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Incremental angular vestibulo-ocular reflex adaptation to active head rotation

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Abstract

Studies on motor learning typically present a constant adaptation stimulus, corresponding to the desired final adaptive state. Studies of the auditory and optokinetic systems provide compelling evidence that neural plasticity is enhanced when the error signal driving adaptation is instead adjusted gradually throughout training. We sought to determine whether the angular vestibulo-ocular reflex (aVOR) may be adaptively increased using an incremental velocity error signal (IVE) compared with a conventional constant and large velocity-gain demand ($\times 2$). We compared the magnitude of aVOR gain change for these two paradigms across different motion contexts (active and passive). Seven individuals with normal vestibular function and six individuals with unilateral vestibular hypofunction (UVH) were exposed to the IVE and $\times 2$ (“control”) aVOR demand tasks. Each subject participated in 10 epochs of 30 active head impulses over a 15 min aVOR gain increase training session separately for the IVE and $\times 2$ paradigms, separated by either seven days (normal subjects) or 14 days (UVH subjects). For both normal and UVH subjects, both paradigms led to aVOR gain increase during the training session. For the normal subjects, the IVE paradigm led to larger aVOR gain change after training compared to the $\times 2$ paradigm, for both active (mean $17.3 \pm 4\%$ vs. mean $7.1 \pm 9\%$, $P = 0.029$) and passive (mean $14.2 \pm 5\%$ vs. $4.5 \pm 8\%$, $P = 0.018$) head impulses. For subjects with UVH, IVE produced a greater change in aVOR gain for active head impulses (mean $18.2 \pm 9.2\%$ vs. mean $-6 \pm 3.8\%$, $P = 0.003$). However, aVOR gains for passive head impulses were less consistent after IVE, with only two subjects displaying greater aVOR gain with this incremental paradigm. Some individuals generated compensatory saccades that occurred in the same direction of the deficient aVOR during either training paradigm. Our data suggest that the aVOR is modifiable when the velocity error signal is presented incrementally, and that this adaptation stimulus is particularly effective in the case of unilateral vestibular hypofunction. This has implications for programs of vestibular rehabilitation, where active head rotation is prescribed as a means to improve gaze stability.

Keywords

Vestibulo-ocular reflex; Saccades; Vestibular rehabilitation; Adaptation

Introduction

Loss of peripheral vestibular function can cause significant disability, in part because of effects on the aVOR, which is the predominant oculomotor system that stabilizes visual gaze during rapid head rotation. Currently, the only available treatment for loss of vestibular function consists of rehabilitation techniques that attempt to improve the aVOR through active exercises requiring stabilization of gaze (eye orientation with respect to space) during head movements, to encourage central aVOR gain (eye velocity/head velocity) adaptation, enlist other oculomotor systems, or employ sensory substitution to compensate for the peripheral vestibular sensory loss. Recently, these gaze stabilization exercises have been shown to improve the aVOR gain during active head rotations (Schubert et al. 2008).

The aVOR retains its adaptive capabilities in the presence of unilateral hypofunction (UVH) and can be enhanced using visual and vestibular stimuli that create retinal image slip (Paige 1994; Szturm et al. 1994; Viirre and Sitarz 2002). This is the basis of vestibular rehabilitation exercises. Retinal slip that induces an aVOR gain change occurs when head and target velocity are incongruent. In humans, a number of aVOR adaptation studies have demonstrated a robust capability for changing the normal aVOR by coupling head motion with target motion (Gauthier and Robinson 1975; Gonshor and Melvill Jones 1976a, b), thereby eliciting retinal slip in the form of a velocity error signal. Although retinal slip is an effective means of aVOR adaptation, other error signals can also be used to modify the aVOR, including position error signals (Eggers et al. 2003) and after-image tracking (Yasui and Young 1975; Shelhamer et al. 1995).

The majority of aVOR gain adaptation studies have been performed using a velocity error signal that seeks a large change in the aVOR “all at once,” such as the $x(-2)$ paradigm. In this paradigm, target and head velocity are equal but opposite in direction, thereby requiring an aVOR eye velocity twice as large as head velocity, with a resulting large demanded change in the aVOR. Non-vestibular motor control studies and auditory perception studies suggest that learning tasks which incorporate an incremental error signal are more effective in driving neural plasticity and learning (Kagerer et al. 1997; Nagarajan et al. 1998, 1999; Kilgard and Merzenich 2002). Preliminary studies suggest that the aVOR, too, can be modified using an incremental retinal slip demand during self-generated head rotations. Two studies investigated changing the aVOR gain during self-generated head motions using an incremental stimulus (magnification factor) that was always 3–5% greater than the prevailing aVOR gain (Viirre et al. 1998; Viirre and Sitarz 2002). Both studies investigated subjects with impaired vestibular function; normal controls were not included. Passive whole-body rotational chair testing was used to determine aVOR gain change. Each study reported that the greatest amount of aVOR adaptation occurred at the highest frequency tested (0.64 Hz), which was much lower than both the frequency content of the self-generated head motion employed in the study and that of quick head movements encountered in daily life (Grossman et al. 1988).

Another commonality among most aVOR gain adaptation studies involves measuring the extent of adaptation using passive, low velocity head rotations. Given the preference of rehabilitation to mimic natural circumstances by prescribing active head rotation exercises, a need exists to understand strategies of gaze stability with active head impulses and to learn of any differences in gaze stability between active and passive head rotations. To our knowledge,

no study has investigated the magnitude of incremental aVOR gain adaptation using head velocities typical of daily life (Grossman et al. 1988).

The purpose of this study was to compare aVOR gain adaptation achieved using an incrementally adjusted velocity error signal with a more conventional, larger velocity error signal in normal and subjects with abnormal vestibular function. We hypothesized that for self-generated head rotations, individuals would have a greater magnitude of adaptation with an incremental aVOR demand task compared with a constant, large aVOR demand task. We measured the extent of aVOR gain adaptation using active and passive head impulses. Our data support the hypothesis that incremental aVOR adaptation is an effective stimulus to enhance aVOR gain in people with normal vestibular function and UVH.

Methods

We studied seven normal subjects (mean age 31.4 ± 9.6 years, range 22–47 years) that had no complaints of vertigo, dizziness, or imbalance. We also studied six subjects with unilateral vestibular hypofunction (UVH, mean age 58.5 ± 12 years, range 38–67 years). The diagnosis of UVH was based on history of vertigo and imbalance, physical exam revealing corrective saccade following head impulse testing (Halmagyi and Curthoys 1998), and abnormal electronystagmography exam ($>20\%$ asymmetry between slow component eye velocity generated with four binaural irrigations at seven degrees Celsius above or below body temperature). Participation in this study was voluntary and all subjects consented to be a part of this project in accordance with a protocol approved by the Johns Hopkins University School of Medicine Institutional Review Board.

Scleral search coil technique

Monocular eye movements were recorded in three rotational dimensions using a pair of search coils embedded in a silicone annulus placed on the left eye. An identical search coil pair embedded in a bite block was used to measure head rotation. Analog signals were low-pass filtered with a single-pole analog filter that had a 3-dB bandwidth of 100 Hz. Eye and head coil data were sampled at 1,000 Hz at 16-bit resolution. Sampled signals were filtered with a zero-phase low pass digital finite impulse response filter with 50 Hz bandwidth, and then 3D rotational positions and velocities were computed using rotation vectors (Migliaccio and Todd 1999). The gain of the system is linear throughout the oculomotor range. The resolution is 0.1° for horizontal and vertical movements.

Each subject was tested while seated upright and centered within a uniform magnetic field, with the interpupillary line in the Earth-horizontal plane. The subject's head was positioned so that Frankfort's line (from the superior-most point of the bony-cartilaginous junction of the external auditory canal to the lowest point of the cephalic edge of the infraorbital rim) was also in the Earth-horizontal plane (Schubert et al. 2006).

Passive and active head impulse test

A passive head impulse consists of an unpredictable, manual head rotation (Halmagyi and Curthoys 1998) useful to examine the angular VOR. The characteristics of our unpredictable head impulses were peak amplitude $\sim 15^\circ$, velocity $\sim 180^\circ/\text{s}$ and acceleration $\sim 3,500/\text{s}^2$. Before the start of each head impulse, the subject's head was realigned as described above for 200 ms, enabling eye and head angular position to be calibrated in vivo while the subject fixated a rear-projected laser target. The laser target was positioned directly in front of the subject at 138 cm along the naso-occipital axis. Passive head impulses were delivered manually in the horizontal canal plane. An active head impulse consisted of having the subject focus on the laser spot target, which flashed when the head was in starting position and had been still for 200 ms.

Once the subject recognized the flashing target, he or she was instructed to rotate the head to the right or left naturally but rapidly. The characteristics of the subjects' predictable head impulses were peak amplitude $\sim 25^\circ$, velocity $\sim 170^\circ/\text{s}$ and acceleration $\sim 1,300/\text{s}^2$. For all head-impulse testing, the room was completely dark with the exception of the laser target, which extinguished during the head rotation. We measured the effect of the IVE and x2 training paradigms with active and passive head impulse testing by comparing aVOR gain before and after the training paradigms.

Laser projection

We used a laser and real-time 2D mirror deflection system for display of a visual target on a rear-projection screen. The laser was placed on the opposite side of the screen from the head and equidistant from the screen. The image from the rear-projected laser was placed at the virtual image point of the head, which pre-compensates for the pincushion and barrel distortion that would otherwise occur in display of images on a flat surface. The sample interval is 1 ms. The input to output settling time is ≤ 3 ms. Therefore, a maximum of 5 ms latency exists between head and target motion. We controlled target position of the laser image using real-time head and eye horizontal and vertical positions. The laser was calibrated to 2D head and eye motion for aVOR adaptation—along both horizontal and vertical directions—to provide a more natural adaptation stimulus, as it may have been difficult for subjects to constrain their heads to one-dimensional motion (horizontal only).

aVOR training paradigms

Order of enrollment in the IVE and x2 paradigms was randomized and separated by seven days for the normal controls and fourteen days for the subjects with UVH. For both aVOR training paradigms, subjects were asked to make self-generated (active) head impulses from a neutral, neck-centered starting position alternating to the left and right. Once the head rotated eccentrically, subjects were instructed to pause and return to center before performing a rotation to the opposite side. The eccentric head rotations were approximately $\pm 25^\circ$ while viewing the laser image. All subjects performed about 300 self-generated head impulses, divided into 10 epochs of 30 head impulses with 30–60 s rest periods between epochs. Visual targets are necessary to change the magnitude of the aVOR; therefore, from this point forward we will use the term vVOR to infer aVOR plus a visual target—which is how we trained the aVOR. However, for post training differences, we refer to the aVOR (absence of a visual target).

Incremental aVOR training

We defined “incremental” as training due to a stimulus that requires gain change in response to a gradual and progressively changing stimulus. For this paradigm, the subject was asked to make 30 self-generated head rotations while viewing a rear-projected laser dot that moved with 10% of the head velocity, in the opposite direction (epoch 1, asking for a vVOR gain increase of 10%). During a brief rest period, the target velocity was manually increased by another 10% (now 20% of the head velocity) for an additional 30 head rotations. This incrementing continued until the subject had made approximately 300 self-generated head rotations (the final 30 asking for a 100% gain increase, or x2 adaptation), which typically occurred within 15 min.

x2 aVOR training

All subjects also participated in the x2 (control) experiment, in which self-generated head impulses were made while viewing a rear-projected laser dot that moved at the same velocity as the subject's head but in the opposite direction (x2 gain demand). Similar to the IVE paradigm, the subject was asked to make 30 self-generated head rotations. After a brief pause, the subject performed another 30 head rotations (epoch 2), and this sequence was repeated until 300 head impulses were achieved. This paradigm was completed within 15 min.

Online horizontal aVOR gain determination

Peak eye velocity, head velocity and vVOR gain were assessed on-line during each epoch of training (every 1–2 min). This enabled us to monitor head velocities during the training epochs, which were encouraged to be greater than 130°/s. This peak head velocity was chosen to impart a stimulus velocity greater than the visual following mechanism (smooth pursuit, <100°/s) in order to produce a vestibular-generated eye rotation. Mean vVOR gain for rightward and leftward head rotations was approximated during data acquisition by calculating the ratio of head and eye velocity at 30 ms prior to peak head velocity for each head impulse.

Offline horizontal aVOR gain data analysis

Angular positions of the eye and head with respect to space, and eye with respect to head, were represented by rotation vectors (Haslwanter 1995; Migliaccio and Todd 1999). Head-in-space, eye-in-space, and eye-in-head velocity vectors were calculated from the corresponding rotation vectors (Hepp 1990) and expressed with reference to the same coordinate frame (Aw et al. 1996).

The time of onset of each head impulse was identified by fitting a polynomial to head-in-space velocity versus time. The time at which the magnitude of the fitted curve became greater than 2% of the curve's peak magnitude (typically this threshold was ~4°/s) was defined as the time of onset. A similar approach was used to identify the time of onset of the eye movement response. In addition, we determined latency of the aVOR by comparing the difference in milliseconds between when the head and eye velocities reached 10°/s.

As the time between the onset of a head impulse and its maximum velocity was less than 150 ms, analysis of the impulse data was restricted to a period of 150 ms from the onset. Trials of head impulse data that included blinks or in which the subject did not fixate the target at the onset of head rotation were not included in the analysis. Depending on the subject, approximately 10–20% of trials were rejected for this reason. Horizontal aVOR gains for head impulses were calculated by dividing inverted horizontal eye velocity by horizontal head velocity during the 30 ms period prior to peak head velocity, and these gains were averaged across trials (Schubert et al. 2006). Positive yaw velocities correspond to head rotations to the left.

Statistical analysis

Based on power analysis using our mean effect size of 0.18 (absolute change in aVOR gain) from the IVE paradigm and –0.06 from the x2 paradigm (and their relative standard deviations), 100% statistical power was established with six UVH subjects (Dawson-Saunders and Trapp 1994).

Analysis of variance (ANOVA) was used to compare difference in age, amplitude, velocity and acceleration of the head rotations between healthy controls and subjects with UVH. Repeated measures multi-variate ANOVA (MANOVA) was used to assess differences across paradigms with respect to VOR gain for epoch (training sessions 1 through 10), test (pre and post), and context (active and passive). When the overall effects of the model were significant, ANOVA and post hoc *t* test were used to assess significances. *t*-test assuming unequal variance was used to compare acceleration, velocity, and position across active and passive head rotations. All levels of significance were assessed at $\alpha < 0.05$. VOR gains are presented as means $\pm$ 1 SD.

Results

Demographic data, caloric asymmetry and directional preponderance are presented in Table 1. One of the subjects with UVH (MM) had difficulty making active head impulses of the velocity we sought and has not been included in the following data.

Normal subjects

Angular vVOR gain change during active head impulse training—There was no difference in head velocity between active head impulse testing and active vVOR gain training (ANOVA, $P = 0.31$). There was no difference in vVOR gain change for head rotations to the right or left for the IVE (two tail t -test $P = 0.77$) or x2 (two tail t test $P = 0.4$) paradigms. vVOR gain data for rightward and leftward head impulses have therefore been combined.

Overall, we found no difference in magnitude of vVOR gain between the IVE and x2 paradigms during the first nine active training head impulses (epochs 1–9, MANOVA $P \geq 0.09$). Four of the seven normal subjects had greater vVOR gain change during the IVE training paradigm (mean $37 \pm 13\%$) compared to their vVOR gain changes during the x2 paradigm (mean $9 \pm 16\%$, $P = 0.03$). Two normal controls had similar vVOR gain change to IVE ($24 \pm 5\%$) and x2 ($33 \pm 9\%$) paradigms ($P = 0.14$), while one subject (CC) did not show an increased vVOR gain during the x2 paradigm (Fig. 1a).

However, the difference between initial vVOR gain and vVOR gain during the final training epoch (last 30 impulses) was greater for the IVE paradigm (mean $32 \pm 12\%$) than the x2 paradigm (mean $19.5 \pm 18\%$, MANOVA, $P = 0.03$). These data suggest that the magnitude of vVOR gain increase is larger with an incremental error signal, though both paradigms do manifest vVOR gain increase.

Post-training angular aVOR gain adaptation—Angular vestibulo-ocular reflex gain adaptation with the IVE paradigm demonstrated a larger aVOR gain change than the x2 paradigm across most subjects, for both active and passive head impulses (Fig. 2a, b). Combined mean aVOR gain change between the IVE and x2 paradigms for active head impulses was $17.3 \pm 4\%$ versus $7.1 \pm 9\%$ ($P = 0.03$) and $14.2 \pm 5\%$ versus $4.5 \pm 8\%$ ($P = 0.02$) for passive head impulses. Two subjects (CC and DD) had no aVOR gain change following the x2 paradigm.

aVOR latency—Angular vestibulo-ocular reflex latencies for rightward and leftward head rotations were lumped for analysis. There was no difference in the latencies of the aVOR for passive head impulses before or after training for the IVE (PRE 6.9 ± 5.4 ms, POST 8.5 ± 5.4 ms) or x2 (PRE 6.3 ± 4.3 ms, POST 8.1 ± 4.3 ms) paradigms in five of seven normal subjects ($P \geq 0.19$). However, two of the normal subjects had evidence for aVOR responses that started before the passive head impulse (-5.2 ± 1.7 ms and -6.7 ± 4.1 ms) during participation in the x2 experiment. After the x2 training, the aVOR latencies in these two subjects were similarly reduced (-5.9 ± 1.8 ms and -6.5 ± 3.5 ms, $P > 0.2$). The aVOR latencies for these two individuals at the time of participation in the IVE paradigm were PRE 14.4 ± 5.7 ms and 6.7 ± 4.1 ms, which were not different from the post measures of 16.1 ± 3.4 ms and 6.6 ± 3.5 ms, respectively ($P > 0.21$). There was no difference between pre and post aVOR latencies for the x2 paradigm ($P > 0.12$).

Compensatory saccades—A compensatory saccade (CS) is a saccade that occurs during the head rotation and in the direction of the deficient aVOR (Tian et al. 2000; Schubert et al. 2006). All normal control subjects used CS during the training session for both paradigms. As a group, normal subjects exhibited no difference in the number of CS generated for either paradigm (IVE 9.6 ± 9.2 vs. x2 26 ± 31 , $P = 0.22$). However, individual differences did exist;

one subject used more CS during the IVE compared with the x2 paradigm, which was useful to assist gaze position error (Fig. 3). Another individual did not initially generate any CS for the x2 paradigm until later in the training session.

Unilateral vestibular hypofunction

Angular VVOR gain change during active head impulse training—Each of the five subjects with UVH demonstrated vVOR gain change to varying amounts during both paradigms (Fig. 1b). There was no difference in the amount of vVOR gain change during training sessions (epoch 1–epoch 10) for the IVE or x2 training paradigms (MANOVA $P > 0.44$). For ipsilesional head rotations, the combined (all UVH subjects) mean vVOR gain change increased from the PRE training measure to the final training session (epoch 10) by $35 \pm 19.7\%$ during the IVE paradigm and by $48 \pm 22\%$ for the x2 paradigm (two tail t test, $P = 0.36$). For contralesional head rotations, the combined mean vVOR gain change increased from the PRE training measure to the final training session by $32 \pm 28\%$ during the IVE paradigm and by $66 \pm 59\%$ for the x2 paradigm (two tail t test, $P = 0.2$). There was no difference in the amount of vVOR gain change between ipsilesional and contralesional head impulses for the IVE (two tail, $P = 0.76$) or x2 (two tail, $P = 0.4$) paradigms. These data suggest that both paradigms lead to increased vVOR gain during the training session.

Post-training aVOR gain adaptation: ipsilesional head impulses—For active head impulses, all UVH subjects had greater mean aVOR gain change to ipsilesional head rotations after participation in the IVE paradigm ($18 \pm 9.2\%$) compared with the x2 paradigm ($-6 \pm 3.8\%$), ($P < 0.002$). After participation in the IVE paradigm, four of five subjects had at least a 10% increase in aVOR gain from pre to post training, while one subject (II) demonstrated a more modest 5% increase, see Fig. 4a. Therefore, although some variability exists in the amount of adaptation, IVE appears to be a superior method to adapt the aVOR in patient subjects.

For passive head impulses, there were no group differences between the IVE and x2 paradigms (MANOVA $P > 0.42$), Fig. 4b. Of note, however, one subject (HH) had a 417% increase to passive head impulses (0.17 – 0.88 , Fig. 5). We were surprised by this large change in aVOR gain for passive head impulses following the x2 paradigm; special attention was paid to this data to ensure that artifacts were not present which would produce an artificially large gain increase. These data suggest this subject's clear preference to use a large velocity error signal for gain modification.

Post-training aVOR gain adaptation: contralesional head impulses—We did not find any differences in aVOR gain adaptation between IVE and x2 paradigms for contralesional active head impulses (IVE $16 \pm 22\%$ vs. x2 $23.4 \pm 29\%$, two-tail, $P = 0.37$), or contralesional passive head impulses ($6 \pm 13\%$ vs. x2 $21 \pm 29\%$, two-tail, $P = 0.28$).

aVOR latency—Although individual variability in aVOR latencies between pre and post measures were considerable; as a group, aVOR latencies for ipsilesional head rotations were larger than for contralesional rotations in both paradigms (ANOVA $P < 0.02$). Interestingly, comparisons between pre and post aVOR latencies within the x2 paradigm showed shorter latencies at the post-training measure for both ipsilesional ($P < 0.0001$) and contralesional ($P < 0.0001$) head rotations when compared with the pre aVOR latencies. This was not the case for the IVE paradigm, Table 2.

Compensatory saccades—There was no difference within the group or within an individual concerning the number of CS generated between the two paradigms for ipsilesional head impulses during the training session (IVE 10.7 ± 7.1 vs. x2 9.1 ± 7.9 $P = 0.29$). Similarly,

there was no difference in the number of CS generated after the training session, for either paradigm (ANOVA $P > 0.7$) or active vs. passive head impulse testing (ANOVA $P > 0.54$).

Discussion

Few data exist exploring the extent of aVOR gain adaptation during self-generated, head-only impulse rotations for normal subjects or individuals with UVH. Our data support earlier work by Viirre et al. establishing that the aVOR can be enhanced in vestibular hypofunction using a retinal velocity error (retinal slip) signal with a gradually increasing adaptive demand (Viirre et al 1998; Viirre and Sitarz 2002). Viirre and colleagues used active head movements coupled with a magnified visual field as the adapting stimulus, however, the extent of aVOR gain adaptation was measured with passive whole-body sinusoidal rotation. Interestingly, the largest magnitude aVOR gain changes reported occurred at the highest frequency tested. This suggests the reported aVOR gain changes may have been greater had the authors tested responses using head velocities of spectral content and peak velocity similar to the stimuli used during training. To our knowledge, no one has used active head impulses to study aVOR gain adaptation nor measured the adaptation with active and passive head impulses.

Our data suggest the ipsilesional aVOR can be adapted in a short time with head velocities similar to those encountered in daily life. Adapting the aVOR with head movements incorporating high-frequency content seems most appropriate since the aVOR remains the primary mechanism of gaze stability for head rotational velocities above 100°/s. Our data support that rehabilitation should incorporate head impulse rotations in addition to the typical sinusoidal head rotations used during gaze-stability exercises (Schubert et al. 2008). It is noteworthy that four of five subjects with UVH had a minimum 10% increase in aVOR gain after just 15 min of training.

We have shown that both an incremental error signal and a large error signal (x2) are effective at changing vVOR gain during the training period in normal and patient subjects. However, only the incremental paradigm elicited an adaptive response to active head rotations that persisted throughout the post-training active head impulse testing in patients with UVH. This suggests that the incremental training paradigm is superior for aVOR gain adaptation to active head impulses testing in UVH. The difference we found in aVOR gain adaptation (post measure) between active incremental compared with active x2 may be a reflection of how the error signal is being perceived by the individual. For the x2 paradigm, the error signal may have been too large for the adaptive process to create a lasting modification—perhaps due to the brain perceiving the stimulus as invalid. In comparison, the incremental paradigm may provide a small enough error signal such that the brain is ‘deceived’ into believing the perceived error signal is legitimate. In this case, the brain may resolve to attempt a more enduring modification. This explanation and our data are related to the “credit assignment” problem in motor learning, where the adaptive processes must determine from which source a given disturbance or perturbation originates—changes in the organism or changes in the environment (Körding et al. 2007). As it relates to our data, the IVE paradigm exposes the adaptive process to a signal that is small enough to appear permanent (i.e., possibly from a pathological condition) and therefore should be remembered, while the x2 paradigm presents a disturbance that is likely to be interpreted as more transient (i.e., an artificial external perturbation) and therefore not to be remembered.

For passive head impulses however, we report mixed results between the two paradigms concerning the magnitude of aVOR gain adaptation in both normal and subjects with UVH. This suggests that prediction is not an exclusive context of motor learning in the aVOR, since both predictable (active) and unpredictable (passive) head impulses manifested aVOR gain adaptation following a predictable (active) training paradigm. One reason for the variety in

aVOR gain adaptation to passive head impulses is that individuals have unique strategies for gaze stabilization (Kasai and Zee 1978). Different strategies include aVOR gain change (Viirre et al. 1998; Schubert et al. 2008), recruitment of CS during the head rotation (Black et al. 2005; Della Santina et al. 2002; Schubert et al. 2008), recruitment of catch up saccades after the head rotation (Eggers et al. 2003), enhancement of the cervico-ocular reflex (Kasai and Zee 1978; Bronstein et al. 1995; Schubert et al. 2004), and increased smooth pursuit for low-velocity head rotations (Bockisch et al. 2004). Together this suggests that aVOR gain adaptation is dependent on unique strategies and preferences within the individual.

aVOR latency

We were surprised to find some normal controls had negative aVOR latencies; the eye rotation preceded the passive head rotation. Careful examination of the traces did not reveal any obvious clues. The eye response was smooth right from the start and did not appear saccadic; neither did the response change when the head started to move. We can not exclude that this response was not due to an inadvertent cue (subtle arm motion or timing difference between the examiners hands contacting the subjects head and eventual head rotation). It is possible these two subjects were able to predict the onset of the head rotation from some proprioceptive cue unintentionally provided to the subjects scalp. This cue may have helped the subject to anticipate the intended head direction and onset, which suggests that proprioceptive cues may also be a mechanism of gaze stability. Barnes and Paige have previously shown that anticipatory smooth eye movements (ASEM) do arise when there is a cued expectation of an intended head motion (Barnes and Paige 2004); however, this occurred only when combined with a visual target and VOR suppression. In contrast, although our paradigm initially Xashes a visual target, this is extinguished during head rotation and therefore the eye rotations we report are not visually guided.

The velocities of the ASEM we report are much higher than previously reported ($<50^\circ/\text{s}$) (Kowler and Steinman 1979; Barnes and Paige 2004, Burke and Barnes 2006). ASEM are believed to be generated from the smooth pursuit system because of their similar velocity magnitudes and latencies (~ 200 ms). Recently however, Burke and Barnes showed smooth pursuit latencies for predictable paradigms are much lower (0–39 ms) than those typically reported for paradigms involving random guided pursuit targets (Burke and Barnes 2006). Our findings of early latency, high velocity ASEM suggests some individuals may be able to use cues to generate an eye rotation that can assist gaze stability, in anticipation of an intended head rotation.

We did not record linear head motion; however it is unlikely that the linear VOR contributed to either aVOR gain change or negative latencies that we report. It has been shown that for self generated head rotations with target distance of 150 cm (similar to our 138 cm), the ratio of RMS linear VOR velocity to RMS angular VOR velocity is 0.1, which indicates very negligible linear VOR contribution on angular VOR (Crane and Demer 1997). In addition, the latency of linear VOR has been reported to be between 10 and 20 ms (Crane and Demer 1997; Ramat and Zee 2003), which does not explain the negative latency behavior we report. Finally, it is likely that any head translation would be phase locked with the inverse of a head rotation (such as occurs during walking, running, and head movement in standing); head rotation to the right is coupled with head translation to the left (Crane and Demer 1997). In this case, the linear VOR would be anticomensatory with the angular VOR.

Influence of visual following on aVOR gain adaptation

Each of our paradigms included certain amounts of time when the relative target velocity (target and head velocity) were less than $100^\circ/\text{s}$, and smooth pursuit (foveal or peripheral) could have contributed to the aVOR gain change we report. While it is possible pursuit contributed to the

aVOR adaptation, we believe the contribution would be negligible. There is no evidence for the pursuit system being 'enhanced' (i.e. a compensatory strategy) in patients with UVH. Although subjects with bilateral vestibular hypofunction have been shown to have 'enhanced' smooth pursuit, this was only at low velocities (<40 d/s, Bockisch et al. 2004). Secondly, while it is true that visual following mechanisms have been shown to increase VOR gain in normal subjects, this occurred at velocities much lower than our training head velocities (50°/s vs. $\geq$ 130°/s) (Shelhamer et al. 1994).

To further investigate the possibility of visual following contributing to the aVOR gain changes we report, we determined the duration the relative target speed was below 100°/s. During active head rotations, the greatest difference in duration of time that the relative target velocity was below 100 d/s for the incremental and x2 paradigms was 48 ms; we have added a Figure to illustrate this point (Fig. 6). Of course, as the incremental paradigm progressed, the duration of time that the target velocity was <100 d/s decreased. This suggests that our two paradigms do provide a duration of time when the peak velocities are within the limits of visual following, however, the difference between the paradigms is relatively small.

Compensatory saccades

Our data suggest that compensatory saccades can be recruited by subjects with vestibular hypofunction during exposure to an aVOR gain adaptation paradigm that uses a velocity error signal to continually drive the aVOR greater than its baseline level. The occurrence of CS helps to reduce gaze position error (Schubert et al. 2002; Black et al. 2005).

Conclusion

In UVH subjects, ipsilesional aVOR gain can be increased in a short time using a visual-vestibular conflict paradigm incorporating quick, active head impulses and an incremental velocity error signal. Presenting the velocity error signal in an incremental manner led to at least a 10% change in aVOR gain in UVH subjects. While we found that use of a velocity error signals is useful to recruit CS for assistance with gaze stability, the data suggest the primary explanation for the gain adaptation is due to aVOR slow phase change, not increased use of compensatory saccades or anticipatory eye rotations. These data suggest that rehabilitation strategies focused on improving aVOR function in patients with UVH should use an error signal that is incrementally adjusted based on the individual's present aVOR performance.

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Fig. 1.

VOR gain during pre-training active head impulse testing (aVOR) and ten training epochs (vVOR) for both incremental (IVE) and x2 paradigms in **a** normal control subjects and **b** subjects with UVH. The first data point in each set of symbols reflects the PRE VOR gain for active head impulses in complete darkness (aVOR), to be compared with the following ten training epochs in the dark while viewing the visual target (vVOR). *Capitalized letters* denote individual subjects. For the normal controls, each data point reflects the mean VOR gain of 30 head impulses in a given epoch for leftward (*Lt*, first series of data) and rightward (*Rt*, second series of data) head rotations for each paradigm. For the UVH subjects, each data point reflects the mean VOR gain of 30 head impulses in a given epoch; both ipsilesional and contralateral head rotations are presented for each paradigm. Note the initial aVOR gains before training in subjects HH, KK, and LL; illustrating that aVOR gain during active head rotation in certain individuals with UVH can be near normal

Fig. 2.

Percent aVOR gain adaptation in normal control subjects after ten training epochs (active head impulses) for active (**a**) and passive (**b**) head impulses. *Capitalized letters* denote individual subjects. Dark vertical line separates group mean with 1 SD error bars. *IVE* incremental velocity error paradigm; *x2* times 2 paradigm

Fig. 3.

Eye and head velocity and position, showing compensatory saccades occurring only during the incremental training paradigm. **a, b** The incremental paradigm for the first and final training epochs. **c, d** The same training epochs for the x2 paradigm. Note that the (inverted) eye velocity is larger than the head velocity in the first and final epochs (**a, b**) for incremental only. Also note the opposing direction of the saccades in (**c, d**). *Position plots* show that the compensatory saccades (arrow) assist in the correction for gaze position error only in the incremental paradigm. Note the reduced aVOR gain from the position plot following the x2 paradigm, the result of the quick phase saccades worsening the gaze position error

Fig. 4.

Percent aVOR gain adaptation in subjects with UVH after ten training epochs (with active head impulses) for active (**a**) and passive (**b**) head impulses. Dark vertical line separates group mean with 1 SD error bars. Capitalized letters denote individual subjects. Only the incremental paradigm was found to have aVOR gain adaptation during active head impulses. Stippled border of x2 bar plot for subject HH in panel B reflects data from UVH subject that had 417% aVOR gain increase, scaled to fit

Fig. 5.

Mean and 1 SD head and eye velocity and acceleration plots illustrating aVOR gain adaptation during passive head-impulse testing after active head-impulse training in one subject with UVH. This subject had 417% aVOR gain increase for ipsilesional head rotations following the x2 paradigm. Data from **a** and **c** are for contralesional head rotations; **b**, **d** are from ipsilesional head rotations. **a**, **b** show eye and head traces during passive head impulse testing before the x2 training paradigm; **c**, **d** illustrate the post aVOR gain training responses. Eye traces inverted for ease of comparison. In **c**, note the eye acceleration precedes the head stimulus; aVOR gain increased by 68% for contralesional head rotations. In **d** note the normalized eye velocity and acceleration traces after the training paradigm

Fig. 6.

Relative target velocity at different gain levels. **a** Graph illustrates difference in target velocity relative to actual head velocity for both the IVE and x2 paradigms. *Bold plot* represent initial head velocity, *red plots* indicate the IVE gain values from 1.1 to 1.9, *green plot* represents the final IVE and x2 relative target velocities. *Stippled drop down lines* indicate the duration smooth pursuit may have contributed toward the adaptation, at velocities less than 100°/s. **b** Outer concentric ring represents data from the x2 paradigm while inner ring represents data from the IVE paradigm. *Each ring* illustrates the training epoch (numbered 1 through 10) and the duration in millisecond that target velocity was at or below 100°/s. Note the initial difference between x2 and IVE paradigms is 48 ms and reduces to 10 ms at the final training epoch

Table 1

Subject characteristics

	<i>N</i>	Age ^a	Percentage of caloric asymmetry (affected side)	Ice water response	Directional preponderance
UVH	6	58.5 ± 12	61.2 ± 32%		38.5 ± 47.7%
HH		61	100 (right)	0	7 left
II		57	33 (left)	n/a	100 left
JJ		55	100 (left)	0	10 right
KK		73	63 (right)	0	100 left
LL		38	32 (right)	Reversal	8 right
MM		67	39	0	6 right
Normal Controls	7	31.4 ± 9.4	n/a	n/a	n/a

Caloric asymmetry, unilateral weakness = [(right cold + right warm) – (left warm + left cold)/right cold + right warm + left cold] × 100; reversal – nystagmus direction reversed between prone and supine irrigations indicating residual function; Directional preponderance = [(right cold + left warm) – (right warm + left cold)/right cold + left warm + right warm + left cold] × 100

UVH unilateral vestibular hypofunction, mean data; n/a not performed

^aSignificant difference between age of UVH and normal control subjects (*P* = 0.0008)

Table 2

aVOR latencies for ipsilesional and contralesional passive head impulse rotations

Subject	<u>INC</u>		<u>x2</u>	
	Ipsilesional PRE (POST)	Contralesional PRE (POST)	Ipsilesional PRE (POST)	Contralesional PRE (POST)
HH	16.5 ± 3.2 (25.4 ± 7.1)	9.2 ± 1.3 (16 ± 6.8)	33.5 ± 5.9 (−4.4 ± 3.2)	6.9 ± 2.2 (−18 ± 2.8)
II	21.8 ± 2.2 (20.1 ± 5.1)	13.3 ± 3.8 (17 ± 3.5)	5.5 ± 1.8 (7.1 ± 2.6)	3.9 ± 2.3 (6.6 ± 2.1)
JJ	35.3 ± 14.4 (32 ± 3.7)	32.3 ± 8.7 (14.2 ± 3.9)	14.9 ± 6.7 (26 ± 7.7)	3 ± 1.5 (8 ± 4.9)
KK	10 ± 6.7 (8 ± 4)	15 ± 4.2 (19 ± 8)	6.6 ± 3.4 (8.5 ± 4.4)	9.8 ± 4.1 (11 ± 4.7)
LL	7.4 ± 2.6 (7 ± 2.2)	3.6 ± 1.1 (3.1 ± 1.8)	8.3 ± 2 (7.8 ± 2.2)	5.3 ± 2 (4.8 ± 1.3)
Mean ± 1 SD	15 ± 10.3 (20.6 ± 11.7) ^b	11 ± 10.2 ^a (11 ± 7.6)	15.4 ± 11 (11.3 ± 11) ^b	6.6 ± 3 ^a (2 ± 10.4)

INC incremental; x2 times 2

^aMean ipsilesional aVOR latencies significantly longer than contralesional latencies for both INC and x2 paradigms ($P < 0.000001$)^bPre and Post comparisons significantly different ($P < 0.02$)