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Examination of utricular response using oVEMP and unilateral centrifugation rotation testing

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Abstract

OBJECTIVE—Significant advancements have been made toward the clinical assessment of utricular function through ocular vestibular-evoked myogenic potentials (oVEMP) and unilateral centrifugation (UCF) testing. To date, no study has examined intra-subject relationships between these measures. The study hypothesis was that intra-subject responses from oVEMP and UCF testing would be correlated inasmuch as both tests have been reported to assess utricular function.

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DESIGN—Unilateral centrifugation rotations and oVEMP testing were performed on healthy volunteers, aged 18–62 years. A within-subject study design compared and correlated UCF outcome measures of ocular counterroll (OCR), subjective visual vertical, and ocular counterroll gravitational inertial acceleration (GIA) slope against peak-to-peak oVEMP N1-P1 amplitude.

RESULTS—Correlational analyses failed to reveal any significant relationships between oVEMP amplitude and UCF responses suggesting these tests may be inciting different response properties within the utricular system.

CONCLUSIONS—Various anatomical and physiological differences within the utricle, in addition to the fundamental differences in stimulus properties between the oVEMP and UCF tests, could explain the lack of significant correlations between these measures and suggest that oVEMP and UCF testing may be complimentary in their evaluation of the utricular system. These data reinforce the complexities of the utricular system and provide further insight into the difficulties encountered in its clinical assessment.

Keywords

Ocular Vestibular Evoked Myogenic Potential (oVEMP); Unilateral Centrifugation (UCF); Subjective Visual Vertical (SVV); Utricle; Ocular Counterroll (OCR)

Introduction

The past two decades have seen significant advancements in the clinical evaluation of the vestibular maculae (Buytaert, Nooij, et al., 2010; Buytaert, Vanspauwen, et al., 2010). Contemporary vestibular assessment has expanded to include cervical vestibular-evoked myogenic potentials (cVEMP) that evaluate the saccule and saccular mediated pathway. Several tests of utricular function have also become available, including ocular vestibular-evoked myogenic potentials (oVEMP) and subjective visual vertical (SVV) testing. However, due to high inter-subject variability, wide normative reference ranges, and poor sensitivity and specificity for the identification and lateralization of otolith disease, most tests of macular function have thus far been limited in their clinical utility (Bronstein et al., 2004).

Investigators have recently reported methods designed to improve the diagnostic accuracy for identifying and lateralizing macular lesions including using techniques such as unilateral centrifugation (UCF) and off-vertical-axis rotations (Akin et al., 2011; Buytaert, Nooij, et al., 2010; Odkvist, 2001; Schonfeld et al., 2011; Valko et al., 2011; Wetzig et al., 1992; Wetzig et al., 1990; Wuyts et al., 2003). During UCF testing, a centripetal linear force can be applied across an eccentrically displaced utricle (Wetzig et al., 1990; Wuyts et al., 2003). The applied centripetal force results in a compensatory utricular-driven contraversive ocular torsion, known as ocular counterroll (OCR). Ocular counterroll is a compensatory vestibular ocular reflex that normally rotates the eyes in the opposite direction of head tilt in an attempt to maintain a true visual horizontal meridian. Although both utricles contribute to this OCR reflex during head tilt, it is possible to isolate an OCR reflex from a single utricle by applying a centripetal force on an eccentrically displaced utricle. During such rotations, the center of rotation is located directly over one utricle, while a centripetally displaced g-force

is subsequently applied over the opposing eccentrically-displaced utricle's epithelium, thus creating a sheering effect as if the single, outwardly displaced, utricle was undergoing a static head tilt. Although the reflex is slow at 300 ms (Gretsy & Lempert, 2001) and expresses a relatively low gain (Ödkvist, 2001), the resulting OCR can be measured during clinical conditions of earth-vertical, eccentric (UCF) rotation (Gresty & Lempert, 2001). Unfortunately, because investigating OCR during eccentric rotations requires specialized rotational equipment and expertise, such reports have been limited (Wuyts et al, 2003). As such, there exists an inherent difficulty for comparison of results secondary to the varying paradigms under which the data were collected (e.g., dynamic centrifugation versus static centrifugation, degree of lateral displacement, degree of angular velocity, monocular versus binocular recording). Finally, variability in OCR measures obtained during eccentric rotation has not been well documented, and may be limited to individual reports (Wuyts et al., 2003), as well as governed by specific rotational protocol parameters.

A linear relationship has been identified between the degree of OCR and the degree of applied centripetal force during eccentric rotations, known as gravitational inertial acceleration (GIA) (Wuyts et al., 2003). During eccentric rotations, the degree of GIA can be mathematically determined from the degree of angular rotation, and the known displacement of the rotational chair from the center of rotation. The further the eccentric displacement, or the higher the rate of angular rotation, the larger the GIA, and, subsequently, the larger the OCR. The resulting OCR-GIA slope has been shown to reflect the sensitivity of the utricular system (Wetzig et al., 1992; Wetzig et al., 1990; Wuyts et al., 2003). A steeper regression slope indicates a more robust OCR with respect to a greater GIA during eccentric rotation, reflecting a stronger utricular response to an applied centripetal acceleration. Conversely, a shallower OCR-GIA regression slope reflects decreased sensitivity of one or both utricles such that a unilateral loss of utricular function results in an OCR-GIA regression that has essentially one-half the slope of a bilaterally intact system (Wuyts et al., 2003). Unfortunately, the stimuli and methods employed during UCF testing require highly advanced rotational equipment and are often only available in research or well-funded clinical settings (Leigh et al., 2006).

In addition to measures of OCR, various reports have also investigated using measures of subjective visual vertical (SVV) tilt during eccentric rotations as a potential proxy for the OCR, given the similar underlying physiologic mechanisms (ocular cyclotorsion) for producing both response measures. The use of SVV as a proxy to measuring OCR has certain advantages inasmuch that it is often easier to record (i.e., precise ocular torsion is not obscured by physiologic artifact such as ocular jitter, blink artifact, or ptosis). However, reports of SVV during subject rotation have varied by as much as 20° from true vertical (Ödkvist, 2001; Tran Ba Huy & Toupet, 2001). Such high variance is likely secondary to differences in rotational paradigms, as well as physiologic co-variables of cognition, memory, and somatosensory cues (Van Nechel, Toupet and Bodson, 2001). Both the OCR and the SVV may have certain advantages, however, the relatively unreported or high variances associated with each, respectively, poses significant challenges with their clinical application.

The recent introduction of oVEMP in the assessment of utricular function has shown promise for a more clinically accessible approach to identifying utricular disease. Ocular VEMPs are a biphasic sonomotor response that can be recorded via surface electrodes from the contralateral inferior oblique muscle. The response has been shown to originate from the utricle in response to high-level, low-frequency acoustic stimuli. Common neurophysiologic response parameters include the amplitude of the biphasic N1–P1 response, the latency of the N1 and P1 response peaks, as well as the interaural amplitude ratio. The interaural amplitude ratio is most often used to identify significant vestibular asymmetries that are attributed to the utricle and/or utricular mediated pathway. However, it has yet to be reported whether any attribute of the oVEMP response, such as the N1–P1 response amplitude, exhibits properties that can be used to represent a graduated degree of utricular sensitivity, similar to the angular vestibular ocular reflex (VOR) response-gain obtained during sinusoidal harmonic acceleration testing. In an attempt to broaden the clinical utility of oVEMP and its response parameters, we investigated the existence of intra-subject correlations between UCF and oVEMP. It would be clinically important to identify whether certain oVEMP response characteristics correspond with a hypo- or hyper-active physiologic response, or if such characteristics can only be identified through more advanced measures like UCF testing. Although data obtained during rotational testing have a high degree of sensitivity and specificity (Brey et al., 2008a), such systems tend to be expensive, accurate administration of the test is often complex, and results may be difficult to interpret (White, 2007). If similar sensitivity and specificity can be extended to tests that are more readily available to the clinician, such as oVEMP, then a greater number of patients could possibly be evaluated and treated for varying degrees of utricular disorders. Furthermore, the segregation or identification of end organ specific (utricular) pathology may serve to elucidate, and possibly even reduce, those diagnoses of non-specific dizziness.

Materials and Methods

Participants and eligibility criteria

Fifty-one healthy volunteers were prospectively recruited and enrolled in the study. Four participants were excluded from the analyses (one individual did not perform rotational testing due to head restraint limitations and data from three individuals were excluded due to eye tracking and chair translation errors), leaving a total of 47 healthy participants (21 male), aged 18–62 years ($M = 27.19$ years, $SD = 9.1$) for whom statistical analyses were conducted (Figure 1). The study protocol (12-DC-0152) was approved by the Combined Neuroscience Institutional Review Board (IRB) at the National Institutes of Health. Informed consent was obtained from all participants. Eligibility criteria included normal hearing and middle ear function, normal vestibular ocular reflexes, and a negative history of neurologic disease and current or past vestibular symptoms. Normal middle ear function, as measured by tympanometry, was defined as tympanometric peak pressure of ± 100 decaPascals, and peak compensated static acoustic admittance between 0.3–1.5 milliliters (Margolis & Heller, 1987). Normal peripheral hearing sensitivity was defined as air-conduction pure-tone thresholds ≤ 25 dB HL for octave frequencies between 250–8000 Hz, and no air-bone gaps > 10 dB from 500–4000 Hz. VOR function was assessed by sinusoidal harmonic acceleration testing from 0.01–0.64 Hz using a peak velocity of $60^\circ/\text{second}$.

Test Procedures

Ocular VEMP testing was conducted using an Intelligent Hearing System Auditory Evoked Potential system (IHS SmartEP version 4.20; Miami, FL). Participant's electrode sites were prepped and single-use, pre-gelled side snap electrodes (Ambu® Neuroline 720) were placed infraorbitally over the inferior rectus / inferior oblique extra-ocular muscle site 1 cm below the lower eyelid (active non-inverting electrode), on the prominence of the chin or sternum in the presence of facial hair (reference inverting electrode), and at Fpz (ground electrode). Individual electrode impedances were confirmed as 10 kOhms and inter-electrode impedances were 5 kOhms. Responses were recorded from the contralateral inferior oblique muscle in response to rarefaction 750 Hz tone-burst stimuli (Blackman gating, 2-ms rise and fall time, 0-ms plateau) presented at 110 dB nHL via Etymotic ER3A insert earphones according to standard methods (119.8 dB pSPL right ear; 119.0 left ear dB pSPL as measured via a KEMAR prior to each day of testing). Stimuli were presented to each participant in a counter-balanced fashion, such that the order of presentation was alternated between the right and the left ears for each successive test session in order to eliminate any possible test order effects. Extraocular myogenic activity was amplified ($\times 100,000$) and analog band-pass filtered (10–300 Hz) with artifact rejection enabled and set to 50 μ V. Ocular VEMPs were recorded from each participant lying supine while maintaining gaze at a targeted position 30° in the upward-midline position (Govender et al., 2009). The biphasic oVEMP response was defined as an initial negative peak (N1) in the recorded activity occurring at approximately 10 ms with a subsequent positive peak (P1) occurring at approximately 15 ms. Individual responses from a minimum of 150 sweeps were replicated and oVEMP N1–P1 peak-to-peak amplitudes were identified for the averaged response. A 0 dB nHL control run was performed for each ear.

Rotational stimuli were presented using a Neuro Kinetics Inc. Neuro-Otologic Test Center (NOTC; NKI, Pittsburg, PA) running a customized VEST™ (v7.0) Research Interface (v3.0) with eye tracking measured at a rate of 100 Hz via biocular infrared digital video-goggles with torsional tracking software (I-Portal-VOG® v2.4.002). The video-goggles were firmly affixed to the head to prevent any slippage during rotation and each participant was individually centered laterally as well as fore and aft using a centering plumb bob to best approximate the exact on-center rotational position. The custom dynamic UCF test paradigm consisted of six independent SVV measures obtained during each of four independent conditions: one static condition and three rotational conditions at an angular velocity of 300° per second ($5^\circ/\text{s}^2$ acceleration). The three rotational conditions were: 1) on-center rotation with clockwise and counter clockwise rotations equally distributed among study cohort 2) left eccentric rotations (UCF-L), and 3) right eccentric rotations (UCF-R) (Figure 2). Test-order for eccentric rotations mirrored the counter-balanced oVEMP ear test-order (e.g. UCF-R was paired with right ear oVEMP stimulation followed by left stimulation, etc.). A relaxation period of no less than five minutes was provided to each participant between each of the three rotational test conditions (Akin et al., 2011). The SVV stimuli consisted of a red 40 cm laser line projected at eye level approximately 80 cm from the participant in the lightproof NOTC enclosure. The starting position of each SVV trial was computer randomized prior to each presentation between ± 30 –50°. Final SVV was recorded for each trial as the degree of skew deviation from true vertical. In addition to measures of SVV, I-

Portal-VOG[®] eye-tracking software also measured the degree of OCR. Specifically, ocular torsion was measured by proprietary software (I-Portal-VOG[®]) designed to identify torsional and linear ocular movements through a precision method of tracking iris edge-based landmarks in eye geometry. Ocular position for horizontal, vertical, and torsional eye movements were recorded using VOG methods, and the raw data (ocular position by time) was saved for off-line data analysis. The degree of OCR was determined by downloading the ocular position torsion data using DIAdem engineering software (National Instruments Corporation, Austin, Texas). Ocular torsion position data were plotted by time, and the degree of ocular torsion was calculated as the change in ocular position just prior to, and after, chair translation from center of on-axis rotation to eccentric position. Degree of ocular torsion in the clockwise direction was a positive value, whereas ocular torsion in the counter clockwise direction was a negative value. The degree of ocular torsion for each eccentric rotation, and for each participant, was then divided by a gravitational inertial acceleration (GIA) constant of 12.14°, in order to calculate the OCR-GIA slope. The GIA constant was derived from the equation $g=(r\omega^2)/G$; where r is the mean radius of eccentric utricle displacement (7.74 cm), G is the velocity of gravity at 9.8m/s², and ω is the angular rotational velocity of 300°/sec.

Data analysis

Data analysis was performed using Prism version 6.00h for Mac, GraphPad Software (La Jolla, California). Statistical analyses were performed using Friedman ANOVA, Wilcoxon matched-pairs signed rank test, simple linear regression, or Mann Whitney U when appropriate, and are identified for each analysis in Tables 1–3. All post-hoc analyses were performed using Tukey's test. Level of significance for all statistical measures was set at $\alpha = 0.05$.

Results

Ocular VEMP data

All 47 participants had a measurable right and left ear oVEMP response to a 110 dB nHL stimulus. N1–P1 amplitudes ranged from 1.42–37.30 μ V. The oVEMP N1–P1 amplitude means were 12.59 μ V (8.4 SD) for the right ear and 8.50 μ V (5.58 SD) for the left ear with a mean amplitude symmetry ratio of 0.24 (0.15 SD). A simple linear regression identified a significant correlation between right and left oVEMP amplitudes ($R^2=0.6980$; $p<0.0001$) (Figure 3).

Rotational SVV data

All 47 participants completed rotational testing and provided an SVV response in all four stimulus conditions (Figure 4). A repeated measures matched-pairs ANOVA and post hoc analyses identified no differences in SVV skew deviations from trials three through six for each of the four test conditions, therefore, an average-SVV (aSVV), based on trials three through six, was calculated for each condition. A repeated measures matched-pairs ANOVA identified a significant difference across rotational conditions for the aSVV ($F(4,47)=104.1$, $p<0.0001$). Post hoc analysis revealed a significant difference between the mean aSVV during UCF-R and UCF-L rotations compared to all other conditions. The mean aSVV for

the static and on-center conditions were not significantly different from each other (Figure 4, Table 1).

Rotational OCR data

Ocular torsion data were analyzed for ocular counterroll (OCR) measures on all 47 participants who completed rotational testing. However, secondary to technical challenges encountered in the measurement of the diminutive OCR, the OCR could reliably be measured (i.e., free from physiologic artifact, tracking noise, or loss of torsional tracking) from at least one eye in only 27 and 20 individuals in response to UCF-R and UCF-L rotations, respectively (Figure 1). Mean OCR and standard deviations for each eye and each eccentric condition are presented in Table 2. Figure 4 depicts the median, quartiles, and range of OCR measures for each eye and each eccentric rotation. For ten individuals from whom biocular OCR measures were successfully measured during UCF-R eccentric rotations, there was no significant difference between the right and left eye OCR (Wilcoxon, $p=0.6250$). However, for 13 individuals from whom biocular OCR measures were successfully measured during UCF-L eccentric rotations, there was a significant difference identified between the right and left eye OCR (Wilcoxon, $p=0.0034$) (Figure 4). Although the median difference between the right and left OCR during UCF-L was small (0.68°), the fact that 12 of the 13 individuals (92%) exhibited a stronger contralateral right eye OCR response likely contributed to the observed statistical significance (Figure 5). In light of the statistical difference in OCR, a comparison of the ocular response between eccentric conditions was performed using only the contralateral eye response, similar to that of the ocular VEMP response. A total of 11 participants provided a measurable OCR from the contralateral eye during both eccentric rotations, which resulted in 11 matched comparisons. Wilcoxon matched-pairs signed ranked analysis revealed a significant difference in the OCR from the contralateral eye between UCF-R and UCF-L rotations ($p=0.0010$) (Table 2).

Rotational OCR-GIA Slope data

The OCR-GIA slope was calculated for each eye in response to each eccentric condition. Mean OCR-GIA slope and standard deviations for each eye and each eccentric condition are presented in Table 2. There was no significant difference in the mean OCR-GIA slope between the right and left eye data in response to UCF-R rotations ($p=0.6777$). However, similar to the OCR measure, there was a significant difference in the mean OCR-GIA slope between the right and left eye data in response to UCF-L rotations ($p=0.0034$). This finding is not surprising given the fact that the OCR-GIA slope is derived from the OCR measure. Similar to the observed OCR, the median difference between the right and left OCR-GIA slope for the right and the left eye during UCF-L was small (0.05°), and the fact that 12 of the 13 individuals with biocular data exhibited a greater (or equal) contralateral right eye OCR-GIA slope likely contributed to the observed statistical significance. Similar to the OCR, a total of 11 matched OCR-GIA slope comparisons were possible using contralateral eye data. A Wilcoxon matched-pairs signed ranked analysis revealed no significant difference between the OCR-GIA slope using contralateral eye data between UCF-R and UCF-L rotations ($p=0.8457$; Table 2).

Regression Analyses (contralateral ocular data)

Given the statistical difference in OCR between the right and left eyes during the UCF-L rotational condition, correlational statistics were performed for OCR and OCR-GIA slope data using contralateral ocular data (i.e., right eye during UCF-L rotations, and left eye during UCF-R rotations). Contralateral eye data were selected when performing regression analyses inasmuch that the oVEMP data were measured from the contralateral eye.

Simple linear regression analyses were conducted between OCR-GIA slope data calculated using contralateral eye data during UCF-L and UCF-R rotation conditions, and the respective left and right oVEMP amplitudes. Regression analyses failed to identify a significant correlation between the right and left oVEMP amplitude and each respective OCR-GIA slope for either the right or the left eccentric rotation (Figure 7; Table 3). To determine if absolute measures of SVV could be used as a proxy for determining utricular sensitivity as defined by the OCR-GIA slope, independent correlations were investigated between the aSVV and oVEMP amplitude, as well as between the aSVV and the OCR-GIA slope, and the OCR derived from the contralateral ocular response (re: the eccentric rotational condition). Linear regression analyses failed to identify any significant correlations for any of these relationships (Table 3). Despite a strong correlation between right and left oVEMP amplitude, simple linear regression failed to reveal a corresponding significant relationship in the aSVV measure between UCF-R and UCF-L rotation conditions ($p=0.1349$) (data not shown).

Regression Analyses (combined contralateral and ipsilateral ocular data)

A simple linear regression analysis between right and left OCR identified a significant coefficient of determination for both UCF-R and UCF-L rotational conditions (UCF-R, $R^2=0.8350$; $p=0.0002$ & UCF-L, $R^2=0.8726$; $p<0.0001$) (data not shown). Given such a strong correlational coefficient, the above analyses were repeated using combined data from both eyes (that is, in the absence of contralateral eye data, ipsilateral data were added to each respective sample). Adding all available ipsilateral eye data was done in order to determine if a larger sample would identify a potential significant effect for any of the analyses.

Supplementing the ipsilateral ocular data from each UCF angular rotation condition (in the absence of contralateral ocular data) effectively increased the total sample size to 37 measurable OCRs during right chair translations (UCF-R), and 33 measurable OCRs during left chair translations (UCF-L), which resulted in 21 matched pairs from individuals for whom a OCR was recorded from *at least one eye* during both eccentric conditions (Figure 1). A Wilcoxon matched-pairs signed ranked analysis revealed a significant difference in the OCR between UCF-R and UCF-L rotations ($p<0.0001$) (data not shown). Moreover, a simple linear regression between the 21 matched pairs of OCR between UCF-R and UCF-L rotation conditions was highly significant ($R^2=0.7502$; $p<0.0001$) (Figure 6).

A simple linear regression also identified a significant coefficient of determination between right and left ocular OCR-GIA slopes for both rotational conditions; UCF-R ($R^2=0.8318$; $p=0.0002$) and UCF-L ($R^2=0.8701$; $p<0.0001$) (data not shown). Therefore, OCR-GIA slope data from both eyes were again combined for each UCF angular rotation, which (similarly)

increased the total sample size to 37 measurable OCR-GIA slopes during right chair translations (UCF-R) and 33 measurable OCR-GIA slopes during left chair translations (UCF-L). Group analysis revealed no significant difference between OCR-GIA slopes between eccentric rotational conditions ($p=0.9324$, Mann-Whitney U ; Figure 1). Similar to the above analyses, a Wilcoxon matched-pairs signed ranked analysis on the larger sample size of 21 matched pairs revealed no significant difference between the OCR-GIA slope between the UCF-R and UCF-L rotations (data not shown).

Non-significant coefficients of determination were also identified between OCR-GIA slope and oVEMP amplitude when using all available OCR-GIA slope data derived from the contralateral eye plus the ipsilateral eye when contralateral OCR-GIA slope data were unavailable (data not shown). Finally, non-significant coefficients of determination were also identified between the aSVV and the OCR-GIA slope when using all available OCR-GIA slope data derived from the contralateral eye plus the ipsilateral eye when contralateral OCR-GIA slope data were unavailable (data not shown). In short, no significant differences were identified for any of the repeated data analyses when using all available data (contralateral eye plus the ipsilateral eye when contralateral OCR-GIA slope data were unavailable).

Discussion

Wyuts and colleagues (2003) were the first to provide evidence suggesting that the sensitivity of the utricular response could be quantified through eccentric rotations by determining the relationship between the degree of OCR and gravitational inertial acceleration (i.e., OCR-GIA slope). We examined the intra-subject relationship between the ocular VEMP amplitude and various outcome measures obtained during eccentric rotations, specifically the OCR-GIA slope data, to determine if utricular sensitivity (gain) could be inferred from oVEMP testing.

oVEMP Data

We report the mean and standard deviation of the oVEMP N1–P1 amplitude at 110 dB nHL. Although it is difficult to directly compare the values obtained in this study against published reports due to slight differences in stimulus characteristics and methodologies (air-versus bone-conduction, click versus tone burst stimuli; seated versus supine, etc.), mean N1–P1 amplitudes and standard deviations are similar to those of Wang and colleagues (Wang et al., 2010), as well as Piker and colleagues (Piker et al., 2011). Not only do these data confirm the feasibility of recording an oVEMP to an air-conducted stimulus, but these data offer significant evidence to suggest the response can be readily obtained, with 100% of the young healthy volunteers in this study exhibiting a response in each ear to 110 dB nHL tone-burst stimulus.

However, despite the feasibility of recording a VEMP response, the current clinical application of VEMP data can be viewed as fairly narrow in scope. Clinicians often use a binary strategy in which they identify the presence or absence of a response, and interpret those results as normal or abnormal, respectively. VEMP threshold is obtained in some cases. However, this binary interpretation of VEMP becomes a significant constraint when

attempting to evaluate the graduated physiology of the utricle (or saccule), similar to VOR gain measured during sinusoidal oscillations. For example, it remains uncertain as to whether a 25 μ V N1–P1 amplitude on oVEMP reflects a stronger utricular end organ response than a 5 μ V N1–P1 amplitude, even though both may be within the normal ± 2 SD reference range. Moreover, identifying weak macular physiology is often difficult as current normative reference limits often identify a lower -2 SD normative reference limit that extends near or even includes 0 μ V.

OCR-GIA Slope Data

In a similar manner to that of Wuyts and colleagues, we examined OCR-GIA slope data from a group of healthy participants in response to both eccentric-right (UCF-R) and eccentric-left (UCF-L) rotations. All OCR-GIA slope data obtained from each eye and each eccentric condition in the current study are within one standard deviation of those obtained from the healthy subjects in Wuyts et al. (2003). No significant differences were observed in the mean OCR-GIA slope when comparing across eccentric conditions. There was a significant difference identified in the OCR-GIA slope between the right and left eye in the UCF-L eccentric condition, with the contralateral right eye exhibiting a greater slope than the ipsilateral left eye. Although it is possible this difference could be explained by the dominating neurophysiologic contralateral oculo-utricular neural pathway previously identified (Curthoys, Vulovic & Manzari, 2012), it is unclear why this difference was also not observed during UCF-R rotations. One possible reason may be the small sample size for whom binocular data was successfully recorded during UCF rotations. Although binocular data was successfully recorded from only 13 individuals during UCF-L rotations, twelve of the 13 individuals exhibited a stronger contralateral eye OCR-GIA slope. This near 100% bias of greater contralateral eye torsion data during UCF-L rotations likely generated sufficient power for significance. However, only five of the ten individuals for whom binocular data was successfully measured during UCF-L rotations exhibited a stronger contralateral eye OCR-GIA slope. As such, the low sample size for which the diminutive

OCR was successfully recorded from each eye likely proved insufficient to demonstrate similar significance during UCF-R rotations. Although a larger sample size is needed to reconcile this difference, the minimal mean difference in OCR-GIA slope between eyes during UCF-L rotations is likely clinically negligent, particularly in light of the strong coefficients of determination observed between both eyes for each eccentric rotation.

Correlations between oVEMP and eccentric outcome measures

The findings of the current study failed to find a significant correlation between the OCR-GIA slope and the oVEMP amplitude. In addition, similar analyses were conducted using the SVV skew as a potential proxy for the measure of OCR. Correlations failed to reveal significant coefficients of determination between the SVV and the OCR-GIA slope, the

OCR, or the oVEMP amplitude. These data suggest that neither the oVEMP amplitude nor the degree of eccentric SVV skew can be used as a direct measure of utricular sensitivity as previously defined by the OCR-GIA slope (Wuyts et al., 2003). Although these findings may have been unexpected, they may not be that surprising. Reasons for a lack of significant correlation may be inherent to the different stimuli employed in each test. Recently, Curthoys (Curthoys, 2010) and Curthoys and colleagues (Curthoys et al., 2014) provided

strong evidence to suggest that the air conduction stimuli used to elicit a myogenic response have response characteristics of jerk stimuli, similar to those recorded from bone-conduction stimuli. Such air-conducted signals would stimulate similar type I vestibular hair cells and their corresponding irregular afferent fibers. Conversely, the acceleration stimulus delivered during on-center rotation and the slow lateral translation of the rotational chair post acceleration (sustained centripetal force) is more inclined to incite a cupular and medial hemi-macular response with subsequent provocation of the VOR via type II hair cells and their corresponding regular afferent fibers (Goldberg, 2000; Goldberg et al., 2012). In review of the characteristic stimuli and responses associated with type I and type II hair cells and their corresponding afferent fibers, it is not surprising or unexpected that different populations of hair cells may preferentially respond to the different stimuli associated with oVEMP and eccentric rotational testing (Baloh et al., 1998; Goldberg, 2000; Gresty et al., 2001; Leigh and Zee, 2006; Minor et al., 1991; Odkvist, 2001). Moreover, differences in epithelial excitation and inhibition are likely insomuch as a centripetal force causes sustained excitation of the eccentrically displaced medial hemi-maculae specifically responsible for the OCR response and inhibition of the lateral hemi-maculae (Leigh and Zee, 2006), as opposed to a more generalized and abrupt epithelial response pattern to air-conducted “jerk” stimuli. Consequently, distinct responses would likely be produced from each test and subsequently would show no relationship. It is, therefore, quite possible that these two tests reflect different response properties of the utricular system that are ultimately governed by the *type* of stimuli.

A second reason for a lack of correlation between rotational measures and oVEMP amplitude may be inherent to the physiologic properties associated with specific neural response characteristics. Response amplitude reflects the number of cells responding to a stimulus and the degree of neural synchrony, whereas threshold reflects a measure of sensitivity (Wang et al., 2012). This suggests that a greater opportunity for a correlation may exist between the oVEMP *threshold* and the OCR-GIA slope versus oVEMP *amplitude* and OCR-GIA slope. The oVEMP threshold was not investigated in this study and this relationship would be worthy of investigation in future studies. An argument, however, could be made as to the origin of the OCR-GIA slope being inherently related to amplitude. This is largely due to the fact that a greater number of hair cell receptors are likely stimulated either by an increase in the velocity of chair rotation or the translational distance from the center of rotation. It is possible that the velocity of chair rotation utilized in this study (300° per second) may have been inadequate to produce a robust and stable OCR that was equivalent to the oVEMP response at 110 dB nHL. Wuyts and colleagues utilized a stimulus velocity of 400° per second, which produces a GIA of 21.7° (Wuyts et al., 2003); nearly twice that of the current study. However, increasing rotational velocity above 300° per second becomes increasingly difficult for individuals (patients) to tolerate. An alternative method of producing a larger GIA is to increase the radial distance of chair translation from on-center rotation. Previous studies have used chair displacements up to 1m (Curthoys et al., 1997; Wade et al., 1997), which can effectively produce a GIA that quickly approaches 70° as the rotational velocity increases to 300°/s. Although rotational velocities rarely exceed 180°/s when employing such large off-center displacements, the effect of eliciting a significantly larger GIA using large radial displacements is certainly advantageous, as it will produce a

larger OCR and SVV with potentially less deleterious variance. This is critical as the degree of OCR gain ascribed to otolith stimulation under dynamic conditions is small, occurring between 0.125 and 0.25 (MacDougall et al., 1999). Consequently, studies that employ robust GIA rotational conditions (i.e., 1m centrifugation at 180°/s; GIA 45.14°) generate a proportionately more robust OCR than those that employ less GIA rotational conditions like this study (i.e., 0.0774m centrifugation at 300°/s; GIA 12.14°). Although the mean OCR responses obtained in this study (3.47° UCF-L; -3.44° UCF-R) demonstrate a similar OCR gain (0.286 & 0.283, respectively) to published reports (MacDougall et al., 1999), the proportionately smaller OCR responses are inherently subject to greater deleterious effects from recording noise and post analysis sampling, thus leading to possibly larger variances and/or loss of data. However, one of the underlying objectives of the current study was to design and evaluate a test paradigm that could be well tolerated by balance-disordered patients. More importantly, it was imperative for the current study's rotational paradigm to parallel that of Wyuts and colleagues (2003) so that an OCR-GIA slope (ie., utricular sensitivity) could be calculated and assigned to the laterally-displaced utricle in the manner which Wyuts and colleagues described.

It is also not surprising that OCR and SVV fail to demonstrate any significant correlation. One reason for this is that they are derived from distinct peripheral and central structures. Ocular counterroll is dependent almost entirely on otolith (utricular) and brainstem processes, whereas SVV also incorporates multiple sensory inputs that include proprioception, cognitive and visual perception (Tarnutzer et al., 2009). This reasoning may also help to explain the lack of significance in the aSVV between the UCF-R and UCF-L rotation conditions versus the highly significant relationship in the OCR between each eccentric rotation condition. Although OCR and SVV responses fail to share a similar gain despite sharing a common peripheral vestibular input, the robust segregation of OCR and SVV data between right and left UCF conditions supports the use of either OCR or SVV for determining utricular *function*. However, the lack of any significant coefficient of determination between either SVV or OCR and OCR-GIA slope would suggest that neither of these response parameters can currently be interpreted as a direct measure of utricular *sensitivity*.

Usefulness of eccentric testing in a comprehensive vestibular assessment

In the absence of any significant correlations between oVEMP and UCF parameters, we suggest that the two tests are complimentary and measure *different* aspects of utricular function that are dependent upon the type of stimulus. Valko and colleagues suggested that use of oVEMP *and* eccentric rotational testing on a group of abnormal balance function and a group of normal participants was able to differentiate the two groups with relatively good specificity and sensitivity (Valko et al., 2011). These results agree with Schönfeld and Clarke who stated that the “measurement of ocular VEMPs must be regarded as a dynamic test involving high frequency [jerk] components, as opposed the static [velocity] condition employed in the unilateral centrifugation test. The two approaches can be regarded as complimentary” (page 10) (Schonfeld and Clarke, 2011). They further explained that eccentric rotational testing has proven very successful in the differentiation between peripheral and central otolith disorders, and can be an effective tool in monitoring the

progression of vestibular rehabilitation as well as supporting medico-legal issues (Schonfeld and Clarke, 2011).

Despite the current challenges associated with measuring the OCR-GIA, these data support previous conclusions that the OCR-GIA slope does offer an increased understanding of utricular physiology, and the subsequent potential for the identification of utricular disease. Although it is clear that certain stimulus and recording obstacles preclude the universal measurement of an OCR-GIA slope from every patient, it is likely that an increase in the appreciation of OCR data could be achieved by increasing the rotational velocity. However, the heightened risks and discomforts associated with increasing the velocity of the chair rotation above 300° per second may not outweigh the clinical benefits. As a result, most clinicians may argue against performing such a labor and stimulus intensive rotational paradigm that is solely reliant on measuring such a subtle and diminutive change in ocular torsion; particularly for balance-disordered patients where a decrease in signal-to-noise ratio may obscure an already diminutive OCR response. Moreover, until the ability to extract a greater degree of noise-free VOG OCR data during high velocity testing improves, the technical difficulty in reliably measuring the miniscule OCR response with greater accuracy and dependability will remain a formidable obstacle. Overcoming such a hurdle may become possible as higher sampling rate VOG goggles become available and more routinely introduced into clinical practice.

Overall, the mean OCR-GIA data presented here do, in fact, agree with that of Wyuts and colleagues (Wuyts et al., 2003). Moreover, these data suggest that, when measured successfully, the OCR-GIA slope may provide additional clinical evidence for utricular function that may not be evident from VEMP testing. Such investigations are warranted on a balance-disordered population to further elucidate this complimentary UCF-cVEMP testing hypothesis.

Study limitations

An *a priori* power analysis was not performed for this study secondary to an absence of studies investigating the relationship between oVEMP and rotational data. Although it is not appropriate to perform a *post hoc* power analysis using the current sample (Hoenig & Heisey, 2001), the published data from studies investigating the relationship between the variability of SVV and OCR (Tarnutzer et al., 2009) were used to estimate the likelihood of finding a false negative in the current sample. In the prior study, the effect size for the behavioral results was large ($R = 0.894$). At $\alpha = 0.05$, 28 participants would be needed to obtain a power equal to 0.80 (Cohen, 1992). Although the variance in our oVEMP data is similar to that reported elsewhere (Wang et al., 2010, Piker et al., 2011) and the test-retest reliability of oVEMP amplitudes has been reported as excellent (Nguyen et al., 2010), the authors recognize that the large inter-subject variance in our data may require a larger sample size to determine the significance of these findings. This is a potential limitation to this study and our ability to understand the importance of this limitation is uncertain.

Conclusion

Results from the current study suggest that oVEMP and UCF responses offer different information regarding the function of the utricle. More research is needed to determine each method's exact contribution within the otolith test battery as well as to identify how these results may correlate with different vestibular phenotypes. Eccentric rotational testing not only offers multiple methods to assess the utricle (SVV, OCR, OCR-GIA slope), but also has the potential to capture even more subtle eye movements with more refined ocular recording techniques, more advanced analytical software, or novel rotational stimuli. The rotational chair's ability to consistently provide stimuli with precision offers a unique opportunity to test the utricular system in ways not always possible with acoustic stimuli (e.g., conductive hearing losses). Additionally, eccentric linear acceleration offers the distinct advantage of producing a more natural and pure-otolithic response (Gresty and Lempert, 2001). The fundamental difference between the response characteristics to both acoustic stimuli (oVEMP) and acceleration stimuli (rotational chair) may offer the simplest reason to support the complimentary use of both tests. Additional measures using larger chair displacements may be useful, although it remains uncertain as to whether or not the OCR-GIA slope accurately reflects utricular sensitivity at such translational distances. Ultimately, the final word on the clinical efficacy of these tests will depend on their application to a disordered population and the ability for each test to more precisely qualify and/or quantify abnormal utricular function.

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Figure 1.

Cohort distribution depicting the sample size for each study portion of the protocol. Dotted lines are used to highlight statistical comparisons. Solid lines are used to track cohort demographics. OCR indicates change in ocular counterroll; OCR-GIA, ocular counterroll-gravitational intertial acceleration; oVEMP, ocular vestibular-evoked myogenic potential; UCF, unilateral centrifugation.

Figure 2.

Rotational paradigms. (A) Clockwise on-center rotation paradigm (counter clockwise rotational paradigm not shown). (B) Left eccentric rotational SVV paradigm with clockwise nasion-centric rotation. (C) Right eccentric rotational SVV paradigm with counter-clockwise nasion-centric rotation. Solid grey lines represent rotational velocity and dashed black lines represent linear chair displacement for each eccentric rotation. Dotted black lines (B & C) represent zero angular velocity (x-axis) and zero displacement (y-axis). Black hash marks represent the time of presentation of each SVV stimuli. SVV indicates subjective visual vertical.

Figure 3.
Right plotted against left oVEMP amplitude for each of the 47 individual participants.
Simple linear regression analysis reveals a significant relationship ($p < 0.0001$).

Subjective Visual Vertical & Ocular Counterroll Measures by Condition

Figure 4.

SVV and OCR skew deviations. Box and whiskers plot showing median, quartiles, 5th / 95th percentile range of values, as well as the individual data points exceeding the 5th and 95th percentile range for the SVV in response to each rotational condition and OCR for each eye and rotational condition. Asterisks (*) indicate statistical significance ($p < 0.05$) between selected measures and rotational conditions. OCR indicates change in ocular counterroll; SVV, subjective visual vertical; UCF, unilateral centrifugation.

Figure 5.

OCR for those participants for whom binocular data was obtained for both UCF-L (n=13) and UCF-R (n=10) eccentric conditions. Wilcoxon matched-pairs signed rank tests reveals a significant difference between right and left eye OCR in the UCF-L condition ($p=0.0034$) and no significant difference between right and left eye OCR in the UCF-R condition ($p=0.6250$). OCR indicates change in ocular counterroll; UCF, unilateral centrifugation.

OCR Change UCF-R versus UCF-L

Figure 6.

Correlation between UCF-R OCR and UCF-L OCR for 21 participants for whom at least one eye OCR was obtained. Contralateral eye data (n=11) is plotted and substituted by ipsilateral eye data (n=10) in cases where matched contralateral eye data was unavailable. Simple linear regression analysis identifies a significant coefficient of determination ($p < 0.0001$). OCR indicates change in ocular counterroll; UCF, unilateral centrifugation.

Figure 7.

OCR slope (both eyes plotted) for each UCF condition versus oVEMP amplitude. N1–P1 oVEMP mean amplitude versus OCR-GIA slope during UCF-R (n=27) and UCF-L (n=20). Discrete data points represent the OCR-GIA slope for each eye during each eccentric condition plotted against the corresponding oVEMP amplitude. Non-significant linear regressions of the plotted data for each ear are shown. OCR indicates ocular counterroll; OCR–GIA, ocular counterroll– gravitational inertial acceleration; oVEMP, vestibular-evoked myogenic potential; UCF, unilateral centrifugation.

Table 1
aSVV skew deviations and statistical comparisons across all rotational conditions

Mean aSVV (and standard deviation) are reported with respective sample sizes by rotational condition. aSVV differences are reported using repeated Friedman ANOVA. aSVV, average subjective visual vertical; UCF, unilateral centrifugation; *SD*, standard deviation

Friedman ANOVA	Static	On-Center	UCF-Right	UCF-Left
Sample Size (n)	47	47	47	47
aSVV[Mean (<i>SD</i>)]	-0.03° (1.5)	0.07° (2.1)	-3.55° (2.1)	3.47° (2.1)
Static	-			
On-Center	Not Significant	-		
UCF-Right	p<0.0001	p<0.0001	-	
UCF-Left	p<0.0001	p<0.0001	p<0.0001	-

Table 2
OCR and OCR-GIA slope group data for each rotational condition

OCR and OCR-GIA slope means and standard deviations for UCF-R and UCF-L for only those individuals for whom data from both the right and left eyes for each eccentric rotation (as well as for each eccentric condition with eyes combined) were obtained. OCR and OCR-GIA slope differences are reported using a Wilcoxon Matched-Pairs Signed Rank. UCF, Unilateral centrifugation; OCR, Change in Ocular Counterroll; OCR-GIA, Ocular Counterroll-Gravitational Inertia Acceleration, *SD*, standard deviation

Wilcoxon Matched-Pairs Signed Rank	UCF-Right / Right Eye	UCF-Right / Left Eye	UCF-Left / Right Eye	UCF-Left / Left Eye	UCF-Right (Left Eye)	UCF-Left (Right Eye)
Sample Size	19	18	17	16	11	11
OCR [Mean (<i>SD</i>)]	-3.40° (2.2)	-3.48° (2.1)	3.62° (1.9°)	3.31° (2.3)	-3.18° (1.9)	3.28° (2.0)
p-value	p=0.6250 (10 matched-pairs)		p=0.0034 (13 matched-pairs)		P=0.0010 (11 matched pairs)	
OCR-GIA Slope [Mean (<i>SD</i>)]	-0.28° (0.18)	-0.29° (0.17)	-0.30° (0.15)	-0.27° (0.19)	-0.29° (0.17)	-0.30° (0.15)
p-value	p=0.6777 (10 matched pairs)		p=0.0034 (13 matched pairs)		p=0.8457 (11 matched pairs)	

Table 3
Linear regression analysis of rotational data and oVEMP amplitude

Linear regression results for OCR-GIA slope versus oVEMP amplitude (μV), aSVV versus OCR, OCR-GIA slope, and oVEMP amplitude for both right and left ear (eccentric rotation). For the OCR-GIA slope data vs oVEMP amplitude, the OCR-GIA slope data were determined using the OCR data from the contralateral eye. For analyses involving OCR data, sample sizes reflect OCR data that was measure from the contralateral eye during each eccentric rotation. aSVV, average subjective visual vertical; OCR-GIA, Ocular Counterroll-Gravitational Intertia Acceleration; OCR, Change in Ocular Counterroll; oVEMP, Ocular Vestibular Evoked Myogenic Potential.

Ear	OCR-GIA Slope vs oVEMP amplitude		aSVV vs OCR		aSVV vs OCR-GIA Slope		aSVV vs oVEMP Amplitude	
	Right	Left	Right	Left	Right	Left	Right	Left
Sample Size	18(contra left eye)	17(contra right eye)	18(contra left eye)	17(contra right eye)	18(contra left eye)	17(contra right eye)	47	47
R ²	0.0058	0.0002	0.0532	0.0340	0.0494	0.0341	0.0185	0.0394
p-value	p=0.7640	p=0.9616	p=0.3570	p=0.5280	p=0.3752	p=0.4778	p=0.3623	p=0.1812