Experimental Brain Research

HUMAN VESTIBULAR PERCEPTUAL THRESHOLDS FOR PITCH TILT ARE SLIGHTLY WORSE THAN FOR ROLL TILT ACROSS A RANGE OF FREQUENCIES

--Manuscript Draft--

Manuscript Number:	EXBR-D-20-00060R2
Full Title:	HUMAN VESTIBULAR PERCEPTUAL THRESHOLDS FOR PITCH TILT ARE SLIGHTLY WORSE THAN FOR ROLL TILT ACROSS A RANGE OF FREQUENCIES
Article Type:	Research Article
Funding Information:	
Abstract:	Vestibular perceptual thresholds measure vestibular sensory and perceptual noise by quantifying how small of a passive self-motion an individual is able to reliably perceive. Vestibular thresholds have clinical and operational relevance, as they are elevated in vestibular migraine patients, and even healthy individuals with higher (i.e., worse) thresholds have degraded balance. Vestibular thresholds have been quantified across a range of frequencies (motion durations) for rotations and translations, with differences identified for different motion directions (e.g., up/down thresholds are higher than those for left/right motions). While roll tilt thresholds have been well quantified, pitch tilt thresholds have not. Here we aim to quantify pitch tilt thresholds across a range of frequencies and test whether they are higher than in those for roll tilt. In ten normal subjects, we found pitch tilt thresholds at 0.15, 0.2, 0.5 and 1 Hz averaged 1.66, 1.61, 0.99, 0.51 degrees, respectively. Using a general linear model, we found subjects' pitch tilt thresholds were slightly, but significantly, higher than their roll tilt thresholds across all frequencies tested. These differences were approximately 10% at 0.15, 0.2, and 1 Hz and 3% at 0.5 Hz. Pitch tilt thresholds exhibited a similar frequency response as in roll tilt (decreasing a higher frequencies). They also had substantial inter-individual variability, which correlated across pitch tilt frequencies and between pitch and roll tilt thresholds. We discuss why pitch tilt thresholds might be higher, including the pitched-up orientation of the utricular plane of the otoliths, compare to previous studies, and discuss functional implications.
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Author Comments:	Enclosed is our revised manuscript. It was originally entitled “Human Vestibular Perceptual Thresholds are Worse for Pitch Tilt than Roll Tilt”. In response to an initial reviewer's comment, we had revised the title to be "Human Vestibular Perceptual Thresholds for Pitch Tilt are Similar to, but Slightly Worse than for Roll Tilt Across a Range of Frequencies". Now, in response to another reviewer's suggestion, we have revised the title to: "Human Vestibular Perceptual Thresholds for Pitch Tilt are Slightly Worse than for Roll Tilt Across a Range of Frequencies" This minor change to shorten the title was the only requested change from reviewers. Please let us know if you need any additional information regarding our submission.

Response to Reviewers:	We agree with the reviewer and have changed the title to shorten it, without losing meaning.

Title: HUMAN VESTIBULAR PERCEPTUAL THRESHOLDS FOR PITCH TILT ARE ~~SIMILAR TO, BUT~~ SLIGHTLY WORSE THAN FOR ROLL TILT ACROSS A RANGE OF FREQUENCIES

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Keywords:
Perception
Signal detection theory
Human performance
Otolith organs
Semicircular canals

ACKNOWLEDGEMENTS

We thank the NASA Johnson Space Center Neuroscience Laboratory, specifically Scott Wood, Ajitkumar Mulavara, and Jacob Bloomberg, for donating the Tilt-Translation Sled. Thank you to Alexander Kryuchkov, Jordan Lerner, Jordan Dixon, Kathrine Bretl, and Emily Matula for their support in data collection.

ABSTRACT

Vestibular perceptual thresholds measure vestibular sensory and perceptual noise by quantifying how small of a passive self-motion an individual is able to reliably perceive. Vestibular thresholds have clinical and operational relevance, as they are elevated in vestibular migraine patients, and even healthy individuals with higher (i.e., worse) thresholds have degraded balance. Vestibular thresholds have been quantified across a range of frequencies (motion durations) for rotations and translations, with differences identified for different motion directions (e.g., up/down thresholds are higher than those for left/right motions). While roll tilt thresholds have been well quantified, pitch tilt thresholds have not. Here we aim to quantify pitch tilt thresholds across a range of frequencies and test whether they are higher than in those for roll tilt. In ten normal subjects, we found pitch tilt thresholds at 0.15, 0.2, 0.5 and 1 Hz averaged 1.66, 1.61, 0.99, 0.51 degrees, respectively. Using a general linear model, we found subjects' pitch tilt thresholds were slightly, but significantly, higher than their roll tilt thresholds across all frequencies tested. These differences were approximately 10% at 0.15, 0.2, and 1 Hz and 3% at 0.5 Hz. Pitch tilt thresholds exhibited a similar frequency response as in roll tilt (decreasing a higher frequencies). They also had substantial inter-individual variability, which correlated across pitch tilt frequencies and between pitch and roll tilt thresholds. We discuss why pitch tilt thresholds might be higher, including the pitched-up orientation of the utricular plane of the otoliths, compare to previous studies, and discuss functional implications.

INTRODUCTION

Vestibular perceptual thresholds quantify how small of a self-motion an individual is able to reliably perceive (Merfeld 2011a). As a measure of sensory noise (Nouri and Karmali 2018) associated with self-motion perception, vestibular perceptual thresholds appear to have clinical, as well as functional (e.g., for balance), significance. For example, vestibular migraine patients, when asymptomatic, have reduced roll tilt thresholds as compared to normal controls (Lewis et al. 2011a, b; King et al. 2019). Further, patients with Menière's disease have elevated linear translation thresholds (Bremova et al. 2016). Individuals that have previously had total bilateral vestibular ablation have substantially elevated thresholds, particularly for superior-inferior (Z-axis) translation and yaw rotation (Valko et al. 2012). Thus vestibular perceptual thresholds may be a tool for clinical diagnosis (Merfeld et al. 2010; Agrawal et al. 2013). Further, thresholds in normal, healthy individuals over the age of approximately 40 have increasingly higher vestibular perceptual thresholds across several motion types, with no significant differences between males and females (Bermúdez Rey et al. 2016). Even when accounting for age, there is substantial inter-individual variation in vestibular perceptual thresholds in normal, healthy individuals, which appears to have a functional impact. Specifically, individuals with higher roll tilt thresholds have an increased likelihood of failing a standard balance test (Bermúdez Rey et al. 2016; Karmali et al. 2017). It is worth noting that vestibular perceptual thresholds qualitatively differ from vestibulo-ocular reflex thresholds, suggesting unique neural processing for the decision-making required of vestibular perceptual thresholds (Merfeld et al. 2005; Haburcakova et al. 2012). Interestingly, individuals with visual impairments were found to have improved vestibular thresholds, suggesting sensory compensation (Hartmann et al. 2014). Finally, an individual's roll tilt threshold correlates with his/her ability to actively null their chair roll tilt using a joystick in response to a random disturbance (Rosenberg et al. 2018). This may be relevant for aircraft pilots, who despite being taught to use their instruments, still are prone to spatial disorientation accidents from vestibular illusions (Pennings et al. 2020).

Given this clinical and operational importance, vestibular perceptual thresholds have been well-quantified for a range of motions, including translations, rotations about an Earth-vertical axis, and tilts relative to gravity (MacNeilage et al. 2010b; Roditi and Crane 2012; Soyka et al. 2012, 2013). These investigations have quantified differences in thresholds for different axes of translation, as well as different axes of rotation. For example, translation thresholds in the Z-axis (superior-inferior, or up/down) are significantly higher than thresholds for translation in the X (fore-aft) and Y (interaural, or left/right) body axes (Jones and Young 1978; Benson et al. 1986; MacNeilage et al. 2010a; Bermúdez Rey et al. 2016; Karmali et al. 2017). Analogously, yaw rotation thresholds about an Earth-vertical axis (subject seated upright) have been observed to differ from those for pitch rotation (subject laying lateral recumbent) and roll rotation (subject laying supine) (Benson et al., 1989).

To date, however, there has been limited investigation of differences in tilt thresholds (e.g., roll tilt vs. pitch tilt, about an Earth-horizontal axis, providing a change in orientation relative to gravity). In particular, while roll tilt thresholds have been well quantified (Valko et al. 2012; Lim et al. 2017; King et al. 2019), pitch tilt thresholds have not been as well studied using modern psychophysical methods. Specifically, two-alternative, forced-choice, motion “direction-recognition” tasks (e.g. did I move left vs. right?) have advantages over motion “detection” tasks (i.e., did I move or not?), particularly when using one-interval presentations (Merfeld 2011a), as they can distinguish perceptual sensitivity from the subject’s (generally arbitrary) selection of a decision boundary (how sure should I be before reporting “yes, I moved”?). Previous pitch tilt threshold tests have primarily involved motion-detection or change in motion-detection tasks, without any trials that have no stimulus (Bronstein 1999; Teasdale et al. 1999; Bringoux 2002; Bisdorff et al. 2018). To our knowledge, one published study has quantified pitch tilt thresholds using the standard forced-choice, direction-recognition task (Hartmann et al. 2014), though it did so in 7-20 year-old subjects, half of whom were gymnasts. Notably, this study did not perform a statistical test to determine if pitch tilt thresholds were higher, lower, or near equivalent to those for roll tilt. Further, this study only assessed roll and pitch tilt motions for motion durations of either 0.5 or 3 seconds (corresponding to 2 or 0.33 Hz “frequencies” for the single-cycle sinusoids of angular acceleration used). Previous studies have found thresholds vary dramatically as a function of motion “frequency” (i.e., vary with motion duration), for yaw rotation (Grabherr et al. 2008), roll rotation (Lim et al. 2017), translations (Valko et al. 2012) and roll tilts (Valko et al. 2012; Lim et al. 2017). Thus, our first objective is to quantify pitch tilt thresholds across a range of frequencies, using modern psychophysical approaches in a cohort of normal, healthy adults. Our second objective is to statistically compare pitch tilt and roll tilt thresholds, in the same cohort of subjects with the same motion device, across these frequencies as differences in axes have been observed for rotation and translation motions. Specifically, we hypothesize that pitch tilt thresholds will be higher (i.e., worse) than roll tilt thresholds. We will elaborate upon potential explanations for why pitch thresholds may be higher than roll tilt in the Discussion. Here we briefly note that the utricular maculae of the otolith is pitched up by ~30 degrees relative to head level (i.e., the Frankfurt plane) (Curthoys et al. 1999), while it is near level in roll, which may reduce the sensitivity to pitch tilt.

MATERIALS AND METHODS

Subjects

A total of ten subjects (nine males and one female; mean age = 25 years-old, min: 22, max: 28) were recruited to participate in this study. We anticipate these subjects would not be confounded by the age-effect previously observed in vestibular perceptual thresholds over the age of 40 (Bermúdez Rey et al. 2016). We did not intentionally recruit a cohort with an uneven gender balance. However, as noted previously, in a large study with 105 subjects (Bermúdez Rey et al. 2016), there was no evidence of a gender difference in yaw rotation, Y-translation, Z-translation, or roll tilt thresholds. Thus, we anticipate our findings to be broadly applicable to males and females. All subjects reported no history of vestibular dysfunction. This study was approved by the University of Colorado Institutional Review Board and all subjects completed a written informed consent form.

Experimental Set-Up

Whole-body tilt motions were generated using a custom human-rated motion device (the Tilt Translation Sled (TTS), without the translation axis activated). The subjects were seated in an upright position and secured with a five-point harness. Subjects' heads were constrained via a custom head restraint securing the head against a cushioned mount. Subjects positioned their heads where they felt was naturally aligned with their bodies (not tilted up or down), the operator visually confirmed the head to be level in pitch, and then the restraint was tightened, thereby holding head position fixed relative to the chair. We estimate the pitch tilt of the head within the restraint was within a few degrees of level. To minimize non-vestibular cues, whole-body tilts (neck receptors did not signal head tilt) were delivered in a completely dark room and subjects listened to white noise via noise-canceling headphones. Two-way auditory communication was maintained between the subject and operator and the operator monitored the subject with an infrared video feed.

Procedure

To precisely estimate thresholds, each subject completed blocks of 200 trials for each tilt axis, pitch tilt (i.e., about an interaural axis) or roll tilt (i.e., about a naso-occipital axis), and stimulus frequency, 0.15, 0.2, 0.5, or 1.0 Hz (1,600 total trials per subject). Before testing, subjects were notified of the axis and frequency of tilt motion for each session and were provided practice trials until they felt comfortable (typically 5-10 trials). All subjects completed all eight conditions (roll and pitch tilt; each at 0.15, 0.2, 0.5, or 1.0 Hz), presented in a counterbalanced order. The start of a trial was indicated by the room lights turning off. A fraction of a second later, the chair passively tilted the subject from upright. The motion profile was a single-cycle sinusoid in angular acceleration (Diaz-Artiles et al. 2017), corresponding to a cosine bell velocity and sigmoidal displacement profile. The tilt axis was located very near the middle of the subject's head (within 1 cm). This was ensured by having the head restraint fixed relative to the tilt axis and instead adjusting the relative height of the chair to comfortably fit subjects with shorter or longer torsos). The direction of the tilt stimuli (e.g., for a pitch tilt block, either forward or backward) was determined randomly. The magnitude of the tilt stimuli was determined using a standard three-down-one-up adaptive staircase (Taylor and Creelman 1967; Leek 2001). The staircase began with a six-degree tilt stimulus, which was well above subjects' thresholds. Upon reaching the final tilt angle for each trial, subjects were haptically cued (vibration on their wrist) to report motion direction (left or right for roll tilt; forward or backward for pitch tilt), in a forced-choice, direction-recognition task (Grabherr et al. 2008; Chaudhuri and Merfeld 2013) . Next, subjects reported the confidence level of their selection (between 50% and 100%, in 5% increments, where 50% means guessing and 100% means certain). The confidence reporting data are not presented here). After reporting, the subject was brought back to upright in preparation for the next trial, which began after at least a three second pause with the lights on.

Data Analysis

Binary data (e.g., for pitch, forward vs. backward responses) collected from subjects was fit using a standard Gaussian cumulative distribution psychometric function defined by standard deviation (σ) and mean (μ). Here, μ corresponds to the "vestibular bias" and σ is the "1-sigma" threshold (MacNeilage et al. 2010a, b; Merfeld 2011a). The 1-sigma threshold corresponds to the subject correctly perceiving the direction of 84.1% of trials at this stimulus level, after adjusting for the vestibular bias. A bias-reduced generalized linear model (Chaudhuri and Merfeld 2013) was used with a probit link function to properly account for the adaptive staircase (Leek 2001). As prior studies have shown vestibular perceptual thresholds are lognormally distributed across subjects, we report geometric means and compute 95% confidence intervals in the log-transformed domain (Bermúdez Rey et al. 2016).

The following general linear model was used to characterize the effect of roll vs. pitch tilt, as well the effect of frequency across subjects:

$$log(\sigma_{ijk}) = \rho_i + \beta_j f_j + \beta_k RP_k + \varepsilon_{ijk} \quad (1)$$

where the individual variables are defined as follows: ρ_i = subject effect coefficients (i=1:10 subjects); β_j = frequency coefficients; f_j = frequency condition (0.15, 0.2, 0.5, or 1 Hz); β_k = axis coefficient; RP_k = axis condition (roll or pitch); and ε_{ijk} = residual error. In this model, the first term characterizes random subject effects, the second and third terms are fixed effects of the frequency and roll vs. pitch, respectively, and the last term characterizes the error.

Previous investigations of roll tilt thresholds have identified a non-linear response as a function of the stimulus frequency. To avoid making an assumption of the mathematical function relating frequency to threshold, we have treated frequency as a categorical variable in Equation 1; the lowest frequency (0.15 Hz) is used as the reference level and its coefficient ($\beta_{j\ @\ 0.15\ Hz}$) set to 0. In this model, the axis effect (pitch vs. roll) is of primary interest. We have assumed pitch versus roll effects to be approximately constant (in the log domain) across frequencies and thus did not include cross-effects of frequency X axis. Assessing the normality and homoscedasticity of the model residuals found this assumption to be reasonable. The model allows 75 degrees of freedom (DOF): from a total of 80 threshold data points (10 subjects * 2 axes * 4 frequencies), the frequency effects absorb 3 DOFs (4 frequencies – 1), the axis effect absorbs 1 DOF (2 axes – 1), and 1 DOF for the reference level y-intercept.

The statistical significance of our hypothesis that pitch tilt thresholds are higher than roll tilt thresholds was analyzed via a one-tailed t-test, given the a priori hypothesis. Furthermore, this effect was analyzed at each frequency via pairwise, paired, one-tailed t-tests. Normality of the log-transformed thresholds was verified via Shapiro-Wilkes tests.

RESULTS

Roll and pitch tilt thresholds for each subject at each frequency are shown in Figure 1.

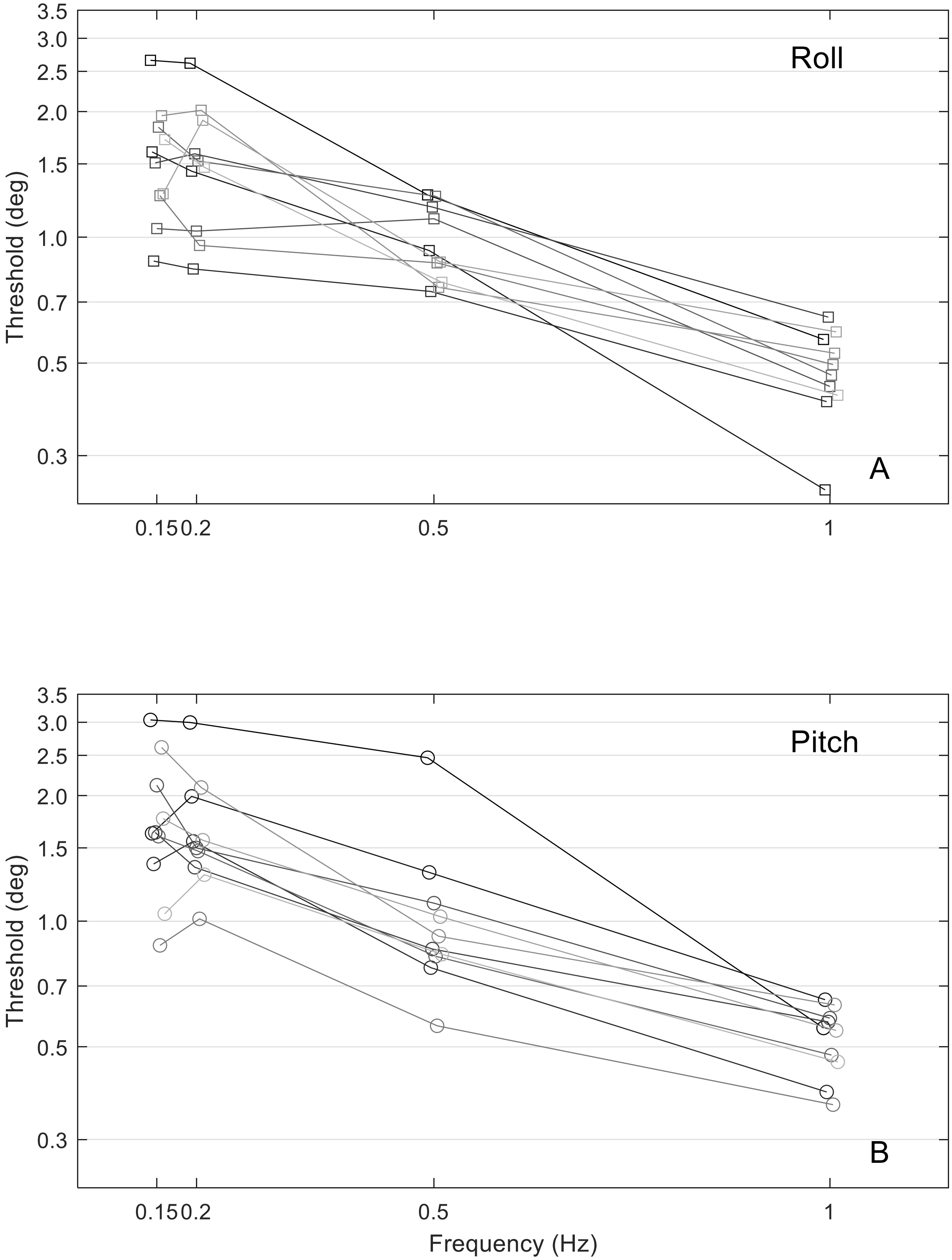
Roll
A
Threshold (deg)
3.5
3.0
2.5
2.0
1.5
1.0
0.7
0.5
0.3
0.150.2
0.5
1
Pitch
B
Threshold (deg)
3.5
3.0
2.5
2.0
1.5
1.0
0.7
0.5
0.3
0.150.2
0.5
1
Frequency (Hz)

Figure 1 Individual tilt thresholds, for roll (Panel A) and pitch (Panel B) for each subject plotted as a function of frequency (0.15, 0.2, 0.5, and 1 Hz, corresponding to 6.67, 5, 2.5, and 1 second duration motions, respectively). Each subject is indicated by a different shade of grey, which is consistent across panels. Data points are shifted slightly horizontally to reduce overlap. Y-axis is plotted on a log axis to capture the log-normal distribution across individuals.

Both roll and pitch tilt thresholds tended to increase as a function of decreasing frequency, stabilizing around 0.15-0.2 Hz. This response across frequencies is very similar to that previously observed for roll tilt (Valko et al. 2012; Lim et al. 2017; King et al. 2019). Also similar to previous studies on roll tilt thresholds (Bermúdez Rey et al. 2016), both roll and pitch tilt thresholds had substantial variability between individual subjects. For example, at 0.15 Hz pitch thresholds varied by 3.5x among our 10 normal, healthy subjects (3.0x at 0.2 Hz, 4.4x at 0.5 Hz, and 1.8x at 1 Hz). Much of this individual variability was maintained across the frequencies tested (e.g., if a subject had a higher (lower) threshold at one frequency, they also tended to have higher (lower) thresholds at the other frequencies. As one method of quantifying this, we found strong correlations between the log-transformed pitch thresholds at each combination of frequencies (0.15-0.2 Hz: correlation coefficient (r) = 0.86, $p = 0.001$; 0.15-0.5 Hz: $r = 0.77$, $p = 0.009$; 0.15-1 Hz: $r = 0.74$, $p = 0.015$; 0.2-0.5 Hz: $r = 0.89$, $p < 0.0005$), though two of the correlations with 1 Hz did not quite reach statistical significance (0.2-1 Hz: $r = 0.60$, $p = 0.065$; 0.5-1 Hz: $r = 0.60$, $p = 0.067$). This pattern of positive correlations between frequencies is similar to that previously observed for roll tilt at 0.2 Hz and 1 Hz (Karmali et al. 2017).

Shapiro-Wilkes tests confirmed the log-transformed data were normally distributed for roll tilt thresholds ($p = 0.62$) and pitch tilt thresholds ($p = 0.41$). The inter-subject variation was somewhat maintained between pitch tilt and roll tilt thresholds (e.g., if a subject had a higher (lower) threshold in pitch tilt, they also tended to have a higher (lower) threshold in roll tilt, at the same frequency). To quantify this, we tended to find positive correlations between log-transformed pitch tilt thresholds and those for roll tilt thresholds, at each frequency (0.15 Hz = 0.46 correlation coefficient, 0.2 Hz =

0.68, 0.5 Hz = 0.47, 1 Hz = -0.07). While the correlation coefficients were positive at each of 0.15, 0.2, and 0.5 Hz, only that at 1 Hz was statistically significant (p = 0.028). The complete lack of correlation at 1 Hz was primarily due to one subject having a very low roll tilt threshold (and moderately high pitch tilt threshold, see Figures 1A and 3D). While post-hoc, if this subject was removed the correlation coefficient was 0.52 between pitch and roll tilt thresholds at 1 Hz. While similar in magnitude to the other correlation coefficients, even after removing this subject for 1 Hz, it was not statistically significant (p = 0.15).

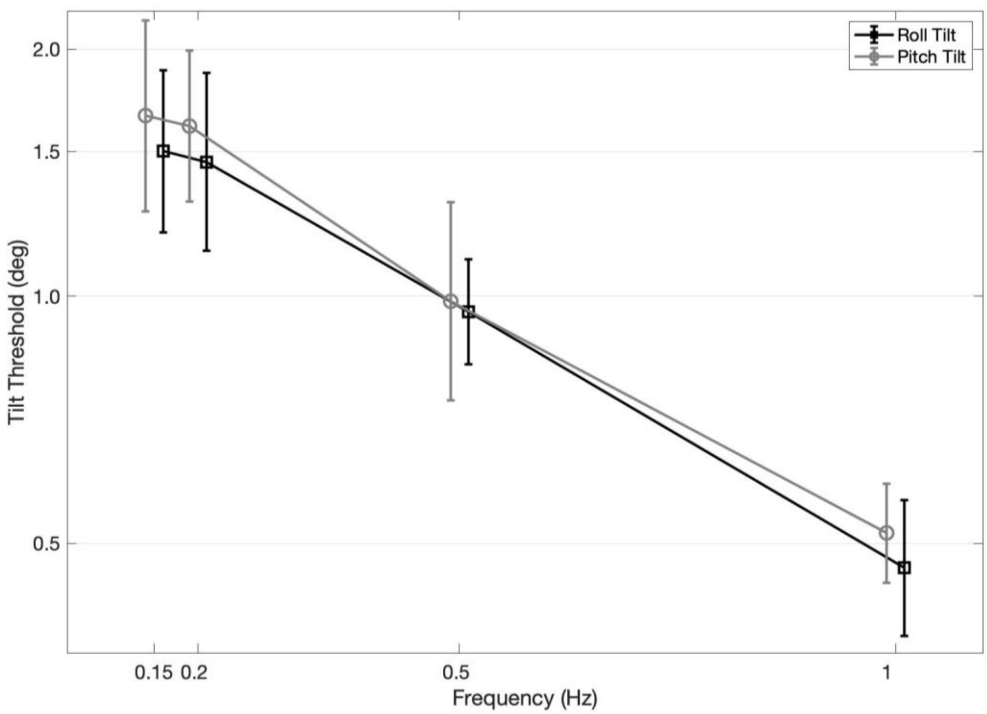

Figure 2 Geometric mean thresholds plotted as a function of frequency with error bars characterizing 95% confidence intervals. The grey circles respresent thresholds in pitch tilt and the black squares represent thresholds in roll tilt. While each are assessed at the same frequencies (0.15, 0.2, 0.5, and 1 Hz), data are slightly shifted on the x-axis to avoid overlap.

The geometric mean thresholds for roll and pitch tilt are compared in Figure 2, across frequencies. The general linear model from Equation 1 was fit and the results are summarized in **Error! Reference source not found.**. As one of our primary findings, pitch tilt thresholds were slightly, but significantly, higher than those for roll tilt, across the frequencies tested (coeff = 0.0821 [units = log(deg)], standard error = 0.0478, t(77) = 1.75, p = 0.045). Furthermore, while there was not a significant difference in thresholds from 0.15 to 0.2 Hz (p = 0.66), they were reduced at 0.5 Hz (p < 0.005) and 1 Hz (p < 0.005).

Table 1 Outputs of the general linear model from Equation 1. The p-value for the statistical significance of the axis effect (pitch tilt thresholds < roll tilt thresholds) is highlighted (*).

	ρ_i (std)	β_j (frequency coefficients)				β_k (roll vs. pitch)	ε_{ijk}
		0.15 Hz	0.2 Hz	0.5 Hz	1.0 Hz		
ESTIMATE	0.2038	0	-0.030	-0.486	-1.17	0.0821	0.21
STANDARD ERROR	-	0	0.068	0.068	0.068	0.048	-
TSTAT	-	0	-0.43	-7.18	-17.3	1.72	-
P-VALUE	-	0	0.66	< 0.005	< 0.005	0.045*	-

To further explore the difference in thresholds for roll vs. pitch tilt, Figure 3 and Table 2 show paired comparisons at each frequency tested. At each frequency, roll tilt thresholds were slightly lower than pitch tilt. At 0.15, 0.2, and 1 Hz, the average difference was approximately 9-10% of the average roll tilt threshold, while at 0.5 Hz the difference was approximately 3%. However, in each case, a paired t-test found these trends did not reach statistical significance (p = 0.21 at 0.15 Hz, p = 0.082 at 0.2 Hz, p = 0.099 at 0.5 Hz, p = 0.057 at 1.0 Hz; these p-values were not adjusted for the four multiple comparisons being made). Failure to reach significance was due to the combination of relatively small differences with very large inter-individual differences (grey shapes and lines represent individual subjects in Figure 3).

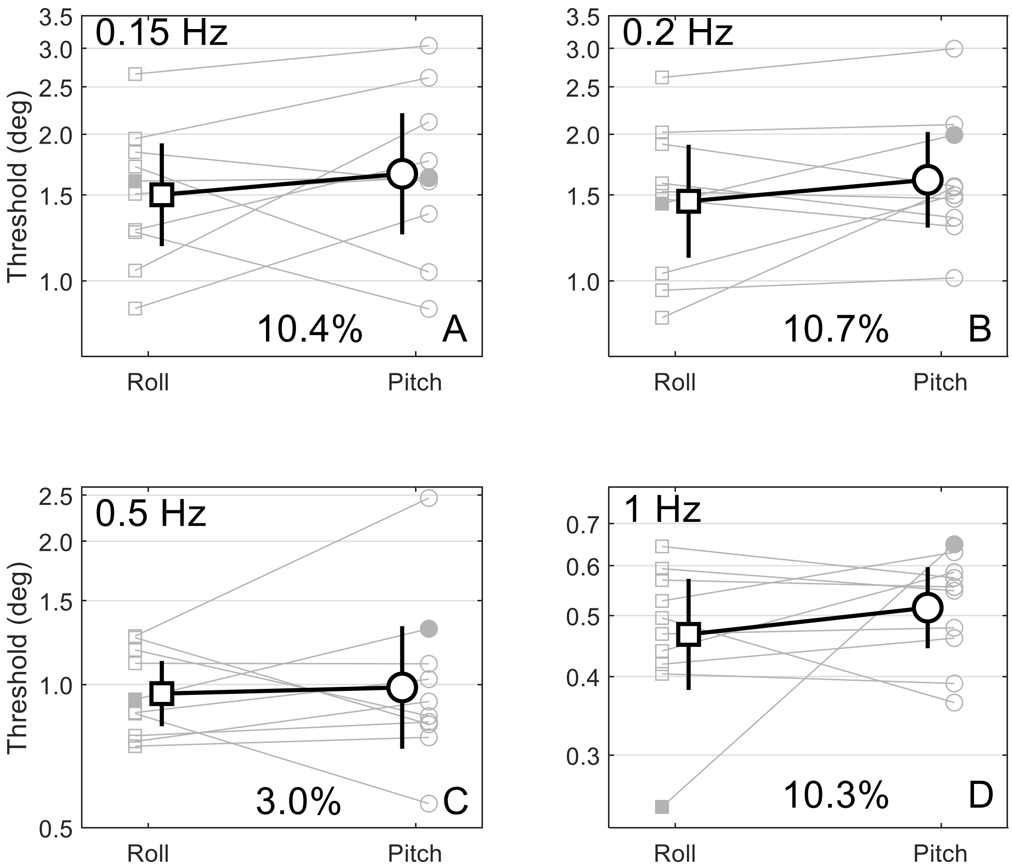

Figure 3 Geometric mean thresholds (black) overlaid on individual subject thresholds (gray) for roll vs. pitch tilt. Error bars characterize 95% confidence intervals. Panel A is data collected at 0.15 Hz, panel B is data collected at 0.2 Hz, panel C is data collected at 0.5 Hz, and panel D is data collected at 1 Hz. The y-axes in each plot are on a log scale, but differ between panels to help distinguish individual subjects. Percent differences are shown between the average roll tilt threshold and pitch tilt threshold (normalized by roll tilt thresholds) at each frequency. For each frequency, the roll tilt thresholds tended to be lower than those for pitch tilt. For roll tilt 1Hz, one subject appears to have an unusually low threshold. This subject's data is identified in all panels with filled shapes.

Table 2 Geometric mean thresholds for roll and pitch tilt. Values are mean [lower-upper 95% confidence interval]. Note that the confidence intervals are not symmetric about the mean when expressed in units of degrees. This is because the mean and the confidence interval at each frequency were calculated using log units as discussed earlier. Data are from 10 normal subjects.

	0.15 Hz	0.2 Hz	0.5 Hz	1 Hz
ROLL THRESHOLD (degrees)	1.50 [1.20-1.88]	1.46 [1.13-1.87]	0.96 [0.83-1.11]	0.47 [0.38-0.56]
PITCH THRESHOLD (degrees)	1.66 [1.27-2.17]	1.61 [1.30-1.99]	0.99 [0.75-1.30]	0.51 [0.45-0.59]

DISCUSSION

Here, we quantified pitch tilt vestibular perceptual thresholds in normal, healthy subjects across a range of frequencies (Figure 1). While this "vestibulogram" had previously been established for roll tilt (Valko et al. 2012; Lim et al. 2017; King et al. 2019), yaw rotation (Grabherr et al. 2008), roll rotation (Lim et al. 2017), and translations (Valko et al. 2012), pitch tilt thresholds had not been quantified as a function of frequency. Furthermore, in the same group of subjects and using the same motion device, we assessed roll tilt thresholds. This allowed for a direct comparison between roll and pitch tilt (Figure 2 and 3 and Table 2). Using a general linear model (Table 1), we found pitch tilt thresholds to be significantly higher (i.e., worse) than roll tilt thresholds across the range of frequencies tested. However, this difference was modest, averaging ~10% for 0.15, 0.2, and 1 Hz and 3% at 0.5 Hz. While pitch tilt thresholds trended to be higher than roll tilt at all four frequencies tested, none of the paired t-tests at each frequency reached significance (p=0.057-0.21).

Why might pitch tilt thresholds be higher than those for roll tilt?

The finding that vestibular perceptual pitch tilt thresholds were slightly higher than those for roll tilt raises the desire for an explanation. While speculative, one explanation involves the anatomical orientation of the otolith organs of the vestibular system. The otoliths consist of two components, the utricular maculae and the saccule. The utricle is thought to be the primary contributor to tilt perception about upright, though the saccule also provides some sensory information (Rader et al. 2009). As noted in the Introduction, the utricular plane is essentially level in roll, but pitched up by approximately 30 degrees relative to head level (i.e., the Frankfurt plane) (Curthoys et al., 1999). (We acknowledge that the concept of a utricular "plane" is a considerable simplification, as the utricule has some three-dimensional structure. However, as an approximation we refer to the principle plane of sensitivity within this structure.) Thus, as seen in Figure 4, a small tilt relative to head level (such as in our threshold testing) produces a larger change in utricular shear stimulation for roll tilt (change is $G*\sin(\theta)$, where G is the magnitude of gravity and θ is the tilt angle) as compared to pitch tilt ($G*(\sin(\theta-30°) - \sin(-30°))$).

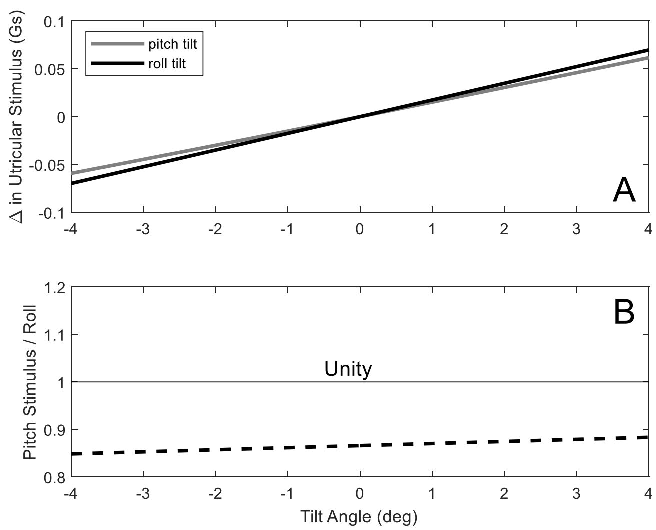

Figure 4 Change in utricular shear stimulus for small tilt angles. Panel A shows the change in utricular shear (in units of G's) for pitch tilt (gray) and roll tilt (black), with positive changes corresponding to shear forward and to the right, respectively. We show small tilt angles ranging from -4 (negative corresponds to tilting backwards or left) to 4 degrees (positive is tilting forward or right). For any given tilt angle, the change in utricular shear for a pitch tilt is slightly smaller than that for the same roll tilt. Panel B shows the ratio of the change in utricular shear from a pitch tilt divided by that for the same roll tilt. At all small angles this ratio is less than unity, corresponding to less sensitivity for pitch tilt than roll tilt. (At zero degrees tilt, the change in utricular shear is zero for both pitch and roll, causing this ratio to be undefined.) While the change in utricular shear is symmetric for roll tilts to the right and left, pitch tilts backward yield a smaller change. Thus, this ratio varies from about 0.85 for a 4-degree pitch tilt backwards up to 0.88 for a 4-degree pitch tilt forwards.

For a given tilt angle, the change in utricular shear is roughly 13% smaller for a pitch tilt than the same roll tilt. (There is a secondary dependence upon whether the pitch tilt is forward or backward and how large the tilt is, but for tilts between -4 and +4 degrees, the difference is 12-15%.) This is roughly similar to our finding that pitch tilt thresholds were ~10% higher than roll tilt at 0.2, 0.15, and 1 Hz (at 0.5 Hz pitch tilt thresholds averaged 3% higher). While of apparently similar magnitude, we note that the empirical difference of ~10% includes substantial uncertainty. The model fit in Table 1 was performed on the log-transformed thresholds and cannot be directly applied to yield an uncertainty percentage, but may be approximated as ± several percent, easily including the expected value of 13%. Further, utricular plane pitch orientation may vary somewhat between individuals, which would modify the expected ~13% difference in the change in utricular shear. To our knowledge, this inter-individual variability has not been quantified in humans.

The geometric analysis of the change in utricular shear stimulation is an appealing explanation for pitch tilt thresholds being slightly higher than those for roll tilt. However, the brain integrates additional sensory information for perception of small tilts. Similar to previous roll tilt threshold testing (Valko et al. 2012; Lim et al. 2017; King et al. 2019), we removed visual cues by keeping the subject in the dark, limited auditory cues by playing white noise during motions, and reduced tactile/proprioceptive cues by supporting the subject in a five-point harness, custom, padded head restraint, and contoured seat. These techniques isolate vestibular cues fairly well, as patients with total bilateral vestibular ablation have significantly higher thresholds than normal controls (Valko et al. 2012), across a range of frequencies (1.88x higher at 0.1 Hz and 2.47x higher at 1 Hz).

However, within the vestibular system, in addition to the otoliths sensing changes in orientation relative to gravity, the semicircular canals sense the angular rotation during pitch and roll tilts. The contribution of otoliths versus canals can be assessed by comparing thresholds for upright roll tilt versus supine, head-centered roll rotation (where the stimulation to the canals is the same, but there is no tilt stimulation to the otoliths) (Lim et al. 2017). Lim et al. found that for roll tilt the contribution from the canals is dominant at higher frequencies (e.g., 1 Hz) where the peak angular velocity is large, while there is a gradual transition until the otolith-contribution is dominant at lower frequencies (e.g., < 0.2 Hz). Assuming similar canal-otolith integration occurs for pitch tilt thresholds, we would expect the ~13% smaller change in utricular shear to impact thresholds at lower frequencies (0.15, 0.2 Hz), as was roughly observed (10.4% higher thresholds at 0.15 Hz and 10.7% higher at 0.2 Hz). Information from sensors other than the utricules (e.g., tactile, somatosensory, neck receptors, and saccule stimulation) could play a role in the slight difference between the empirical effect (~10%) and that expected from the geometric analysis (~13%).

Conversely, at higher frequencies (e.g, 0.5 and 1 Hz), we would expect the semicircular canals to be dominant and therefore the pitched up orientation of the utricular plane to not impact pitch versus roll tilt thresholds. Thus, if each of the three semicircular canals are equally sensitive, we would anticipate pitch tilt thresholds to be roughly equal to roll tilt thresholds at 1 Hz. Pitch rotation thresholds (i.e., about an Earth-vertical axis, where there is no tilt stimulation to the otoliths) have only been compared to roll rotation at 0.3 Hz, but no difference was found (Benson, Hutt, & Brown, 1989). Yet, here we still observed 10.3% higher pitch tilt thresholds at 1 Hz (and 3.0% higher at 0.5 Hz), as compared to those for roll tilt. While this suggests another mechanism than the pitched-up orientation of the utricles, we note that the 10.3% difference at 1 Hz did not reach statistical significance. It is possible the 10.3% average difference we observed at 1 Hz is greater than the true value simply due to measurement variability. If the true value were actually smaller (or near zero), the observed differences of 10.4% at 0.15 Hz, 10.7% at 0.2 Hz, and the smaller difference of 3.0% at 0.5 Hz would be consistent with an increasing contribution from the canals at higher frequencies reducing the impact of the pitched up orientation of the utricular plane. We note that the 10.3% average difference at 1 Hz is predominantly due to one subject having a much lower threshold for roll tilt than pitch (Figure 3D, highlighted with filled gray shapes). While post-hoc, excluding this subject reduces the average difference at 1 Hz to only 0.2% among the remaining nine subjects. (Removing this subject entirely causes the average difference at 0.5 Hz to also reduce to only -0.05%, while remaining substantial at 0.15 Hz (11.5%) and 0.2 Hz (8.0%)). While this is consistent with that expected from the "utricular geometry"-hypothesis, our data remain inconclusive.

In addition to simply testing more subjects in standard pitch and roll tilt thresholds, this hypothesis could also be tested using another configuration. If the subject's head is configured pitched nose-down by 30 degrees, this effectively places the utricular plane in the Earth-horizontal plane. From this initial configuration, the utricular sensitivity to small pitch tilts should be identical to that for roll tilt. As such, we would expect thresholds for pitch tilt relative to this initial configuration (head pitched forward 30 degrees) to be similar to roll tilt, even at lower frequencies.

Comparison to threshold values in previous studies

As previously noted, this is the first published study to have quantified pitch tilt vestibular perceptual thresholds across a range of frequencies, using modern psychophysical techniques. However, one previous study (Hartmann et al. 2014) did quantify pitch tilt thresholds with 0.5 second motions (2 Hz) and 3 second motions (0.33 Hz). While we did not test at these frequencies, to compare, we interpolated between the threshold values at 0.2 and 0.5 Hz that we did test at (Figure 2 and Table 2), which yields 1.34 degrees at 0.33 Hz. Hartmann et al. reported an average threshold based upon staircase reversals of 0.61 degrees per second. Converting to our angular tilt 1-sigma threshold yields 1.13 degrees, which compares fairly well to our interpolated value of 1.34 degrees. We note that Hartmann et al. tested subjects ages 7-20 years, which may not be a direct comparison to our subjects (ages 22-28, mean = 25 years).

As a primary conclusion, we found that pitch tilt thresholds were higher (i.e., worse performance) than roll tilt thresholds. To our knowledge this is the first study to systematically assess this using signal detection theory methods. However, this conclusion tends to be consistent with previous studies. For example, Hartmann et al. 2014 tested both pitch and roll tilt thresholds at 2 Hz and 0.33 Hz but were not interested in differences between the axes and did not perform a statistical test. Nonetheless, at 0.33 Hz they report pitch tilt thresholds averaged 0.61 degrees per second, while for roll tilt they were 0.53 degrees per second (15% difference). At 2 Hz, thresholds were 0.33 degrees per second for pitch and 0.30 for roll (10% difference). In the subset of "older" subjects (ages 14-19), which may be more comparable to our adult subjects, pitch tilt thresholds also tended to be higher (at 0.33 Hz: 0.52 versus 0.43 degrees per second or 20.9% higher for pitch; at 2 Hz: 0.28 versus 0.22 degrees per second or 27.2% higher for pitch).

A few other studies have compared pitch versus roll tilt by investigating how quickly subjects can sense they are being tilted in response to a constant velocity tilt that continues until the subject responds (Bronstein 1999; Teasdale et al. 1999; Bringoux 2002; Bisdorff et al. 2018). Unlike our direction recognition task (e.g., did I move left or right?), these motion detection-type tasks do not directly measure sensitivity to self-motion in that they required the subject to set a criteria (i.e., decision boundary) for how much evidence is needed before responding (e.g., how confident they must be). For example, in Bringoux 2002, subjects were tilted at 0.05 degrees per second and "they were encouraged to give their response as soon as they reached a confidence level of 4 on a 5 points scale". In such a task subjects are required to make a speed-accuracy tradeoff; nonetheless, Bringoux found subjects responded more quickly (at smaller tilt angles) for roll versus pitch. This is analogous to Teasdale et al. (1999), who tilted a platform under the subject either standing, on their knees, or seated and their heads free. In four subjects, Teasdale et al. concluded subjects responded at smaller angles for roll tilt compared to pitch. In two other studies (Bronstein 1999; Bisdorff et al. 2018), subjects were tilted back and forth (+/- 15 degrees) and were tasked with responding when they were tilted versus felt they were upright. Here, no differences between pitch and roll tilt were identified. Our measures of "1-sigma" thresholds, an emerging standard in the field which directly quantifies sensitivity, appear consistent with these studies in which subjects tended to respond to detection of roll tilt more quickly or at smaller angles than for pitch.

While our primary objective was not to reassess roll tilt thresholds, we did quantify them using the same motion device, for comparison to our subjects' pitch tilt thresholds. Table 3 shows our subjects' roll tilt thresholds are roughly comparable to several previous studies across the range of frequencies tested. Our roll tilt thresholds were slightly higher than previous studies at 0.2 and 0.5 Hz, but were comparable to most other studies at 1 Hz and the one other study that tested at 0.15 Hz (though other studies that tested at 0.1 Hz, which we would anticipate would be similar to 0.15 Hz, reported lower threshold values). All studies consistently found increasing thresholds with decreasing frequency (i.e., longer motions) that tend to level off below 0.1 – 0.2 Hz.

Table 3 Comparison of roll tilt thresholds across studies, assessed at various frequencies. Thresholds are for roll tilt displacement (degrees), reported as "1-sigma" thresholds, and calculated as the geometric mean across the number of subjects tested.

	Current study	**Hartmann et al. 2014 [1,2]**	**Valko et al. 2012 [1]**	**Lim et al. 2017 [6]**	**King et al. 2019 [6]**	**Bermudez Rey et al. 2016 [1]**
Number of subjects	10	24 controls [12 ages 14-19][3]	14	6	12	105 [29 ages 18-29][4]
Number of trials per threshold test[5]	200	9 reversals, avg. 64	CV<0.2, 70-80	5 reversals, est. 40-50	CV<0.2, 70-80	100
0.1 Hz	-	-	1.25	1.6	1.35	-
0.15 Hz	1.50	-	-	1.6	-	-
0.2 Hz	1.47	-	1.125	1.1	1.05	1.15 [0.925][4]
0.5 Hz	0.96	-	0.64	0.7	0.8	
1 Hz	0.47	-	0.375	0.48	0.45	0.465 [0.35][4]
2 Hz	-	0.091 [0.067][3]	0.1375	0.2	0.1	

[1]Hartmann et al. 2014, Valko et al. 2012, and Bermudez Rey et al. 2016 reported thresholds as peak angular velocity (degrees per second) and we converted them to roll tilt displacement (degrees): Angular tilt threshold = peak angular velocity threshold / frequency / 2)

[2]Hartmann et al. 2014 reported thresholds as the average of the last two reversals of a 3 down 1 up staircase and we converted them to a "1-sigma" threshold. On average, the final reversals of a 3 down 1 up staircase converge to a stimulus producing 79.4% correct responses, while the 1-sigma threshold which we report corresponds to 84.1% correct. The reversal threshold can be converted by dividing by 0.82 (Merfeld 2011a).

[3]Hartmann et al. 2014 tested subjects ages 8-19 years. They also reported thresholds for the subset of "older" subjects (ages 14-19), which are given in brackets.
[4]Bermudez Rey et al. 2016 tested subjects ages 18-80 years, but also reported thresholds for the subset of subjects ages 18-29, which are given in brackets.
[5]The number of trials used to test each subject's threshold affects the precision of each estimate (Karmali et al. 2016). In some studies each test was concluded based upon another stopping criteria. For example, Hartmann et al. 2014 stopped after 9 reversals in their 3 down 1 up staircase. Valko et al. 2012 and King et al. 2019 concluded after the coefficient of variation (CV) of the fitted threshold was less than 0.2. In these cases, the approximate, average number of trials used is provided.
[6]Threshold values for Lim et al. 2017 and King et al. 2019 were estimated from graphs and should be considered approximate.

Pitch Tilt "Vestibulogram" and Inter-Individual Variability

Having quantified pitch tilt thresholds across a range of frequencies provides a normal, baseline (Figure 2 and Table 2), which can be compared to responses in various patients group. Of note, pitch tilt thresholds varied dramatically as a function of frequency (i.e., inverse of motion duration). At 0.15 Hz, the geometric mean threshold (1.66 [1.27-2.17, 95% confidence interval]) was over 3x higher than that at 1 Hz (0.51 [0.45-0.59]). The pattern of increasing thresholds with decreasing frequency until 0.1-0.2 Hz, previously observed for roll tilt, was found to be very closely replicated for pitch tilt. As discussed above, the variation of roll tilt thresholds as a function of motion frequency can be explained by decreased semicircular canal sensitivity with decreasing frequency until ~0.2 Hz, below which the threshold is primarily determined by otolith sensitivity to the angular tilt (frequency-invariant) (Lim et al. 2017). Pitch rotation thresholds have not been characterized across a range of frequencies. However, at 0.3 Hz pitch rotation thresholds were not found to be statistically significantly different from those for roll rotation (Benson et al. 1989). Thus, we anticipate the same canal-otolith integration mediates the frequency-effect on pitch tilt thresholds, as identified for roll tilt thresholds.

We also found substantial inter-individual variability in pitch tilt thresholds, again similar to that previously observed in roll tilt thresholds. We note our subject pool consisted of apparently normal subjects, with no reported history of vestibular dysfunction. Previous studies have identified an age-effect on vestibular perceptual thresholds, with substantial increases above the age of 40 years (Bermúdez Rey et al. 2016; Karmali et al. 2017). However, we tested a relatively narrow age range of

22-28 (mean = 25 years), intentionally below that which we would anticipate aging-effects. Furthermore, we specifically tested each subject with a fairly large number of trials (200) per condition in order to produce a precise threshold estimate. With 200 trials and our 3 down 1 up staircase sampling method, we would expect the coefficient of variation in our threshold estimates to be less than 0.13 (Karmali et al. 2016). Thus, the large variation between individuals is not due to age and minimally influenced by measurement variability. Identifying causes of these innate inter-individual variations in pitch tilt thresholds remains an open research objective. However, here we find that whenever an individual has a higher (lower) pitch tilt threshold at one frequency it tends to persist they will have a higher (lower) pitch tilt thresholds at other frequencies. Further, these individual differences persist to some extent across axes, with individuals with higher (lower) pitch tilt thresholds at a given frequency also tending to have higher (lower) roll tilt thresholds at that frequency. Similar correlations between individuals' thresholds have been observed between roll tilt (0.2 and 1 Hz), yaw rotation, y-translation, and z-translation (Bermúdez Rey et al. 2016; Karmali et al. 2017).

Functional Implications of Higher Pitch Tilt Thresholds?

While we found that pitch tilt thresholds were higher than roll tilt thresholds, consistently across a range of frequencies, it was a difference of only approximately 10% and one might ask if this has any functional implications. To address this, we summarize a few previously found operational impacts of inter-individual differences in roll tilt thresholds. First, individuals with higher thresholds have an increased likelihood of failing condition 4 of the modified Romberg balance test (standing on a foam pad with eyes closed) (Bermúdez Rey et al. 2016; Karmali et al. 2017). Performance on this balance test strongly correlates with the likelihood of a fall within the last year (Agrawal et al. 2009). If the relationship between vestibular perceptual thresholds, the modified Romberg balance test, and likelihood of falls applies to the pitch axis, it is possible falls are more likely to occur (in those susceptible) in the fore-aft direction rather than to the side. There are obvious biomechanical differences, in terms of controlling and stopping falls, between fore-aft and lateral directions (e.g., knee and ankle joints have greater range of motion for responding to fore-aft falls). However, higher pitch tilt thresholds suggest worse sensory precision (i.e., higher sensory noise) for pitch versus roll, particularly when other balance sensory information is reduced (e.g., in the dark). Better understanding the contributing factors for falls (e.g., sensory versus motor), as they vary by direction, may be helpful for developing approaches to prevent falls.

In addition, an individual's roll tilt threshold correlates with his/her ability to actively null their chair roll tilt using a joystick in response to a random disturbance (Rosenberg et al. 2018). This may have important implications for pilots of aircraft, spacecraft, or other vehicles. Specifically, higher pitch tilt thresholds may yield worse manual control nulling performance in the pitch axis. Manual control scenarios may be particularly susceptible to even slight increases in sensory noise (thresholds) since there is little biomechanical differences between pitch vs. roll for a seated subject controlling self-tilt with a joystick. Such piloting scenarios could be altered to take advantage of more precise tilt perception in the roll axis. For example, adjustments in helicopter hovering position could be done by first aligning the desired adjustment with the roll axis.

Limitations and Future Work

We aimed to quantify pitch tilt thresholds across a range of frequencies and compare them to roll tilt thresholds. However, we only tested frequencies of 0.15, 0.2, 0.5, and 1 Hz (corresponding to motion durations of 6.67, 5, 2, and 1 seconds). Previously studies have investigated a much wider range of frequencies, from 0.05 to 5 Hz (Valko et al. 2012; Lim et al. 2017) or even as low as 0.03 Hz (King et al. 2019). We did not test higher frequencies (e.g., >1 Hz) due to concerns about our motion device effectively replicating these very small, but very fast motions. Further, we did not test lower frequencies (e.g., <0.15 Hz) due to the much longer motion durations, which yield very long test sessions. Instead, we prioritized all of our subjects completing all eight of the conditions (four frequencies, each tested in pitch and roll tilt) and thus keeping the length of the testing sessions manageable. Finally, we used previous studies of roll tilt thresholds to help inform the frequency range of interest. Greater than ~1-2 Hz roll tilt thresholds are roughly constant in terms of peak angular velocity, while less than ~0.1-0.2 Hz they plateau in terms of angular displacement (Valko et al. 2012; Lim et al. 2017). From our initial investigation, pitch tilt thresholds have a similar frequency-response.

With our general linear model, we found pitch tilt thresholds were statistically significantly higher than those for roll tilt. However, in pairwise comparison t-tests at each individual frequency, none of these differences reached statistical significance ($p = 0.057 – 0.21$), though the average pitch tilt thresholds were ~10% higher at 0.15, 0.2, and 1 Hz and 3% higher at 0.5 Hz. We suggest this is due to the substantial inter-subject variability in thresholds and encourage future studies to test additional subjects, in order to determine if these differences at each frequency reach significance. This is a substantial effort, as each subject was tested with a total of 1,600 trials (200 trials per condition, with four frequencies for each roll and pitch tilt), requiring approximately 8-10 hours of testing across multiple sessions. However, this will be critical to determine if the difference between pitch and roll tilt thresholds is consistent across frequencies or becomes less pronounced at higher frequencies, as expected if due to the utricular plane being pitched up.

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