groups. No gender or ear-related differences were detected in the VEMP responses. There was a significant decline in DVA with speed (0.75 m/s & 1.5 m/s) during “near” (0.5 m) and “far” (3 m) DVA while an interaction between speed and age was seen only in the “near” conditions. There was also a significant decline in DVA with fixed neck condition in the “near” DVA trials. A significant negative correlation between DVA and VEMP was seen in

the “near” condition which is consistent with postulated underlying effectors for the VEMP and “near” DVA. Results of this study provide preliminary normative data across age ranges for DVA and VEMP along with evidence that both of these measures can be used to assess age-related changes in vestibular function.

The views expressed in this dissertation are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the United States Government.

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## I. Introduction

Dizziness and balance disorders constitute a major public health concern due to the debilitating effects and decrease in quality of life experienced by individuals afflicted with these conditions (Rosenhall & Grimby, 1995). The incidence of dizziness in the United States is approximately 5.5%, which means that more than fifteen million Americans develop some type of symptom each year (Yardley, Owen, Nazareth, & Luxon, 1998). Roydhouse (1974) reported that as much as 30% of the United States population will have dizzy-related symptoms by the age of 65. Although dizziness has many different etiologies, abnormalities in vestibular function constitute a significant cause.

As the population continues to age, dizziness and balance disorders become an important area of emphasis for the safety and well being of the public, especially for the elderly population. Epidemiologic studies have shown that balance disorders dramatically increase the probability of fall related injuries and that these types of falls are a major cause of morbidity in the elderly (Blake et al., 1988; Sloane, Coeytaux, Beck, & Dallara, 2000). Important aspects related to avoiding injury-related falls include the abilities to adapt quickly to unexpected conditions and maintenance of clear vision during head movements (Heasley, Buckley, Scally, Twigg, & Elliot, 2004). These abilities are important for all age groups and especially the elderly

whose skeletal muscular systems are weaker and less responsive to unexpected change.

The vestibular system, located in the inner ears, analyzes angular and linear motion of the head. The three semicircular canals detect angular acceleration while the utricle and saccule, known as the otolith organs, detect linear acceleration. This system is utilized to help maintain equilibrium, spatial orientation of the head and also provide the central nervous system with information which allows eye adjustments to be made with respect to a moving head in relation to the body and space during daily activities (Schubert & Minor, 2004). Stabilization of the eye is achieved through compensatory eye movements with respect to the visual target and is essential for controlling retinal slip and oscillopsia (movement of the visual field which causes blurriness) thus preserving visual acuity. The initial muscle activation necessary to adjust and help prevent unexpected falls by stabilizing the head in space depends heavily on the activation of the vestibular otolith system, possibly through the reticular formation and the spinal cord (Greenwood & Hopkins, 1976). Thus, the linear and angular parts of the vestibular system work together to achieve the visual stabilization necessary for maintaining balance.

**The Vestibulo-Occular Reflex (VOR) and Dynamic Visual Acuity (DVA)**

The majority of clinical vestibular testing today has been centered on the evaluation of the vestibulo-ocular reflex, which is studied by analyzing the integration of the horizontal semicircular canals in patients with vestibular hypofunction. The VOR is most often evaluated in dizzy patients using clinical tests such as videonystagmography (VNG) and sinusoidal rotational chair testing but can also be evaluated using a more functional test such as dynamic visual acuity. A VNG consists of a series of tests, using videooculography (VOG) for eye movement recordings, to estimate the position of the eyes as a function of time. The main subtests of the VNG consist of ocular-motor evaluations (smooth tracking, saccades, gaze fixation, and optokinetics), positional nystagmus, and caloric irrigations. The slow component of the nystagmus in these tests reflects the portion of the nystagmus generated by the VOR (Shepard & Telian, 1996).

Rotational chair testing is used to expand the evaluation of the peripheral vestibular system often in conjunction with VNG testing. Rotary chair testing also uses video or electro-oculography to track eye position while the subject is rotated in a sinusoidal manner at different frequencies. The parameters phase, gain, and symmetry are used to characterize the function of the VOR in rotary chair testing (Shepard & Telian, 1996). VOR phase is a measure of the timing relationship between head velocity and slow-phase eye velocity that is typically measured in degrees. VOR gain is the ratio of peak slow-phase eye velocity and peak head velocity while

symmetry gives an index of whether rightward or leftward eye movement peak velocities are consistent (Stockwell, 1988).

For an individual to visually resolve details the target must be stabilized on the fovea portion of the eye. Relative motion of the target greater than 2 degrees per second has been shown to degrade visual acuity (Demer & Amjadi, 1993). Gaze stabilization processes such as the VOR are thus needed to maintain proper position of the target on the fovea while the body is in motion. The ability to maintain visual acuity during head movements is called DVA and has been shown to rely on the VOR (Schubert & Minor, 2004). DVA testing allows clinicians a way of assessing the functional impact of vestibular abnormalities in more of a "real world" situation than typical VOR tests such as Rotary Chair and VNG. Though age-related deterioration of the vestibular system has been documented in the literature, it was unknown if these changes are associated with deterioration of DVA in healthy older adults. People with vestibular disorders often experience debilitating illusionary movement or blurring of vision during physical activities. DVA also has been shown to be poorer in patients with vestibular abnormalities when compared to age-matched peers (Tian, Shubayev, Baloh, & Demer, 2002). In clinical environments DVA is most often tested in a stationary environment where the head is rotated sinusoidally in an active or passive manner. Literature on patients with vestibular abnormalities has shown discrepancies between clinically tested DVA and subjective reports of oscillopsia and

blurred vision during dynamic tasks (Herdman, Schubert, Das, & Tusa, 2003). During real life situations such as walking the head movements are multidirectional and head stabilization in space relies on the vestibulocollic reflex (VCR) (Melvill Jones, Fletcher, Weber & Block, 2000). These differences between clinical testing and subjective reports could be due to other underlying mechanisms not captured in the standard clinical procedure for obtaining DVA. Studying a person's visual acuity while participating in a common activity such as walking, which is often associated with oscillopsia, may provide a better functional assessment than traditional DVA testing. Hillman, Bloomberg, McDonald, & Cohen (1999) studied DVA while walking in subjects with vestibular deficits versus normal age matched peers, although significant differences between groups were found, comparisons to clinically assessed DVA were not reported. Therefore it is still unknown how well static DVA tests can predict DVA measures during functional activities such as walking.

Many functional activities involving visual acuity and resultant gaze stabilization happen at multiple visual distances and may involve contributions from different portions of the vestibular system. Previous research has shown that this change in distance may be relevant when looking at DVA measures. Moore, Hirasaki, Cohen, & Raphan (1999) have shown that phase relationships between the head and eyes can be dramatically affected by visual target viewing distances. During "far" (> 2 m) distances the relationship

between the eyes and head has been shown to be close to 180° out of phase while at “near” (< 1 m) distances essentially no phase differences were detected. It is hypothesized that these phase differences are related to contributions from the otoliths and semicircular canals. Contributions from the near distance are likely driven by activation of linear VCR and linear VOR (otoliths) while contributions from the far distance are likely generated by the angular VOR (semicircular canals). Synder & King (1996) also have shown differences in otolith contribution with viewing distance. Peters & Bloomberg (2005) developed a protocol for testing “near” and “far” targets and have reported that otolith contributions during near target fixation are not sufficient to maintain proper eye stability as measured by DVA. Similar DVA measures had not been studied in an aging population. Developing testing protocols/techniques that can detect differences between otolith and semicircular canal function may become a valuable tool in the future evaluation of populations required to maintain proper visual acuity under dynamic conditions.

Age-related morphological changes affecting the vestibular system are well documented. Vestibular hair cell loss (Rosenhall, 1973), vestibular nerve fiber loss (Bergstrom, 1973) and a reduction in cell bodies in Scarpa’s ganglion (Richter, 1980) all have been reported. Although these changes are significant, tests of VOR function have reported only modest changes with age. The effects of age on traditional VNG and rotational chair vestibular

tests of the VOR often have not correlated well with the morphological changes seen in the vestibular system (Peterka, Black, & Schoenhoff, 1990; Mulch & Petermann, 1979). It is unknown whether reduced DVA in healthy older adults is associated with this morphological decline in the vestibular system. Older adults are highly dependent on visual information for their overall postural control (Anand, Buckley, Scally, & Elliott, 2003) and blurring of vision during dynamic tasks can significantly jeopardize their stability (Heasley et. al, 2004). Future research on tests such as DVA may be able to provide better functional data on aging effects in patients with vestibular deficits and additional information regarding predicting functional DVA measures from standard static DVA tests.

The common clinical evaluation of DVA involves the patient remaining stationary while the head is rotated back in forth in a sinusoidal manner (Herdman et al., 2003). Proprioceptive input from neck muscles and neck joint structures may also be contributing to improvement of DVA measures through the cervico-ocular reflex (COR). The COR is a reflexive eye response elicited by neck movement that also helps stabilize the eye and can work in conjunction with the VOR (Kelders et al., 2003). There are questions surrounding whether contributions from COR could be compensating for reduced vestibular function seen in elderly adults. Studies have shown a compensatory increase in COR with age and in subjects with vestibular deficits (Bronstein & Hood, 1986). It is unknown whether the proposed

increase in neck proprioceptive input has any implications on improving DVA during functional activities such as walking.

**The Vestibular Evoked Myogenic Potential (VEMP)**

During functional activities the ability to maintain head stability is regulated by the VCR, which is not directly evaluated in the traditional clinical vestibular test battery. The VEMP is a measurement that can be used to assess the quick reflexive change in muscle tone that occurs to stabilize the head following an unexpected movement (Colebatch, Halmagyi, & Skuse, 1994; Uchino et al., 1997). In fact, vestibular tests of saccular/VCR function were rarely seen until the recent emergence of VEMPs. VEMPs represent short-latency muscular responses recorded over the sternocleidomastoid (SCM) muscle in response to saccular stimulation (Brantberg, Tribukait, & Fransson, 2003). The emergence of VEMPs has created new opportunities to gain insight into the functional status of the saccule (Murofushi & Curhoys, 1997; Murofushi, Curthoys, Topple, Colebatch, & Halmagyi, 1995; Young, Fernandez & Goldberg, 1977) and the inferior vestibular nerve (Murofushi, Halmagyi, Yavor, & Colebatch, 1997; Murofushi, Matsuzaki, & Mizuno, 1998). There is an increasing amount of literature providing evidence that VEMPs recorded from the SCM muscle are altered by pathologic processes affecting the vestibular end organs and pathways. Abnormal responses have been reported in cases of Meniere's disease (de Waele, Tran Ba Huy, Diard,

Freyss, & Vidal, 1999; Heide et al., 1999), acute peripheral vestibulopathy (Heide et al., 1999), vestibular neuronitis (Murofushi et. al, 1996; Halmagyi & Curthoys, 1999), vestibular hypersensitivity disorders (Minor, Cremer, Carey & Santina, 2001; Brantberg, Bergenius, & Tribukait, 1999), vestibular schwannomas (Matsuzaki, Murofushi, & Mizuno, 1999), and central nervous systems disorders (Itoh et al., 2001; Chen & Young, 2003). Although VEMP latencies can be affected in brainstem disorders, amplitudes are more commonly used to assess peripheral vestibular function (Welgampola & Colebatch, 2001a).

VEMP importance also stems from the fact that the neural pathway of the response is different from that of the VOR, which is routinely evaluated using a standard vestibular test battery. The VOR reflects vestibular information processed in a pathway rostral from the level of the vestibular nuclei through the midbrain (Shepard & Telian, 1996), while the VEMP reflects a pathway organized caudally from the vestibular nuclei through cervical portions of the spinal cord (Buttner-Ennever, 1999). The neural pathways also differ in relation to the portion of the vestibular nerve they activate. The superior vestibular nerve branch innervates the superior and horizontal semicircular canal ampulla and utricle and is the source of the rostral pathway. The inferior branch innervates the posterior semicircular canal ampulla and the saccule (Buttner-Ennever, 1999). The VEMP also may help us better understand the vestibulospinal system and pathologic

processes involved. The medial vestibulospinal system is thought to help with fine eye, head, and neck movements while the lateral vestibulospinal system is thought to direct extensor tone to the neck and antigravity muscles (Zapala & Brey, 2004). Although the exact nature of the VEMP reflex pathways are not known it appears that the VEMP should be sensitive to lesions involving the saccule, inferior vestibular nerve, and vestibulospinal pathways (Shimizu, Murofushi, Sakurai, & Halmagyi, 2000).

The magnitude of the VEMP response is directly correlated with the degree of tonic muscle contraction of the SCM muscle in the neck. This feature has prohibited the full diagnostic value of the VEMP to be realized in the clinical setting. Specific electromyography (EMG) recording systems are needed to monitor tonic muscle contraction and these devices are not routinely found in most clinical settings. Vanspauwen, Wuyts & Van De Heyning (2006a) developed a technique for monitoring SCM muscle contraction using a clinically available blood pressure manometer (BPM) cuff and have shown that this technique is a valid alternative to the EMG measurement. Maes et al. (2009) have also shown that VEMPs recorded with this new BPM method have excellent between-subject and within-subject reliability and result in similar response parameters when compared with current VEMP data in the literature utilizing EMG monitoring. Maes et al. (2009) confirmed that the current BPM feedback method is a suitable alternative in a controlled clinical setting.

There have been several reports on age-related negative changes in VEMP parameters (i.e. reductions in amplitudes and increases in absolute wave latencies) in the literature (Ochi & Ohashi, 2003; Su, Huang, Young, & Cheng, 2004; Welgampola & Colebatch, 2001(b): Zapala & Brey, 2004). Thus, when interpreting whether a VEMP response is abnormal the patient's age must be considered since none of the previous studies have been conducted utilizing the clinically assessable blood pressure cuff feedback procedure. In addition, measures from EMG studies are typically not directly comparable (Maes et al., 2009).

**Summary and Goals**

With the recent establishment of a more clinically accessible feedback method (i.e., using a blood pressure cuff to monitor SCM muscle contraction) and the lack of comparable age-related VEMP data, it is important to establish age-related changes in normal subjects and to compare these changes with measures of VOR function measured from vestibular tests such as DVA. Thus, the main goal of this study was to evaluate age-related changes in VEMP and DVA responses with focus on the following specific objectives:

1. Quantify physiologic changes which occur in the vestibular (specifically saccular pathways) system with aging utilizing the VEMP.

2. Establish preliminary age-related data for VEMPs utilizing the BPM method with 500 Hz tone bursts.
3. Evaluate the effects of normal aging on DVA at “near” and “far” distances and the indirect contributions from underlying reflexes such as the COR.
4. Evaluate the effects of speed of locomotion on gaze stabilization in young and older healthy adults.
5. Analyze the relationship between a static physiologic otolith test, VEMP, and a functional otolith test, DVA at “near” distances, in normal aging adults.

Accomplishing the above goals will provide critical age-related information on the process of gaze stabilization and on clinical tests such as the VEMP. The results of this study also will provide insight into the relationship between physiologic and functional measures of the vestibular system. The establishment of appropriate age-related data and clinically assessable recording techniques are essential to improving and expanding the diagnostic capabilities of the VEMP and tests of DVA.

## II. Methodology

### A. Subjects

All subjects recruited for this study were required to have no history of vestibular and/or neuromuscular pathologies, cervical complaints, dizziness, or greater than 1 fall within the past year. Subjects were required to walk on a treadmill and were therefore also screened for symptomatic lower limb arthritis, frequency of physical activities, and underwent an assessment of cognitive function (Mini Mental State Examination (MMSE, Folstein M., Folstein S. & McHugh, 1975)). Screening tympanometry (Grason Stradler Inc. TympStar, Madison, WI.) and 500 Hz air/bone conduction pure tone thresholds (Grason Stradler Inc. 61 Clinical Audiometer, Madison, WI.) were performed bilaterally on all study subjects to verify appropriate middle ear function and to confirm that no air/bone gap greater than 10 dB HL was present at the test frequency of 500 Hz (Green, 1978). Subjects were assigned to three groups using a non-probability static group assignment based on their age. Based on a review of similar VEMP literature, a medium effect size was estimated. Thirty-five total subjects were tested which provided a power level of 0.8 for this study. Three subjects in the oldest group were not comfortable walking on the treadmill at the required speeds and thus their data were not analyzed for this study. Group 1 consisted of 12 young adults (7 females & 5 males) between the ages of 20 and 30 years (range 23-30 mean 26.83). Group 2 was comprised of 10 adults (5 females &

5 males) between the ages of 65 and 74 years (range 65-71 mean 67.7), and Group 3 consisted of 10 adults (5 females & 5 males) between the ages of 75 and 85 years (range 75-84 mean 78.7). Significant changes in the VEMP response have been shown to exist as subjects reach their 60's and 70's (Lee, Cha, Jung, Park & Yeo, 2007; Su et al., 2004; Welgamapola & Colebatch, 2001). In addition, significant changes in gait and walking patterns have been shown to begin around 60 years of age and decline at accelerated rates thereafter (Berry, Fisher & Lang, 1981; Murray, Kory & Clarkson, 1969; Murray, Drought, A., & Kory, R., 1964; Hageman & Blanke, 1986). Young subjects were recruited from the graduate student population at the University of Kansas Medical Center (KUMC) and the older subjects were recruited from the Grayhawk Laboratory database at the Landon Center of Aging, KUMC. All subjects used in this study signed an informed consent approved by the KUMC Human Subjects Committee before participating.

B. VEMP Stimuli

All VEMP testing was completed using a standard auditory-evoked potential (AEP) system (Bio-Logic Navigator, Mundelein, IL). The sound stimulus used for VEMP testing was a 500 Hz rarefaction tone burst (rise/fall time = 2 millisecond (ms), plateau = 1 ms). The electrophysiological response was band-pass filtered between 10-1500 Hertz (Hz), and amplified 5,000 times. These parameters have been shown to provide the most robust

VEMP responses at the lowest sound intensities (Akin, Murname, & Proffitt, 2003; Wu, Young, & Murofushi, 1999; Cheng & Murofushi, 2001; Welgampola & Colebatch, 2001a). The 500 Hz tone bursts were presented initially at 95 dB normal hearing level (nHL), reduced in 10 dB steps until the VEMP was unrecognizable, and then increased in 5 dB steps until the response reappeared. Threshold was defined as the lowest intensity level where the VEMP response could be visually identified and replicated (Ochi & Ohashi, 2003; Welgampola & Colebatch, 2001a; Su et al., 2004). The responses to 150 stimuli were averaged for each repetition, and at least two repeatable repetitions of the VEMP were verified at each stimulus level. With the SCM muscle activated by pushing against the blood pressure cuff, 500 Hz tone bursts were presented to the ipsilateral ear through an Etymotic ER-3A insert earphone (Etymotic Research, Elk Grove Village, IL) at a rate of 5.1/second.

C. VEMP Recordings

All VEMP recordings were performed in a sound treated booth (AEP laboratory, Department of Hearing and Speech, KUMC). Single channel recordings of the surface electromyographic activity were obtained using 10 millimeter (mm) gold plated disc electrodes from the right and left sides of the subject's neck. The primary (non-inverting) electrode was placed on the skin at the prominent mid-point of the SCM muscle, the secondary (inverting) electrode was placed at the sternoclavicular junction, and a ground electrode

was placed on the forehead (Maes et al., 2009; Vanspauwen et al., 2006a; Vanspauwen, Wuyts & Van De Heyning, 2006b). Impedance of the recording electrodes was maintained below 5 kΩ by cleansing the skin thoroughly with an impedance lowering gel (Omni Prep, D.O. Weaver Co., Aurora, CO) prior to electrode application.

D. SCM Muscle Contraction Procedure

The BPM feedback method was used to monitor SCM muscle contraction throughout the VEMP testing. A blood pressure manometer with inflatable cuff (Welch-Allyn, Skaneateles Falls, NY) with an extra large manometer dial was used. The subjects were seated in a comfortable chair with their back against the back support and no head or neck support. The blood pressure cuff was securely attached around a wall mounted 1.5 inch round metal bar (Figure 1) and the cuff was inflated to a standard pretest level of 20 mm Hg to form a cushion (Maes et al., 2009; Vanspauwen et al., 2006a; Vanspauwen et al., 2006b). Previous studies using the BPM method have had the subject hold the BPM in their hand which could introduce additional variability if the subject applies force directly to the BPM with their hand instead of their turning their chin.


Figure 1. Blood pressure cuff attached to a secure metal bar to ensure stability/consistency during VEMP testing.

When testing the ipsilateral ear, the subject was required to flex his/her head down approximately 30 degrees and rotate it approximately 30 degrees toward the contralateral shoulder, without bending the ear down towards the shoulder. While securing the cuff to the bar with their contralateral hand the subject would push his/her chin against the cuff to generate a pressure of 40mm Hg on the extra-large dial of the manometer (Figure 2).

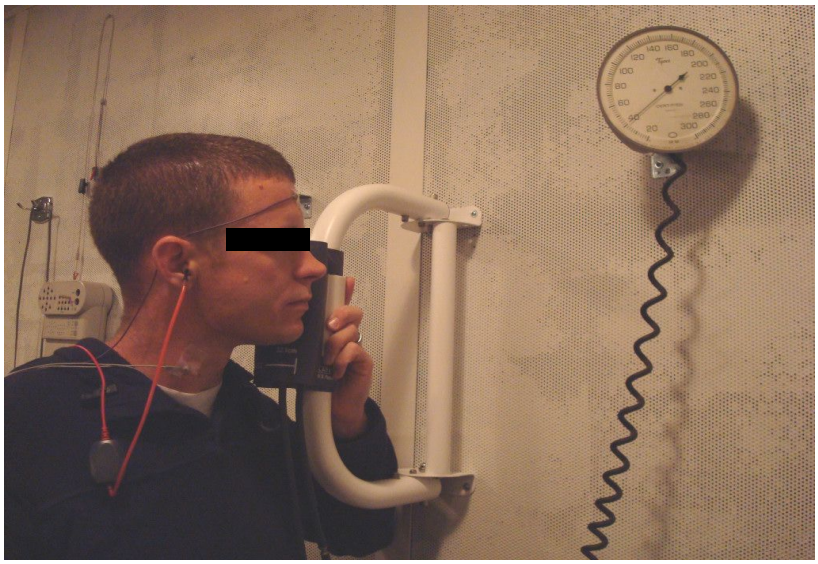

Figure 2. The BPM feedback method utilized to control contraction of the SCM muscle. The subject presses his/her chin against the blood pressure cuff to create the appropriate pressure and then visually monitors this pressure to ensure that it remains constant throughout the testing by looking at the extra-large manometer dial.

40 mm Hg has been shown to be a more reliable median pressure than 30 or 50 mm Hg when using the BPM method (Maes et al., 2009; Vanspauwen et al., 2006a; Vanspauwen et al., 2006b). Subjects were instructed to maintain this 40 mm Hg of pressure throughout the testing by monitoring the manometer dial (small variations of 2 mm Hg above and below 40 mm Hg were accepted). Subjects were monitored by a research assistant at all times to make sure the target was maintained. Subjects were allowed a brief period of rest between repeated VEMP recordings at each intensity level. Each subject was instructed on the procedure and shown a demonstration of proper position. Each subject then practiced the proper head position to ensure understanding and comprehension prior to the testing.

E. VEMP Response Parameters

The VEMPs were analyzed and considered present if the peaks were reproducible. P1-N1 peak to peak amplitude was measured from the average of two repetitions of 150 stimuli. Absolute P1 and N1 peak latencies also were measured. The averaged waveforms were analyzed and the first positive peak was labeled P1 and the first negative peak was labeled N1. The Interamplitude difference (IAD) ratios between ears were calculated (100 [(AR-AL)/(AR+AL)]) where AR = P1-N1 peak to peak amplitude of right ear and AL = P1-N1 peak to peak amplitude of left ear). Thresholds for the right and left ears were obtained for the VEMP response (threshold = the lowest intensity level where the VEMP can be visually identified and replicated (Ochi & Ohashi, 2003)) (Figure 3).

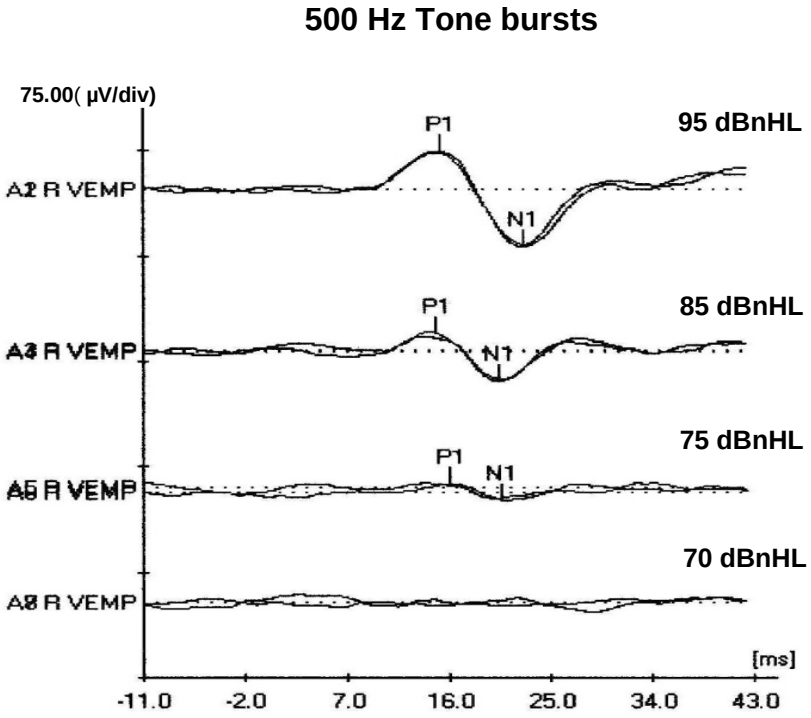


Figure 3. Typical VEMP response with an initial positive polarity (P1) and subsequent negativity (N1). A clear relationship can be seen between intensity and peak to peak amplitude.

E. DVA Instrumentation and Software

The DVA instrumentation and software used in this study were developed and engineered at the Neuroscience Laboratories, Johnson Space Center, NASA, Houston, TX. This instrumentation and software have been thoroughly explained by Peters & Bloomberg (2005) and will only be summarized here. DVA software was displayed on a Dell laptop computer (Dell, Inc., Round Rock, TX) and a mini screen (Model CO-3: The MicroOptical Corporation, Westwood, MA). In the past, resolution of available laptop computer screens has limited their use in DVA to far viewing distances

only. Typical laptop pixel density has been insufficient to clearly display the optotypes at near distances such as the 0.5 meters used in this study. The mini screen utilized in this study had a video graphics display that was able to display optotypes ranging in size from 0.8 to -0.4 logMAR (logarithm of the minimum angle of resolution) (Peters & Bloomberg, 2005). The Dell laptop computer was supported by a tripod (Allsportsystems, Inc., Willow Springs, NC) while the mini screen was supported by a tripod for the sitting conditions and supported by a custom-made wooden stand for the walking conditions. A variable speed treadmill (Biodex Medical Systems, Shirley, NY) was used to regulate walking speed while performing DVA at near and far distances.


Figure 4. Photos of display devices and treadmill used for DVA testing.

E.1. DVA Optotype Generation.

A computer generated Landolt ‘C’ optotype program was developed utilizing Matlab (The Mathworks Inc., Natick, MA). The optotypes were presented at various sizes and orientations to the subject. The gap in the ‘C’ optotype was randomly alternated between four positions: up, down, left or right (Figure 5) and varied between 15 different sizes ranging from 1.0 to -0.4 logMAR. In the logMAR scale 1.0 is equivalent to a 20/200 Snellen ratio, while 0.0 is equivalent to a Snellen ratio of 20/20 (Peters & Bloomberg, 2005).

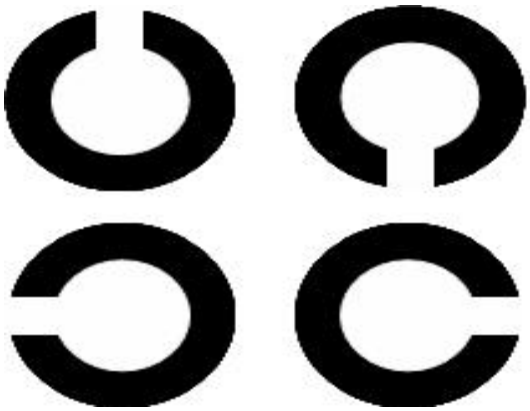

Figure 5. Example of possible Landolt “C” optotype orientation during acuity threshold determination (Miller, Feivesen, & Bloomberg, 2009).

E.2 Visual Acuity Threshold Determination

The displayed optotypes were controlled using a custom-written LabView (National Instruments, Austin, TX) program. An algorithm used to estimate psychophysical threshold detection was used to determine the visual acuity threshold for each condition used in the study (Lieberman & Pentland, 1982). This threshold was calculated as the optotype size in which half of the

responses are correct. This process was accomplished by presenting a large number of optotypes near the projected threshold to enhance accuracy of the fit with the fewest presentations possible. Following each optotype presentation a threshold probability was calculated for each of the 15 different optotype sizes and the next optotype presented was equal to the optotype with the highest probability. Subjects responded verbally after each 500 ms presentation. Responses were entered into the computer by a test administrator using a numeric keypad. Entering the response on the keypad immediately triggered the next randomly oriented optotype in the series.

A DVA score was calculated for each testing condition by taking the static visual acuity (SVA) threshold of the subject and subtracting this score from his/her DVA threshold. This delta score was then reported in a linear logMAR (Log (Decimal Acuity)) scale (Table I). The delta value was used as the DVA outcome measure for all analyses and calculations.

Table I. Conversion of visual acuity in feet (ft) to logMAR.

| Visual Acuity (ft) | logMAR (rounded) |
|---|---|
| 20/8 | - 0.4 |
| 20/10 | - 0.3 |
| 20/13 | - 0.2 |
| 20/15 | - 0.1 |
| 20/20 | 0.0 |
| 20/25 | +0.1 |
| 20/30 | +0.2 |
| 20/40 | +0.3 |
| 20/50 | +0.4 |
| 20/60 | +0.5 |
| 20/100 | +0.7 |
| 20/200 | +1.0 |

F. DVA Procedure

DVA data collection was carried out at the Landon Center of Aging Human Performance Laboratory, KUMC. The subjects were allowed to use their normal vision correction during the DVA testing. Two DVA trials were performed at each condition to ensure repeatable measures of DVA were obtained. SVA was assessed in a sitting position at 0.5 meters (m) ("near") and 3 m ("far") at the beginning of the DVA testing and was used as a baseline for the analysis. All subjects wore a head mounted eye tracker system (Applied Science Laboratories, 175, Middlesex Turnpike, Bedford, MA) and were linked to an Optotrak video system (Northern Digital Inc, Waterloo, Ontario), which was used to determine eye position with respect to head position for future analysis. Eleven Optotrak infrared markers were placed on their bodies (above each ear, right and left acromium process, vertex, spine of $7^{th}$ cervical vertebrae, $12^{th}$ thoracic vertebrae, heal and $5^{th}$ metatarsal of each foot).

DVA was assessed while walking using a variable speed treadmill at two distances ("near" & "far"), two test conditions: head fixed to trunk ("fixed")(standard foam cervical collar, Procare, Vista, CA), and head free from trunk ("free") and at two different speeds (0.75 (speed 1) & 1.50 (speed 2) meters per second (m/s)). All subjects wore a light-weight harness system during the testing on the treadmill to ensure safety. The "near" and "far" distances were chosen based on previous research describing the

relationships between viewing distance and generation of eye movements during locomotion. Eye velocity has been shown to be significantly affected by viewing distance (Moore et al., 1999). Near distances have been shown to rely more heavily on the linear VOR (lVOR) while far distance rely more on angular VOR (aVOR) (Gresty, Bronstein & Barratt, 1987; Telford, Seidman, & Paige, 1996,1997; Paige, Barnes, Telford, & Seidman, 1996; Busettini, Miles, Schwarz & Carl, 1994). The "fixed" versus "free" head-to-trunk conditions were included in the analysis to help identify possible contributions from the COR (Bronstein & Hood, 1986).

The walking speeds chosen provided a range of slow to moderate walking speeds for adults (aged 20-60 years), average speeds have been shown to range from 1.3 - 1.6 m/s (Finley & Cody, 1970; Perry, 1992) and velocities between 1.2 - 1.8 m/s have been shown to provide an area where head translation and pitch are most highly correlated (Hirasaki, Moore, & Raphan, 1999). The subjects first practiced treadmill locomotion until they could walk comfortably without using the handrails. A randomized block design was used for testing to control for possible learning effects. Initial distance and speed order was randomized and then followed throughout the testing procedure while keeping the near and far testing consolidated to minimize time constraints and patient fatigue. This consolidation also likely reduced the overall variability in the fixed condition data by minimizing the number of times the cervical collar was adjusted on the subject's neck. SVA

assessment was performed again at the conclusion of the dynamic testing. This post test also served as an internal check to control for fatigue or eye strain that could potentially affect visual acuity measures.

G. Covariate Measures

Demographic variables were collected which included: age, height, and weight. Knee extensor torque measures were collected to serve as an experimental control to ensure homogenous lower body strength in the subject pool. Knee extensor torque was measured using a portable dynamometer (CSD 400, Chatillon, Largo, FL). Lower-extremity strength has been shown to decline with age and has been associated with reduced performance on functional tasks such as balance and gait speed (Wang, Olsen, & Protus, 2002; Fransen, Crosby & Edmonds, 2003). Touch sensation was measured on the plantar aspect of the distal phalanx of the right great toe with a standard monofilament protocol using a set of three Semmes-Weinstein monofilaments (10.0 g, 4.0 g, & 2.0 g). Vibration sensation was measured on the dorsum of the right great toe at the bony prominence of the distal interphalangeal joint using a standard 128 Hz tuning fork (McCoy Medical, Maryland Heights, MO). Cutaneous sensitivity from the lower extremities can play a significant role for an individual in maintaining balance during locomotion and have a significant effect on gait speed (Deshpande et al., 2008; Resnick, Stansbery, & Harris, 2002). VOR function was evaluated

using a standard rotary chair (NeuroKinetics, Pittsburgh, PA) protocol in the Vestibular Diagnostics Laboratory, Dept of Otolaryngology, KUMC. Seatbelts and straps were utilized to ensure that subjects were secured to the chair. EOG activity was recorded from disposable disc electrodes placed just lateral to each eye (centered on the pupil) and a ground electrode placed on the forehead. VOR phase and gain measures were obtained from each subject at five standard clinical sinusoidal chair rotation frequencies (.01, .02, .04, .08 & .16 Hz).

H. Data Analysis

The goals of this study are summarized below:

1. Provide measures of physiologic changes occurring in the saccular system with age as measured by the VEMP.
2. Establish initial normative data on VEMPs in different age groups using the BPM method to provide additional clinical diagnostic value to current vestibular testing.
3. Evaluate the effects of normal aging on DVA at “near” and “far” distances and possible contributions from the COR.
4. Analyze the effect of speed of locomotion on gaze stabilization in healthy young and older adults.
5. Evaluate the relationship between a static and functional otolith measure in healthy aging adults.

To achieve these goals several statistical procedures were used. Distributions of continuous variables were evaluated for normality through skewness and kurtosis testing. A repeated measures General Linear Model (GLM) (SPSS version 16.0) was used to test for differences in DVA between age-groups (3(groups) x 2(head-trunk coupling) x 2(speeds)). The study of age-related changes in VEMPs in recent research literature has traditionally been analyzed using a set of linear regression models with age as the main independent variable and P1-N1 amplitude, latencies, and thresholds as dependent variables (Ochi & Ohashi, 2003; Su et al., 2004; Zapala & Brey, 2004). This technique was not pursued in the present study due to a lack of a continuum of age categories (groups of 20-30 years, 65-74 years and 75-85 years). It would have been inappropriate to make predictions based on age groups not included in the study but follow-up studies may be able to provide data for missing age categories.

A between-subjects multivariate analysis of variance (MANOVA) (SPSS version 16.0) was used to test for differences in VEMP (amplitude, latency, threshold, & IAD) parameter means among the three age groups in the study. Post hoc Tukey HSD procedures were used to test pair wise specific age-group differences. Differences were considered significant at $p < 0.05$. The association between changes in DVA with age and VEMP responses with age was also evaluated. Due to possible changes in the association between DVA and VEMPs in the head-trunk coupling conditions,

correlation coefficients between DVA (head-fixed to trunk and head not fixed to trunk conditions) and VEMP was computed and tested for significance using a t-test.

## III. Results

### A. VEMP Data

#### A.1 Overall Data

VEMPs were successfully recorded bilaterally on 29 of the 32 subjects. Three subjects (one from each age category) had attenuated or absence responses unilaterally due to reduced middle ear function and thus data from these three ears were excluded from further analysis. Thus there were a total of 32 subjects (61 ears) with measureable VEMP responses. Mean values were determined at intensity sound level of 95 dBnHL consistent with previous studies using BPM (Maes et al., 2009; Vanspauwen et al., 2006b) and at a level where a 100% response rate was obtained for ears with normal middle ear function. The overall mean P1 and N1 latencies were 16.0 ± 2.2 ms and 24.2 ± 2.7 ms, respectively; the mean peak-to-peak P1/N1 amplitudes were 103.1 ± 75.6 µV; the overall mean thresholds were 80.6 ± 5.2 dBnHL and the mean IADs for the total group were 15.7 ± 13.9 % (Table II). No significant right-left or gender differences were demonstrated in any of the before mentioned response parameters (Table II). Since no significant differences were detected in left-right and gender categories, ear and gender data were combined for all other analyses.

Table II. Overall, Left-Right & Gender specific VEMP parameters: Latency, Amplitude, Threshold and IAD.

| | P1 (ms) | N1 (ms) | Amplitude (μV) | Threshold (dBnHL) | IAD (%) |
|---|---|---|---|---|---|
| Overall (n = 61) | 16.0±2.2 | 24.2±2.7 | 103.1±75.6 | 80.6±5.2 | 15.7±13.9 |
| Right (n = 32) | 16.1±2.1 | 24.3±2.8 | 104.0±75.3 | 80.8±5.4 | |
| Left (n = 29) | 15.9±2.3 | 24.2±2.8 | 99.2±69.0 | 80.2±5.2 | |
| | p = 0.698 | p = 0.975 | p = .349 | p = 0.475 | |
| Male (n = 30) | 15.8±1.4 | 23.5±1.8 | 93.3±60.7 | 80.3±4.1 | 18.2±14.4 |
| Female (n = 31) | 16.3±1.9 | 24.8±2.8 | 114.1±92.3 | 80.9±5.1 | 13.1±13.3 |
| | p = 0.399 | p = 0.156 | p = 0.464 | p = 0.741 | p = 0.323 |

***IAD, Interaural Amplitude Difference. (n = ears)***
***Data are expressed as mean ± SD, *p < 0.05.***

## A.2 Group Data

The P1 and N1 latencies measures did not show any statistical significant differences among the three age groups (p = 0.446 & p = 0.119) (Figure 6, Table III). The IAD percentage also was statistically equivalent across age groups (p = 0.234) (Table III). There was a statistically significant difference in VEMP peak-to-peak amplitudes among groups (f = 19.68, p = 0.000). Tukey HSD post hoc pair wise comparisons showed Group 1 amplitude was significantly greater than Group 2 & Group 3 (p = 0.000) (Figure 7, Table III). As shown in Figure 8, there was also a statistically significant increase in VEMP threshold among age groups (f = 8.82, p =

0.001). Post hoc comparisons confirmed that Group 1 thresholds were significantly lower when compared to Groups 2 & 3 (Tukey HSD, p = 0.002 & p = 0.008, Table III).

Table III. Parameters of VEMP: latency, amplitude, threshold, and IAD by age group.

| Age Groups | P1 (ms) | N1 (ms) | Amplitude (μV) | Threshold (dBnHL) | IAD |
|---|---|---|---|---|---|
| 1 (20-30 yrs) | 16.2±1.3 | 24.6±1.1 | 180.1±67.9 | 77.1±4.4 | 10.1±7.0 |
| 2 (65-74 yrs) | 16.5±2.3 | 25.0±3.6 | 59.9±40.3 | 83.3±3.7 | 18.8±15.4 |
| 3 (75-85 yrs) | 15.5±1.5 | 22.9±1.7 | 57.9±41.8 | 82.3±2.8 | 19.6±17.5 |
| p value | p = 0.446 | p = 0.119 | p = 0.000* | p = 0.001* | p = 0.234 |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10).***
***Data are expressed as mean ± SD, *p < 0.05.***

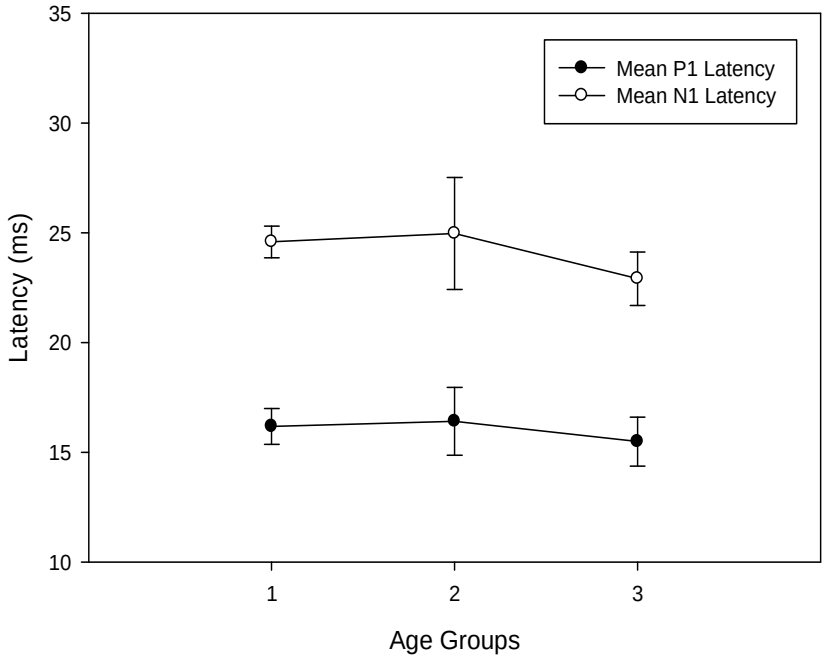


Figure 6. P1 (filled circles) and N1 (open circles) latencies among groups. Reported as Mean ± Standard Error Measurement (SEM). Latencies were not statistically differenct across age groups.

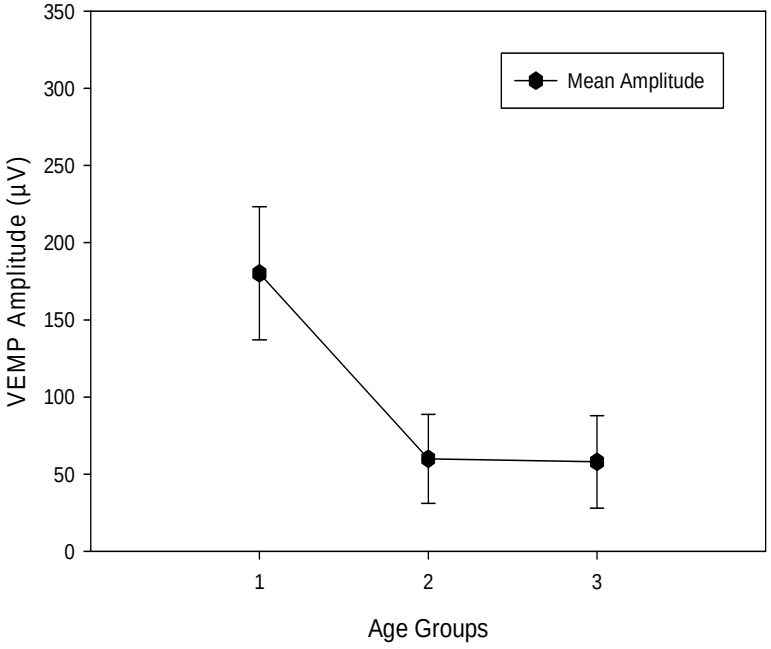


Figure 7. VEMP peak-to-peak amplitudes are shown for each group reported as Mean ± SEM. There were statistically significant differences detected between Group 1 & 2 (p = 0.000) and Group 1 & 3 (p = 0.000).

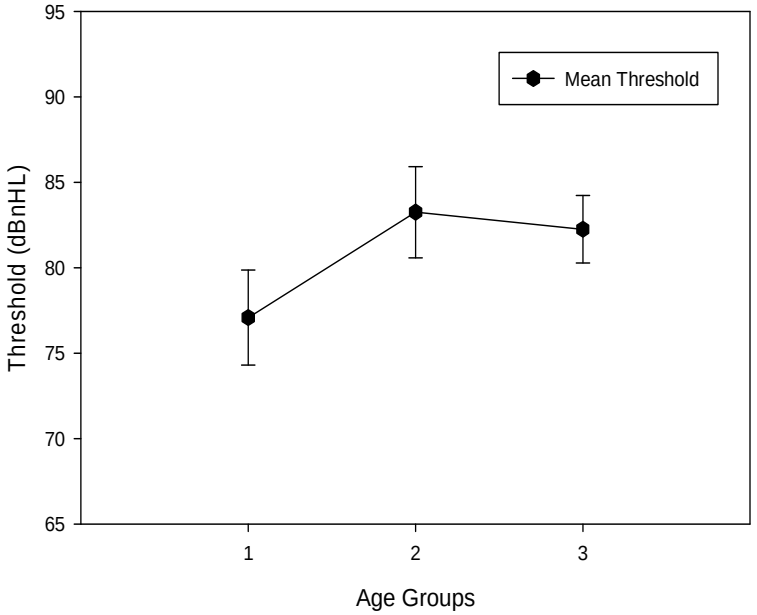


Figure 8. VEMP thresholds are shown for each age group reported as Mean ± SEM. A statistically significant difference was shown between Group 1 & 2 and Group 1 & 3 (Tukey HSD, p = 0.002 & p = 0.008, respectively).

B. DVA Data

DVA was successfully obtained in 32 subjects; three subjects were unable to comfortably walk at 1.5 m/s on the treadmill and were thus excluded from the analysis. Two acuity trials were recorded at each position throughout the study to ensure quality of data and to control for possible learning effects. When compared, trial 1 (0.19±0.22) was not statistically different from trial 2 (0.011±0.21) ($t = 1.96$, $p = 0.480$) and thus the two trials were combined for all visual acuity analysis. In instances where data from trial 1 or trial 2 were compromised due to the DVA software, the intact trial was used in the analysis.

SVA was obtained pre and post DVA testing at near and far distances. Pre SVA (-0.04±.21) and post SVA (-0.07±.21) at near distances were not significantly different ($t = 1.58$, $p = 0.124$). Pre SVA (-0.01±.16) and post SVA (-0.04±.18) at far distances also were not significantly different ($t = 1.98$, $p = 0.057$). Therefore, pre and post measurements of SVA were combined within their respective categories and used to calculate the delta (DVA – SVA) value used in the analysis.

DVA data were analyzed using the general linear model (GLM) and a mixed design ((3(groups) x 2(head-trunk coupling) x 2(speeds)) for the near and far distances separately, since direct comparisons should not be made between these distances due to luminance and/or viewing distance differences.

Based on self reports from study subjects regarding oscillopsia during testing and evidence reported from previous studies (Bloomberg, Reschke, Huebner, & Peters, 1992; Peters and Bloomberg, 2005), near DVA was much more challenging for all participants when subjectively compared to far DVA.

B.1 Near DVA

Mean ± one standard deviation measures and corresponding p values for near DVA results are presented below in Table IV. There was a significant decline in DVA score with increasing speed ($p = 0.000$, Table IV, Figure 9) and a significant interaction effect was seen between speed x group ($p = 0.031$, Table IV). A loss/decline in DVA was discovered between the "fixed" versus "free" neck conditions ($p = 0.013$, Figure 10). There was not a significant interaction relationship between condition and age group ($p = 0.621$) but previous literature (Kelders et al. 2003) and trends in the current study data suggest that there could be some underlying interactions between group and neck condition in larger sample sizes of healthy adults. The between subjects omnibus test revealed significant differences in DVA among age groups ($p = 0.046$). Post Hoc analysis using Tukey HSD revealed a significant decrease in visual acuity between group 1 (young) and group 3 (oldest group) ($p = 0.044$). The quasi linear relationship between near DVA and age groups can be seen below in Figure 11.

Table IV. Near DVA results expressed in logMAR units. Displayed as Condition vs. Speed (1 = 0.75 & 2 = 1.5 m/s).

| Age Groups | Free_1 | Fixed_1 | Free_2 | Fixed_2 |
|---|---|---|---|---|
| 1 (20-30 yrs) | 0.01±0.13 | 0.03±0.15 | 0.13±0.15 | 0.16±0.12 |
| 2 (65-74 yrs) | 0.12±0.11 | 0.14±0.10 | 0.19±0.10 | 0.21±0.12 |
| 3 (75-85 yrs) | 0.10±0.12 | 0.14±0.13 | 0.26±0.13 | 0.31±0.09 |
| Within Subjects | | | | |
| | Speed | p = 0.000* | Speed x Group | p = 0.031* |
| | Condition | p = 0.013* | Condition x Group | p = 0.621 |
| | Cond. x Speed | p = 0.778 | Cond. x Speed x Group | p = 0.875 |
| Between Subjects | **Overall** | | | |
| | Groups | p = 0.046* | | |
| | Post Hoc | **1 vs 2** | **1 vs 3** | **2 vs 3** |
| | | p = 0.197 | p = 0.044* | p = 0.753 |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10).***
***Data are expressed as mean ± SD, *p < 0.05.***

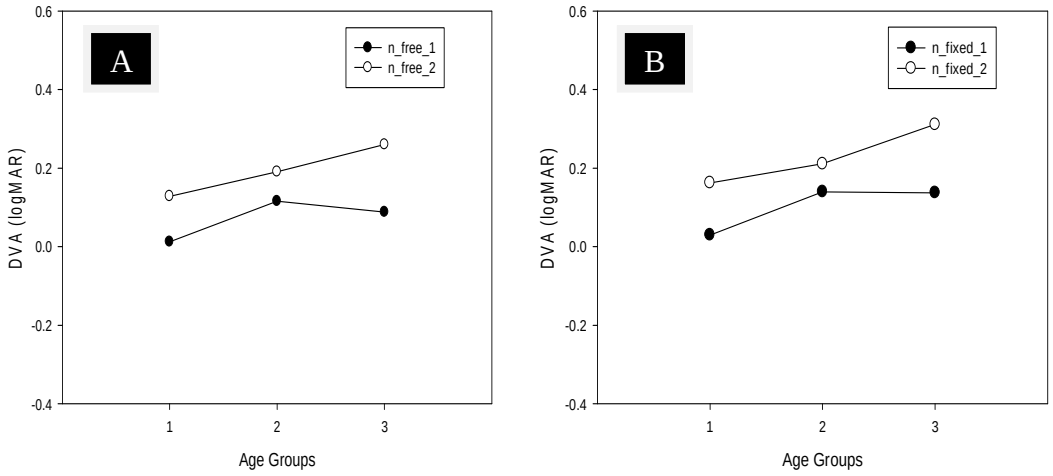


Figure 9. (A. Free condition & B. Fixed Condition). Near DVA results showing changes in visual acuity between walking speeds by group (0.75 and 1.5 m/s).

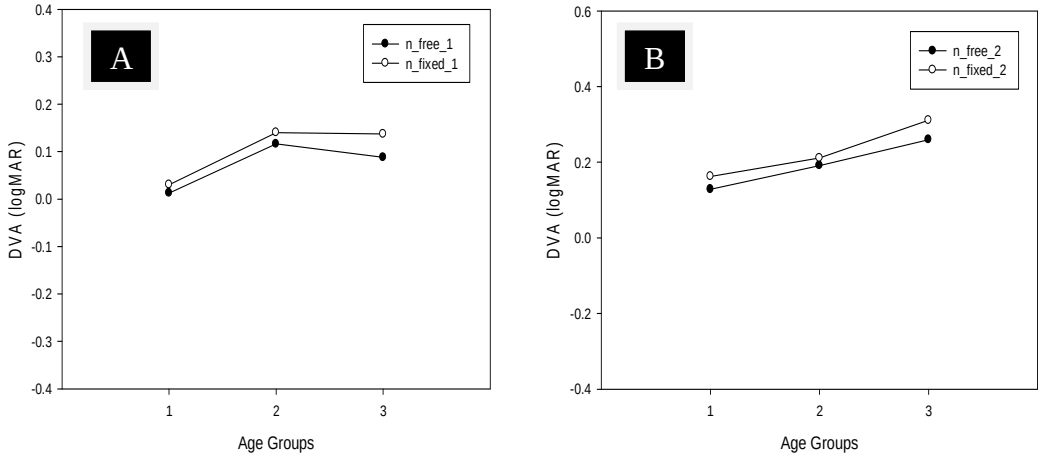


Figure 10. (A. Speed 1 & B. Speed 2). Near DVA results showing changes in visual acuity between “fixed” and “free” neck conditions at 0.75 and 1.5 m/s by group.

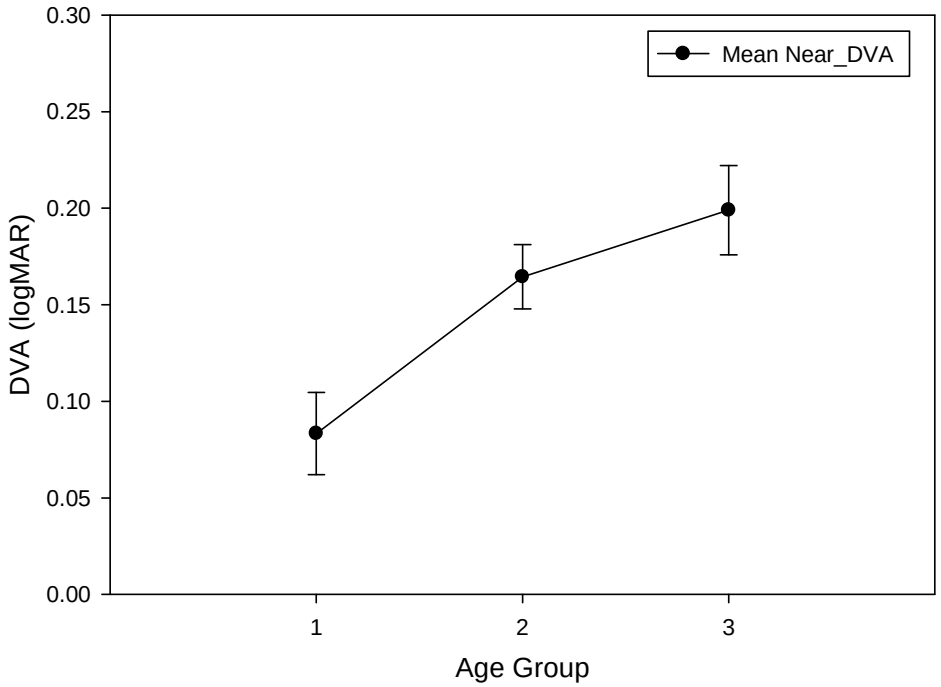


Figure 11. Mean near DVA scores are shown for each age group reported as Mean ± SEM. A quasi linear relationship is seen between age group and near DVA. A statistical difference was found between groups 1 and 3 (p = 0.044).

B.2 Far DVA

Mean ± one standard deviation measures and corresponding p values for far DVA results are presented below in Table V. Similar to the near DVA results, there was a significant deterioration in DVA scores with increasing speed (p = 0.001) (Table V., Figure 12) but no significant interaction effect was seen between speed x group (p = 0.365). Contrary to the near results, there were no significant changes detected in DVA when "fixed" versus "free" neck conditions were analyzed (p = 0.412, Figure 13) and no interaction effects between condition and age group (p = 0.399). No differences in DVA among age groups were detected with the between subjects omnibus test (p

= 0.441). The relationship between far DVA and the three age groups are show below in Figure 14.

Table V. Far DVA results expressed in logMAR units. Displayed as Condition vs. Speed (1 = 0.75 & 2 = 1.5 m/s).

| Age Groups | Free_1 | Fixed_1 | Free_2 | Fixed_2 |
|---|---|---|---|---|
| 1 (20-30 yrs) | - 0.02±0.04 | -0.02±0.05 | -0.01±0.04 | 0.02±0.12 |
| 2 (65-74 yrs) | -0.07±0.11 | -0.06±0.08 | 0.00±0.10 | -0.03 ±0.10 |
| 3 (75-85 yrs) | -0.03±0.10 | -0.01±0.06 | 0.01±0.11 | 0.02±0.08 |
| Within Subjects | | | | |
| | Speed | p = 0.001* | Speed x Group | p = 0.365 |
| | Condition | p = 0.412 | Condition x Group | p = 0.399 |
| | Cond. x Speed | p = 0.715 | Cond. x Speed x Group | p = 0.388 |
| Between Subjects | | | | |
| | Groups | p = 0.441 | | |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10).***
***Data are expressed as mean ± SD, *p < 0.05.***

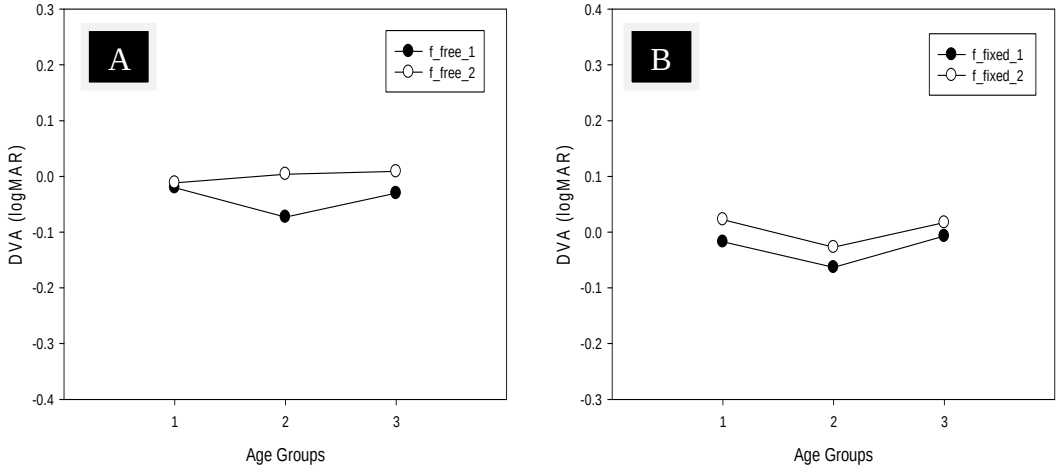


Figure 12. (A. Free condition & B. Fixed Condition). Far DVA results showing changes in visual acuity between walking speeds by group (0.75 and 1.5 m/s). There was a significant decline in DVA scores with increased speed (p = 0.001).

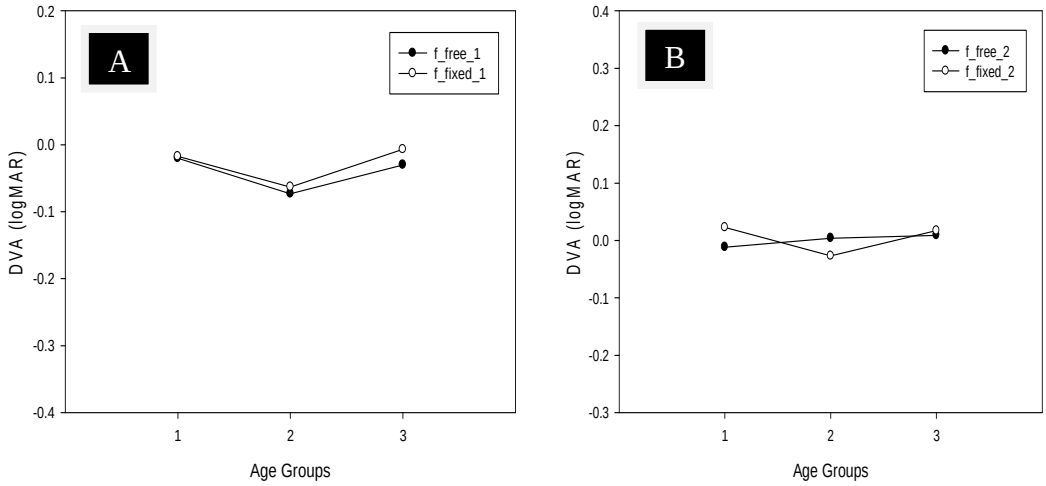


Figure 13. (A. Speed 1 & B. Speed 2). Far DVA results for "fixed" and "free" neck conditions at 0.75 and 1.5 m/s by group. No significant changes were detected between conditions or groups.

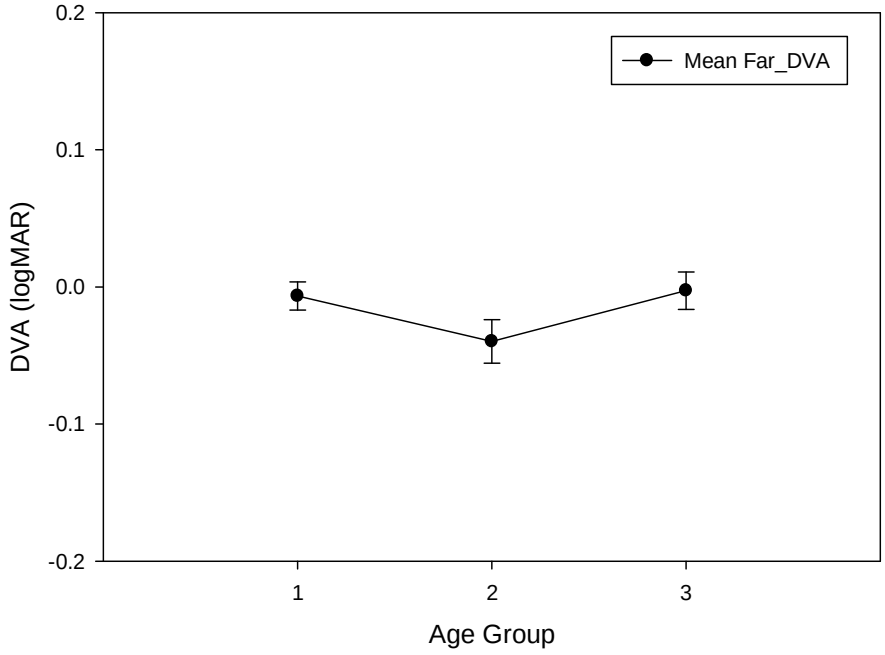


Figure 14. Mean far DVA scores are shown for each age group reported as Mean ± SEM. No significant differences were detected among age groups.

C. VEMP Amplitude and DVA Correlation Data

Due to similar underlying linear otolith mediated mechanisms thought to contribute to the VEMP and possible DVA responses, Pearson's Correlation Coefficients were used to analyze these relationships and are shown in Table V1 and VII below.

Table VI. Pearson's Correlation results for VEMP amplitude versus near DVA.

| | Free_1 | Fixed_1 | Free_2 | Fixed_2 |
|---|---|---|---|---|
| **VEMP Amplitude** | r = -0.269 | r = -0.314 | r = -0.357* | r = -0.304 |
| | p = 0.136 | p = 0.080 | p = 0.045 | p = 0.090 |

***p < 0.05.***

Table VII. Pearson's Correlation results for VEMP amplitude versus far DVA.

| | Free_1 | Fixed_1 | Free_2 | Fixed_2 |
|---|---|---|---|---|
| **VEMP Amplitude** | r = 0.158 | r = 0.139 | r = 0.008 | r = -0.116 |
| | p = 0.387 | p = 0.449 | p = 0.967 | p = 0.528 |

There was an overall negative relationship between VEMP amplitude and near DVA, which was expected based on previous literature on generator sites for near DVA and VEMPs. VEMP amplitude and far DVA did not show any discernable linear relationships. The only significant linear relationship between VEMP amplitude and DVA was detected in the near distance, free neck condition and 1.5 m/s (r = - 0.357, p = 0.045, Figure 16A). Though not statistically significant, there were also moderate levels of correlation with VEMP amplitude at the near, fixed, 0.75 m/s & 1.5 m/s conditions (r = - 0.314,

p = 0.080, Figure 15B and r = - 0.304, p = 0.090, Figure 16B) and a somewhat weak correlation between VEMP amplitude and near, free, 0.75 m/s conditions (r = - 0.269, p = 0.136, Figure 15A).

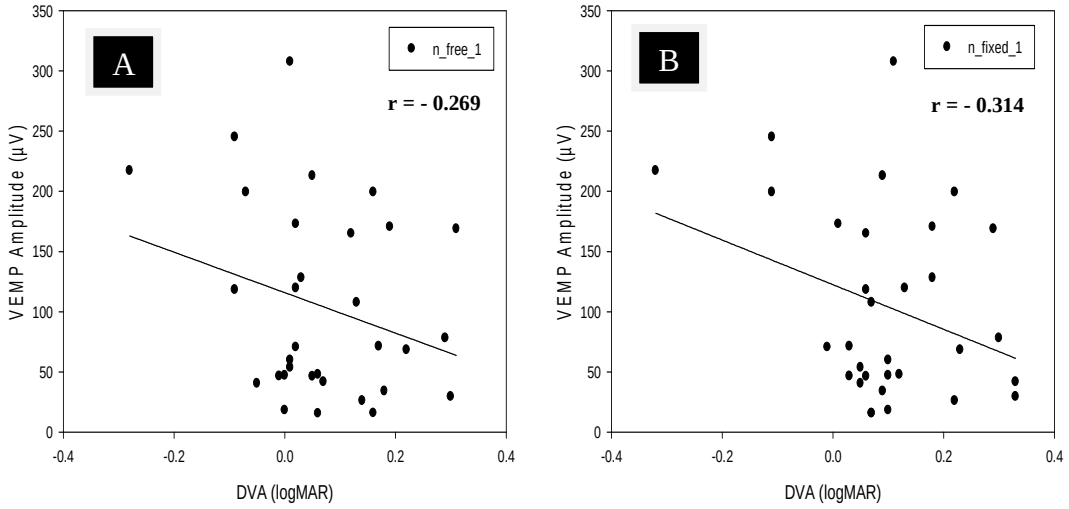


Figure 15. (A. Free condition & B. fixed condition). Relationships between VEMP amplitude and near DVA are shown at 0.75 m/s. A weak relationship was seen in the free position and a moderate relationship in the fixed condition.

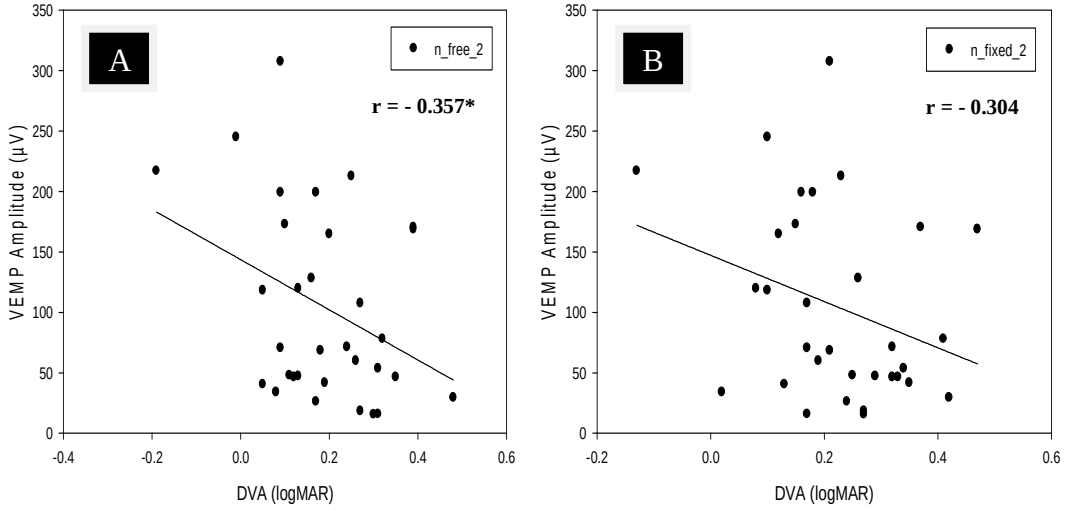


Figure 16. (A. Free condition & B. fixed condition). Relationships between VEMP amplitude and near DVA are shown at 1.5 m/s. A significant relationship was discovered in the free condition and a non-significant but moderate relationship was identified in the fixed position.

The relationship between VEMP amplitude and far DVA was much weaker overall when compared to near DVA. No significant linear relationships were discovered and all VEMP amplitude and far DVA relationships were weak or non-existent (Figures 17 & 18 and Table VII).

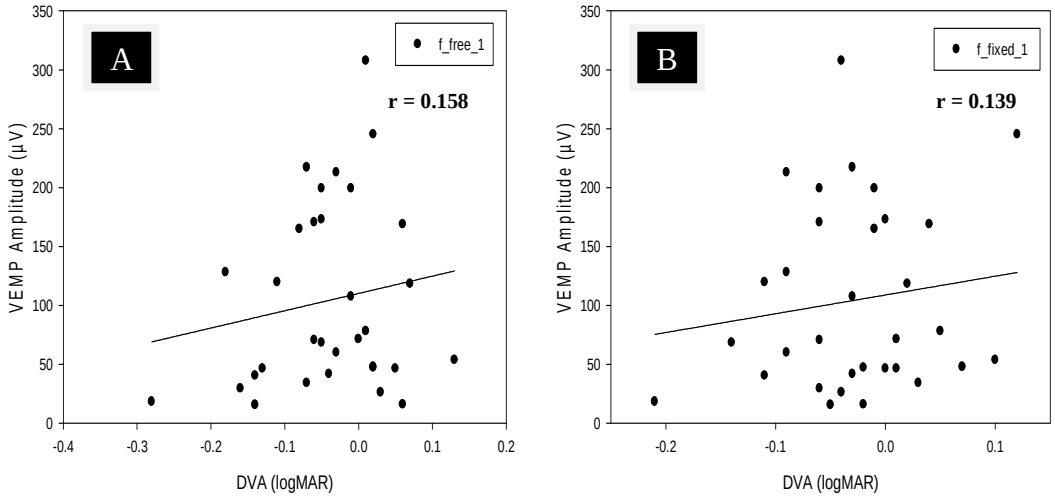


Figure 17. (A. Free condition & B. fixed condition). Relationships between VEMP amplitude and far DVA are shown at 0.75 m/s. A weak relationship was discovered for both free and fixed conditions.

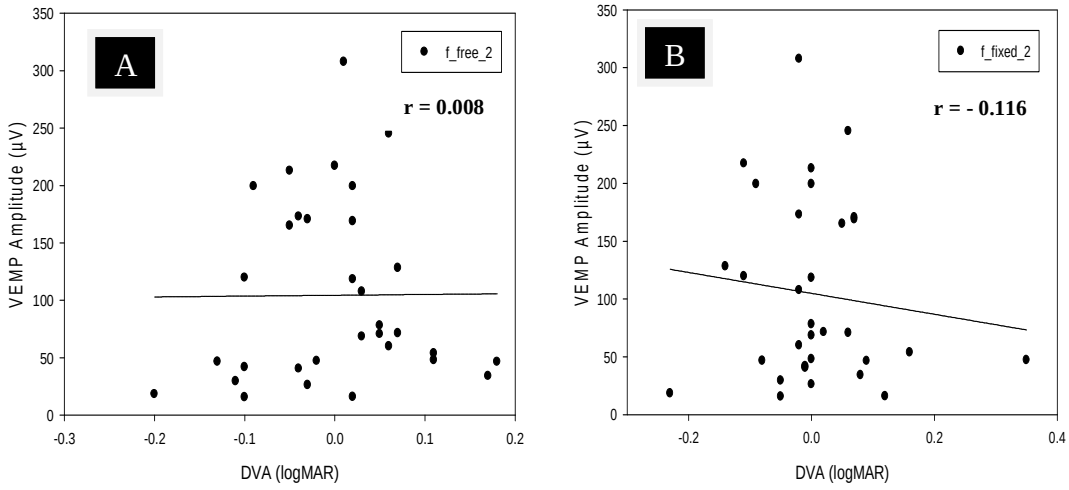


Figure 18. (A. Free condition & B. fixed condition). Relationships between VEMP amplitude and far DVA are shown at 1.5 m/s. Essentially no linear relationship was noted in the free condition and a weak relationship in the fixed condition.

## D. Covariate Data

Demographic and covariate clinical data were collected to analyze and control for underlying possible confounding factors associated with increased aging in a healthy population. These factors and demographic information are displayed in Tables VIII, IX and X. There were no significant differences between groups for height, average walking speed or knee extensor torque (Table VIII). Rotary Chair VOR gain was also unchanged across age groups in the present study ($p = 0.998$, Table IX). There was a significant difference in VOR phase between age groups ($p = 0.034$, Table X, Figure 19) and post hoc analysis revealed the detected differences were between groups 1 and 3 ($p = 0.026$).

Table VIII. Covariate Measures displayed by age groups.

| Groups | Age (yrs) | Height (in) | Average Walking Speed (m/s) | Knee Extensor Torque (Nm) |
|---|---|---|---|---|
| 1 (20-30 yrs) | 26.8±2.7 | 66.9 ±3.06 | 1.34±0.18 | 62.3±19.4 |
| 2 (65-74 yrs) | 67.7±2.0 | 68.3±4.81 | 1.39±0.15 | 75.4±21.3 |
| 3 (75-85 yrs) | 78.7±3.0 | 66.6±2.59 | 1.23±0.18 | 67.4±21.6 |
| p value | p = 0.000* | p = 0.531 | p = 0.106 | p = 0.446 |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10).***
***Data are expressed as mean ± SD, *p < 0.05.***

Table IX. Rotary Chair VOR Gain displayed by age group.

| Age Groups | 0.01 (Hz) | 0.02 (Hz) | 0.04 (Hz) | 0.08 (Hz) | 0.16 (Hz) |
|---|---|---|---|---|---|
| 1 (20-30 yrs) | 0.30±0.12 | 0.35±0.14 | 0.45±0.17 | 0.51±0.16 | 0.57±0.20 |
| 2 (65-74 yrs) | 0.27±0.10 | 0.36±0.09 | 0.46±0.15 | 0.53±0.16 | 0.55±0.15 |
| 3 (75-85 yrs) | 0.26±0.12 | 0.37±0.15 | 0.47±0.18 | 0.52±0.17 | 0.57±0.19 |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10), gain = eye velocity/head velocity.***
***Data are expressed as mean ± SD.***
***No significant group differences were detected (p = 0.998).***

Table X. Rotary Chair VOR Phase displayed by age group.

| Age Groups | 0.01 (Hz) | 0.02 (Hz) | 0.04 (Hz) | 0.08 (Hz) | 0.16 (Hz) |
|---|---|---|---|---|---|
| 1 (20-30 yrs) | 31.8±7.12 | 17.3±5.68 | 9.08±4.25 | 3.58±5.21 | -0.92±5.09 |
| 2 (65-74 yrs) | 40.2±9.11 | 22.4±9.14 | 10.9±4.77 | 3.40±3.34 | -0.20±3.94 |
| 3 (75-85 yrs) | 43.4±12.0 | 27.5±13.5 | 16.8±8.69 | 5.80±5.71 | 0.90±4.93 |

***Group 1 (n=12), Group 2 (n=10), Group 3 (n=10), phase are reported as degrees.***
***Data are expressed as mean ± SD.***
***Significant between group differences were detected (p = 0.034).***
***Post Hoc tests revealed differences were between groups 1 & 3 (p = 0.026).***

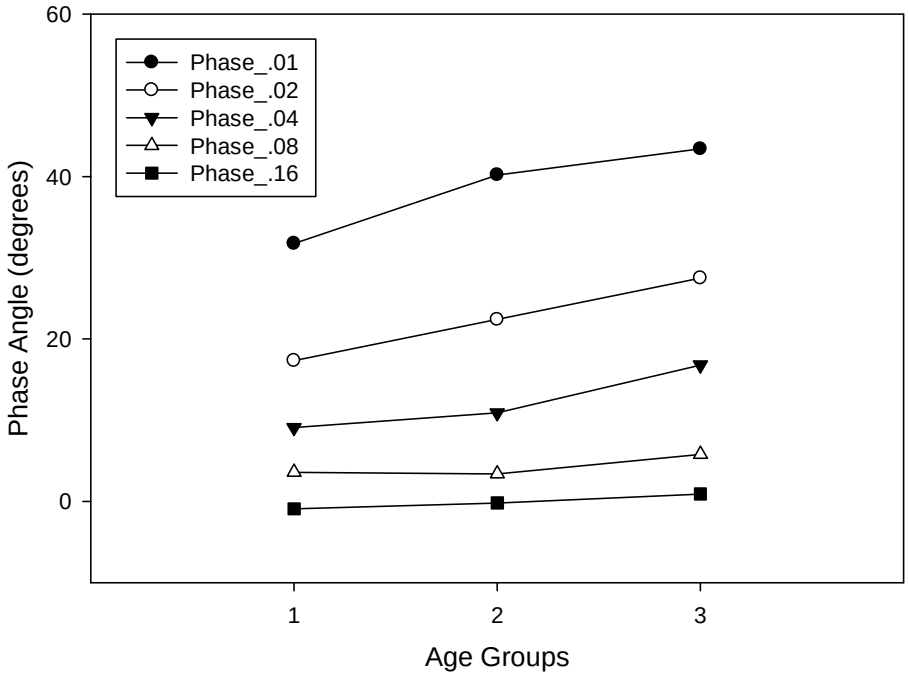


Figure 19. The relationship between rotary chair phase angle and age groups are shown by frequency. An increase in phase angle was seen with increasing age.

## IV. Discussion

### A. Measurement of the Vestibular Evoked Myogenic Potential Utilizing BPM Feedback

The mean absolute interaural amplitude difference measured using the BPM feedback method for our subjects was 15.7 ± 13.9 μV. This value is smaller and less variable than the differences observed by Maes, et al. (2009) of 33.80 ± 28.33 μV and Vanspauwen et al. (2006a) of 40.2 ± 29.5 μV using a similar approach even though our age groups were much broader (both previous BPM studies were conducted only on young healthy adults). In addition, the blood pressure cuff in our study was attached securely to a stable metal bar which provided a constant, repeatable position for testing. This protocol insured that the subject could only apply the appropriate cuff pressure with a head turn due to precise head positioning. It was possible for subjects in the Vanspauwen et al. study to inadvertently confound the response by applying force to the cuff with their hand. Our protocol also provided a stable forward flexion of the neck which resulted in a subjectively "simpler" muscle contraction per anecdotal evidence from testing, whereas the Maes et al. study used a "lateroflexion" movement. Thus, differences in testing protocols could have contributed to a more uniform muscle contraction throughout the data collection for the present study.

#### A.1 Gender Effects

There were no differences in VEMP response parameters (amplitude, latency, threshold or IAD) for gender or ears (left versus right) discovered among groups. Previous studies (Akin et al., 2003; Lee et al., 2007; Brantberg et al., 2007; Brantberg & Fransson, 2001; Welgampola & Colebatch, 2001) have also found equivalence between genders with amplitude and threshold. There have been some reported latency differences between genders by Brantberg et al. (2007) and Lee et al. (2007) but these results have been contradictory with other research showing no latency differences (Akin et al., 2003 & Basta et al., 2005). Differences in latency between genders have been reported in auditory evoked potentials due possibly to differences in head sizes, distances to the brainstem structures, and possible faster potential transmission (Nikifordis et al., 1993). It should be noted that these results are contrary to recent VEMP research which showed increased component latencies in females (Lee et al., 2007). Thus, additional research needs to be accomplished in this area before appropriate judgments can be made on the significance of possible gender effects.

### A.2 Amplitude

VEMP interpeak amplitude measures have been reported as the most reliable parameter for comparison among subjects (Isaradisaikul et al., 2008; Maes et al., 2009). This study revealed a decline in VEMP amplitude in the two older groups when compared to the mean amplitude of the young group

(see Figure 7). There were no differences detected between the two older groups. This age-related decline is consistent with previous amplitude data using EMG monitoring (Lee et al., 2008; Welgampola & Colebatch, 2001; Su et al., 2004; Ochi & Ohashi, 2003; Zapala & Brey, 2004) and has been shown to be unrelated to any age-related reduction in muscle tone/strength (Brantberg et al.,2007; Welgampola & Colebatch, 2001). Ours is the first study to collect age-related VEMP data utilizing the BPM method of monitoring, and VEMP amplitude means and standard deviations collected were comparable to other EMG monitored aging studies (Wang & Young, 2003, 2004; Basta et al., 2005; Isaradisaikul et al., 2008; Cheng et al., 2003; Wu et al., 2007).

Similar to results from morphological studies of the vestibular system, VEMP amplitude has been shown to decline slightly with age until around the 6$^{th}$ decade of life, at which time the reductions become more evident (Welgampola & Colebatch, 2001; Su et al., 2004; Basta et al., 2005). This increase in slope following the 6$^{th}$ decade has not been consistently shown in other functional vestibular data such as VOR gain (Peterka et al., 1990) but is even more pronounced than anatomical changes seen in the vestibular system. The increased decline in VEMP amplitude could be an indication of functional saccular loss prior to histological degenerative changes (Welgampola & Colebatch, 2001a). Previous aging literature has also shown similar declines in gait and walking patterns predominantly after the 6$^{th}$

decade of life (Murray et al. 1969; Blanke & Hageman, 1989). Contrasting increases in slope cannot be visualized in the present data due to the limited range of age groups tested, but is a feasible assumption based on current data trends and previous literature. The small inconsistent differences seen between other vestibular function tests and morphological changes have been attributed to possible redundancy and central adaptations within the vestibular system (Peterka et al., 1990; Enrietto et al., 1999). It is possible that these assumed central adaptive features are less prevalent in the otolith portion of the vestibular system. The decline in VEMP amplitude has largely been attributed to the afore mentioned reduction of vestibular hair cells, neurons in Scarpa's ganglion, changes in the vestibular nuclear complex, and possible degeneration of the saccule (Merchant et al., 2000, Tang et al., 2001; Johnson, 1971). Another possible factor for amplitude decline could be a reduction in specific saccular hair cells (possibly type I hair cells in the saccular macula) or specific inferior vestibular nerve fibers (irregularly discharging primary afferents) that are reportedly related to VEMP responses (Brantberg et al., 2007; Murofushi & Curthoys, 1997). Specific anatomical sites have not been histologically singled out and thus it is most likely a combination of multiple areas and mechanisms within the VEMP neural pathway that account for age-related declines in component amplitudes. The VEMP neural pathway has been shown to include: saccular macula, Scarpa's

ganglion, inferior vestibular nerve, vestibular nuclear complex, medial/lateral vestibulospinal tract, and motor neurons of the SCM muscle.

### A.3 Latency

There were no differences in P1 or N1 latencies detected among age groups (see Figure 6). This finding is consistent with many previous studies involving VEMP parameters (Basta et al., 2005; Su et al., 2004; Welgampola & Colebatch, 2001), but contrary to the results from other studies that reported age-related latency prolongations (Zapala & Brey, 2004; Brantberg et al., 2007; Lee et al., 2007). Differences in VEMP latencies have been shown to vary based on stimulus (i.e. click verse tone bursts) and stimulus parameter (rise/fall times) variations. The contradictory results reported on latency could be due to small differences in stimulus parameters and thus it is important to compare results utilizing identical stimulus parameters (Akin et al., 2003; Basta et al., 2005; Zapala & Brey, 2004). Alternatively, these changes also could be related to altered central nervous system processing of otolithic changes or changes in peripheral conduction rates along the pathway. In addition, pathological changes associated with demyelinating diseases such as multiple sclerosis (Shimizu et al., 2000) and other central nervous system disease such as tumors (Murofushi et al., 2001), have been shown to prolong VEMP latency measures. Future research should focus on evaluating differences in VEMP latency for use as a clinical tool.

Comprehensive prescreening regimens, such as utilized in this study, can exert increased control over obtaining subjects without underlying vestibular pathology and standardized testing protocols should provide opportunities to better understand these differences.

### A.4 Threshold

VEMP thresholds provide information on minimal levels of stimulation needed to activate saccular vestibular afferents. There was a significant increase in VEMP thresholds noted among the groups in our study. The thresholds for the two older groups were less sensitive when compared to the young group (see Figure 8). Thresholds in adults have been shown to range between 75 and 100 dBnHL but have rarely been reported in VEMP studies (Akin et al., 2003). Ochi et al. (2001) indicated that thresholds were the most useful and reliable VEMP parameter although they have not often been reported due to the fear of muscle fatigue. Results from this study are consistent with age-related changes in VEMP thresholds reported by Ochi & Ohashi (2001). Changes in thresholds with age are presumably secondary to the afore mentioned degeneration in the vestibular system and possibly are related to broadening of vestibular tuning curves following neuronal changes due to aging and/or pathology.

### A.5 Interamplitude Difference Ratio

IAD ratios show the relationship between side differences in VEMPs. IAD ratios have been shown to range from 0-40% in normal healthy adults regardless of method used to account for muscle activity (Akin & Murnane, 2001). Li et al. (1999) reported IADs of 37% while monitoring SCM EMG level and Welgampola & Colebatch (2001) reported similar average IADs of 22%. The average IAD in this study was 15.7 ± 13.9%, which is moderately lower than most published VEMP reports and suggests good agreement between ears using the BPM method of muscle monitoring. There were no IAD differences among groups, which is also consistent with previous age-related VEMP studies (Ochi & Ohashi, 2003; Su et al., 2004; Basta et al., 2007; Lee et al., 2007). Thus, it seems that age-related changes in the vestibular system detected with VEMPs affect both sides equally. This information could be important for the clinical usefulness of VEMPs as comparisons between ears can be made without regard to changes in age when a unilateral pathology or deficit is suspected. Age must still be taken into account for suspected bilateral lesions, however.

B. Dynamic Visual Acuity

Though interest in DVA was identified many years ago, there have been relatively few studies on age-related changes in this factor (Long & Cramber, 1990). DVA assessment has improved throughout the years but these measures have largely been static in nature. Our study employed a

functional approach described by Peters and Bloomberg (2003) for DVA testing but also is the first to apply measures associated with distance, walking speed and neck contributions. This study evaluated how these factors are affected by natural age-related changes in healthy adults. Thus, our data provide valuable insight into the functional benefits this particular test provides regarding changes in visual acuity.

## B.1 DVA Distance

DVA was recorded at two distances in the current study ("near" and "far") while subjects walked on a variable speed treadmill, and was measured at two different speeds under two neck conditions. Grossman et al. (1989) reported that during natural head movements from walking and running angular motion is stabilized by the VOR. This angular motion of the head is analyzed by the semicircular canals and results in compensatory eye movements initiated by the angular VOR (Moore et al., 1999; Paige, 1989). The pitching movement of the head generated during walking also stimulates the otolith system which is responsible for linear motion through contributions from the linear VOR (Telford et al., 1997). Thus, to maintain proper focus on targets of varying distances, the central nervous system must generate appropriate eye movements based on both aVOR and lVOR contributions.

Differences in aVOR gain (eye/head velocity) with distance have been shown previously (Demer & Viirre, 1996; Paige, 1989). While walking and

viewing “far” targets aVOR velocity has been shown to be 180 degrees out of phase with head pitch which is consistent with typical measures of aVOR (Grossman et al., 1989). In contrast, “near” targets have shown an in phase relationship (eye/head pitch velocity) which is consistent with a linear VOR contribution (Moore et al., 1999). These observed differences in VOR responses are thought to be related to possible contributions from semicircular canal (aVOR) and otolith (lVOR) responses (Peters & Bloomberg, 2005). Moore et al. (1999) and Paige (1989) have proposed that linear otolith mediated responses are related to the vestibulocollic reflex, particularly saccular input, which can be directly measured with the VEMP. Thus, we would expect a much greater relationship between VEMP and near DVA then VEMP and far DVA, which will be discussed in depth later in this paper. Hirasaki et al. (1999) also has shown that there is an interactive effect of walking speed on the previously mentioned linear contributions and that at an ideal walking speed (1.2 - 1.8 m/s) the corresponding head pitch is most highly compensatory for vertical head translation. These identified differences in possible generator sites for “near” and “far” DVA have led to the assumption that DVA recorded at multiple distances could be used to distinguish between possible otolith and semi-circular canal function in the future.

## B.2 Aging Effects

All visual acuity measures were recorded while subjects wore their appropriate corrective lenses and all subjects self reported visual acuity at normal levels. Pre and post static visual acuity measures were obtained while sitting in the "near" and "far" condition to account for possible learning effects and signs of possible eye fatigue from the extensive visual testing. No differences were detected between pre and post measures of SVA and thus it was assumed that possible learning effects and fatigue did not skew the results. SVA results also confirmed that mean visual acuity scores were within normal limits across age groups before and after DVA testing. All subjects were prescreened for muscle strength, cognition, peripheral sensitivity, physical activity level and average walking speed. No differences were detected between these factors among age groups. These factors have been shown to be important in maintaining proper gait/stability and upright locomotion (Laufer, 2005; Berry et al., 1981; Murray et al., 1969). This comprehensive screening procedure helped confirm that the changes detected were most likely directly related to changes in postural reflexes or similar functional mechanisms and not due to physical/ muscular differences between young and older subjects.

There was a significant decline in near DVA detected with age. Post Hoc analyses revealed that age-related differences detected in near DVA were between the younger group (20-30 yrs) and the oldest group (75-85 yrs) (see Figure 11). Age-related decline in DVA has received scarce attention in

the literature and has never been reported utilizing a functional protocol as described here, although changes with age have been reported with traditional DVA testing (Ishigaki & Miyao, 1994; Long & Crambet, 1990; Long & Penn, 1987; & Burg, 1966). Originally, these studies related decline in DVA to possible luminance changes and underlying changes in eye movement, but several studies also have shown declines at low frequencies which are thought to be vestibular mediated (Miller & Ludvigh, 1962; Burg, 1966; Reading, 1972). The above findings confirm that declines in DVA cannot be solely related to deterioration in the ocular system but most likely are significantly related to a combination of degenerative changes in the sensory/peripheral vestibular and ocular systems. Declines in DVA also have been reported in cases of vestibular pathology and post space flight due to changes in the vestibular system (Herdman et al., 1998; Schubert et al., 2008; Hillman et al., 1999; Cohen et al., 2007; Bloomberg et al., 2003).

The measurement of far DVA remained constant across age groups (see Figure 14). As mentioned above, VOR function in far DVA has been shown to be closely related to angular VOR mediated by the semicircular canal afferents. The decline in traditional VOR function with age has resulted in inconsistencies in the literature. Small declines in caloric responses have been seen after the $5^{th}$ and $6^{th}$ decades (Mulch & Petermann, 1979) and small reductions in VOR gain have been shown in older patients (Peterka et al., 1990). Reports of greater decreases in VOR function have been seen in

response to high amplitude and high acceleration rotational stimuli (Tian, Shubayev, Baloh, & Demer, 2001). The minimal decline in VOR with aging has been suggested to be related to central adaptive mechanisms that can increase semicircular canal input to help maintain VOR function at acceptable levels for compensatory eye movements (Herdman et al., 2003; Peterka et al., 1990).

The ability to maintain a stable visual field during locomotion is a complex phenomenon that requires extensive integration and coordination from multiple mechanisms. These mechanisms may include contributions from: elastic properties of neck musculature; cervicocollic reflexes; vestibulocollic reflexes; voluntary and anticipatory motor control strategies; along with centrally controlled visual/vestibular inputs (Patten et al., 2003). Breakdowns in these systems due to pathology and/or degeneration from aging can cause decreased head stability (Grossman & Leigh, 1990). A better understanding of the underlying mechanisms involved in these changes will provide insight into the role of possible adaptive strategies/techniques that may help compensate for these deficits.

### B.3 Speed

A decline in DVA was discovered with increased speed at near and far distances. This decrement was also shown to interact significantly with age in the near condition leading to poorer DVA scores in the oldest groups at 0.75

& 1.5 m/s (see Figure 9). An interaction with age was not seen in the far DVA trials (see Figure 12) leading to assumptions of possible age-related differences between aVOR and lVOR generator sites as discussed in the previous aging section. Such differences could be due to physiologic differences in aging rates between the semicircular canals and otolith systems or to differences in central adaptive features within the two systems (Schuknecht, Igarashi, & Gacek, 1965). Age-related changes in gait and walking patterns have been extensively reported in the literature (Laufer, 2005; Bohannon, 1997; Berry et al, 1981). Decreases in self-selected walking speeds, stride length, stride width, and walking cycle duration have been noted especially as individuals' age beyond 65 years (Murray et al. 1969). Maintaining proper gaze stabilization during locomotion requires extensive coordination between multiple sensorimotor systems within the body. Contrary to previous literature, the prescreening protocol data employed in the current study revealed no differences in self-selected walking speed, peripheral sensation, or muscle strength for healthy aging adults. This finding supports the idea that changes detected in DVA may be related to neural declines in the vestibular system with aging as opposed to possible physical declines related to muscle strength, as described in previous studies.

Natural high frequency head movements during walking can cause retinal slip which could lead to decreases in visual acuity (Demer & Amjadi, 1993). The current study is the first one to evaluate a functional DVA protocol

with multiple walking speeds and thus can provide important baseline information for future studies. The two speeds utilized in this study were 0.75 m/s and 1.5 m/s. Walking speeds of 1.5 m/s have been shown to be similar to average walking speeds in adults (aged 20-60 yrs), which range from 1.3 to 1.6 m/s (Finley & Cody, 1970; Perry, 1992). Thus, by choosing speeds similar to everyday function these results provide valuable information predictive of daily activities for an aging population. Walking speeds between 1.2 - 1.8 m/s have been shown to be ideal speeds for better correlation between head pitch and vertical head translations and thus have been defined as an optimal range of walking velocity with regard to head-trunk coordination (Hirasaki et al., 1999). Based on the frequency of these characteristics, Hirasaki et al. (1999) has also suggested that head pitch movements are controlled by the angular vestibulocollic reflex at slow walking speeds while the linear vestibulocollic reflex contributes more to faster walking speeds.

B.4 Condition

A standard foam cervical collar was used to restrict yaw neck movements during half of the trials. This approach allowed us to indirectly evaluate possible contributions from the COR in gaze stabilization for healthy aging adults. A significant decline in near DVA was detected in the “fixed” condition when compared to the “free” condition (see Figure 10). This finding

was consistent with subjective reports of difficulty level while performing the “near” and ”fixed” trials. No differences between “fixed” and “free” conditions were noted in the far DVA trials (Figure 13). No interaction effects with age on neck conditions were revealed even though previous studies have shown significant COR age effects. The COR is a reflexive eye movement that is activated by lateral neck movement and is thought to help optimize the ocular response (Hikosaka & Maeda, 1973). Schweigart et al. (2002) has reported that neck proprioceptive gain increases with age which is contradictory to most age-related functional changes in postural reflexes. COR function has also been shown to be increased in subjects with vestibular hypofunction (Bronstein & Hood, 1986; Heimbrand et al., 1996). Kelders et al. (2003) has shown increases in COR gain with age and essentially negligible COR gain in young healthy adults. Kelders et al. (2003) revealed a negative co variation between VOR and COR function (as VOR gain declines, COR gain increases) and postulated that the COR may be a compensatory function for decreases in VOR function with aging. The extra ocular muscles are the effector mechanism for VOR and COR function, thus it can be assumed that declines in VOR are not necessarily related to motor decline but likely result from sensory loss (as mentioned previously).

Several factors could have led to the unexpected findings revealing no age-related interactions in neck condition in this study. First, trends in the data show a possible relationship developing between age and condition

(especially in the near trials) but could be limited by the sample size or unknown underlying individual factors. Secondly, the current study used an indirect measure of COR function by limiting yaw movement in a functional protocol while previous COR studies measured COR gain directly utilizing a bite board and sinusoidal chair rotation. Though our testing was conducted using a more functional measure than previous studies, possible restrictions to vertical head movement (from placement of the cervical collar under the chin of the subject) could have contributed to reduced DVA measures across groups. This restriction could have caused increased restriction of pitch movement thus allowing for less separation in the young versus older group results. Finally we cannot rule out minimal inconsistencies in collar placement and/or collar stability during testing due to unexpected patient adjustments and/or patient-requested modifications during the testing protocol.

C. DVA and VEMP Amplitude Correlation

Various relationships between DVA and VEMPs were analyzed utilizing Pearson's Correlation Coefficients. Of special interest was the relationship between a "static" clinical test of otolith function (VEMP) and a "functional" clinical test of otolith function (near DVA). Previously reported research has shown that DVA recorded at near distances receives substantial contributions from the linear VOR system, more specifically the linear

vestibulocollic reflex (Takahashi et al., 1990; Moore et al., 1999). Similar to near DVA function, the VEMP has been identified as resulting from saccular afferents and is a measurement of vestibulocollic function (Kushiro et al., 1999; Uchino et al., 1997; Murofushi & Curthoys, 1997). A common limitation of tests of vestibular function has been their static nature. Static tests provide opportunities to conveniently test patients in limited clinical space but also leave room for speculation as to the effectiveness of these tests in everyday settings. By evaluating a functional and static test on the same population, important information could be inferred on the effectiveness of these and similar clinical measures.

There was a significant negative correlation between near DVA and VEMP amplitude at 1.5 m/s (see Figure 16A, $r^2 = 0.13$). Thus, approximately 13% of the variability in the near DVA data at this speed/distance could be explained by VEMP amplitude. Though correlation levels did not reach significance for the other near DVA conditions, moderate levels of correlation were shown to exist (see Figure 15 A&B, 16B) which was contrary to the correlation results obtained for the far DVA data. The negative relationships detected in the data are consistent with expected values. As morphological changes in the vestibular neural pathways develop a decrease in VEMP amplitude and increase in DVA scores (an increase in logMAR scores signifies a decrease in visual acuity) were observed. It was hypothesized a priori that this relationship would be stronger in the fixed neck position due to

a focus on vertical pitch motion. However, possible restrictions in head pitch movement with the cervical collar utilized are a probable explanation for not seeing a dramatic difference. The fact that no discernable relationships were seen in the far condition is also consistent with findings in the literature that far DVA utilizes the angular portion of the VOR (Moore et al., 1999) and would therefore be less closely related to VEMP amplitude measures.

D. Covariate Measures

As mentioned previously, demographic and covariate measures were recorded to control for any underlying differences between groups that could possibly confound the age related changes that were detected. Subject height, walking speed, and knee extensor torque were all statistically equal across age groups. Data from our study helped confirm that differences detected in DVA were age related and not due to underlying physical limitations that can often develop with increasing age. VOR function was also measured using a standard sinusoidal rotary chair. Similar to previous VOR studies, gain measures did not differ among age groups. There were group differences detected in VOR phase (Table X & Figure 19) (a measure of the timing relationship between head velocity and slow-phase eye velocity measured in degrees) which were seen as an increase in phase lead for the oldest group. An increase in phase lead has been shown to be related to a decline in the velocity storage mechanism associated with the vestibular

nuclei. The velocity storage mechanism helps store motion activity that produces slow phase eye velocity (Raphan et al., 1979). These changes in VOR, similar to detected VEMP and DVA measures, are most likely due to anatomical changes in the vestibular system with aging.

E. Conclusions and Future Research

This study aimed to explore the use of DVA (utilizing a functional paradigm) and the VEMP (utilizing the BPM feedback method) to document changes in the vestibular system for healthy aging adults. The significant findings are summarized below:

1. A functional test of DVA and static VEMP test can provide data on relevant age-related changes in vestibular function between young and older healthy adults.

2. There is a significant age-related decline in VEMP amplitude and increase in VEMP threshold due to neuronal degeneration in the vestibular system.

3. The VEMP BPM method utilized for controlling SCM muscle contraction provided less variability than previous BPM methods (Maes et al., 2009; Vanspauwen et al., 2006) while detecting

age appropriate declines in healthy aging adults. Results were consistent with previous EMG monitored VEMP recordings.

4. The protocol we employed demonstrated that there is a decline in DVA associated with speed of locomotion and a significant interaction between speed and age category (greater DVA decline with speed in older compared to younger adults).

5. A significant relationship was shown between a static otolith measure (VEMP) and a functional otolith measure (near DVA) providing additional support for the reported relationship between near DVA and linear otolith contributions.

6. A significant reduction in DVA was found when lateral neck movement was restricted with a cervical collar at a near distance but no age-related interaction was detected.

Based on these and previous findings this protocol can provide a positive mechanism for future research on otolith function and its contribution to postural stability during upright locomotion. The ability to record repeatable and reliable VEMP data without EMG rectifying equipment will allow VEMPs

to become a more clinically viable option for studying vestibular disorders. Age appropriate normative data are necessary, especially in older patients, and can provide an opportunity for much needed standardization of the VEMP procedure. The data obtained in this study can help preliminarily satisfy the need for clinical norms, though future research utilizing this protocol is needed to populate missing age categories to ensure a continuous range of ages.

The base DVA protocol used in this study was adapted from Peters & Bloomberg (2005) and has been shown to be a reliable functional measure of visual acuity. Future analysis is needed to quantify the underlying changes responsible for the decline seen in DVA with speed and age. DVA is the overall functional output to a combination of possible physiologic underlying mechanisms, which could include changes in kinematic gait adjustments and/or gaze stabilization adjustments with age. Due to differences in generator sites for far and near DVA, the potential for differentially testing semicircular canal versus otolith function is a future possibility through manipulations in the testing protocol. As underlying mechanisms related to declines in DVA and VEMPs are identified (aside from neuronal degeneration), a better understanding of the relationships between static and functional vestibular tests will be obtained.

## VI. Literature Review

### A. History of VEMPS

Although the vestibular system is physiologically responsive to head accelerations (angular and linear), vestibular afferents have also been shown to be responsive to non-physiologic mechanisms such as loud sounds, vibration, and electrical stimulation. The VEMP response is based on the acoustic responsiveness of the sacculus, which is thought to respond to loud sounds due to its proximity to the footplate of the stapes. The saccule for some lower vertebrates, such as amphibians and fish, is still considered the primary organ of hearing (Popper, Platt, & Saidal, 1982). The cochlea is the primary organ of hearing in mammals but studies in guinea pigs and monkeys have shown that the saccule continues to be responsive to sounds in the frequency and sound intensity range of human hearing sensitivity (Young et al., 1977; Murofushi et al., 1995).

Evidence that loud sounds can evoke vestibular symptoms in humans has been reported as early as 1929 by Tullio. In 1958, Geisler, Frishkoph, & Rosenblith claimed to have recorded cortical responses to auditory clicks, while measuring a response from the inion. Following this discovery there was interest in the possible application for study of central auditory function with this response. A few years later this idea was discounted by the initial work of Bickford, Jacobson, & Cody (1964). Bickford et al. made recording to loud clicks with an electrode just below the inion, which they termed the “inion

response". These short latency potentials were not, as originally thought, from the auditory cortex but were instead generated by reflex changes in the level of muscle contraction in the neck, and thus were "myogenic" in nature. Bickford et.al studied 30 normal subjects and found the inion responses were greatly affected by alterations in the tension in the neck muscles. They studied subjects with various auditory and vestibular lesions and discovered that the inion response was of vestibular origin instead of cochlear, as was originally thought. Later studies by Cody and Bickford (1969) and Townsend and Cody (1971) helped to confirm that the inion response was indeed of vestibular origin, specifically the saccule. Following these studies other research presented ideas that the inion response could be nonspecific and inconsistent partly due to its midline recording site and thus was not pursued thoroughly until many years later. In 1992 Colebatch & Halmagyi introduced a new recording site for the inion response utilizing the SCM muscle in the neck. They studied humans with well documented audio and vestibular lesions and again confirmed the vestibular origin of the VEMP. Additional studies have confirmed that the VEMP response is present with profound sensorineural hearing loss and normal vestibular function (Colebatch et al., 1994; Murofushi, Matsuzaki, & Chih-Hsiu, 1999; Colebatch & Halmagyi, 1992). The findings from these studies suggest that the response is not of cochlear origin.

B. VEMP Response

The VEMP response is characterized by a biphasic wave form (positive-negative) that occurs within 30 milliseconds of the stimulus. The most standard way of labeling this biphasic waveform is to use P1 (first positive wave) and N1 (first negative wave). These waveforms are sometimes labeled the p13 - n23 complex as seen below (Figure 20).

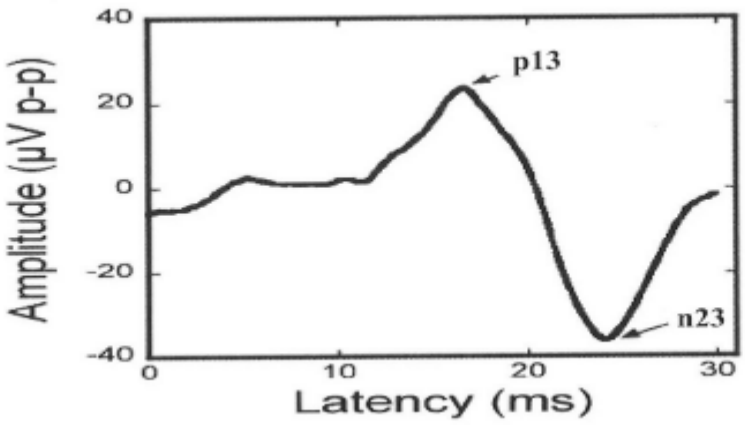


Figure 20. A typical VEMP response waveform from a normal subject. The response is displayed with the positive peak up (Adapted from Zhou & Cox, 2004).

B.1 Recording Site

The original inion response was measured with the active electrode placed on the back of the scalp at the inion with the reference electrode placed on the nose or earlobe and a ground electrode placed on the forehead. Utilizing this configuration VEMPs are present in approximately 90% of normal subjects. Colebatch et al. (1994) showed that using the SCM muscle recording site the VEMP could be recorded in 100% of normal

subjects in their study. Using this configuration the active electrode (non-inverting) is placed in the middle of the belly of the SCM muscle with the reference electrode (inverting) placed at the sternoclavicular junction. The ground electrode is placed on the forehead. This recording configuration allows for greater certainty as to the specific muscle responsible for the recording and helps to avoid uncertainties involved with a midline recording site while investigating a unilateral stimulus.

B.2 Stimulus Factors

Auditory clicks or tone bursts can be used to elicit the VEMP response. Responses can be obtained monaurally or binaurally using clicks or tone bursts. Welgampola and Colebatch (2001a) conducted studies utilizing tone burst and click stimuli. Both click and tone burst stimuli can elicit the VEMP but thresholds were obtained at lower stimulus intensities with tone bursts when compared to clicks. Todd, Cody, & Banks (2000) have shown that the VEMP response have a well-defined frequency tuning with a maximum response between 300-350 Hz.

Due to this information, 500 Hz tone bursts allow VEMPs to be recorded at the lowest thresholds and with the largest magnitude of response (Akin et al., 2003). Due to these and similar finding in the literature (Cheng et al., 2003; Sheykholeslami, Murofushi, Kemany, & Kaga, 2000) the current study utilized 500 Hz tone bursts as the preferred stimulus to ensure the largest VEMP

magnitude while maintaining subject comfort with a lower stimulus presentation level. VEMPs can also be recorded by bone-conducted stimuli and skull taps (Halmagyi & Colebatch, 1995) in patients with conductive hearing loss. The response amplitude of the VEMP increases with stimulus level while the latency of the P1 and N1 waveforms does not shift with intensity changes, as seen in typical auditory evoked potentials (Akin et al., 2003).

### B.3 Effects of Muscle Tension

Bickford et al. (1964) first reported that the amplitude of the inion response was influenced by muscle tension in the neck. Increased tension in the neck produced increases in response amplitude even though the stimulus intensity remained constant. Colebatch et al. (1994) monitored the electromyographic activity with an oscilloscope and quantified the muscle activity. They had subjects alter their muscle contraction between trials by switching between pressing their forehead against a bar and simply turning their head toward their shoulder. They found a strong linear relationship between amplitude of the VEMP and mean level of muscle activity. This finding has been replicated in many studies establishing a clear relationship between muscle contraction and the VEMP amplitude (Welgampoloa & Colebatch, 2001a; Robertson & Ireland, 1995; Ochi, Ohashi, & Nishino, 2001). Thus, in order to obtain correct interpretation of proper left-right

amplitude differences or attempt to compare amplitude differences between subjects it is important to monitor the muscle activity while performing VEMPs. Without monitoring the muscle contraction the VEMP would be relegated to a binary (present or absent) outcome measure. A large added amount of variability is introduced if this muscle contraction is not controlled for by some measure. The instrumentation necessary for EMG monitoring during VEMPS is not readily available in most standard audiology clinical settings because most commercial evoked-potential systems have not incorporated simultaneous EMG recording with VEMP recording yet.

Vanspauwen et al. (2006a) proposed a feedback method which consisted of using a blood pressure manometer (BPM) and cuff to keep the SCM muscle contraction at a specified consistent level throughout the VEMP testing. The subjects would turn their head away from the stimulus ear and press their chin against the blood pressure cuff until a specific target pressure was obtained and then maintain this target throughout the testing. Through their studies utilizing the BPM method, Vanspauwen et al. showed that the BPM method could be used as a feedback technique to monitor SCM contraction. A linear relationship was shown for BPM pressure and the VEMP amplitude similar to the linear relationship reported for EMG and VEMP amplitude. Three different BPM pressures were tested (30, 40, & 50 mmHg) in these studies and like the EMG studies, the VEMP latencies were not affected by this change in muscle contraction. Maes et al. (2009) recently

confirmed the reliability of the VEMP response using the BPM method and showed that similar amplitude and latency responses can be obtained using this technique. Due to the relative newness of these studies it is necessary to continue to study this procedure to ensure that it is sensitive to changes in the VEMP due to vestibular pathology and other factors such as age. The current study will continue this process by using the BPM method to study age-effects on the VEMP and to establish appropriate age-related normative values for clinical use.

C. VEMP Neural Pathways

The saccule is one of the otolith organs and is part of the membranous labyrinth. Sensory hair cells project into a gelatinous material that has calcium carbonate crystals (otoconia) embedded in it, which provide the otolith organ with its internal mass (see Figure 21 below).

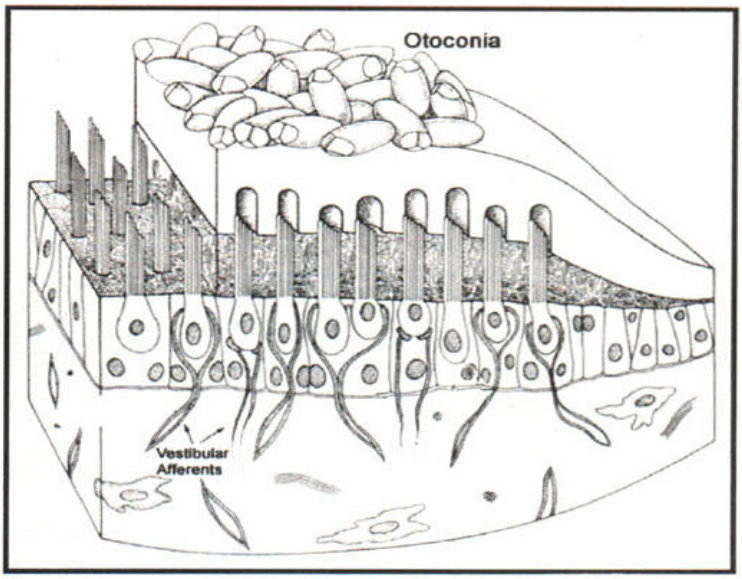


Figure 21. Otoconia are embedded in a gelatinous material and provide an inertial mass. Linear acceleration shifts the material and excites or inhibits the vestibular afferents (Schubert & Minor, 2004)

Hair cell motion towards the taller hair cells (kinocilia) causes excitation in the saccule. Saccular excitation occurs during vertical linear acceleration whereas horizontal linear acceleration stimulates the utricle. Bickford et al. (1964) provided the initial information about possible neural pathways for the VEMP response. They ruled out the response being from the startle and voluntary system (due to its quick latency). They concluded that it was of vestibular origin since subjects with profound sensorineural hearing loss but normal vestibular function showed normal responses. Townsend and Cody (1971) suggested a saccular generator site due to their findings of preserved responses after semicircular canal ablation and benign paroxysmal positional vertigo, but an absence response with Meniere's disease (MD) and MD subjects who had a cochleosacculotomy. Animal research has also

confirmed the hypothesis of a saccular origin (Young et al., 1977, in monkeys; Cazals, Aran, Erre, Guilhaume, & Aurousseau, 1983, in guinea pigs). Single motor unit recordings in response to clicks have confirmed the inhibitory response underlying the VEMP (see Figure 22 below).

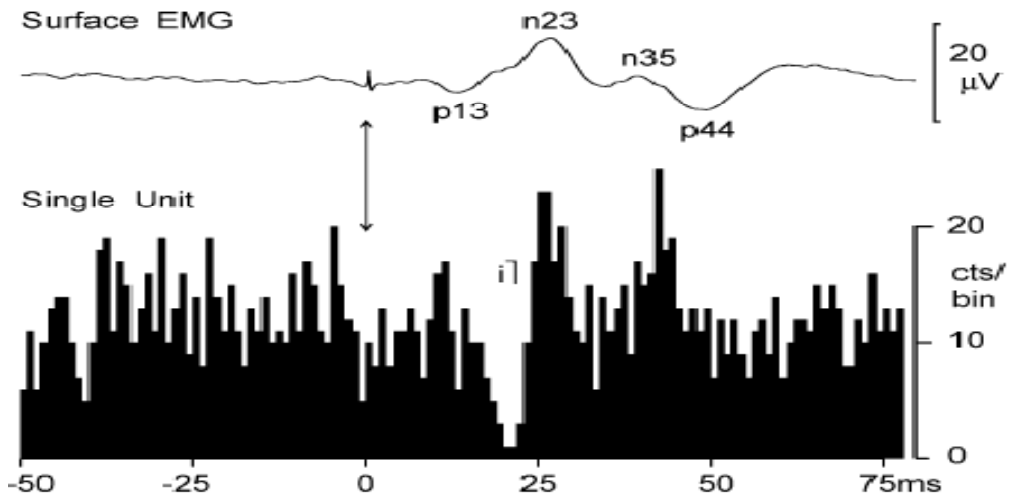


Figure 22. Recordings from the SCM muscle on the surface and intramuscularly from single motor units in response to clicks. The surface recording shows the typical potentials seen. The first excitability change on the histogram is a short-duration period of inhibition (Colebatch & Rothwell, 2004).

The study of the saccular system in cats has also confirmed that saccular nerve stimulation mainly evokes inhibitory postsynaptic potentials in the ipsilateral SCM muscle motoneurons (Kushiro et. al, 1999). It has also been reported that VEMP responses are mediated by the vestibular nerve. Studies of VEMPs before and after vestibular nerve section and neuritis have revealed absent responses on the surgical side and reduced amplitude or

absent responses in patients who had neuritis (Halmagyi & Colebatch, 1995). The VEMP has been suggested to follow the inferior division of the vestibular nerve up to the vestibular nuclei; this was confirmed by studying patients with vestibular schwannomas. VEMPs were only present on the unaffected side (Murofushi et al., 1998). The primary afferent pathway from the saccule is found in the inferior vestibular nerve. The vestibular nuclei that receive afferent fibers from the saccule have a major descending connection to spinal motor neurons. The lateral vestibulospinal tract (LVST) and medial vestibulospinal tract (MVST) are considered possible efferent pathways for the SCM muscle. Both the LVST and MVST project to motor neurons of the cervical cord, which control neck muscles. A schematic of this pathway is shown below highlighting the disynaptic inhibitory response alluded to previously (Figure 23).

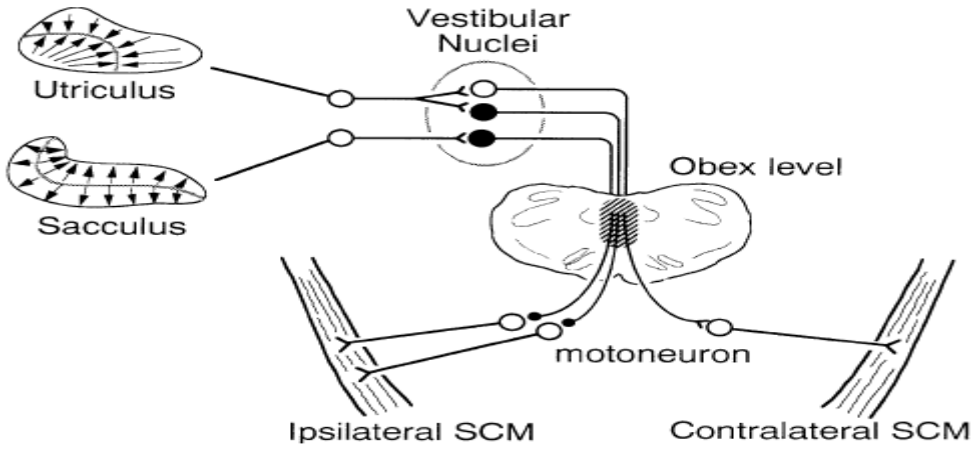


Figure 23. Diagram of the sacculo-sternocleidomastoid pathway. Filled neurons are inhibitory and open neurons are excitatory. Also shown is the ipsilateral nature of the saccular pathway (Kushiro et al., 1999).

Thus the literature has shown that the main VEMP response is generated by a disynaptic pathway originating in the saccule, passing through Scarpa's ganglion, through the inferior portion of the vestibular nerve, lateral vestibular nucleus, MVST, and finally arriving at the motor neurons of the SCM muscle (Kushiro et al., 1999; Uchino et al., 1997; Murofushi & Curthoys, 1997).

D. Dynamic Visual Acuity

DVA is the ability to discriminate or resolve the details of a moving object while there is relative motion between the target and the observer (Miller & Ludvigh, 1962). The early research conducted on DVA was accomplished by Miller & Ludvigh in the late 1940s and early 1950s. Their research, as well as other investigators through the early 1960s, established some basic ideas that are generally accepted today: (a) As target speed is increased the viewer's acuity decreases, (b) Similar measures of static acuity, as measured with a Snellen chart, do not always correlate with similar results of DVA in individuals, and (c) DVA appears to be more closely related to "real world" functional activities than traditional visual assessment procedures.

DVA has been measured in subjects in several different ways over the years including moving a display in front of the subject (Longridge & Mallinson, 1984), having the subject make active sinusoidal head movements, or walking in place while reading a visual display (Grossman & Leigh, 1990). Some of the earliest tests involved moving Snellen letters or

Landolt Cs in the horizontal plane with a stationary subject attempting to discriminate the moving target (Ludvigh, 1948). Later investigators used rotating mirrors and slide projectors to project moving targets on a screen while other researchers had moved the observer rather than the target (Long & Crambert, 1990; Miller, 1958). More recently, rotational chairs have been used to move subjects while discriminating a stationary target (Demer & Amjadi, 1993).

In the 1980s the study of DVA was significantly restricted to work in the fields of sports vision and its use as a predictor of performance in various athletic settings (Hoffman, Rouse, & Ryan, 1981). In 1985, the Committee on Vision described DVA as one of their four emergent techniques for the assessment of visual performance that may more reliably predict visual function in applied settings when compared with traditional assessment methods. The committee gave a strong recommendation for additional work to be done in this area of research. With this idea of more functional measures in mind, research has began to focus more on dynamic activities while evaluating DVA in hopes of getting a more precise idea of true subjective function. On a daily basis most subjects perform tasks that require seeing clearly while moving their head. Situations such as standing and walking, which were evaluated in this study, require the integration of all the systems normally involved in maintaining visual acuity.

D.1 DVA Distance

Grossman et al. (1990) has shown that during natural movements from walking and running angular motion is stabilized by the VOR. This angular motion of the head is picked up by the semicircular canals and results in compensatory eye movements initiated by the aVOR (Moore et al., 1999; Paige, 1989). The pitching movement of the head generated during walking also stimulates the otolith system which picks up linear motion through contributions from the linear lVOR (Telford et al., 1997). In order to focus properly on targets of varying distances the central nervous system must generate appropriate eye movements based on both aVOR and lVOR contributions.

Differences in aVOR gain (eye/head velocity) with distance have been shown previously (Demer & Viirre, 1996; Paige, 1989). While walking and viewing “far” targets aVOR velocity has been shown to be 180 degrees out of phase with head pitch consistent with typical measures of aVOR (Grossman, Leigh, Bruce, Huebner, Lanska, 1989) while “near” targets have shown an in phase relationship (eye/head pitch velocity) consistent with a more linear contribution (Moore et al., 1999). These observed differences in VOR responses are thought to be related to possible contributions from semicircular canal (aVOR) and otolith (lVOR) responses (Peters & Bloomberg, 2005). Moore et al. (1999) and Paige (1989) have proposed that these linear otolith mediated responses are related to the vestibular-colic

reflex, particularly the saccular input, which as discussed previously, can be directly measured with the VEMP. Hirasaki et al. (1999) has also shown that there is an interactionary effect of walking speed on these before mentioned linear contributions and that at an ideal walking speed (1.2 - 1.8 m/s) the corresponding head pitch is most highly compensatory for vertical head translation. These identified differences have led to the assumption that "near" and "far" DVA recording could be used to distinguish between possible otolith versus semicircular canal function in the future.

E. DVA Neural Pathways

Physiologic movement of the head can decrease acuity in subjects by degrading their ability to keep retinal images stabilized if compensatory eye movements are not properly executed. The VOR is the major reflex producing these compensatory eye movements in these types of situations (Herdman et al., 1998). The relationship of DVA and retinal image motion allows researchers and clinicians to make inferences about the effectiveness of these compensatory eye movements, since DVA should be independent of this motion if the ocular motor reflexes are working appropriately. DVA has been used as an indirect measure of the VOR in stabilizing gaze during head rotation (Demer, Honrubia, & Baloh, 1994; Benson & Barnes, 1978; Longridge & Mallinson, 1984; Barber, 1984). Because DVA is a more direct

measure of function, it has been recommended as a technique to study functional vestibular impairment.

In an ideal situation the VOR would compensate fully for any arbitrary movement of the head in space and would generate eye rotations at the same speed, but in an opposite direction of head rotation. The goal of the VOR is to keep the eye still in space during head motion so that clear uninterrupted vision can be utilized. The main physical property detected by the VOR is angular motion which is picked up by the semi-circular canals. This angular detecting VOR is primarily responsible for gaze stabilization. The VOR is composed of three main components which are: the peripheral sensory system (the labyrinth), a central processing mechanism, and the motor output (the eye muscles) (Fetter, 2007). The sensory input of the VOR response is furnished by a set of motion sensors which provide information about angular velocity, linear acceleration, and orientation of the head with gravity to the central nervous system. The central nervous system can combine this sensory information with other provided information to estimate head orientation. This central nervous system information is then sent to the ocular motor muscle system and the vestibulospinal reflex (VSR). The VSR is used to create compensatory body movements in order to maintain head and postural stability. This information is integrated with other important information such as visual, proprioceptive, auditory and tactile input to generate the best estimate of motion and space orientation (Grusser, Pause,

& Schreiter, 1990). The performance of these reflexes are monitored and readjusted as necessary through an adaptive process with the capability of repair and modification involving cerebellar function (Figure 24 below).

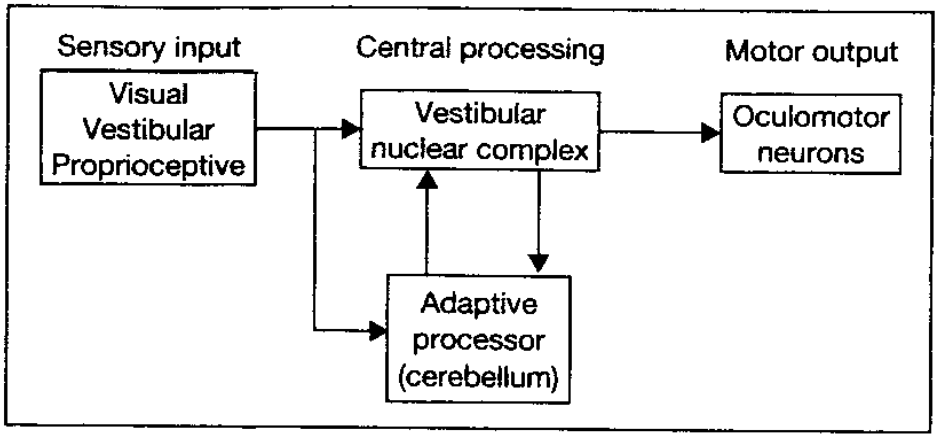


Figure 24. Schematic drawing of VOR components (Fetter, 2007).

The peripheral vestibular system involved in the VOR response consists of contributions from the membranous and bony labyrinths and the hair cells, which are the motion sensors of the system. Each labyrinth contains three semicircular canals (SCC), the cochlea, and the vestibule containing the utricle and saccule. The arrangement of SCC geometry allow for detection of head rotation about any axis in space. These SCCs are set up in a paired fashion between the left and right labyrinths to function as angular accelerometers working in a push-pull manner (right superior-left posterior, right lateral-left lateral and left superior and right posterior). These planes are similar to the planes of the ocular muscles allowing for relatively simple neural connections between individual canals and motor output

neurons (Blanks, Curthoys, & Markham, 1975). One end of each SCC has a widened diameter ampulla which contains the cupula. The cupula causes endolymphatic pressure differences, elicited by head motion, to be detected by vestibular hair cells embedded in the cupula. These specialized hair cells are biological mechanical sensors which create changes in neural firing following displacement of the hair cells by endolymph movement. As hair cells are bent towards their tallest member an increased firing rate (excitation) is created and as these hair cells are bent away from their tallest member a decrease in firing rate (inhibition) is created (Goldberg & Fernandez, 1971).

The responses from the peripheral system are picked up through a central processing system. With the rotation of the head, neural firing increases, from the resting state, in one vestibular nerve and decreases in the opposite vestibular nerve. The pairing of the SCCs provide important sensory redundancy and allows the central processing system to receive information from one member of the pair if the other is affected by disease, which helps provide added sensitivity in the system. The pairing of the canals also allows the brain to ignore changes in neural firing that occur on both sides at the same time, these types of changes could be seen with body temperature changes etc. The vestibular nuclear complex and the cerebellum are the two main targets of primary afferents from vestibular input. The nuclear complex is the primary processor and implements direct, fast connections between incoming information and motor neurons. The cerebellum is an adaptive

processor, which monitors vestibular input and readjusts central vestibular processing if necessary. At both locations vestibular information is processed in association with somatosensory and visual sensory input (Robinson, 1976). The vestibular nuclear complex consists of 4 major nuclei (superior, medial, lateral, and descending) and at least 7 minor nuclei. The vestibular nuclei are connected via a system of commissures. The commissures allow information to be shared between the two sides of the brainstem and implement the push-pull system of the SCCs. Extensive connections between the nuclear complex, cerebellum, ocular motor nuclei, and brainstem reticular activating systems convey the efferent signals to the VOR and the extra ocular and skeletal muscles (Figure 25 below). The output neurons of the VOR are the motor neurons of the ocular motor nuclei, which drive the extra ocular muscles resulting in conjugate eye movements in the same plane as head motion (Fetter, 2007).

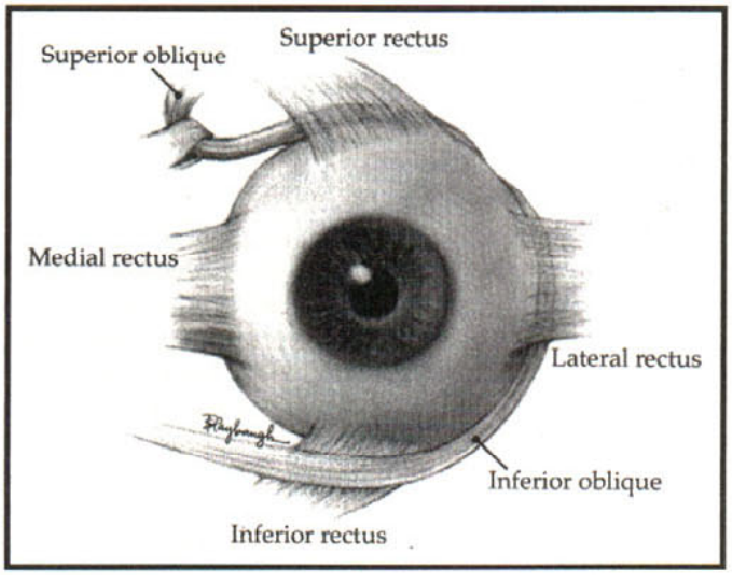


Figure 25. Schematic of the six extra-ocular muscles of a left eye involved in stabilizing gaze during the VOR (Schubert & Minor, 2004).

F. Vestibular Age-related Changes

Complaints of dizziness and disequilibrium are extremely common in the elderly population and associated falls are a major cause of morbidity and mortality (Tinetti, Speechley, & Ginter, 1988). In order to better understand these vestibular difficulties in aging populations testing procedures must be developed that are sensitive to vestibular changes. Previous research throughout the years has documented age-related morphological changes affecting the vestibular system. As early as 1965, Schuknecht et al. found cochleo-saccular degeneration in an aged cat, an aged dog and an 85-year-old man. This study discovered wide-spread deterioration in the cochlea of all three cases and found a loss of about half the vestibular hair cells in the macula sacculi, while the macula utriculi appeared normal. They concluded the sacculus may be more susceptible to aging than other vestibular organs.

Vestibular sensory cells have been analyzed by Rosenhall (1973) and clear degenerative changes were found with age. The reduction in sensory cells amounted to approximately 40% on the cristae and 20% on the maculae. Rosenhall discovered sensory reductions beginning as young as 40 years of age, with the older subjects showing as much as a 37% reduction in sensory cells and nerve fibers compared to a young group. This study reported vestibular hair cell loss of 6% per decade between the ages of 40 and 90 years. Bergstrom (1973) also reported changes in the vestibular system with age. Bergstrom reported a decrease in the number of vestibular nerve fibers by 5% per decade in similar age categories as Rosenhall. In a temporal bone study of the human peripheral vestibular system, Merchant et al. (2000) reported that vestibular hair cell counts and densities declined steadily from birth to old age. Decreases in cell bodies in Scarpa's ganglion with age have also been reported (Velazquez et al., 2000) as well as losses of approximately 5% per decade of neurons in the medial vestibular nucleus (Tang et. al, 2001/2002). Despite these studies showing morphological changes occurring, tests of vestibular function have been reported to show only small changes with age. Small declines in caloric responses have been seen after the $5^{th}$ and $6^{th}$ decades (Mulch & Petermann, 1979) and small reductions in VOR gain have been shown in older patients (Peterka et al., 1990). Reports of greater decreases in VOR function have been seen in

response to high amplitude and high acceleration rotational stimuli (Tian et. al, 2001).

F.1 Age-related VEMP Changes

Aging effects have been noted using the VEMP as a clinical measure of change. The most consistent finding of age-affect on the VEMP is the reduction of amplitude with age (Ochi & Ohashi, 2003; Su et al., 2004; Welgampola & Colebatch, 2001a; and Zapala & Brey, 2004). Amplitude decreases with age are not related to changes in muscle tension (Welgamapola & Colebatch, 2001b) but most likely due to morphological reductions in vestibular sensory cells discussed previously. P1 and N1 latencies have also been shown to be significantly increased with age (Brantberg et al., 2007; Zapala & Brey, 2004; Ochi & Ohashi, 2003). Latency changes with age could be due to altered central processing of otolithic signals (Su et al., 2004). Measures of inter-aural amplitude differences (IAD; 100[ampL-ampR/ampL+ampR]) were also analyzed by Su et al. (2004). IAD ratios did not differ with age, suggesting that bilateral saccular pathways were affected to a similar extent with aging. Due to the changes in the VEMP response discussed, it has been recommended by most VEMP researchers that reference values from different age groups be used in the clinical evaluation of patients. All of the age-related VEMP studies in the literature were conducted using the EMG method of muscle monitoring. As discussed

previously, though effective, this EMG method is not readily available in most clinical settings. This study proposed the use of the BPM method of muscle monitoring that is available in most clinical settings and is easily obtainable for minimal cost if not already available. Normative data for age specific groups was obtained, which will allow for more valid comparisons when evaluating an aging clinical population with vestibular abnormalities.

## F.2 Age-related DVA Changes

As mentioned before, significant well documented morphological changes occur in the human vestibular system with age. If reflex function depends directly on an intact peripheral vestibular system, then we would expect to see a significant decline in measures such as the VOR, and ultimately measures such as DVA, in parallel with this anatomical change. But along with these morphological changes there is also a possibility that central adaptive mechanisms may remain intact in older subjects, which could allow the VOR and similar reflexes to remain relatively stable regardless of peripheral deterioration.

Literature on age-related changes in vestibular function is much more limited than the morphological literature. Much of the literature in this area has been focused on the use of caloric measures (Mulch & Petermann, 1979). Though most of the caloric results are ambiguous and include increased, decreased, and unchanged responses with increasing age. Test

results using rotational testing have been less complete but have revealed small age-related declines in VOR (Peterka et al., 1990). Age-related changes in VOR with rotational testing has resulted in a steady slow decline throughout the age categories as opposed to a more drastic drop off seen after 60 years of age in the anatomical data.

As individuals age there is a gradual loss of peripheral canal input due to cellular death and it has been shown that possible adaptive mechanisms in the central nervous system may be able to increase contributions of high gain canal nerve input to help compensate for this loss. The cervico-ocular reflex (COR) is an ocular stabilization reflex that is elicited by rotation of the neck and works in conjunction with the VOR to help prevent visual slip on the retina. The COR, which is essentially negligible in healthy humans, has been shown to have increased gain in patients with vestibular deficits (Bronstein & Hood, 1986). Kelders et al., (2003) also found a significant co variation of VOR and COR, meaning that when VOR decreases, COR increases and vice versa. This notion could possibly account for part of the discrepancy between anatomical data and current vestibular function data differences. However it is still not known whether these changes in the COR dealing with neck proprioceptive information has any implications for improving DVA during functional activities.

One of the largest studies on age-related DVA was conducted by Burg (1966). Burg measured static and dynamic visual acuity of 17,500 male and

female subjects and reported that both static and dynamic visual acuity decreased with age, but that dynamic visual acuity was greater than the decline in static acuity in individuals over 40 years of age. In 1967, Farrimond also reported on age-related changes in DVA and speculated that the decline in DVA with age might be solely due to changes in the efficiency of the visual processes with age. Long and Crambert (1990) reported on differences in DVA in younger versus older subjects and concluded that some of these differences with age were due to illuminating changes in the optical system. Ishigaki & Miyao (1994) studied the age-related changes in DVA and concluded that DVA shows rapid development between the ages of 5 and 15 years and then gradually declines after 20 years of age. Most of these historical studies where performed in static positions and did not take into account changes occurring during functional activities. Hillman et al. (1999) have shown that DVA during walking is significantly worse in patients with vestibulopathy compared to age-matched pairs, but they did not perform DVA while sitting to get a direct comparison of differences in functional activities.

G. VEMP Clinical Significance

The vestibular system can be complex and difficult to understand. The clinical tests used to evaluate the vestibular system are also less concrete and less reliable than many clinical tests used to evaluate the auditory system. Current testing to evaluate the electrophysiological properties of the

vestibular system, such as VNG and Computerized Dynamic Posturography (CDP) are not able to assess all functional structures and pathways. Reliable measures for evaluating the otolith organs (saccule and utricle) have not been readily available until recently (Halmagyi & Curthoys, 1999). Since the revised recording procedure utilizing the SCM muscle was re-introduced by Colebatch et al. (1994), VEMP testing has become a popular clinical test for the evaluation of peripheral vestibular pathologies.

There are several possible reasons as to why the VEMP is potentially important in the clinical evaluation of the dizzy patient. First, the response (P1-NI) is repeatable and consistent. Despite variations in amplitude, the latency and threshold is relatively stable. Second, the VEMP is thought to reflect activity of the sacculus, which is not evaluated through typical VNG methods (Colebatch et al., 1994). Due to its vertical orientation, the saccule is thought to play an important role in maintaining proper head and body position against vertical/linear changes and gravity (Uchino et al., 1997). There is an increasing body of literature providing evidence that the VEMP recorded from the SCM muscle, can be altered by pathologic processes affecting the vestibular end organ, specifically the saccule (Itoh et al., 2001; Ochi et al., 2001). A third reason the VEMP might be important stems from the fact that the neural pathway of the VEMP response is different from the VOR response routinely used. The VOR reflects vestibular information processed in a pathway rostral from the level of the vestibular nuclei through

the midbrain (Shepard & Telian, 1996), while the VEMP reflects a pathway organized caudally from the vestibular nuclei through cervical portions of the spinal cord (Buttner-Ennever, 1999). The neural pathways also differ in relation to the portion of the vestibular nerve they activate. The superior vestibular nerve branch innervates the superior and horizontal semicircular canal ampulla and utricle while the inferior branch innervates the posterior semicircular canal ampulla and the saccule (Buttner-Ennever, 1999). A fourth reason for the clinical importance of the VEMP is that it may help us better understood the vestibulospinal system and pathologic processes involved. The MVST is thought to help with fine eye, head, and neck movements while the LVST is thought to direct extensor tone to the neck and antigravity muscles (Zapala & Brey, 2004). Although the exact nature of the VEMP reflex pathways are not known it appears the VEMP should be sensitive to lesions involving the saccule, inferior vestibular nerve, and vestibulospinal pathways (Shimizu et al., 2000).

G.1 Vestibular Hypersensitivity Disorders

Very loud sounds can cause vestibular symptoms in subjects. In 1929, Tullio discovered that if a small window was made in the bony capsule of the lateral semicircular canal in pigeons, the vestibular system would become responsive to sound. Clinically, patients can present with vertigo and oscillopsia in response to loud sounds (Tullio phenomenon). This is often the

presentation of superior canal dehiscence (SCD). SCD was first identified by Minor et al. (2001). The dehiscence is thought to create a low-impedance "third window" in the vestibular system that makes it more sensitive to sound. The diagnosis is often made on the basis of high-resolution CT scans, which can show the dehiscence. Conventional tests of vestibular function often give normal responses for these patients but the VEMP has been shown to be highly sensitive to SCD. Colebatch et al. (1994) studied VEMPs in SCD patients and the testing revealed extremely large amplitudes and abnormally low thresholds with normal wave configuration. Normal VEMP thresholds range between 70-90 dBnHL and SCD patients routinely have thresholds between 50-60 dBnHL (Watson, Halmagyi, & Colebatch, 2000). VEMP responses are typically absent in patients with conductive hearing loss due to an attenuation of the sound, but SCD patients with conductive hearing loss have been reported to have VEMPs due to their increased vestibular sensitivity to sound (Streubel, Cremer, Carey, Weg, & Minor, 2001).

G.2 Meniere 's disease (MD) (endolymphatic hydrops)

MD is a fairly common disorder characterized by fluctuating hearing loss, tinnitus, aural fullness, and episodic rotary vertigo. The etiology of MD is still not completely known though endolymphatic hydrops has been confirmed in some cases with histopathology. The clinical diagnosis of MD currently relies on symptoms, electrocochleography (ECochG), and VNG/caloric

testing. Studies of MD utilizing VEMPs may provide an additional tool to help diagnose this disorder. De Waele et al. (1999) reported absent VEMPs in 54% of patients with MD using click stimuli and Robertson and Ireland (1995) reported absent VEMPs in their 3 MD patients. MD can be classified into four stages which are based on the degree of hearing loss (Black, 1982). Patients in early stages of MD are often hard to diagnose due to normal hearing and normal VNG/Calorics. Young, Huang, & Cheng (2003) studied MD using the IAD ratio of the VEMP response. Young et al. found a significant correlation between stage of MD and IAD ratio. In this study 82% of MD patients were identified by the VEMP procedure. Young et al. contributed the differences in positive rates between their study and previous studies to the stages of MD. Differences in VEMP thresholds and amplitudes have also been found in MD (Rauch, Zhou, Kujawa, Guinan, & Herrmann, 2004). Subjects with MD showed elevated VEMP thresholds and decreased 500 Hz amplitude as compared to normal subjects and unaffected ears of Meniere's patients.

G.3 Vestibular Neuritis

As discussed previously, the vestibular nerve has two branches (superior & inferior) and each branch innervates a different portion of the vestibular system. The VEMP may be able to help with differential diagnosis of vestibular neuritis due to these distinctions of the vestibular nerve since disruption to any of the vestibular organs could cause dizziness and vertigo.

Halmagyi and Colebatch (1995) studied VEMPs in patients with vestibular neuritis. Their study revealed VEMPs present in 50% of these patients while all had absent caloric responses. Heide et al. (1999) studied dizzy patients and all their subjects with benign proximal positional vertigo (BPPV) had present VEMPs, thus it seems that an intact inferior vestibular nerve is necessary to generate BPPV. It has been shown that most neuritis cases involve the superior portion of the vestibular nerve and thus VEMPs provide information regarding the function of the inferior portion (Brantberg et. al, 2003).

G.4 Vestibular Schwannomas

Since the neural pathways of the VEMP include the vestibular nerve it would seem like a logical choice for evaluation of vestibular nerve function. Magnetic Resonance Imaging (MRI) with contrast continues to be the gold standard for diagnosing vestibular schwannomas. Auditory Brainstem Response (ABR) is also often used due to its lower cost and high sensitivity but can be problematic in localizing small tumors (<1cm). Murofushi et al. (1998) reported abnormal VEMPs in 80% of 17 patients with vestibular schwannomas. 15 of the 17 patients had absent VEMPs and the other two patients had significantly reduced VEMP amplitudes. Matsuzaki et al. (1999) reported absent VEMPs in two patients with normal ABR measures. At this point there have not been any correlations reported in the literature between

VEMPs and tumor size. Today VEMPs are not appropriate as a stand-alone test but may provide useful information in diagnosing vestibular schwannomas.

### G.5 Central Nervous System (CNS) Disorders

The neural pathways of the VEMP include the CNS thus it seems plausible that VEMPs may provide some information in the diagnosis of CNS disorders. Shimizu et al. (2000) reported delayed P1-N1 wave latencies in patients with multiple sclerosis. They suggested that prolonged latencies could be used to evaluate the vestibulo-spinal tract. Prolonged wave latencies have also been reported with large tumors and may suggest compression of the brainstem (Murofushi et. al, 2001). VEMPs have also been reported absent in brainstem lesions such as Wallenberg's syndrome and strokes (Itoh et al., 2001; Chen & Young, 2003).

## H. Summary

As can be seen from this review, VEMPs are a relatively new tool for the clinical evaluation of vestibular disorders but possibly a promising tool. Future research on VEMPS should focus on obtaining VEMP standardization. Critical normative data utilizing the BPM method, due to its clinical availability, is an important step and discovering the relationship of this measure with current tests of vestibular function such as DVA should also provide unique

positive information. The use of these tests together hand in hand may provide the researcher and clinician additional valuable information about the overall status of the VOR, saccule and inferior vestibular nerve which may be used to establish proper diagnosis and treatment strategies. This study has attempted to fill some of these before mentioned gaps in vestibular testing and provide an avenue for future functional vestibular testing.

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