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Velocity-selective adaptation of the horizontal and cross-axis vestibulo-ocular reflex in the mouse

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Abstract

One commonly observed phenomenon of vestibulo-ocular reflex (VOR) adaptation is a frequency-selective change in gain (eye velocity / head velocity) and phase (relative timing between the vestibular stimulus and response) based on the frequency content of the adaptation training stimulus. The neural mechanism behind this type of adaptation is not clear. Our aim was to determine whether there were other parameter-selective effects on VOR adaptation; specifically velocity-selective and acceleration-selective changes in the horizontal VOR gain and phase. We also wanted to determine whether parameter-selectivity was also in place for cross-axis adaptation training (a visual-vestibular training stimulus that elicits a vestibular-evoked torsional eye movement during horizontal head rotations). We measured VOR gain and phase in 17 *C57BL/6* mice during baseline (no adaptation training) and after gain-increase, gain-decrease and cross-axis adaptation training using a sinusoidal visual-vestibular (mismatch) stimulus with whole-body rotations (vestibular stimulus) with peak-velocity 20°/s and 50°/s both with a fixed frequency of 0.5 Hz. Our results show pronounced velocity-selectivity of VOR adaptation. The difference in horizontal VOR gain after gain-increase versus gain-decrease adaptation was maximal when the sinusoidal testing stimulus matched the adaptation training stimulus peak-velocity. We also observed similar velocity-selectivity after cross-axis adaptation training. Our data suggest that frequency-selectivity could be a manifestation of both velocity- and acceleration-selectivity because when one of these is absent, e.g., acceleration-selectivity in the mouse, then frequency-selectivity is also reduced.

Keywords

VOR; visual-vestibular training; vestibular adaptation; oculomotor learning; plasticity; afferent pathways

Introduction

The vestibulo-ocular reflex (VOR) generates gaze (vision) stabilising eye movements in response to sudden unpredicted head perturbations to keep images stable on the retinae. Optimal gaze stabilisation during typical (i.e., far) viewing conditions requires that the VOR generates a three-dimensional (horizontal, vertical and torsional component) eye movement with equal velocity magnitude, but with opposite direction, to head velocity, so that the VOR gain (eye velocity / head velocity) is equal to unity. Because of the "open circuit" nature of the VOR it relies on calibration / adaptation mechanisms to adjust gain, phase and rotation axis to minimize retinal image slip. Changes in viewing conditions or in peripheral vestibular organ and optical plant function due to, e.g., ageing or illness, can affect this calibration and result in a retinal slip error signal (Angelaki and Hess 1998). This error signal drives VOR adaptation to adjust to the new condition. Under laboratory conditions VOR adaptation can be induced by deliberately producing a mismatch between head movement and movement of the visual scene that demands a change in VOR gain, phase or rotation plane.

One commonly observed phenomenon of VOR adaptation is a frequency-selective change in gain and phase (relative timing of the vestibular stimulus and response) based on the frequency content of the adaptation stimulus. For example, sinusoidal VOR adaptation training at a frequency of 1 Hz will produce a maximum change in gain at the same frequency. VOR adaptation training using a more complex stimulus, for example, a step impulse, will evoke an adaptation effect across the frequency spectrum of the stimulus (Powell et al. 1991). The bandwidth around the training frequency in which an adaptation effect is observed varies between species. Rabbits, for example, develop a sharply tuned gain change at the adaptation frequency (Collewijn and Grootendorst 1979; Angelaki and Hess 1998), while studies in the monkey generally report a very broad frequency-

selectivity (Lisberger et al. 1983; Powell et al. 1991; Raymond and Lisberger 1996). It is not clear what neural mechanisms are responsible for this frequency-selectivity. Several studies suggest that neural pathways in the cerebellum and brainstem form "frequency-channels", however frequency-selectivity of individual cells or synapses has never been demonstrated (Lisberger et al. 1983; Straka et al. 2009; Dean et al. 2009). On the other hand, there is a basis for the existence of "velocity-channels" mediated by regularly-discharging primary afferents that encode head velocity and "acceleration-channels" mediated by irregularly-discharging afferents that encode head acceleration (Holstein 2004; Minor and Lasker 2009). One hypothesis of context specific adaptation suggests that VOR adaptation is dependent on modification of these tonic (velocity sensitive) and phasic (acceleration sensitive) afferent signals from the vestibular periphery (Clendaniel et al. 2001; Clendaniel et al. 2002). This theory is supported by the presence of cell populations with different response dynamics at each level of the vestibulo-motor pathway, such as type-I and type-II hair cells in the peripheral sensory organs, regularly- and irregularly-discharging primary vestibular afferents, subgroups of second-order vestibular neurons (i.e., type A and type B) and extra-ocular motor neurons with different discharge dynamics (Straka et al. 2009). In contrast to the "frequency-channel theory" which only explains frequency-selective VOR adaptation, the "tonic/phasic pathway theory" also predicts selective modification of the VOR based on stimulus velocity and acceleration. The majority of studies that investigated selective VOR adaptation (e.g., monkeys: Lisberger et al. 1983; Raymond and Lisberger 1996, cats: Godaux et al. 1983; Powell et al. 1991; Titley et al. 2009, mice: De Zeeuw et al. 1998; Iwashita et al. 2001; Kimpo et al. 2005, fish: Yoshikawa and Hirata 2006 and humans Shelhamer et al. 1992; Watanabe et al. 2003), have only tested frequency-selectivity, or other modes of context specific adaptation, but do not report on effects of stimulus parameters such as velocity and acceleration. Furthermore, these studies exclusively tested VOR adaptation for horizontal

visual-vestibular training. It is unclear if parameter-selectivity is a neural strategy unique to horizontal VOR adaptation, or if similar parameter-selectivity exists for cross-axis adaptation (e.g., horizontal vestibular stimulation paired with vertical movements of the visual scene).

Our first aim was to determine whether VOR adaptation was exclusively frequency-selective by testing velocity- and acceleration-selective adaptation. Second, we wanted to determine whether selective adaptation could also occur in response to cross-axis visual-vestibular adaptation training. We kept the adaptation training stimulus frequency constant at 0.5Hz but peak-velocity was 20°/s or 50°/s for separate training sessions. Following adaptation we measured 3D VOR eye movements in response to sinusoidal stimuli between 0.1 - 10Hz with peak-velocity 10, 20, 50 or 100°/s, as well as in response to transient steps of acceleration at 1500, 3000 and 6000°/s² reaching a velocity plateau of 100, 150 and 300°/s respectively. We compare these results with baseline (no adaptation) data collected under identical conditions. We show that the effect of horizontal adaptation training, measured as the difference in horizontal VOR gain after gain-increase versus gain-decrease adaptation training, was largest when tested across frequencies that had the same peak-velocity used during adaptation training.

Materials and methods

Animal Groups

Data were obtained from 17 *C57BL/6* mice (both sexes, aged 13-15 weeks), of which 9 contributed to the horizontal adaptation data, and 8 contributed to the cross-axis adaptation data. Mice in the horizontal adaptation group were tested over five separate sessions, each session separated by at least two days. These mice were tested prior to adaptation training (baseline VOR, ideal gain = 1) and after sinusoidal VOR gain-increase (x1.5) and gain-decrease (x0.5) adaptation training at 0.5Hz with peak-velocity 20°/s or 50°/s. Mice in the cross-axis adaptation group were tested after adaptation training consisting of pure torsional visual stimulation synchronized to pure horizontal vestibular stimulation. The stimulus gain for cross-axis adaptation (torsional visual stimulus velocity / horizontal vestibular stimulus velocity) was set to unity and vestibular stimulus frequency and peak-velocity were kept constant at 0.5Hz and 20°/s, respectively. VOR measurements after cross-axis adaptation were compared to baseline VOR data from the horizontal adaptation group. Following all adaptation training we measured the sinusoidal (0.1 - 10Hz, at peak velocities 10, 20, 50 and 100°/s) and transient (1500 - 6000°/s² at velocity plateaus 100 - 300°/s) VOR gain and phase (or latency) in darkness using a binocular 3D video-oculography system.

Animal Preparation

Similar to previous studies (Migliaccio et al. 2005; Migliaccio et al. 2011; Hübner et al. 2013) we prepared each animal for restraint during VOR adaptation training and eye movement recording by mounting a lightweight, low profile head-post adapter plate on the skull under general inhalation anaesthesia (Isoflurane 2-3%). After surgery, mice were returned to their cage where they recovered for a minimum of three days. During this time the animal's well-being was assessed by monitoring body posture, alertness and appetite. Prior to

each experimental session a head-post was attached to the previously implanted adapter plate using a magnet and screw. The mouse was restrained within a Fick gimbal superstructure (from here on referred to as the vestibular gimbal) atop a high torque rotary servomotor (GOLDLINE DDR D083, Danaher). In this restrained position the head was tilted ‘nose-down’ by $\sim 30 \pm 5^\circ$, to align the plane of the animal’s horizontal semicircular canals to within 10° of the earth horizontal plane (Calabrese and Hullar 2006, see Figure 1E). The animal’s body and extremities were restrained in a plastic cylinder, which was firmly attached to the rotation platform (Figure 1D).

All surgical and experimental procedures were approved by the Animal Care and Ethics Committee of the University of New South Wales.

Visual-Vestibular adaptation training

The visual adaptation training stimulus was generated using a two-axis “planetarium projector” (Figure 1A), designed to project a field of random light spots onto a dome (Figure 1B) surrounding the animal. Similar systems have been successfully used in other adaptation studies (Simpson et al. 1988; Khater et al. 1993). A spherical shell (29mm diam.) with numerous small holes was used as the aperture of the projector. The centre of the projector shell housed 8 bright surface mount LEDs (0603 package size), arranged in a sphere ($\sim 2.5\text{mm}$ diam.) to approximate a point light source. Varying the size of the holes in the projector shell allowed us to adjust the spatial coherence of the light and thus maximise contrast.

[Figure 1]

The projection unit was mounted on a two-axis gimbal (from here on referred to as the projector gimbal), mounted on the vestibular gimbal superstructure. Both gimbal axes were rotated using a small brushless direct drive motor (EC Flat, Maxon Motor) fitted with a high-

resolution (65,000 counts/rev) laser interference encoder (M1500P, MicroE Systems). This technology was chosen over a normal DC motor because of its superior performance during low velocity profiling and low latency response times during fast changes of accelerations and direction (i.e. no torque ripple or gear backlash). By generating combined movements of the two projector-gimbal axes it was possible to perform phase-locked (± 0.5 ms latency) visual-vestibular adaptation training in multiple planes (horizontal, vertical, torsional, right-anterior and left posterior canal plane [RALP], left-anterior and right-posterior canal plane [LARP]) with respect to head. In this study we used horizontal and torsional visual projections in response to horizontal head rotations to perform in-plane and cross-axis adaptation respectively.

Adaptation procedure

Only whole-body sinusoidal oscillations at 0.5Hz reaching a peak-velocity of 20°/s and 50°/s were used as the VOR adaptation training stimuli. The peak-velocity and direction of the visual stimulus was altered to gain-increase, gain-decrease or cross-axis adapt the VOR. For gain-increase and gain-decrease adaptation the projector unit was configured to perform phase-locked rotations in the opposite direction to head rotation. The amplitude of the projector unit could be altered using a gain parameter (ratio projector velocity / vestibular gimbal velocity) so that a gain of 1 produced perfectly compensatory rotation of the visual projection resulting in a static field of light spots in earth coordinates. During gain-increase adaptation training the visual projector was set to rotate with a gain of 1.5. Similar, during gain-decrease adaptation training the visual projector was set to rotate with a gain of 0.5. Cross-axis adaptation training was achieved by rotating the visual projection with a gain of 1 around the roll (x) axis of the head fixed coordinate frame while keeping the vestibular

stimulus around the horizontal (z) axis (coordinate frame see Figure 1). Adaptation training was kept strictly to 40 and 60 minutes for horizontal and cross-axis adaptation respectively.

Eye movement recording

Eye movements were recorded using a 3D video-oculography technique described previously (Migliaccio et al. 2005; Migliaccio et al. 2011; Hübner et al. 2013). This technique relies on a marker array that is securely affixed to the eye. While this marker array can easily be removed without damage to the eye, it can still cause some irritation and tearing for a short time after removal. To ensure optimal vision during visual-vestibular adaptation training we measured VOR eye movements only after adaptation training, i.e., baseline (before adaptation) VOR data was recorded during a separate experimental session. All VOR data were recorded in darkness using two high-speed infrared sensitive cameras (Figure 1C) to capture binocular eye movements at 200fps.

We tested the VOR in response to horizontal whole-body: sinusoidal oscillation at 0.1, 0.2, 0.4, 0.5, 0.8, 1, 2, 5 and 10Hz with peak-velocities of 10, 20, 50 and 100°/s, and transient acceleration stimuli at 1500, 3000, 6000°/s² reaching a velocity plateau of 100°/s (for 1500°/s²), 150°/s (for 3000°/s²) and 300°/s (for 6000°/s²). From here on after we refer to transient stimulus conditions using the following abbreviations: 1.5k100, 3k150 and 6k300.

Data analysis

Head and eye velocity traces of each stimulus cycle (10-100, depending on stimulus) were superimposed and quick-phases were removed using an algorithm we previously developed (Hübner et al. 2013). Three dimensional eye movements were divided into horizontal (z), vertical (y) and torsional (x) VOR components (in head coordinates) (see Figure 1 for coordinate frame). VOR components were analysed separately with each component having their own gain and phase parameter (G_X , G_Y , G_Z and P_X , P_Y , P_Z respectively). In this system a

change in VOR alignment, as induced by cross-axis adaptation, is represented as a gain increase of one component accompanied with a gain decrease of another component.

Analysis of sinusoidal rotations

Least-square pure sine waves (frequency was a fixed variable, amplitude and phase were free variables) were fit to each head and eye velocity cycle to compute gain (eye velocity magnitude / head velocity magnitude) and phase. Positive phase lead denotes eye velocity leading head velocity. Mean and standard deviation of gain and phase across cycles are reported for each stimulus frequency and peak-velocity combination. To analyse acceleration-selectivity we chose peak-accelerations that occurred at all tested stimulus velocities (10, 20 50 and 100 deg/s) at their respective frequency combinations (see table below). This approach allowed us to nullify the effects of velocity-selectivity to better examine the effect of acceleration-selectivity. Table 1 summarises the frequency-velocity combinations that result in the peak-accelerations reported.

[Table 1]

Analysis of transient acceleration steps

VOR responses to acceleration step stimuli were fit using least-square linear regressions to the acceleration component (10-30ms after stimulus onset) and constant-velocity component (200-400ms after stimulus onset) of eye and head velocity traces. The fits were used to extract acceleration gain (G_A), latency and constant-velocity gain (G_V) respectively. G_A was calculated as the mean ratio of horizontal eye / head acceleration (using the slopes of the fitted lines) during the 10-30ms interval after stimulus onset. G_V was calculated as the mean ratio of horizontal eye / head velocity during the 200-400ms interval after stimulus onset. Stimulus and response onsets were calculated as the times at which the respective acceleration line-fits intercept with the zero velocity axis. The latency of the VOR was

defined as the time difference between stimulus (head rotation) and response (eye rotation) onset. All values, unless otherwise stated, are reported as mean $\pm$ standard deviation.

Analysis of Adaptation Selectivity

We compared VOR adaptation selectivity between gain-increase versus gain-decrease adaptation training, by calculating a generalisation index across frequencies and velocities for each individual animal. The generalisation index (see Kimpo et al. 2005) is defined as the fraction of adaptation at the training frequency and velocity compared to the average adaptation at frequencies and velocities other than the adaptation training frequency and velocity.

$$\text{Generalisation index} = \frac{\frac{1}{j}(\sum_i \Delta gain_i)}{\Delta gain_{training}}, \text{ where } i \neq \text{training}$$

$\Delta gain_{training}$ represents the amplitude of VOR gain adaptation at the same frequency/velocity used during adaptation training. $\Delta gain_i$ represents the amplitude of VOR gain adaptation at one of j stimulus frequencies/velocities other than the adaptation training frequency/velocity (e.g., for adaptation training peak velocity 20°/s, $i = 10, 50, \text{ and } 100^\circ/\text{s}$, $j=3$). A generalisation index close or equal to 1 (*average gain adaptation* $\Delta gain_i \approx \Delta gain_{training}$) indicates broad generalisation of VOR gain adaptation, while a generalisation index close or equal to 0 indicates stimulus specific VOR adaptation. A generalisation index <0 occurs if the change in VOR gain at non-adaptation frequencies/velocities is maladaptive (e.g., decrease of VOR gain after gain-increase adaptation training).

Statistical analysis

Data were analysed using a general linear mixed model with two-factor interactions (The R Project for Statistical Computation). Independent factors included: Animal ID, training (gain-increase, gain-decrease, cross-axis) and training peak-velocity (20°/s or 50°/s). For sinusoidal

stimulus analysis additional independent factors were (testing): frequency, peak-velocity and peak-acceleration, and dependent factors were: gain and phase. For transient stimulus analysis an additional independent factor was (testing): stimulus (1.5k100, 3k150, 6k300), and dependent factors were: G_A , G_V and latency. All variables were included in the model initially and those found insignificant were subsequently removed. All values are reported as mean $\pm$ standard deviation.

Results

[Figure 2]

Horizontal Adaptation

Sinusoidal rotations

Each mouse in the horizontal adaptation group (n=9) was tested over five separate experimental sessions (separated by at least two days), to acquire VOR data without prior adaptation (baseline VOR) and over two sessions of gain-increase (x1.5) and gain-decrease (x0.5) adaptation, with adaptation training stimulus peak-velocity 20°/s and 50°/s, respectively. Figure 2 shows representative unprocessed data recorded in one mouse (ID#6) before adaptation (baseline) and after gain-increase and gain-decrease adaptation respectively. Analysis of the post-adaptation VOR response showed a strong adaptation training effect (factor “Training”: $F_{1,613}=144.6$, $P<0.001$) with pronounced velocity-selectivity (interaction of “Training Velocity” and “Testing Velocity”: $F_{1,1617}=20.6$, $P<0.001$). The difference in post-adaptation VOR gain (in darkness) after gain-increase versus gain-decrease adaptation (total adaptation training effect) was maximal when the sinusoidal testing peak-velocity matched the adaptation training peak-velocity (see Figure 3 and Figure 4). The difference reached a maximum of 0.31 ± 0.14 (average across all frequencies) when the adaptation training peak-velocity was 20°/s and post-adaptation VOR was tested with peak-velocity 20°/s (Figure 4, left). At peak-velocities of 10, 50 and 100°/s (after adaptation training at 20°/s) this difference was significantly lower at 0.11 ± 0.18 , 0.13 ± 0.14 and 0.09 ± 0.11 , respectively. Similarly, when the adaptation training peak-velocity was 50°/s and post-adaptation VOR was tested with peak-velocity 50°/s this difference was maximal at 0.21 ± 0.17 (Figure 4, right). At peak-velocities of 10, 20 and 100°/s (after adaptation training at 50°/s) this difference was significantly lower at -0.02 ± 0.05 , 0.07 ± 0.13 and 0.09 ± 0.11 , respectively.

[Figure 3]

Comparison of the generalisation index between gain-increase versus gain-decrease adaptation indicated that velocity-selectivity was mostly caused by selective VOR gain adaptation in response to gain-increase (from baseline), rather than gain-decrease (from baseline), adaptation training. After adaptation training with peak-velocity 20°/s the generalisation index across velocities was 0.01 ± 0.56 in response to gain-increase adaptation as compared to 0.58 ± 0.59 in response to gain-decrease adaptation. Similarly, after adaptation training with peak-velocity 50°/s the generalization index across velocities was -0.60 ± 1.05 in response to gain-increase adaptation as compared to 1.05 ± 2.37 in response to gain-decrease adaptation ($T_{16,54}=2.04$, $P=0.057$).

[Figure 4]

Comparison of the maximal difference between gain-increase versus gain-decrease adaptation training at peak-velocities 20°/s and 50°/s revealed a ~47% stronger adaptation of VOR gain at 20°/s compared to at 50°/s (factor “Training Velocity”: $F_{1,1617}=85.0$, $P<0.001$). We did not observe frequency-selectivity of VOR adaptation. . As can be seen in Figure 3, there was no difference in adaptation across testing frequencies (“Frequency”: $F_{1,168}=1.91$, $P=0.169$). There was no significant interaction between “Frequency” and “Training Velocity”, indicating that frequency did not affect adaptation differently depending on the test stimulus peak-velocity (“Frequency” interaction with “Training Velocity”: $F_{1,129}=0.73$, $P=0.394$). Also, there was no significant interaction between “Frequency”, “Training Velocity” and “Testing Velocity”, indicating that frequency did not affect adaptation at only one specific combination of adaptation training and testing peak-velocity (*‘Frequency’ interaction with “Training Velocity” and “Test Velocity”*: $F_{1,129}=0.67$, $P=0.413$). Similarly, we did not observe acceleration-selectivity of VOR adaptation (“Acceleration”: $F_{1,5}=0.84$,

$P=0.401$; “Acceleration” interaction with “Training Acceleration”: $F_{1,37}=0.89$, $P=0.353$, see bottom panel of Figure 4).

Unlike VOR gain, VOR phase showed no velocity-selective differences between the two adaptation conditions (interaction “Training Velocity” and “Testing Velocity”: $F_{1,129}<0.01$, $P=0.976$). However, we identified a frequency-selective difference in VOR phase ($F_{1,168}=50.53$, $P<0.001$). Mice that received gain-increase adaptation showed an increase in phase at low frequencies and a decrease in phase at high frequencies, when compared to the gain-decrease group. The crossover of phase increase to phase decrease approximately coincided with the frequency that was used during VOR adaptation training.

Transient rotations

The VOR gain response to constant angular acceleration (G_A) was significantly different between gain-increase and gain-decrease conditioning when the adaptation training stimulus peak-velocity was $50^\circ/\text{s}$ ($F_{1,372}=9.6$, $P<0.01$). Adaptation only affected the lowest acceleration response ($1500^\circ/\text{s}^2$), and was not present for acceleration stimuli of $3000^\circ/\text{s}^2$ and $6000^\circ/\text{s}^2$ (see bottom-left panel of Figure 5). In contrast, adaptation training with stimulus peak-velocity $20^\circ/\text{s}$ did not affect G_A at any acceleration (top-left panel of Figure 5).

The VOR gain response to constant angular velocity (G_V) showed a similar pattern after VOR adaptation. We measured significant adaptation of G_V only when adaptation stimulus peak-velocity was $50^\circ/\text{s}$ ($F_{1,372}=26.0$, $P<0.001$, bottom-right panel of Figure 5). Adaptation using stimulus peak-velocity $20^\circ/\text{s}$ did not result in adaptation of G_V (top-right panel of Figure 5). But even for adaptation stimulus peak-velocity $50^\circ/\text{s}$, adaptation only affected the lowest constant-velocity response ($100^\circ/\text{s}$). G_V did not adapt for constant-velocity stimuli of $150^\circ/\text{s}$ and $300^\circ/\text{s}$.

[Figure 5]

Cross-Axis Adaptation

We measured the 3D VOR response of 8 mice that received cross-axis adaptation training and compared results with baseline VOR data from mice in the horizontal adaptation group.

Sinusoidal rotations

The baseline torsional gain (G_X) in the horizontal control group was similar across stimulus frequencies and velocities and averaged -0.041 ± 0.052 . In contrast, G_X in the cross-axis adaptation group was on average ~ 0.073 larger compared to the horizontal control group. ($F_{1,10} = 261.51$, $P < 0.001$). This difference was constant over the frequency spectrum tested (“Frequency” interaction with “Training”: $F_{1,10} = 0.015$, $P = 0.905$). However, the adaptation effect was larger when tested at $20^\circ/\text{s}$ (same peak-velocity as cross-axis adaptation training stimulus) with a difference of ~ 0.093 compared to when tested at $50^\circ/\text{s}$ where the difference was only ~ 0.053 (“Training Velocity” interaction with “Testing Velocity”: $F_{1,10} = 15.21$, $P < 0.01$, compare Figure 6 top-left and bottom-left). Analogous to G_X we analysed vertical gain (G_Y). In the horizontal control group we measured a baseline G_Y of 0.012 ± 0.069 (left eye positive, right eye negative) while in cross-axis adapted mice G_Y was 0.053 ± 0.053 , a significant increase ($F_{1,10} = 62.51$, $P < 0.001$). We also identified an interaction between the factors “Training” and “Velocity”. The gain increase was larger when tested at $20^\circ/\text{s}$ with a difference of ~ 0.056 compared to when tested at $50^\circ/\text{s}$ with a difference of ~ 0.026 (“Velocity” interaction with “Training”: $F_{1,10} = 9.01$, $P < 0.05$, compare Figure 6 top-centre and bottom-centre).

The gain increase of G_X and G_Y after cross-axis adaptation was accompanied by a decrease in horizontal gain (G_Z , Figure 6 right). Mice in the horizontal adaptation group had an average G_Z of 0.756 ± 0.191 while the average for the cross-axis adaptation group was only 0.576 ± 0.153 , a significant difference of ~ 0.18 ($F_{1,10} = 256.0$, $P < 0.001$). Furthermore, this

difference was consistent over all frequencies and both velocities tested (see Figure 6 top-right and bottom-right panel).

[Figure 6]

Transient rotations

In contrast to horizontal adaptation training, where single-frequency training resulted in adaptation of the acceleration component G_A of transient step stimuli, cross-axis adaptation training had no effect on these high acceleration responses. Similarly, there was no effect of adaptation training on the constant-velocity gain G_V and a pairwise comparison of factors “Training” and “Stimulus” did not show a significant interaction.

Discussion

This study demonstrates velocity-selectivity of VOR adaptation as a result of sinusoidal visual-vestibular adaptation training with fixed frequency and peak-velocity of the vestibular stimulus. The difference in horizontal VOR gain after gain-increase versus gain-decrease adaptation training (across frequencies of 0.1 – 10 Hz) was maximal when tested at the same peak-velocity used during training. When the adaptation training stimulus peak-velocity was 20°/s, the VOR response was 2.5 – 3.5 times larger than when tested at 20°/s as compared to the other stimulus peak-velocities. Similarly, when the adaptation training stimulus peak-velocity was 50°/s, the VOR response was 1.5 – 2.5 times larger when tested at 50°/s as compared to the other stimulus peak-velocities. The maximal adaptation training effect was ~47% larger for adaptation training at peak-velocity 20°/s versus 50°/s (Figure 4). This preferential adaptation at lower peak-velocities is consistent with other mice studies (Koekkoek et al. 1997; De Zeeuw et al. 1998; Iwashita et al. 2001; Kimpo et al. 2005), which used similarly low peak-velocity (between 3-18°/s) adaptation training stimuli. Our results also suggest that velocity-selectivity is more pronounced for gain-increase adaptation. Only training at 50°/s resulted in significant adaptation of the constant-acceleration and constant-

velocity gains in response to transient step stimuli. Studies investigating frequency-selectivity of VOR adaptation have also reported reduced frequency-selectivity at higher frequencies (> 2 Hz) (Raymond and Lisberger 1996). Thus, our finding that velocity-selectivity is reduced for higher adaptation training peak-velocities is consistent with previous studies. Similar to horizontal adaptation we observed velocity-selectivity after cross-axis adaptation training. The difference in torsional gain component (G_x) during sinusoidal testing at $20^\circ/\text{s}$ was $\sim 75\%$ larger compared to testing at $50^\circ/\text{s}$, whereas there was no difference during transient testing with peak-velocities of $100^\circ/\text{s}$ and over.

Two specific hypotheses have been proposed regarding the neural mechanism that guides parameter-selective VOR adaptation. The “frequency-channel theory” postulates that parallel adaptive filters with overlapping bandwidths carry information about the frequency content of head movements and that central adaptation mechanisms modify the tuning of these individual “channels” (for a review see: Fujita 1982; Straka et al. 2009; Dean et al. 2009). This hypothesis explains why the VOR gain in monkeys changes significantly more at the training frequency as compared to other frequencies. It can also provide an explanation for the generally observed phase crossover at the training frequency. However, the velocity-selective adaptation effects observed in this study cannot be explained by a simple change of adaptive filter characteristics. Rather they imply that other mechanisms alongside these frequency-channels are necessary to facilitate velocity-selectivity. The “frequency-channel theory” has also been weakened by the lack of reports of cell groups with selective responses to narrow windows of head movement frequencies as one might predict frequency-channels operate (Jones and Milsum 1971; Schneider and Anderson 1976; Buettner et al. 1978; Angelaki and Dickman 2000; Dickman and Angelaki 2004; Lasker et al. 2008). Instead, vestibular primary afferents, second-order vestibular neurons (e.g., flocculus target neurons) and neurons in the cerebellum were found to modulate their spontaneous firing rate as a

function of head velocity or head acceleration (Raymond and Lisberger 1996; Serafin et al. 1999). A signal transformation of afferent firing rate, which primarily modulates with head velocity and acceleration, into channels that encode the frequency content of a head movement (i.e., Fourier analysis) is an unlikely mechanism for encoding frequency channels.

Minor and colleagues put forward an hypothesis which conjectures that tonic and phasic signal pathways under individual adaptive control are the main mechanism of VOR adaptation (Minor et al. 1999; Clendaniel et al. 2001; Clendaniel et al. 2002). There are several anatomical and behavioral features that support a separation into tonic and phasic pathways. Both, regularly- and irregularly-discharging primary vestibular afferents demonstrate a linear relationship between head velocity and corresponding inter-spike interval (ISI) (i.e. doubling the head velocity without changing the acceleration results in doubling of the afferent firing rate). However, the sensitivity, measured as the change in ISI per head velocity unit differs between regularly- and irregularly-discharging afferents. Regularly-discharging vestibular afferents show low sensitivity to head velocity, but constant sensitivity across a wide range of head accelerations with dynamic properties consistent with tonic pathways. Irregular-discharging vestibular afferents on the other hand show higher sensitivity to changes in head velocity, sensitivity that increases considerably with head acceleration with dynamic properties consistent with phasic pathways (Minor et al. 1999; Lasker et al. 2000; Hullar et al. 2005; Sadeghi et al. 2006). It is hypothesized that VOR adaptation is achieved by individual modification of central tonic and phasic signal gains probably caused by long-term depression (LTD) and long-term potentiation (LTP) at secondary vestibular neurons and Parallel fibre/Purkinje cell synapses (Marr 1969; Albus 1971; Ito 1982; Ito 2002; Boyden et al. 2004; Straka et al. 2009; Menzies et al. 2010; Broussard et al. 2011). Studies in monkeys have shown that these central changes in signal gain are substantially greater in phasic pathways compared to tonic pathways (420% vs. 28%

post gain increase adaptation, 100% vs. 30% post decrease adaptation) (Clendaniel et al. 2001; Clendaniel et al. 2002).

These findings together with the assumption that tonic and phasic afferent signals can be divided into parallel pathways that carry signals with ISI within a defined bandwidth, i.e., velocity and acceleration channels, similar to frequency channels as proposed by earlier studies (Lisberger et al. 1983; Raymond and Lisberger 1996), can explain both velocity-selective as well as frequency-selective effects observed in this and earlier studies, respectively. In a manner analogous to the frequency channel theory, we hypothesize that maximum adaptation is observed when the vestibular testing stimulus has similar acceleration and velocity content as the training stimulus. The velocity and acceleration channel pathways most stimulated by adaptation training are the pathways that are most likely to adapt. So the VOR adaptation effect decreases as the difference between testing and training stimulus velocity and acceleration increases. Because sinusoidal frequency is a function of sinusoidal velocity and acceleration, frequency-selectivity could be a manifestation of combined velocity and acceleration-selectivity. Our data support this hypothesis because we observed good velocity-selectivity, but poor acceleration-selectivity in mice. Without good velocity- and acceleration-selectivity one would predict poor frequency-selectivity, which is what we observed. Conversely, if velocity- and acceleration-selectivity were not the basis for frequency-selectivity, then one would predict that frequency-selectivity would be present even when velocity- and acceleration-selectivity was not, which is not what we observed. Previous studies have shown that for sinusoidal rotations, irregularly-discharging vestibular afferents phase lead regularly-discharging vestibular afferents. This phase lead increases with frequency from $\sim 15^\circ$ at 0.5Hz to $\sim 40^\circ$ at 10Hz (macaque monkey: Sadeghi et al. 2009, squirrel monkey: Minor and Lasker 2009, chinchilla: Hullar et al. 2005 and mouse: Lasker et al. 2008). If velocity-selective adaptation is primarily mediated by the phasic component (and

irregularly-discharging afferent pathways) then one might expect increased phase leads at x1.5 compared to x0.5 adaptation at higher frequencies. However, our phase data, showed increased phase lag at x1.5 compared to x0.5 adaptation at higher frequencies suggesting that velocity-selectivity is mediated by the tonic component (and regularly-discharging afferent pathways).

Lack of frequency-selectivity in mice

The range and magnitude of frequency-selectivity reported in other studies strongly depends on the species and adaptation method used and can range from no measurable selectivity to a highly selective change in VOR gain. While our data clearly shows parameter-selective adaptation as result of training velocity, it also shows reduced frequency selective adaptation. Mice, in contrast to other mammalian species like the chinchilla, rabbit or monkey, have a very low sensitivity of regularly- and irregularly-discharging primary vestibular afferents and irregularly-discharging primary vestibular afferents show only little change in their sensitivity with increasing acceleration (Lasker et al. 2008). Therefore frequency-selectivity, which probably depends on both velocity- and acceleration-selectivity, in mice is very broadly tuned. Results from other mouse studies vary widely, from absence of frequency-selectivity to precise frequency-selectivity as seen in the rabbit (Koekkoek et al. 1997; De Zeeuw et al. 1998; Iwashita et al. 2001; Kimpo et al. 2005). The variation in these results might be explained by the differences in adaptation and eye movement recording techniques. Two out of three studies that investigated frequency-selectivity in the mouse used implanted search coils for VOR recording. While this technique is commonly used in larger animals and humans where it provides unsurpassed precision of eye movement recordings, it is unsuitable for studies in animals with small eyes (Stahl et al. 2000). Studies employing the search coil technique in mice report significantly smaller VOR gains and unusual distorted eye

movements compared to studies using video-oculography. Coil studies also have the potential to produce frequency selective artifacts due to increased inertia at high frequencies. Besides differences in eye-movement recording techniques the studies also vary in their approach to VOR adaptation. None of these previous mouse studies accounted for changes in peak-velocity with increasing frequency, i.e., they kept peak-position constant. Since the stimulus peak-velocity changed with frequency it is likely that velocity-selectivity was incorrectly interpreted as frequency-selectivity.

Conclusion

In this study we show velocity-selective adaptation of VOR gain in the mouse. We hypothesize that frequency-selective adaptation reported in other species is a result of the individual adaptation of signal pathways that encode head velocity and head acceleration, i.e., velocity- and acceleration-selective adaptation. Our mouse data suggests that frequency-selectivity is a function of both velocity- and acceleration-selectivity because when one of these is absent, i.e., acceleration-selectivity in the case of the mouse, then frequency-selectivity is also reduced.

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Table 1: Sinusoidal peak-acceleration

Acceleration	Velocity			
	10 °/s	20 °/s	50 °/s	100 °/s
63 °/s ²	1 Hz	0.5 Hz	0.2 Hz	0.1 Hz
126 °/s ²	2 Hz	1 Hz	0.4 Hz	0.2 Hz
251 °/s ²	5 Hz	2 Hz	0.8 Hz	0.5 Hz
628 °/s ²	10 Hz	5 Hz	2 Hz	1 Hz

Figure Legends

Figure 1. A planetarium projector unit (A) mounted on a gimbal arm was used to project a 360° star field on a dome shaped screen surrounding the head of the mouse (B). Using the gimbal arm the projection unit can be positioned so that the adaptation training is purely horizontal (rotation around z axis) to torsional (rotation around x axis) to allow cross axis adaptation. The mouse (E) was restrained above the projection unit, so that the semicircular canals were aligned with the centre of rotation of the vestibular stimulus and the projection unit. The body of the mouse was held secure in a plastic tube (D) to prevent movement. Upon completion of the adaptation training the projector screen (B) was removed and the two high speed cameras (C) were moved forward for eye-movement recording.

Figure 2. VOR eye movements (inverted) in response to sinusoidal head rotation. Left and right graph show response after 40 minutes gain-decrease (x0.5) and gain-increase (x1.5) adaptation training respectively (head velocity – black; eye velocity – white [mean] and grey [standard deviation]). The middle graph shows the baseline VOR response without prior adaptation (x1).

Figure 3. Comparison of post-adaptation VOR gain for gain-decrease (x0.5) and gain-increase (x1.5) adaptation (gain-decrease – filled circles, gain-increase – open circles). The baseline VOR response without prior adaptation is shown as a dashed line (mean). The surrounding grey area marks the standard deviation of the baseline VOR response. Adaptation (difference between x0.5 and x1.5) was significantly increased when tested at the same velocity used during training (equal adaptation training peak-velocity and testing peak-velocity is marked with #). Our data did not show significant frequency-selectivity of VOR

adaptation, which is apparent by the absence of increased adaptation about the vertical dashed line indicating the adaptation training frequency of 0.5Hz.

Figure 4. Comparison of gain-increase ($\times 1.5$ – open circles) versus gain-decrease ($\times 0.5$ – filled circles) adaptation across testing stimulus peak-velocities (top) and testing stimulus peak-accelerations (bottom). The baseline VOR response is shown by the dashed line (mean) surrounded by a grey area (standard deviation). The adaptation training peak-velocity and peak-acceleration is shown by a vertical dashed line. Peak-acceleration of the sinusoidal testing stimulus was calculated using the first derivative of the velocity stimulus. Peak-acceleration of the adaptation training stimulus was $63^\circ/\text{s}^2$ for adaptation at frequency 0.5Hz and peak-velocity $20^\circ/\text{s}$, and $126^\circ/\text{s}^2$ for adaptation at frequency 0.5Hz and peak-velocity $50^\circ/\text{s}$. There was a significant velocity-selective effect on VOR gain adaptation (see increased adaptation effect when testing peak-velocity matched adaptation training peak-velocity; top row) but no significant acceleration-selective effect (see bottom row).

Figure 5. Comparison of acceleration gain (G_A) and velocity gain (G_V) after sinusoidal gain-increase and gain-decrease horizontal adaptation with adaptation training peak-velocity $20^\circ/\text{s}$ and $50^\circ/\text{s}$. Sinusoidal horizontal adaptation training with low peak-velocity ($20^\circ/\text{s}$) had no effect on G_A and G_V during high velocity, high acceleration transient VOR testing. However, horizontal adaptation training at peak velocity $50^\circ/\text{s}$ had a significant effect on the acceleration component (G_A) and velocity component (G_V) of the transient VOR response when the acceleration stimulus was $1500^\circ/\text{s}^2$ and velocity plateau was $100^\circ/\text{s}$. In contrast, accelerations of $3000^\circ/\text{s}^2$ and $6000^\circ/\text{s}^2$ as well as velocities of $150^\circ/\text{s}$ and $300^\circ/\text{s}$ were not affected by sinusoidal adaptation training.

Figure 6. Results after 60 minutes cross-axis visual-vestibular adaptation training (vestibular stimulus around z axis, visual projection around x-axis). The adaptation training peak-velocity for cross-axis adaptation was 20°/s (first row). Vertical dashed lines indicate the adaptation training frequency of 0.5Hz. The eye-velocity vector has horizontal, vertical and torsional components in head coordinates (z, y and x respectively). Cross-axis VOR testing data (post adaptation training, open circles) was compared to horizontal VOR baseline data (no adaptation training, dashed line [mean] surrounded by grey area [standard deviation]). Adaptation training resulted in an increase of the gain-x (torsion) of the VOR accompanied by a decrease of the gain-z (horizontal). The adaptation effect was significantly larger at 20 °/s (same velocity used during adaptation training) compared to 50 °/s. Training frequency did not affect cross-axis VOR adaptation.

Figure 1 (colour version and black and white version)

Figure 2

Adaptation Training and Testing stimulus had equal frequency and peak-velocity

Figure 3

Figure 4

Figure 5

Figure 6