Title:

Older adults demonstrate superior vestibular perception for virtual rotations.

Authors:

Ryan M. Peters¹, Jean-Sébastien Blouin^{1,2,3}, Brian H. Dalton⁴ J. Timothy Inglis^{1,3,5}

Author Affiliations:

¹ School of Kinesiology, University of British Columbia, Vancouver, BC, Canada.

² Institute for Computing, Information, and Cognitive Systems, University of British Columbia, Vancouver, BC, Canada.

³ Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada.

⁴ Department of Human Physiology, University of Oregon, Eugene, OR, USA.

⁵ International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada.

Corresponding Author:

Jean-Sébastien Blouin

University of British Columbia
School of Kinesiology
Vancouver Campus
210-6081 University Boulevard
Vancouver, BC Canada V6T 1Z1
Office: D.H. Copp Building – Room 3506
Phone: 604-827-3372
Fax: 604-822-6842
Email: jsblouin@mail.ubc.ca

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1. ABSTRACT

Adult aging results in a progressive loss of vestibular hair cell receptors and afferent fibres. Given the robustness of vestibulo-ocular and vestibular-evoked whole-body responses to age-related deterioration, it was proposed that the vestibular system compensates centrally. Here we examine the potential for central compensation in vestibular sensitivity with adult aging by using a combination of real and virtual rotation-based psychophysical testing at two stimulus frequencies (0.1 & 1 Hz). Real rotations activate semi-circular canal hair cell receptors naturally via mechanotransduction, while electrical current used to evoke virtual rotations does not rely on mechanical deformation of hair cell receptors to activate vestibular afferents. This two-pronged approach allows us to determine the independent effects of age-related peripheral afferent receptor loss and potential compensatory mechanisms. Older adults had thresholds for discriminating real rotations that were significantly greater than young adults at 0.1 Hz (7.2 vs. 3 °/s), but the effect of age was weaker (non-significant) at 1 Hz (2.4 vs. 1.3 °/s). For virtual rotations, older adults had greater thresholds than young adults at 0.1 Hz (1.2 vs. 0.5 mA), however, older adults outperformed young adults at 1 Hz (0.6 vs. 1.1 mA). Based on these thresholds, we argue that central vestibular processing gain is enhanced in older adults for 1 Hz real and virtual rotations, partially offsetting the negative impact of normal age-related hair cell receptor and primary afferent loss. We propose that the frequency dependence of this compensation reflects the physiological importance of the 1-5 Hz range in natural vestibular input.

2. INTRODUCTION

The vestibular system transduces linear and angular head motion and plays a role in stabilization of the eyes and head, standing balance control and the perception of head motion. Our focus is on the angular rotation signals provided by the 6 semi-circular ducts bilaterally. Much like in other sensory systems, age-related deterioration of the human peripheral vestibular sensory apparatus is well documented (for review see Ishiyama, 2009). Consistently, anatomists report a decline in human hair cell receptor number within the crista ampullaris of the semi-circular ducts by 40% beyond the age of 70. *Type 1* receptors in the central crest zone of the crista show a more rapid decline in number than *type 2* receptors, which decline at a similar rate across all 10 vestibular sensory end organs (Rosenhall, 1973; Richter, 1980; Merchant et al., 2000; Rauch *et al.*, 2001; Ishiyama, 2009). Concomitantly, peripheral afferent number decreases by ~40% starting around age 50 (Richter, 1980), being most pronounced for the central crest zone of the crista ampullaris which is primarily innervated by large, irregularly discharging afferent fibres. Neuron counts in Scarpa's ganglion also decline with adult aging (Richter, 1980), with the reported losses mirroring those in the peripheral branch of the vestibular nerve (Bergström, 1973). Given this, we would expect healthy aging to lead to a large decrement in the sensitivity to head rotation required for accurate vestibular perception.

However, only small increments in perceptual thresholds have been observed previously with age (Seemungal *et al.*, 2004; Roditi & Crane, 2012), suggesting that an adaptive neural mechanism counteracts the anatomical loss of hair cell receptors and primary afferents. The presence of an age-related central gain enhancement mechanism has previously been proposed for vestibulo-ocular (Peterka *et al.*, 1990; Jahn *et al.*,

2003), and vestibulo-motor (Welgampola & Colbatch, 2002; Dalton *et al.*, 2014) function. Here we investigate the potential for this gain enhancement to influence vestibular perception. Loss of hair cell receptors would be predicted to result in elevated thresholds for real rotations by increasing the noise in the afferent population response (Goldberg *et al.*, 2012). If older adults are as sensitive as younger adults at detecting real rotary stimuli despite the loss of vestibular hair cell receptors and primary afferents this would imply the population signal is being enhanced relative to the noise centrally, which could be accomplished through central response gain enhancement in neurons that remain connected to functioning hair cells receptors (Phillips *et al.*, 2015).

Recently, we have deployed a combination of real and virtual rotation-based psychophysical testing to examine peripheral and central contributions to vestibular processing (Peters *et al.*, 2015). Real kinetic rotations activate hair cell receptors within the semi-circular canals via mechanical shearing forces, whereas electrical vestibular stimulation (EVS) used to evoke virtual rotations does not rely on mechanical deformation of hair cell receptors to activate vestibular afferents (Goldberg *et al.*, 1984; Fitzpatrick & Day, 2004; Kim & Curthoys, 2004). Pitching the head down towards the lap brings the net EVS-evoked response vector (Fitzpatrick & Day, 2004) in-line with a rotary chair or platform's earth-vertical axis of rotation, giving rise to the distinct sensation of virtual rotation that is indistinguishable from real kinetic rotation (Wardman *et al.*, 2003; Day & Fitzpatrick 2005; St. George *et al.*, 2011; Fitzpatrick & Watson, 2015; Peters *et al.*, 2015). We utilize this two-pronged approach of homologous real and virtual rotation testing to examine the differential effects of age-related hair cell receptor loss or dysfunction, and potential adaptive compensatory mechanisms. Given the deterioration of

the peripheral vestibular apparatus with age, we hypothesized older adults would exhibit greater thresholds on real rotation testing relative to young adults. In light of the central gain enhancement mechanism suggested in vestibulo-ocular (Peterka *et al.*, 1990; Jahn *et al.*, 2003) and vestibulo-motor (Welgampola & Colbatch, 2002; Dalton *et al.*, 2014) function, we hypothesized that older adults would exhibit lower discrimination thresholds for virtual rotations relative to young adults.

3. MATERIALS AND METHODS

3.1 Participants

Ten healthy older adults (4 men, 6 women) between the ages of 69 and 81 years (mean = 74.6, SD = 3.6), and ten healthy young adults (4 men, 6 women) between the ages of 20 and 30 years (mean = 25.2, SD = 3.6), with no known history of otologic or neurologic diseases or of falling participated in this study. Experimental protocols were explained to each subject and their written, informed consent was obtained. All procedures conformed to the standards of the World Medical Association Declaration of Helsinki and were approved by the University of British Columbia's Clinical Research Ethics Board.

3.2 Real kinetic rotations

To deliver whole-body yaw rotations, we used a custom-built rotary chair (see Figure 1A), which we drove with a real-time motion controller (PXI-7350 Motion Controller, National Instruments, USA; Universal Motion Interface UMI-7774, National Instruments, USA) running in-house LabVIEW software built with the NI Motion

programming suite (National Instruments, USA). The motion controller sent torque commands to a servo amplifier (SGDV-200A01A, Yaskawa, Japan), which powered a large AC motor (SGMCS-2ZN3A-YA21, Yaskawa, Japan; encoder angular resolution 0.00034° , continuous torque 200 Nm). Rotation stimuli consisted of raised-cosine bell curves, with the peak angular velocity adaptively adjusted (from 0.1 to 15 $^\circ/\text{s}$) across trials. The predicted movement of the cupula that results from this sinusoidal velocity pulse is a sinusoidal monophasic deflection (see rightmost column plots in Figure 5 from Guedry, 1974). Afferent firing rate will be proportional to cupular deflection, thus showing a monophasic increase/decrease following such a sinusoidal velocity pulse pattern. To mitigate non-vestibular (somatosensory) cues, additional dual-layer memory foam padding depicted in Figure 1A was added beneath the participant's socked feet and around their chest, forearms, and shanks, and was secured firmly to the chair using adjustable strapping. The participant was further strapped to the device using a five-point racing harness. Testing was carried out in a dark, electrically shielded room, with the participant blindfolded and wearing earplugs. Before each testing block, 5 to 10 practice trials were given at clearly discernable stimulus amplitudes for each participant to ensure they were entirely comfortable with the task.

Figure 1.

3.3 Electrical vestibular stimuli

Electrical vestibular stimulation was delivered in a binaural bipolar electrode configuration. Carbon rubber electrodes (9 cm²), coated with Spectra 360 electrode gel (Parker Laboratories, USA), were secured over participants' mastoid processes with surgical tape and an elastic headband. Vestibular stimuli were generated on a PC computer using custom LabVIEW software (National Instruments, USA) and were sent

to a constant current isolation unit (STMISOLA; Biopac Systems Inc., USA) via a multifunction data acquisition board (PXI-6289; National Instruments, USA). Vestibular stimuli consisted of raised-cosine bell curves, with the peak current amplitude adaptively adjusted (from 0.1 to 5 mA) across trials. We note that the activation of vestibular afferents to real motion (see above) is predicted to be very similar to the activation pattern evoked by a sinusoidal EVS pulse (our virtual stimuli; see Goldberg et al., 2012). Additionally, we have demonstrated that EVS is perceived as an angular velocity signal over the frequency range tested here (Peters et al., 2015). Therefore, the pattern of afferent activation is expected to be similar between stimulus types. As with real rotation testing, before each virtual testing block, 5 to 10 practice trials were given at clearly discernible stimulus amplitudes to ensure the participant was comfortable performing the task. To minimize any non-vestibular cues associated with skin tingling under the electrodes, we anesthetised the skin over the mastoid processes bilaterally using AMETOP (Tetracaine HCl Gel 4% w/w; Smith & Nephew Inc., UK), which was applied 30-45 minutes prior to each experiment. Given the low amplitude of currents applied during sensory testing ($\sim 0.5 - 1.5$ mA at peak), tingling under the electrodes was rarely reported, and all participants reported performing the task based on their vivid perception of chair rotation.

3.4 Direction discrimination threshold estimation

Participants attempted to discern whether the direction of real or virtual whole-body rotation was to the right or left. Participants were seated comfortably atop the rotary chair with their head facing down towards their lap and immobilized. The experimenter ensured that the head was pitched down 71° aligning the angle of the EVS-evoked

rotational vector (Fitzpatrick & Day, 2004) with an earth-vertical axis through the center of the chair's axis of rotation (see Figure 1B). Applying electrical vestibular stimulation in a binaural bipolar configuration with the head pitched downward evokes an illusion of whole-body rotation around an earth-vertical axis, providing the sensation of whole-body motion induced by the motor. For this study, the participant's head was held fixed in-place with a helmet (Pro-Tec, China) that was braced firmly to the rotary chair carriage. Correct head pitch was confirmed periodically throughout testing using a protractor. We asked each participant to complete a series of trials wherein they were given a single-cycle of a raised-cosine bell electrical vestibular stimulation or real angular velocity pulse (with electrode polarity and rotation direction randomized across trials), and were required (forced choice) to indicate which direction they were rotated with a verbal response ("right" or "left"). With electrical vestibular stimulation, participants reported vivid sensations of chair rotation, although the chair remained stationary. The direction of virtual rotation was always toward the cathode side for supra-threshold stimuli (see Figure 1A). Each participant completed testing blocks of real and virtual rotations at 0.1 and 1 Hz (4 blocks total; 40 trials per block). 40-trial testing blocks were performed at one frequency before switching to the other frequency, and the order of these blocks was randomized (i.e., some subjects did the 0.1 Hz 40-trial block first, others did 1 Hz 40-trial block first). Real rotation testing always preceded virtual rotation testing to allow an adequate duration of time for the topical anaesthetic to become active.

The peak electrical vestibular stimulus current and angular velocity across trials was adjusted across trials using a Bayesian adaptive procedure (Kontsevich & Tyler, 1999). This psychophysical testing method efficiently estimates each participant's

function relating stimulus amplitude (in mA or °/s) to their proportion of correct direction discriminations, and from this function a threshold-level of performance can be extracted (see Figure 2). To improve the robustness of the Bayesian procedure (Goldreich *et al.*, 2009), we parameterized each participant’s sigmoidal psychometric function online as a mixture model of the probability for a correct response by chance (0.5) given the participant had an attention lapse ($\delta/2$), or given they were performing the task (modified Weibull function; see Tong *et al.*, 2013),

$$P(\text{correct}|x, \text{no attention lapse}) = \gamma + (1 - \gamma - \delta) \left(1 - 2^{-(x/a)^b}\right) \quad (\text{Eq. 1})$$

and therefore,

$$P(\text{correct}|x) = \left(\frac{\delta}{2}\right) + (1 - \delta) \left(\gamma + (1 - \gamma - \delta) \left(1 - 2^{-(x/a)^b}\right)\right) \quad (\text{Eq. 2})$$

Here the γ -parameter sets the y-intercept of the curve, the a -parameter determines the lateral position of the curve along the x-axis, the b -parameter determines the shape (slope) of the curve, and the δ -parameter represents the lapse rate. The lapse rate term accounts for the realistic possibility of occasional attention lapses, resulting in 50% correct response probability, regardless of the peak stimulus amplitude. The algorithm, which we programmed in LabVIEW (National Instruments, USA), adaptively adjusted the peak stimulus level from trial-to-trial, presenting the stimulus expected to yield the greatest information regarding the participant’s psychometric function parameters (expected entropy minimization; Kontsevich & Tyler, 1999). The algorithm began with uniform priors over the a (real: 0.1 to 15°/s in 100 steps; virtual: 0.1 to 5 mA in 100 steps), b (real and virtual: 0.5 to 15 in 50 steps), and δ (real and virtual: 0.01 to 0.05 in 20 steps) parameters. These parameter ranges were carefully chosen based on pilot testing such that participants were not “maxing- or bottoming-out” (i.e., threshold value out-of-

range), and such that the parameter space provided a broad range of slopes spanning the range of possibilities (from a nearly flat line, to a step function). The γ -parameter was held fixed at 0.5 for this experiment because this represents chance performance; thus, the Bayesian adaptive procedure made hypotheses only on the possible a , b , and δ parameters of each participant's psychometric function, and returned the joint posterior probability distribution function (PDF) over these three parameters, along with the best-estimated psychometric function.

The direction discrimination threshold was defined as the peak stimulus level at which the participant could correctly discriminate direction with 69% probability, which corresponds to $d' = 1$ on this single-interval task (Gescheider, 1997). To extract the 69% correct threshold, we marginalized each participant's joint posterior PDF over the δ -parameter, plotted the best-fit psychometric function for each (a,b) pair, and interpolated to find the stimulus amplitude corresponding to 69% correct performance. We then averaged the 69% correct stimulus amplitude across the (a,b) posterior PDF, and took this as the participant's threshold estimate.

3.5 Statistical analysis

The dependent variables we extracted were each participant's mean 69%-correct direction discrimination threshold for real ($^{\circ}/s$) and virtual (mA) rotations. To compare performance of young and older adults, we performed a mixed model ANOVA for each stimulus type with frequency (0.1 & 1 Hz) as a within-subject factor, age group (young & older) as a between-subject factor, and 69%-correct discrimination threshold as the dependent variable. When interaction effects were identified, post-hoc planned comparisons were performed to assess age group differences at each stimulus frequency.

Statistical analyses were performed using Statistica 6.0 (StatSoft, USA), and in all cases we used an alpha level of 0.05.

4. RESULTS

4.1 Real Rotation Perception

On each trial, we rotated the chair randomly to either the left or right, and asked participants to discern the direction. The peak velocity of the rotation was adjusted across 40-trial blocks using a Bayesian adaptive procedure. The best-estimated psychometric functions for real motion are shown for all participants in Fig. 2. At 0.1 Hz, 95% confidence intervals for the threshold value in young adults spanned on average ± 0.88 deg/s, and at 1 Hz they spanned ± 0.49 deg/s; in the older adults, the corresponding values were ± 3.52 deg/s (0.1 Hz) and ± 1.28 deg/s (1 Hz). As expected, all 10 young and 10 older participants had lower peak velocity thresholds at 1 Hz (mean young = 1.3 °/s, SD = 0.4 °/s; mean older = 2.4 °/s, SD = 1.8 °/s), than at 0.1 Hz (mean young = 3 °/s, SD = 1.1 °/s; mean older = 7.2 °/s, SD = 3.9 °/s). In addition, older adults exhibited higher peak velocity thresholds than young at 0.1 Hz, but the difference between age groups was smaller at 1 Hz (Fig 4A). A mixed model ANOVA revealed a significant effect of stimulus frequency ($F_{1,18} = 27.391$, $p < 0.001$), a significant effect of age group ($F_{1,18} = 11.791$, $p = 0.003$), and a significant stimulus frequency by age group interaction ($F_{1,18} = 6.33$, $p = 0.022$). Planned comparisons between age groups at each frequency revealed that older adults had higher thresholds than young adults at 0.1 Hz ($F_{1,18} = 10.841$, $p = 0.004$), however, the age group difference failed to reach statistical significance at 1 Hz ($F_{1,18} = 3.336$, $p = 0.084$).

Figure 2.

4.2 Virtual Rotation Perception

To measure the perception of virtual rotations, we used a homologous forced choice task. Instead of rotating the chair, we applied binaural bipolar electrical current over the mastoid processes giving rise to an illusory perception of whole-body rotation. All participants reported a distinct perception of chair rotation that was indistinguishable from real rotation stimuli. The best-estimated psychometric functions for virtual motion are shown for all participants in Fig. 3. At 0.1 Hz, 95% confidence intervals for the threshold value in young adults spanned on average ± 0.25 mA, and at 1 Hz they spanned ± 0.41 mA; in the older adults, the corresponding values were ± 0.8 mA (0.1 Hz) and ± 0.27 mA (1 Hz). The thresholds for virtual rotations differed between age

groups across the two stimulus frequencies (Fig 4B). All 10 young participants had higher peak current thresholds at 1 Hz (mean = 1.1 mA, SD = 0.6 mA), than at 0.1 Hz (mean = 0.5 mA, SD = 0.4 mA). In contrast, all 10 older participants had lower peak current thresholds at 1 Hz (mean = 0.6 mA, SD = 0.3 mA), than at 0.1 Hz (mean = 1.2 mA, SD = 0.7 mA). The mixed model ANOVA revealed no significant effect of stimulus frequency ($F_{1,18} = 0.094$, $p = 0.762$), nor age group ($F_{1,18} = 0.497$, $p = 0.49$), but a significant stimulus frequency by age group interaction ($F_{1,18} = 21.968$, $p < 0.001$). Planned comparisons between age groups at each frequency revealed that older adults had higher virtual rotation thresholds than young adults at 0.1 Hz ($F_{1,18} = 9.240$, $p = 0.007$), however, older adults outperformed young adults on 1 Hz virtual rotations ($F_{1,18} = 4.920$, $p = 0.040$).

Figure 3.

5. DISCUSSION

We used a combination of real and virtual rotation-based testing to investigate the effect of normal adult aging on vestibular perception. For real rotations, older adults exhibited elevated direction discrimination thresholds at 0.1 Hz relative to the young – an effect that we argue is the result of sensorineural deterioration in the peripheral vestibular apparatus (Bergström, 1973; Rosenhall, 1973; Richter, 1980; Merchant *et al.*, 2000; Rauch, 2001; Ishiyama, 2009). However, older adults performed as well as young adults with 1 Hz rotations, suggesting a compensatory mechanisms has maintained function at this frequency, in the face of age-related vestibular sensorineural losses. All participants, regardless of age, had lower thresholds at 1 Hz compared to 0.1 Hz, as would be

predicted from the high-frequency gain of vestibular mechanotransduction (Benson *et al.*, 1989; Grabher *et al.*, 2008; Soyka *et al.*, 2012). For virtual rotations, at 0.1 Hz the young outperformed the older adults, however, at 1 Hz the older adults outperformed the young. This interaction, especially in light of age-related sensorineural deterioration, is likely the result of central processing gain compensation occurring within the vestibular system for the 1 Hz stimuli with age.

5.1 Perception of real rotations: age-related deterioration of the peripheral vestibular system

We found that the older adults had significantly elevated thresholds for real rotations at 0.1 Hz, but similar thresholds at 1 Hz, relative to their young adult counterparts. We suggest that this impairment in perceptual performance, which appears most pronounced at lower frequencies, is linked to the well-established reduction in the number of human hair cell

Figure 4.

receptors (Rosenhall, 1973; Merchant *et al.*, 2000; Rauch *et al.*, 2001; Ishiyama *et al.*, 2009) and peripheral afferent fibres (Bergström, 1973; Richter, 1980) with normal adult aging. Given this sensorineural deterioration with age, the robustness of perceptual sensitivity to real 1 Hz rotations suggests that a compensatory gain enhancement mechanism might be at play, without which, performance would be predicted to decline to a greater extent given anatomical losses alone.

Only a small number of studies have investigated the perception of rotation in older adults. Seemungal *et al.* (2004) had participants discern the direction of 0.1 Hz triangle wave velocity pulses, and obtained threshold estimates for fourteen young (mean age = 23 years), and nine older (mean age = 63 years) adults using an adaptive staircase psychophysical method. Direction discrimination thresholds were $1.2\text{ }^{\circ}/\text{s}^2$ ($1.9\text{ }^{\circ}/\text{s}$) for young and $1.4\text{ }^{\circ}/\text{s}^2$ ($2.2\text{ }^{\circ}/\text{s}$) for the older adults: a difference that failed to reach significance. Roditi & Crane (2012) used sinusoidal stimulus pulses akin to those used in the present study and also found only weak (insignificant) differences between young ($1.2\text{ }^{\circ}/\text{s}$) and older ($1.5\text{ }^{\circ}/\text{s}$) adults at 0.5 Hz. Roditi & Crane (2012) tested eight older adults in total (mean age = 61), but only one older adult at 1 Hz; thus, age group statistical comparisons are not available at either of the frequencies tested in the present study. Their findings, however, are consistent with ours in that the effect of age on real rotation sensitivity appears to be small at frequencies above 0.1 Hz. We suggest that differences in stimulus profiles, psychophysical procedures, equipment, and precautions taken to reduce non-vestibular cues could plausibly explain why we found a significant age difference at 0.1 Hz, and Seemungal *et al.* (2004) did not, though the effect they observed was in the same direction. In addition, our older adult group was more than 10

years older on average than these two previous studies, aiding our ability to detect any age effects.

Furthermore, all participants in our study, regardless of age, exhibited lower thresholds at 1 Hz than 0.1 Hz for real rotations. Many previous investigations into the perception of whole-body yaw rotations have shown that human sensitivity to real motion increases at higher stimulus frequencies. Based on a combination of non-human primate neurophysiological recordings (Goldberg *et al.*, 1982; 1984; Dickman & Angelaki, 2004; Haque *et al.*, 2004), human psychophysical experiments (Benson *et al.*, 1989; Grabher *et al.*, 2008; Soyka *et al.*, 2012), and computational modelling of cupular biomechanics (Guedry, 1974; Mayne, 1974; Grabher *et al.*, 2008; Soyka *et al.*, 2012), it is clear that increased sensitivity to higher frequency (1 Hz) motion profiles is explained by the high-frequency gain of vestibular afferent mechanotransduction. There is general agreement between studies regarding young adult data (see Benson *et al.*, 1989; Grabher *et al.*, 2008; Soyka *et al.*, 2012); for example, our threshold values fit well onto Figure 2 from Grabher *et al.* (2008), and Figure 6 from Soyka *et al.* (2012).

5.2 Perception of virtual rotations: central gain compensation in the vestibular system

Similar to the real rotations, we found that the young outperformed the older adults for the 0.1 Hz virtual rotations. The comparable age-related performance decrements for 0.1 Hz real and virtual rotations in the older adults suggests a common neural mechanism (e.g., afferent receptors loss), and that there is little or no central gain enhancement at this frequency. The lower thresholds observed in older adults to 1 Hz virtual rotations, on the other hand, suggest central gain compensation occurs with adult aging. Given vestibular afferents begin to decline in number later in life than hair cell

receptors (Richter, 1980; Bergström, 1973), and are still likely activated by electrical current without functioning hair cells (Jahn *et al.*, 2003; Phillips *et al.*, 2015), older adults should be close-to as good, but worse at discriminating virtual motion direction provided they have lost only a small proportion of afferent fibres (at around age 50-60). However, the fact that older adults outperformed the young on 1 Hz virtual rotations cannot be explained by the remaining afferents alone, and suggests another adaptive neural mechanism is at play. This central compensation may partially offset the sensitivity impairments to real rotation owing to anatomical deterioration of vestibular end organs and primary afferents. In other words, we propose that vestibular thresholds for the 1 Hz real rotations would have been higher in older adults had this compensation not occurred.

Why is there central vestibular gain compensation with age at 1 Hz, but not 0.1 Hz? While we can only speculate as to why the vestibular system may prioritize a particular frequency bandwidth, it is suggestive to us that the compensated bandwidth coincides with particularly important frequencies of natural vestibular input. Using accelerometry in young adults, the frequency content of head movement during locomotion (i.e., while walking, running, and hopping) displays the vast majority of power distributed within the 1 to 5 Hz range (Grossman *et al.*, 1988; Pozzo *et al.*, 1990), which has been corroborated in older adults performing the same tasks (Hirasaki *et al.*, 1993). Further, in activities of daily life such as switching between workstations in the kitchen, or maneuvering the head to the left and right at an intersection while driving, the frequency content was again found to be within the 1 to 5 Hz range (Land, 2004). Therefore, from an adaptive neural plasticity perspective, targeting and enhancing the transmission of inputs within the 1 to 5 Hz range would likely be advantageous for

maintaining natural vestibular function in older adults. Conversely, the internal representation of 0.1 Hz might not be re-mapped in normal aging because this is likely not an important frequency in natural vestibular stimulation.

Age-related loss of central vestibular neurons has been documented in the lateral, medial, and inferior compartments of the human vestibular nucleus (Alvarez *et al.*, 2000). However, the superior vestibular nucleus (SVN) which receives input from the more-rapidly deteriorating central crest zone of the crista ampullaris (Brodal, 1974; Gacek, 1969) does not show any decline in cell counts up to the tenth decade (Alvarez *et al.*, 2000). The SVN is the first central processing stage of the semi-circular canal evoked vestibulo-ocular reflex (Baloh & Honrubia, 1990) and of the vestibulo-cortical pathway presumed to underlie the sensation of angular rotation (Purves *et al.*, 2012). The SVN receives input from all other vestibular nuclei, in addition to the cerebellum (Alvarez *et al.*, 2000). The preservation of the SVN with age could explain observations that vestibulo-motor function (Peterka *et al.*, 1990; Jahn *et al.*, 2003; Welgampola & Colbatch, 2002; Dalton *et al.*, 2014), and now vestibular perception, appears to be maintained longer than would be expected based on hair cell receptor loss alone.

All 10 young adults performed worse on 1 Hz virtual rotations than they did on 0.1 Hz rotations. We have proposed that low-pass filtering of the electrical stimulus by the skull and tissue overlying the vestibular afferents may explain this increase in thresholds with higher stimulation frequencies in young adults (Peters *et al.*, 2015). Alternatively, the central vestibular system may decrease the gain at 1 Hz relative to 0.1 Hz in young adults to flatten the gain spectrum over a broader range of frequencies downstream of the vestibular nucleus. This alternative mechanism is supported by the

responses seen in the vestibular nucleus to irregular afferent input (Dickman & Angelaki, 2004), where gain enhancement was observed at 0.1 Hz and not at 1 Hz in young rhesus monkeys. Furthermore, all 10 older adults performed worse on 1 Hz virtual rotations than they did on 0.1 Hz rotations. Regarding the influence of the skull and overlying tissue as a potential alternative hypothesis for our aging results, we further point out the age by frequency interaction we observed could not simply be explained by a simple decrease in the amount of filtering, for example due to a change in bone density with age. For a change in bone density to explain the age group differences we observed, it would have to turn the skull and overlying tissue from a low-pass filter to a high-pass filter over the 0.1 to 1 Hz range, which while plausible, seems less likely than a frequency-specific adaptive change in central gain.

5.3 Converging evidence for a frequency-specific central compensation mechanism

Based on the robustness of vestibular-based reflexes in the face of age-related decline in peripheral receptor number, it was previously proposed that the central vestibular system might compensate for age-related sensorineural deterioration by enhancing the gain of vestibular afferent input (Peterka *et al.*, 1990; Jahn *et al.*, 2003; Dalton *et al.*, 2014). Peterka *et al.* (1990) considered 0.05, 0.2, and 0.8 Hz real rotations, in addition to caloric vestibular testing, in their investigation of age-related gain compensation. While caloric testing showed no correlation with age, they did observe that the slope of the decline in vestibulo-ocular reflex gain to real rotations was steeper at 0.05 Hz (-0.003 units/year), than at 0.2 Hz (-0.0026 units/year), and 0.8 Hz (-0.0022 units/year). The slower decline in reflex gain with age at 0.8 Hz further supports the influence of a frequency selective central gain compensatory mechanism, as reported

here. Jahn *et al.* (2003) used square wave EVS to evoke torsional eye movements, and measured response gain in participants age 20 to 69 years. Their findings suggest that the gain of the vestibulo-ocular reflex to electrical stimulation increased, and was greater than that observed in the young from the third to sixth decade, but then declined in the seventh decade. Jahn *et al.* (2003) provided evidence that the central gain enhancement follows an inverse U-shape over normal adult aging, such that central gain enhancement is peaked around age 50, then declines later in life. Dalton *et al.* (2014) computed the gain between stochastic electrical vestibular stimulation and resultant ground reaction forces during quiet standing, considering frequency components ranging from 0.5 to 25 Hz. The observed relative gain spectrum for older adults was condensed to frequencies between 1 and 5 Hz. Therefore, converging evidence from vestibular-evoked ocular and postural reflexes, and now vestibular perception, suggests that there is a frequency-specific central compensatory mechanism occurring within the vestibular system during normal adult aging. Beyond frequency specificity, it would be optimal for any central gain compensation mechanism to selectively enhance the input from the remaining intact, sensitive afferent fibres for the detection real kinetic motion.

When hair cell receptors are functionally destroyed via gentamycin injection, the afferents maintain a baseline firing rate ~10-20% lower than normal, but are insensitive to mechanical perturbations (for discussion see Goldberg *et al.*, 2012). Despite the noise added by the afferents deprived of their hair cell receptors, Phillips *et al.* (2015) reported that loss of vestibular afferent activity due to gentamycin injection produces an increase in the efficacy of a prosthetic neurostimulator to drive oculomotor behaviour but no increase of electrical afferent activation in the periphery. These authors argued that the

increase in efficacy of the neurostimulator was due to central adaptive changes to the reduced peripheral vestibular input to the central nervous system. We propose that a similar mechanism explains our observations such that the gain of the information transmitted by functioning peripheral vestibular afferents in older adults is enhanced centrally.

This frequency-specific central gain enhancement targeting the information transmitted by functioning vestibular afferents might occur via connections between the vestibular nucleus and cerebellum (Alvarez *et al.*, 2000). In a recent non-human primate neurophysiological study, Brooks *et al.* (2015) demonstrated that an experimental alteration in the mechanics of self-generated head movements resulted in an error signal generated within the rostral fastigial nucleus. One of the major outputs of this cerebellar nucleus is the vestibular nucleus, which is where Brooks *et al.* (2015) observed gain adjustments such that the discrepancy in re-afferent signals was corrected (i.e., the altered mechanics of self-generated neck movements were “learned” by the vestibular nucleus circuitry). It seems plausible that similar mechanisms might bring about adaptive gain adjustments at the vestibular nucleus to partially offset the effect of gradual age-related sensorineural deterioration. Such vestibular gain enhancement may be associated with re-mapping vestibular cues of self-motion to other sensory cues (e.g., vision, audition and proprioception) in adult aging, a process akin to what we have previously shown in young healthy adults (Heroux *et al.*, 2015).

5.4 Conclusion

Here we find support for the hypothesis that central gain enhancement is occurring in the vestibular system with normal adult aging. There is now evidence for a

frequency-specific adaptive gain enhancement mechanism with age in three major vestibular functions: vestibulo-ocular reflexes, vestibular-evoked balance responses and vestibular perceptual sensitivity. While sensory aging research is all too often a story of deterioration, we found older adults were actually more sensitive to electrical vestibular stimulation at 1 Hz, re-mapping them to a faster head movement relative to young adults, a finding that supports the existence of a central compensatory mechanism. Future studies are needed to characterize age-related changes in vestibular function by considering different frequencies and planes of rotation, as well as linear motion. Furthermore, the experimental approach developed in this, and a companion paper (Peters *et al.*, 2015), provides a theoretical and methodological framework that can now be readily applied for investigation into various clinical and practical applications.

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8. FIGURE LEGENDS

Figure 1. Experimental setup and Bayesian adaptive procedure. **A.** Participants were seated comfortably on a memory foam-padded rotary chair. The chair was custom-designed to provide earth-vertical yaw rotations via a servo-controlled electric motor. Illustrated above the participant is the perceived virtual direction for the 2 different electrode polarities; virtual head rotation was always felt toward the cathode side for suprathreshold stimuli. **B.** Head pitch angle was specifically chosen to align the EVS-evoked net rotational vector (see Fitzpatrick and Day 2004) with the chair's axis of rotation, producing the illusion that the chair was rotating when binaural bipolar EVS was applied over the mastoids (cathode right/ anode left = rightward virtual rotation, cathode left/anode right = leftward virtual rotation). Anterior (A), horizontal (H), and posterior (P) semicircular canal rotational vectors are drawn for the left side; the net EVS-evoked rotation vector summed across all 6 semi-circular ducts bilaterally is shown as a solid black arrow. To estimate real and virtual motion direction discrimination thresholds, we used a Bayesian adaptive procedure. **C.** Examples of different peak-amplitude EVS waveforms (raised-cosine bell curves) used to evoke virtual rotations (stimulus frequency = 0.1 Hz). **D.** Performance plot demonstrating how peak amplitude was adaptively adjusted across 40-trial blocks with the Bayesian adaptive procedure (+ = correct response; X = incorrect response). **E.** The end-of-block a parameter probability distribution function (normalized to the maximum value for plotting purposes) corresponding to the performance plot shown in **D**. **F.** Best-estimated psychometric function relating the peak EVS current to the proportion of correct responses for the same block of trials as **D** and **E**.

Figure 2. Best-estimated psychometric functions for real motion. Individual participants (thin lines), and mean (thick line) best-estimated psychometric functions (shaded regions: ± 1 SD) for real rotation experiments. Gray curves and shaded regions show data from older adults (right column of panels); black curves and shaded regions show data from young adults (left column of panels). Stimulus frequency is displayed in the bottom right corner of each panel.

Figure 3. Best-estimated psychometric functions for virtual motion. Individual participants (thin lines), and mean (thick line) best-estimated psychometric functions (shaded regions: ± 1 SD) for virtual rotation experiments. Data plotted as in Figure 2.

Figure 4. Comparison of young and older adult direction discrimination thresholds for real (A) and virtual (B) yaw rotation. Young adult data (squares) are on the left and older adult data (circles) are on the right for both panels. Each thin line is an individual participant and the thick line connects the mean threshold values at 0.1 and 1 Hz. Note in panel **A** that all young and older adults have lower threshold values at 1 Hz relative to 0.1 Hz; however, older adult threshold values are elevated at both stimulus frequencies. Also note in panel **B** that all 10 young adults performed worse on average at 1 Hz relative to 0.1 Hz; however, all 10 older adults performed better at 1 Hz relative to 0.1 Hz.