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**Title:** Binocular Coordination of the Human Vestibulo-Ocular Reflex during Off-axis Pitch Rotation

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## **ABSTRACT**

**Introduction.** Head movements in the sagittal pitch plane typically involve off-axis rotation requiring both vertical and horizontal vergence ocular reflexes to compensate for angular and translational motion relative to visual targets of interest. The purpose of this study was to compare passive pitch VOR responses during rotation about an Earth-vertical axis (canal only cues) with off-axis rotation (canal and otolith cues). **Methods.** Eleven human subjects were oscillated sinusoidally at 0.13, 0.3 and 0.56 Hz while lying left-side down with the interaural axis either aligned with the axis of rotation or offset by 50 cm. In a second set of measurements, twelve subjects were also tested during sinusoidally varying centrifugation over the same frequency range. The modulation of vertical and horizontal vergence ocular responses was measured with a binocular videography system. **Results.** Off-axis pitch rotation enhanced the vertical VOR at lower frequencies and enhanced the vergence VOR at higher frequencies. During sinusoidally varying centrifugation, the opposite trend was observed for vergence, with both vertical and vergence vestibulo-ocular reflexes being suppressed at the highest frequency. **Discussion.** These differential effects of off-axis rotation over the 0.13 to 0.56 Hz range are consistent with the hypothesis that otolith-ocular reflexes are segregated in part on the basis of stimulus frequency. At the lower frequencies, tilt otolith-ocular responses compensate for declining canal input. At higher frequencies, translational otolith-ocular reflexes compensate for declining visual contributions to the kinematic demands required for fixating near targets.

## INTRODUCTION

The vestibulo-ocular reflex (VOR) must compensate for head motion relative to visual targets of interest in order to stabilize gaze. In foveate animals, the characteristics of the VOR are driven by the functional demand to maintain binocular fixation (7, 12). Compensating for visual target distance is particularly important to coordinate stereoscopic vision during translational movements (20). Since the eyes are in front of the usual axes of head rotation, the VOR presumably compensates for translation during most natural head turns. Head movements in the sagittal (pitch) plane involve rotations about multiple vertebrae in the cervical column (21), as well as rotations about the hip and ankles (16). As the head is farther displaced from the axis of rotation, commonly referred to as *off-axis* rotation, the eye movement response must be modified to adjust for the greater translational components incurred.

If one rotates about an axis that passes through the eyes, the ideal eye movement required for stabilizing a retinal image of a straight ahead target would be simply equal and opposite to the angle of head rotation. However, the ideal compensatory eye movements during off-axis rotation is no longer dependent on rotation angle alone, but also on the radius of rotation, distance to the target, interpupillary distance, and target eccentricity (10, 20, 24, 29). Viirre and Demer (30) observed an enhanced gain of the vertical VOR during off-axis pitch rotation about an Earth-horizontal axis over a frequency range 0.8 - 2.0 Hz. The modulation of horizontal vergence has also been observed during off-vertical axis rotation (8) and during straight-ahead translation (2). Based on these results, we hypothesized an enhancement of both the vertical and vergence eye responses during off-axis rotation in the pitch plane.

Otolith-ocular reflex pathways are responsible for compensating for the translational components of head movements (3, 18). Interestingly, previous research suggests that human translational otolith-ocular reflexes are characterized by high-pass filtering (36), with large phase leads and negligible amplitude at low frequencies but increasing in fidelity at frequencies above 0.3 Hz. Below 0.3 Hz the otolith input is interpreted as tilt. Since canal cues appear to be critical to discriminate between tilt and translational motion (3, 15, 34), we were interested in comparing pitch VOR responses during rotation about an Earth-vertical axis (canal only cues) with off-axis

rotation (canal and otolith cues). Therefore, one objective of our study was to compare vertical VOR and horizontal vergence ocular responses obtained during passive on-axis and off-axis rotation. We were specifically interested in the effects of stimulus frequency around the range where there is a cross-over of tilt and translation otolith-ocular responses.

Head movements in altered gravity phases of high performance aircraft operations challenge the central integration of otolith and canal inputs. For example, shifts in perceived attitude during hypergravity have been attributed to vestibular G-excess effects (9). To further examine the interaction of angular and linear inputs to the VOR during different gravitoinertial loads, a second set of off-axis VOR measurements were obtained during sinusoids with a bias velocity, i.e., sinusoidally varying centrifugation. We predicted that the effects of this additional gravitoinertial input would vary as a function of stimulus frequency.

## **METHODS**

Experiments were conducted on eleven human subjects (3F, 8M, age range 26-50 yrs) to compare the VOR during on-axis and off-axis rotation (study 1), and on twelve subjects (5F, 7M, age range 24-50 yrs) to examine the effects of sinusoidally varying centrifugation (study 2). Six subjects participated in both sets of measurements. Each participant was required to pass a medical examination (Air Force Class III) and to have no history of balance or visual disorders. All subject selection criteria and experimental procedures were approved in advance by the NASA Johnson Space Center (JSC) Committee for the Protection of Human Subjects. Each subject provided written informed consent before participating.

*Motion stimuli.* The motion stimuli were provided by the NASA JSC Short-Arm Centrifuge Facility, which includes a 300 ft-lb direct drive motor with high precision tachometer-based servo controller for motor control and stability (Neuro Kinetics, Inc., Pittsburgh, PA). Subjects were rotated in the sagittal plane while lying left side down, i.e., about an Earth-vertical axis. Operator instructions as well as background masking noise were provided via a chair-fixed speaker to minimize any extraneous auditory orientation cues. Subjects were restrained using a quick release harness with straps and padding around their legs and feet. An adjustable head

restraint was used to fixate the subject's head relative to the chair. During study 1, on-axis and off-axis comparisons were obtained by positioning the chair using a manual screw drive so that the interaural axis was either centered over the axis of rotation (Figure 1A) or 0.5 m off-axis (Figure 1B). Subjects were rotated with sinusoidal oscillation at 0.13, 0.3, or 0.56 Hz at a peak velocity of  $\pm 40^\circ/\text{s}$  using custom data acquisition and control software. The centripetal acceleration ( $\omega^2 r$ ) along the longitudinal axis was constant across the three frequencies, while the tangential acceleration ( $\alpha r$ ) increased as a function of frequency (Figure 1C left side).

*Insert Figure 1 about here*

During study 2, the effect of sinusoidally varying centrifugation was examined using the same rotator system with the interaural axis positioned 0.5 m off-axis. During these trials, subjects were accelerated in darkness at  $25^\circ/\text{s}^2$  to a constant rate of  $140^\circ/\text{s}$  in either forward-facing (FF) or backward-facing (BF) directions for 60s, followed by superimposed sinusoidal oscillation at 0.13, 0.3 or 0.56 Hz and  $\pm 40^\circ/\text{s}$  peak velocity. These six trials were typically completed over two sessions separated by 10 days ( $\pm 1.0$  sem). As seen in Figure 1C, the rotational velocity (sinusoidally varying between 100 and  $180^\circ/\text{s}$ ) and centripetal ( $+a_z$ ) linear acceleration at the interaural axis (sinusoidally varying between 1.5 and  $4.9\text{m}/\text{s}^2$ ) were held constant across frequencies, while the sinusoidal modulation of the tangential acceleration ( $\pm a_x$ ) increased with frequency (from  $\pm 0.29\text{ m}/\text{s}^2$  at 0.13 Hz to  $\pm 1.23\text{ m}/\text{s}^2$  at 0.56 Hz). For each stimulus frequency, data were also obtained during vertical optokinetic stimulation and again in the dark (data not reported here) before decelerating at  $25^\circ/\text{s}^2$  to a complete stop. Post-rotatory responses were recorded for at least 2 min between runs. The sequence of trials for both study 1 and 2 was counter-balanced across subjects.

*Eye measurement and analysis.* During the oscillations in darkness, subjects were instructed to imagine Earth-fixed objects on the laboratory wall. Eye movements were recorded with a binocular video camera system which used dichroic mirrors to allow a full field of view (37). Small monochrome video cameras were used with near-infrared emitting diodes to allow eye recording in darkness. A time code was digitally overlaid on each video field by a video inserter (Video Data System 523A, H.E. Inc., Las Vegas, NV) to permit off-line processing and

synchronization with the tachometer signals. Eye data were recorded on video cassette tapes and processed off-line using an eye tracking system (25) implemented on a Macintosh PowerPC platform with an image frame grabber (LG-3, Scion Corp., Frederick, MD). The eye tracking algorithm used a least squares fit to track the pupil from these binary images based on a clipped circular disk model. This algorithm was used to derive the horizontal and vertical image coordinates of the pupil center, the pupil radius, and the degree to which the upper eyelid has occluded the pupil. Eye data during upper eyelid closure were excluded using minimal pupil radius criteria.

Eye measurement calibrations were made by having subjects fixate a series of targets placed over a range of  $\pm 20^\circ$  horizontally and vertically on the laboratory wall at 1.8 m distance.

Interpupillary distances were measured for each subject (mean = 6.18 cm  $\pm$  0.08 sem) using a digital corneal reflection pupilometer (Essilor, France), and these values were used to calculate the visual angle of each calibration target for left and right eyes separately. The signals were linearly scaled to express eye position in degrees using head-fixed coordinates with the convention that downward and leftward movements were positive. Following calibration, conjugate horizontal and vertical measurements were obtained from the average of left and right eye data from each video field (60 Hz sample rate), and vergence was obtained from the difference of left and right horizontal eye position. Vergence was normalized for different interpupillary distance by using meter angles, or the reciprocal of fixation distance (18). Eye position was then differentiated, and desaccaded using acceleration and velocity thresholds, and then verified using a custom interactive script (MATLAB; The MathWorks).

VOR response parameters (amplitude, phase and bias) were derived from sinusoidal curve fits of vertical and vergence eye velocity over successive cycles of centrifuge oscillation. Gains and phase shifts relative to the chair velocity were calculated, with the convention that phase leads were positive. Separate gains were also derived for pitch forward and backward rotations to quantify VOR asymmetry (22). Gains and time constants were also estimated from single exponential fits to vertical slow phase velocity over the first 20s following the end of acceleration or deceleration. The VOR response parameters were then used in repeated measures multivariate analyses of variance (MANOVAs) to assess the effects of frequency for each

rotation condition using StatView (SAS Institute, Inc.), with Wilks' Lambda serving as the critical statistic (significance level of 0.05). Comparisons across rotation conditions at specific stimulus frequencies were performed with paired t-tests. However, due to the uneven variability across frequencies, Wilcoxon signed-rank tests were performed on the VOR asymmetry measures to compare across conditions. Central tendencies are presented as mean  $\pm$  sem.

## RESULTS

### *Study 1: On-axis versus Off-axis VOR*

The vertical VOR gain during on-axis rotation (primarily canal cues) increased as a function of stimulus frequency (open squares, Figure 2A). The vertical VOR phase and bias remained relatively constant over this same frequency range, averaging  $11.7 \pm 1.2^\circ$  and  $-1.7 \pm 0.4^\circ/\text{s}$  respectively. The VOR was more asymmetrical at lower frequencies, with the gain being greater during pitch forward, i.e., upward > downward slow phase velocity. As seen in Figure 2B, the vertical VOR asymmetry at 0.13 Hz was also highly variable, which was expected in part due to the relatively lower gain at this stimulus frequency (Figure 2A).

*Insert Figure 2 about here*

The presence of otolith cues during off-axis rotation tended to enhance the vertical VOR gain and significantly reduce the up-down asymmetry at the lower stimulus frequencies (filled circles, Figure 2). The vertical VOR phase and bias remained unchanged across frequency and relative to on-axis rotation, averaging  $14.8 \pm 2.1^\circ$  and  $-1.8 \pm 0.2^\circ/\text{s}$  respectively. Although there continued to be a significant effect of frequency on the vertical VOR gain, the asymmetry between pitch forward and backward was negligible during off-axis rotation. This was consistent with a lack of vertical VOR gain difference between forward-facing and backward-facing centrifugation (see below).

As expected, the modulation of horizontal vergence was negligible during on-axis rotation in the absence of translation motion (open squares, Figure 3). Vergence responses were also negligible at 0.13 Hz during off-axis rotation, but then increased with stimulus frequency (filled circles,

Figure 3). This enhancement of the horizontal vergence response during off-axis rotation is striking since the fixation distance in the dark was greater than 1 m for all subjects.

*Insert Figure 3 about here*

#### *Study 2: Sinusoidally Varying Centrifugation*

The initial per-rotatory eye responses decayed to negligible levels within the first minute of rotation, persisting longer in the forward-facing (FF) direction (time constant =  $8.0 \pm 0.8$  s) than in the backward-facing (BF) direction (time constant =  $4.2 \pm 0.5$  s). This is consistent with the pitch asymmetry described above. Since the per-rotatory response to the initial acceleration might persist longer than 1 minute and influence the responses during the superimposed oscillation, we analyzed successive cycles separately. Beyond the first several cycles needed for response stabilization, the VOR gain was stable across oscillations in darkness and therefore appears to reflect steady state conditions.

*Insert Figure 4 about here*

The vertical VOR phase and bias were not different during centrifugation, although the upward (pitch forward) slow phase bias at 0.13 Hz tended to be greater ( $-2.9 \pm 0.5$  °/s FF and  $-3.0 \pm 0.7$  °/s BF versus  $-1.4 \pm 1.0$  °/s without centrifugation). There were negligible differences between vertical VOR response parameters obtained with and without centrifugation at the lower two frequencies (Figure 4). On the other hand, the vertical VOR gain was significantly decreased at the higher frequency during centrifugation for both FF and BF directions.

*Insert Figure 5 about here*

While there was general trend for off-axis vergence responses to increase with stimulus frequency when elicited without an off-set velocity (filled circles, Figure 5), the opposite trend was observed during centrifugation in either FF or BF directions. The modulation of vergence tended to be greater in the FF direction at the lower frequencies. Vergence responses significantly decreased at 0.56 Hz during centrifugation in both FF and BF directions. The



phases of the vergence responses were highly variable across all conditions, with average phase leads comparable to the vertical VOR responses.

## DISCUSSION

One major finding of this study is that off-axis pitch rotation enhances the vertical VOR at frequencies below 0.3 Hz and enhances the vergence VOR at frequencies above 0.3 Hz. These differential effects of off-axis rotation over the 0.13 to 0.56 Hz range are consistent with the hypothesis that otolith-ocular reflexes are segregated in part on the basis of stimulus frequency (13, 36). At the lower frequencies, tilt otolith-ocular responses compensate for declining canal input. At higher frequencies, translational otolith-ocular reflexes compensate for declining visual contributions to the kinematic demands required for fixating near targets. The suppression of both vertical (angular) and vergence (translational) VORs at the higher frequency during centrifugation may reflect a conflict induced by the presence of additional low frequency tilt graviceptor input with concomitant higher frequency translational components resulting in a novel motion path.

### *Otolith enhancement of low frequency vertical VOR*

The relatively short vertical VOR time constants (<50% of horizontal time constants) observed in the present study and reported previously (5, 14) reflect the poor dynamics in the pitch plane during rotation about an Earth-vertical axis with canal inputs alone. Most natural pitch head movements involve changes in head orientation relative to gravity. Angelaki and Hess (1) proposed that one function of the otolith-ocular reflex is low-frequency enhancement of the VOR dynamics. It is interesting to note that the largest changes we observed between on-axis and off-axis vertical VOR measures were at the lower frequencies, while differences at 0.56 Hz were negligible.

Previous studies have demonstrated that gravity-sensitive mechanisms make the vertical VOR more compensatory, including increased gains, with more symmetrical responses that are more in phase with the stimuli (6, 27). Pitch VOR differences between rotation about an Earth-horizontal axis (upright) versus Earth-vertical axis (onside) are greater at lower frequencies,

similar to the off- and on-axis comparisons in the present study. Human VOR responses between upright and onside pitch during voluntary (4) or passive (28) head movements at higher frequencies ( $\geq 0.3$  Hz), on the other hand, are not substantially different. We conclude that the contribution of the otolith-ocular reflexes to the vertical VOR is primarily enhancement of the low frequency responses.

#### *Otolith-mediated vergence VOR*

Increases in vergence VOR we observed at the higher frequency were consistent with the kinematic gaze demands during translation along the naso-occipital axis. Previous studies have measured average vergence in order to infer the effect of fixation distance on the translational VOR (23, 26, 31). The modulation of vergence we observed suggests the human translation VOR in darkness is capable of compensating for changes in fixation distance as one translates forward and backward relative to a target of interest. A modulation of vergence during translational motion in the naso-occipital direction has been previously observed in the squirrel monkey (19) and the rhesus monkey (2), and during off-vertical axis rotation in the rhesus monkey (8). Consistent with other translation otolith-ocular reflexes (18), the vergence VOR reflects high-pass properties becoming more robust at frequencies greater than 0.3 Hz.

One consequence of open loop recording of the VOR is that the visual target of interest may not be maintained during the oscillations in darkness. However, it has been observed that human vergence in the dark is maintained in the dark to a distance consistent with the known distance to surroundings previously viewed in the light (17, 35). The subjects in our study were asked to imagine Earth-fixed targets on the wall at a distance  $>1$  m. The effect of off-axis rotation on the vergence VOR is striking given that the imagined targets of interest were relatively far away. The sensitivity to fixation distance varies as a function of stimulus frequency (26), and so it would be arguably more critical to control for fixation distance at higher frequencies than used in the present study.

#### *Suppression of the VOR during Sinusoidally Varying Centrifugation*

Difference in translation VORs as a function of body orientation relative to gravity, i.e., static loading of the otoliths, tend to be fairly small over the frequency range included in our study

(26). It has been shown that the angular VOR gain, on the other hand, is modulated by gravitational state during parabolic flight, increasing during hypergravity (directed downward) and reduced during microgravity phases (32). Extending these parabolic results to centrifugation, it is perhaps not surprising that the VOR would be suppressed with the force directed headward. However, the suppression was most striking at the highest frequency.

The effect of sinusoidally varying centrifugation resulted in a complex motion path, with greater tangential accelerations at the higher frequency. At 0.56 Hz, subjects often reported perceived translation along an elliptical path, with comparable amplitude along both longitudinal and naso-occipital axes. The trend for the translational vergence VOR during sinusoidally varying centrifugation to decrease with increasing frequency may be related to the changing ratio of centripetal and tangential linear accelerations (see Figure 1C). Another possible factor for the VOR suppression observed at this frequency may be that subjects had difficulty imaging Earth-fixed targets, but instead tended to fixate on a targets moving with the head as they moved about this complex path (11).

### *Conclusions*

Without offset velocity or during low frequency of varying centrifugation, both otolith and canal-mediated VORs operate synergistically to compensate for linear and angular accelerations within the plane of rotation. The increased vertical VOR gain and improved symmetry at lower frequencies and increased vergence responses at higher frequencies during off-axis rotation are compensatory for the increased translational components incurred. The impaired VOR responses during sinusoidally-varying centrifugation at 0.56 Hz, on the other hand, suggest that otolith-canal integration may be transiently compromised during passive rotation at higher frequencies within altered gravito-inertial states. Active head movements include a motor command contribution that is important for gaze stabilization during translational movements (33). As vestibular signals are just one of many inputs to a spatial localization process (7), contributions of other sensory and motor inputs during active head movements in aerospace operations must be relied on for gaze stabilization within these altered gravito-inertial states.

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## **LEGENDS FOR FIGURES**

Figure 1. Schematic of rotation stimuli presented with subject lying on left side, view from above. A. Rotation on-axis (radius = 0) results in no centripetal or tangential linear acceleration. B. During rotation off-axis, both centripetal and tangential accelerations are a function of the radius of rotation. C. Centripetal and tangential accelerations are represented for off-axis rotation without an offset velocity (left side) and for ramp up, sinusoidally varying centrifugation, and ramp down (right side). Note that centripetal acceleration, a function of angular velocity, is consistently unidirectional (towards the rotation axis). Centripetal acceleration was identical across all three frequencies but substantially greater during centrifugation. Tangential acceleration, a function of angular acceleration, was bidirectional, increased as a function of stimulus frequency and did not change during centrifugation.

Figure 2. Comparison of the vertical VOR gain (A) and asymmetry (B) observed with the interaural axis aligned over the axis of rotation (on-axis, open squares) and located 50 cm off-axis (filled circles). The gain is the ratio of peak vertical eye velocity to peak head velocity. Negative VOR asymmetry indicates the vertical VOR gain is greater during pitch forward (upward > downward slow phase velocity). Asterisk indicates significant difference between on-axis and off-axis ( $p < 0.05$ ). Error bars represent  $\pm$  sem.

Figure 3. Comparison of vergence amplitude (MA/s) observed for on-axis and off-axis pitch rotation (symbols and error bars as in Figure 2).

Figure 4. Comparison of the vertical VOR gain (A) and asymmetry (B) observed during off-axis rotation without an offset velocity (filled circles) versus during sinusoidally varying centrifugation in forward-facing (rightward triangles) or backward-facing (leftward triangles) directions. Note the filled circles are the same data presented in Figure 2 for comparison. Asterisk indicates significant difference between no offset velocity and FF/BF ( $p < 0.05$ ). Error bars represent  $\pm$  sem.

Figure 5. Comparison of vergence amplitude (MA/s) observed during off-axis rotation without an offset velocity versus during sinusoidally varying centrifugation (symbols and error bars as in Figure 4). Note the filled circles are the same data presented in Figure 3 for comparison.

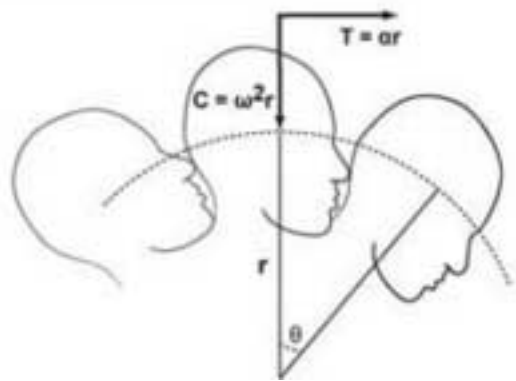


### A. On-axis Rotation



Radius ( $r$ ) = 0  
No Centripetal (C) or  
Tangential (T) Acceleration

### B. Off-axis Rotation



### C. Off-axis linear stimuli

