

Research Article

Human Vestibulo-Ocular Reflex Adaptation Training: Time Beats Quantity

M. MUNTASEER MAHFUZ,^{1,2} MICHAEL C. SCHUBERT,^{3,4} WILLIAM V. C. FIGTREE,^{1,2}
CHRISTOPHER J. TODD,^{1,2} AND AMERICO A. MIGLIACCIO^{1,2,5} 

¹*Balance and Vision Laboratory, Neuroscience Research Australia, Cnr Barker Street & Easy Street, Randwick, NSW 2031, Australia*

²*University of New South Wales, Sydney, NSW 2033, Australia*

³*Laboratory of Vestibular NeuroAdaptation, Department of Otolaryngology—Head and Neck Surgery, Johns Hopkins University, Baltimore, MD 21205, USA*

⁴*Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD 21205, USA*

⁵*Department of Otolaryngology—Head and Neck Surgery, Johns Hopkins University, Baltimore, MD 21205, USA*

Received: 1 March 2018; Accepted: 4 July 2018; Online publication: 24 September 2018

ABSTRACT

The vestibulo-ocular reflex (VOR) is the main gaze stabilising system during rapid head movements. The VOR is highly plastic and its gain (eye/head velocity) can be increased via training that induces an incrementally increasing retinal image slip error signal to drive VOR adaptation. Using the unilateral incremental VOR adaptation technique and horizontal active head impulses as the vestibular stimulus, we sought to determine the factors important for VOR adaptation including: the total training time, ratio and number of head impulses to each side (adapting and non-adapting sides; the adapting side was pseudo-randomised left or right) and exposure time to the visual target during each head impulse. We tested 11 normal subjects, each over 5 separate sessions and training protocols. The basic training protocol (protocol one) consisted of unilateral incremental VOR adaptation training lasting 15 min with the ratio of head impulses to each side 1:1. Each protocol varied from the basic. For protocol two, the ratio of impulses were in favour of the adapting side by 2:1. For protocol three, all

head impulses were towards the adapting side and the training only lasted 7.5 min. For protocol four, all impulses were towards the adapting side and lasted 15 min. For protocol five, all head impulses were to the adapting side and the exposure time to the visual target during each impulse was doubled. We measured the active and passive VOR gains before and after the training. Albeit with small sample size, our data suggest that the total training time and the visual target exposure time for each head impulse affected adaptation, whereas the total number and repetition rate of head impulses did not. These data have implications for vestibular rehabilitation, suggesting that quality and duration of VOR adaptation exercises are more important than rapid repetition of exercises.

Keywords: Vestibulo-ocular reflex (VOR), VOR adaptation, VOR training, Head impulses, Optimising training parameters

Correspondence to: Americo A. Migliaccio · Department of Otolaryngology—Head and Neck Surgery · Johns Hopkins University · Baltimore, MD 21205, USA. Telephone: +61 2 9399 1030; email: a.migliaccio@neura.edu.au

INTRODUCTION

The vestibulo-ocular reflex (VOR) maintains images stable on the retina during head movement by rotating the eyes in the opposite direction to the head. During far-viewing, the magnitude of eye

velocity matches head velocity, so that the gain (eye/head velocity) equals unity. The VOR gain can be increased via adaptation training, which employs a vestibulo-visual mismatch stimulus. For example, a mismatch stimulus can be provided using magnifying lenses, so that the visual world appears to move more for a given head rotation than it would without lenses. Under this circumstance, the VOR initially produces an eye movement that does not stabilise images on the fovea of the retina, which generates a retinal image slip error signal used to drive adaptive change within the VOR (Gauthier and Robinson 1975). Prior studies have used visual-vestibular mismatch to induce VOR adaptation via lenses (e.g. Gauthier and Robinson 1975; Paige and Sargent 1991), reversing prisms (e.g. Gonshor and Melvill-Jones 1976a, b), moving visual displays (e.g. Shelhamer et al. 1992 and 1994) or a moving visual laser target paired with head movement (Schubert et al. 2008; Migliaccio and Schubert 2013 and 2014, Fadaee and Migliaccio 2016; Mahfuz et al. 2018).

The main difference between the moving laser target method and prior methods is that the laser target moves in the opposite direction to the head at an incrementally increasing percentage of head speed, which causes VOR gain demand for stable vision to gradually increase (Schubert et al. 2008; Migliaccio and Schubert 2013 and 2014; Fadaee and Migliaccio 2016). The moving laser target method generally employs active (self-generated) transient head impulses rather than sinusoids as the vestibular training stimulus. Head impulses (Halmagyi and Curthoys 1988) are considered to be a more physiologically relevant vestibular stimulus than sinusoids, because they have the same frequency and velocity content as head motion encountered in daily life (Grossman et al. 1988). The head impulse training lasts 15 min with the laser target velocity, initially equal to head velocity, increasing by 10% every 90 s. This method drives the passive VOR gain to increase significantly towards the side being actively trained (left, right or both) by ~10% (Mahfuz et al. 2018; Schubert et al. 2008).

The neural basis of plasticity and motor learning within the VOR pathways has been extensively examined. Short-term VOR adaptation results in changes in the floccular target neurons (Lisberger et al. 1994a), Purkinje cells in the cerebellar flocculus and ventral paraflocculus (Lisberger et al. 1994b) and vestibular-only neurons in the vestibular nuclei (Sadeghi et al. 2011). VOR plasticity is affected by ageing (Khan et al. 2017), vestibular stimulus characteristics (Hubner et al. 2014) and the cholinergic vestibular efferent system (Hubner et al. 2015). Animal studies suggest that changes in the central

vestibular pathways occur before changes at the level of the vestibular periphery (Primates: Carriot et al. 2015; Mitchell et al. 2017), and that repeated exposure to a visual-vestibular mismatch stimulus results in changes in synaptic transmission and the intrinsic properties of central vestibular neurons in the direct pathway of the VOR (Mouse: Carcaud et al. 2017).

Motor learning studies suggest that learning tasks which incorporate an incremental error signal are more effective at driving neural plasticity and learning. This has been shown in visuo-motor (Kagerer et al. 1997), somatosensory (Nagarajan et al. 1998), auditory (Kilgard and Merzernich 2002) and vestibular (Schubert et al. 2008) learning tasks. When the error signal during learning is too large, adaptive processes may assign the stimulus as invalid. In contrast, incremental learning provides a valid small error signal that adaptive processes recognise because small adaptive changes are constantly required, e.g. due to ageing and injury. Known as the “credit assignment” problem, such adaptive processes must determine that the error signal is valid and due to internal changes as opposed to an artificially altered external environment (Körding et al. 2007). The moving laser target method exposes adaptive processes to a signal that is small enough to appear permanent and internal.

The goal of the present study was to determine some of the essential training parameters for optimal VOR adaptation in healthy controls. Using the principles of motor learning, we sought to provide proof of concept on whether the total number of stimulus presentations had a greater effect on VOR adaptation than the total training time. Specifically, if the stimulus repetition rate was increased, then could the total training time be reduced to produce the same level of VOR adaptation? Also, given that the typical duration of a head impulse is about 200 ms and the latency of other non-vestibular vision stabilising systems such as smooth pursuit is > 100 ms (e.g. Krauzlis and Lisberger 1994), does providing a visual-vestibular mismatch stimulus after peak-head velocity, i.e. ~100 ms after head impulse onset, result in greater VOR adaptation? We hypothesised that the number of head impulses would affect VOR adaptation, but not the total training time per se, and that extending the duration of the visual-vestibular mismatch stimulus to the second half of each head impulse would not affect VOR adaptation. Five training protocols were designed to determine the effect of each parameter on VOR adaptation. Over separate days, the active and passive VOR gains were measured before and after each adaptation training protocol.

METHODS

Subjects

Eleven normal subjects (mean age 33 years, range 25–46 years, all male) were recruited to participate in this study. Each subject participated in five separate sessions, separated by at least 3 days with sessions not repeated. All subjects had performed basic unilateral incremental adaptation training previously, but not during the 6 weeks prior to commencement of this study. Five subjects regularly wore corrective lenses with diopter ranging –2.25 to –1.5. These subjects did not have any history or clinical signs of vestibular abnormality. Participation in this study was voluntary and subjects gave written informed consent before participating as approved by the University of New South Wales, Human Ethics Committee.

Recording System

Head and eye rotations were measured using the EyeSeeCam system (Denmark), with the camera placed over the left eye (Bartl et al. 2009). The EyeSeeCam system consisted of a 220 Hz digital video camera, an infrared mirror to reflect the eye image to the camera and an inertial measurement unit to measure 3D (yaw, pitch and roll) angular head velocity. All components were rigidly mounted onto a lightweight swim goggle frame to minimise camera slippage relative to the head. The eye was illuminated via two on-board infrared LEDs. Horizontal and vertical eye positions were calibrated by having subjects fixate (goggle-mounted laser projected) visual targets at known angles with respect to the subject. The calibrated data were digitally filtered with a 50-tap zero-phase low pass FIR filter with a bandwidth of 50 Hz.

Training System

A digital laser target system described in Mahfuz et al. (2018) controlled the position of a laser target directed onto a matte-white projection screen (2.4×2.4 m) 1 m in front of the subject. The device consists of a head unit (strapped securely to the forehead) and a base (or control) unit. The head unit consists of a laser mounted in a fixed position relative to, and aimed at the centre of, an electrostatic MEMS micro mirror (Mirrorcle Technologies Inc., USA) and a 9D IMU (3D accelerometer, gyroscope and magnetometer; STMicroelectronics, USA). Information from the IMU is processed, so that 3D head orientation with respect to space can be calculated at 250 Hz to within 0.1° . The head orientation is used to drive the mirror and hence laser target position with respect to the head. The base unit provides auditory feedback when

head impulse peak-velocity is below $120^\circ/\text{s}$ or above $180^\circ/\text{s}$. The peak-amplitude of a head impulse with peak-velocity $150^\circ/\text{s}$ and 200 ms duration is $\sim 10^\circ$.

Active and Passive VOR Adaptation Training Protocols

Each subject underwent five test sessions on separate days in pseudo-randomised order. For each session, a variant of the unilateral incremental VOR adaptation training protocol as previously described (Migliaccio and Schubert 2013 and 2014; Fadaee and Migliaccio 2016) was employed. In brief, using the head impulse test (Halmagyi and Curthoys 1988), the active and passive VOR gains were measured before and after active VOR adaptation training. Passive VOR gain testing prior to (and after) training required head impulses delivered manually in the horizontal canal plane, i.e. leftward and rightward. Subjects were trained to perform active head impulses similar in profile to the passive head impulses (per Figure 1 in Migliaccio and Schubert 2013). During VOR testing, a visual fixation target (laser target) located straight ahead and at eye level was provided. This target disappeared when the head rotated 0.6° away from neutral.

Unilateral VOR adaptation training consisted of a series of active only head impulses from a neutral starting position, i.e. only outward impulses were applied. The adapting side was pseudo-randomised, leftward or rightward, across subjects (e.g. leftwards for 5/11 subjects). For each head impulse, subjects were instructed to maintain visual fixation of the laser target whose horizontal position was a function of horizontal head position, head impulse direction and adaptation gain (eye/head angular speed) demand. The basic adaptation training protocol consisted of unilateral incremental VOR adaptation training lasting 15 min with the ratio of head impulses to each side kept at 1:1. To maintain this ratio, subjects were instructed to alternate the head impulse direction. Protocol one followed the basic protocol. Protocol two followed the basic protocol with one difference: the ratio of head impulses were in favour of the adapting side by 2:1. To maintain this ratio, subjects repeated the following pattern: two head impulses towards the adapting side followed by one impulse to the non-adapting side. Protocol three followed the basic protocol with two differences: all head impulses were towards the adapting side and the training only lasted 7.5 min. Protocol four followed the basic protocol with one difference: all head impulses were towards the adapting side for 15 min. Finally, protocol five followed the basic protocol with two differences: all head impulses were towards the adapting side and the exposure time to the visual target during each head impulse was doubled (see Table 1).

TABLE 1

The five protocols shown were performed over separate days and sessions in pseudo-randomised order. The differences between each protocol and the basic protocol (protocol 1) are highlighted in italics. The approximate number of head impulses towards the adapting and non-adapting sides is based on the assumption that 400 active head impulses are performed during 15 min. Exposure to the target from onset to head peak-velocity, which occurs approximately half way during a head impulse, is ~ 100 ms in duration. Exposure to the target from onset to head peak-amplitude (and zero head velocity), which occurs approximately at the end of a head impulse, is ~ 200 ms in duration

Protocol	Duration (min)	Head rotation side ratio (adapting side:non-adapting side)	Exposure to target during head impulse
1	15	1:1 (~ 200 impulses to each side)	Onset to peak-velocity
2	15	2:1 (~ 266 impulses to adapting side and ~ 133 impulses to non-adapting side)	Onset to peak-velocity
3	7.5	1:0 (~ 200 impulses to adapting side only)	Onset to peak-velocity
4	15	1:0 (~ 400 impulses to adapting side only)	Onset to peak-velocity
5	15	1:0 (~ 400 impulses to adapting side only)	Onset to peak-amplitude

For protocols 1–4, the laser target was extinguished once head peak-velocity was detected, i.e. mid head impulse, whereas for protocol five, the laser target was extinguished once head peak-amplitude was detected, i.e. the zero velocity crossing denoting the end of head impulse. The target reappeared only after the head returned slowly back to its neutral position. The gain demand is the VOR gain required to stabilise the image of the target on the fovea. For all rotations towards the non-adapting side, the target was kept stationary in space, so that the gain demand was fixed to unity, i.e. driving no adaptation because a gain of unity is the typical far-viewing gain in a normal subject. In contrast, for rotations towards the adapting side, the target moved, so that the gain demand increased from 1 (epoch 1) to 1.9 (epoch 10) in increments of 0.1 every 90 s (i.e. the duration of each epoch). Apart from the laser target, all training and testing was performed in complete darkness.

Data Analysis

Horizontal angular eye position was differentiated and the onset of each head impulse was calculated by fitting horizontal angular head velocity magnitude to a polynomial curve versus time. The point where the magnitude of the fitted curve was greater than 2% of the curve's peak magnitude (typically this threshold was 4°/s) was defined as the impulse onset. Only head impulses with peak magnitude between 150°/s and 300°/s were included in the analysis. Traces with saccades occurring inside a window starting at 100 ms before impulse onset and ending at impulse peak magnitude (typically 100 ms after onset) were also removed. Eye traces containing blinks and other artefacts were removed, along with their corresponding head traces. The instantaneous VOR gain was calculated as the magnitude of eye velocity divided by head velocity. The impulse VOR gain was calculated as the median of the instantaneous VOR gains

calculated during the 30 ms period (at 220 Hz this corresponds to 6 to 7 instantaneous gain values) immediately prior to impulse peak magnitude (Carey et al. 2002; Mahfuz et al. 2018). The percentage of VOR gain change for each side (adapting or non-adapting) was calculated by dividing the post-training by the pre-training VOR gain, subtracting by 1 and multiplying by 100. A positive percentage indicated an increase in VOR gain due to adaptation training.

Statistical Analysis

Statistical analysis was performed using SPSS version 23 (IBM, USA) and Excel 2013 (Microsoft, USA) software. We used a linear mixed model (LMM) with repeated measures to analyse the VOR gain data. Independent variables included: subject ID, VOR protocol type ('1', '2', '3', '4', '5'), VOR testing type ('active', 'passive'), head rotation side ('adapting', 'non-adapting') and time ('pre-training', 'post-training'). The number of head impulses towards each side during training was a covariate in the analysis. The dependent variable was either gain or percentage gain change. All variables were included in the LMM initially and those found insignificant were subsequently removed. Only the interaction effects found to be significant are included in the results. Paired *t* tests were performed on the pre-training and post-training VOR gains and the percentage increases for each protocol using Least Significant Difference (LSD) to correct for multiple comparisons. Pooled data are described as mean ± 1 SD.

RESULTS

Pre-adaptation Training VOR

There were no differences in pre-adaptation VOR gains between leftward and rightward (LMM $F_{1,42} =$

0.3, $P=0.57$) and between active and passive (LMM $F_{1,42}=0.03$, $P=0.86$) head impulses. However, there were between-subject differences in pre-adaptation gains (LMM $F_{10,47}=2.8$, $P<0.01$), with means (\pm SD) ranging from 0.90 ± 0.03 to 0.96 ± 0.02 . The mean pre-adaptation VOR gain pooled across subjects was 0.93 ± 0.06 . Power analysis indicates that with 11 subjects, a 7.7% increase in VOR gain would be detected with 80% power ($\mu_1=0.93$, $\mu_2=1.002$, $SD=0.06$, $\alpha=0.05$, 2-sided test). However, after normalising gains (scaling by a fixed number for each subject) so that the pooled (left/right, active/passive, across all protocols) mean pre-adaptation gain was equal to unity for each subject, SD across subjects reduced to 0.03, and a 3.6% increase in VOR gain could be detected with 80% power ($\mu_1=1.0$, $\mu_2=1.036$, $SD=0.03$, $\alpha=0.05$, 2-sided test).

Passive VOR Gain Adaptation for Each Training Protocol in a Typical Subject

Figure 1 shows the passive VOR responses immediately before (left column) and immediately after (right column) active adaptation training for each of the five protocols (rows 1–5) in one subject. For protocol one (top row), two (second row) and four (fourth row), the VOR gain increased significantly (t test $P<0.05$) and similarly at about 10% (LMM $F_{2,3}=0.4$, $P=0.70$) as a result of adaptation training. For protocol three (third row) the VOR gain did not significantly increase (t test $P=0.15$). Whereas for protocol five (fifth row), the about 20% VOR gain increase was significantly higher (LMM $F_{3,4}=6.7$, $P<0.05$) than protocols one, two and four. The actual and ideal number of head impulses during training towards the adapting side (assuming an ideal of 400 head impulses over 15 min of training) for protocols one to five were: 166 (ideal 200), 270 (266), 172 (200), 317 (400) and 393 (400).

Number of Head Impulses for Each Training Protocol Across Subjects

The training duration (7.5 or 15 min) and the exposure to the visual target during each head impulse were controlled, however, the number of head impulses during training was allowed to vary between subjects. There was no difference in the average number of head impulses towards the adapting side during training protocols one and three (206 ± 39 vs 207 ± 43 , t test $P=0.96$). Similarly, there was no difference between training protocols four and five (383 ± 67 vs 362 ± 58 , t test $P=0.44$). The number of head impulses during training protocol two (289 ± 59) was larger than protocols one and three (t test $P<0.001$, $P<0.002$) and smaller than protocols four

and five (t test $P<0.005$, $P<0.01$) and lay in between those two protocol pairs (i.e. 1/3 pair and 4/5 pair).

Active and Passive VOR Gain Adaptation for Each Training Protocol Across Subjects

Figure 2 shows VOR gain data from training protocols one (top-left panel), two (top-right panel), three (middle-left panel), four (middle-right panel) and five (bottom-left panel). For each protocol (i.e. panel), the active (left graph) and passive (right graph) VOR gain pre-training (white boxplot) and post-training (grey boxplot) are shown for head impulses towards the adapting (left side of graph) and non-adapting (right side of graph) sides. Data analysis showed *time* ('pre' vs 'post' training $F_{1,90}=36.4$, $P<0.001$), *protocol* (1–5 $F_{4,136}=7.2$, $P<0.001$) and *side* ('adapting' vs 'non-adapting' $F_{1,153}=34.3$, $P<0.001$) significantly affected the VOR gain. There were significant interactions between *protocol* and *time* (LMM $F_{4,120}=5.6$, $P<0.001$), *protocol* and *side* (LMM $F_{4,163}=3.4$, $P<0.02$) and *protocol*, *side* and *time* (LMM $F_{4,120}=2.5$, $P<0.05$), suggesting that the gain change on the adapting side due to training depended on the protocol. There was also a significant interaction between *time* and *side* (LMM $F_{1,90}=29.8$, $P<0.001$), indicating that the training only affected the adapting side. There was no difference between the active and passive VOR gains (LMM $F_{1,90}=0.01$, $P=0.91$), and the number of head impulses during training did not affect the VOR gain (LMM $F_{1,125}=1.1$, $P=0.31$).

Due to the variability of pre-adaptation gains across subjects, data were normalised for each subject/session by calculating the percentage VOR gain increase for each side (adapting, non-adapting). Using the normalised data, the difference between the active and passive VOR gains (LMM $F_{1,58}=0.01$, $P=0.98$) remained insignificant and so did the effect of number of head impulses during training on the VOR gain (LMM $F_{1,72}=0.03$, $P=0.87$). Significant factors were *protocol* (LMM $F_{4,63}=10.7$, $P<0.001$), *side* (LMM $F_{1,88}=61.5$, $P<0.001$) and an interaction between the two (LMM $F_{4,66}=7.5$, $P<0.001$). Protocols three and five had the smallest and largest effects on VOR gain change, respectively (see Fig. 2, middle-left panel and bottom-left panel). Removing the protocol three data only (LMM $F_{3,55}=3.1$, $P<0.05$) or removing the protocol five data only (LMM $F_{3,61}=5.4$, $P<0.005$) had little effect on the significance of *protocol*, however, removal of both protocols three and five data resulted in *protocol* becoming highly non-significant (LMM $F_{2,50}=0.03$, $P=0.97$).

Figure 3 shows the normalised active (top panel) and passive (bottom panel) VOR gain percentage increases towards the adapting side only. Training protocols one, two and four result in $\sim 10\%$ increases

Passive VOR gain pre- and post-training for each protocol

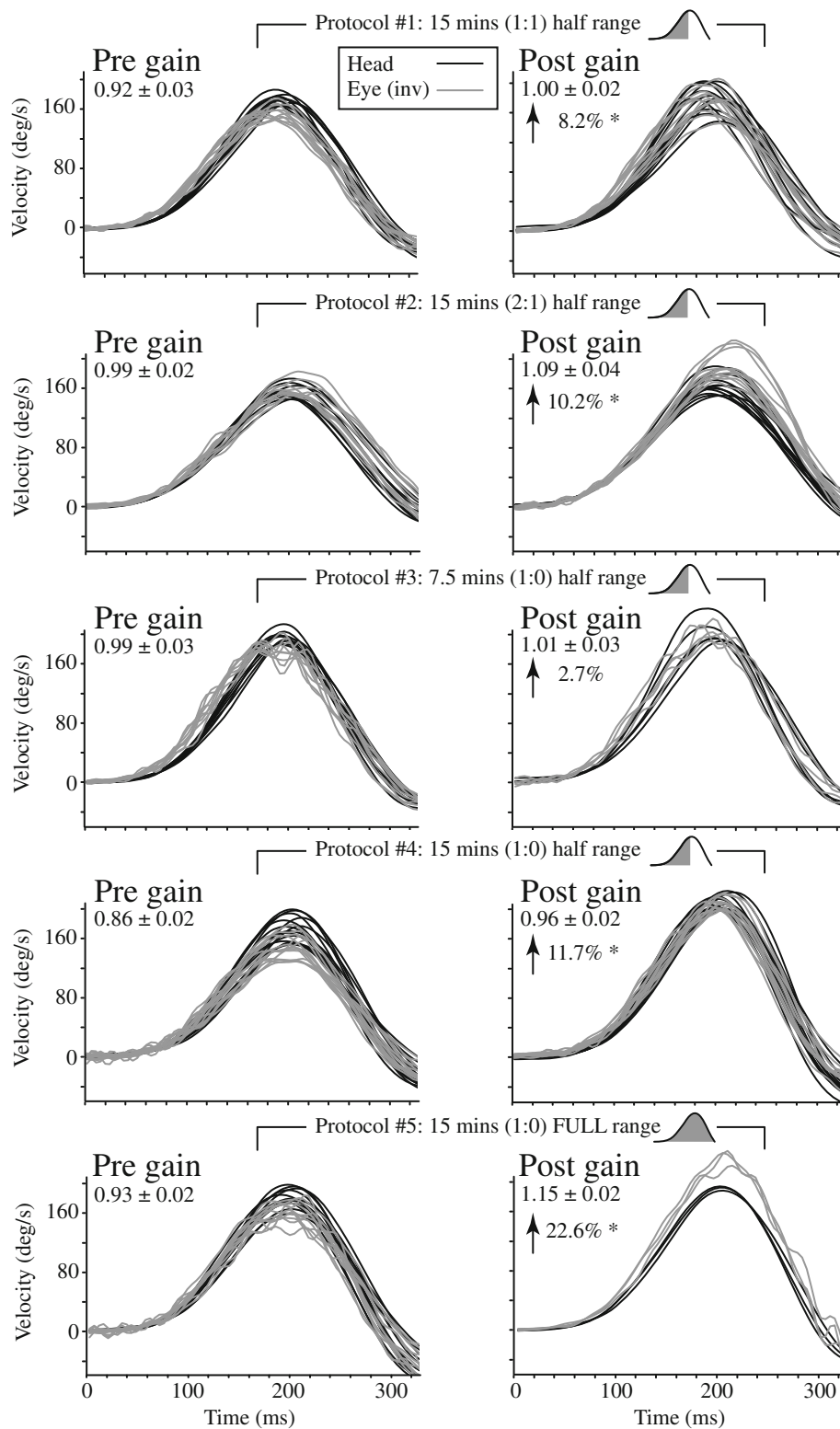


FIG. 1. Passive VOR responses immediately before (left column) and immediately after (right column) active adaptation training for each of the five protocols (rows 1–5). The mean \pm SD VOR gains are shown in each panel, plus the percentage VOR gain increase from pre-training to post-training is shown. The head impulse icon on the

right side of each protocol description denotes whether the laser target was on during the first half of the head impulse (half range, first half of impulse shaded) or the entire head impulse (full-range, entire impulse shaded). An asterisk (*) denotes a significant (t test $P < 0.05$) increase in gain as a result of the training

VOR gains pre- and post-training for each protocol

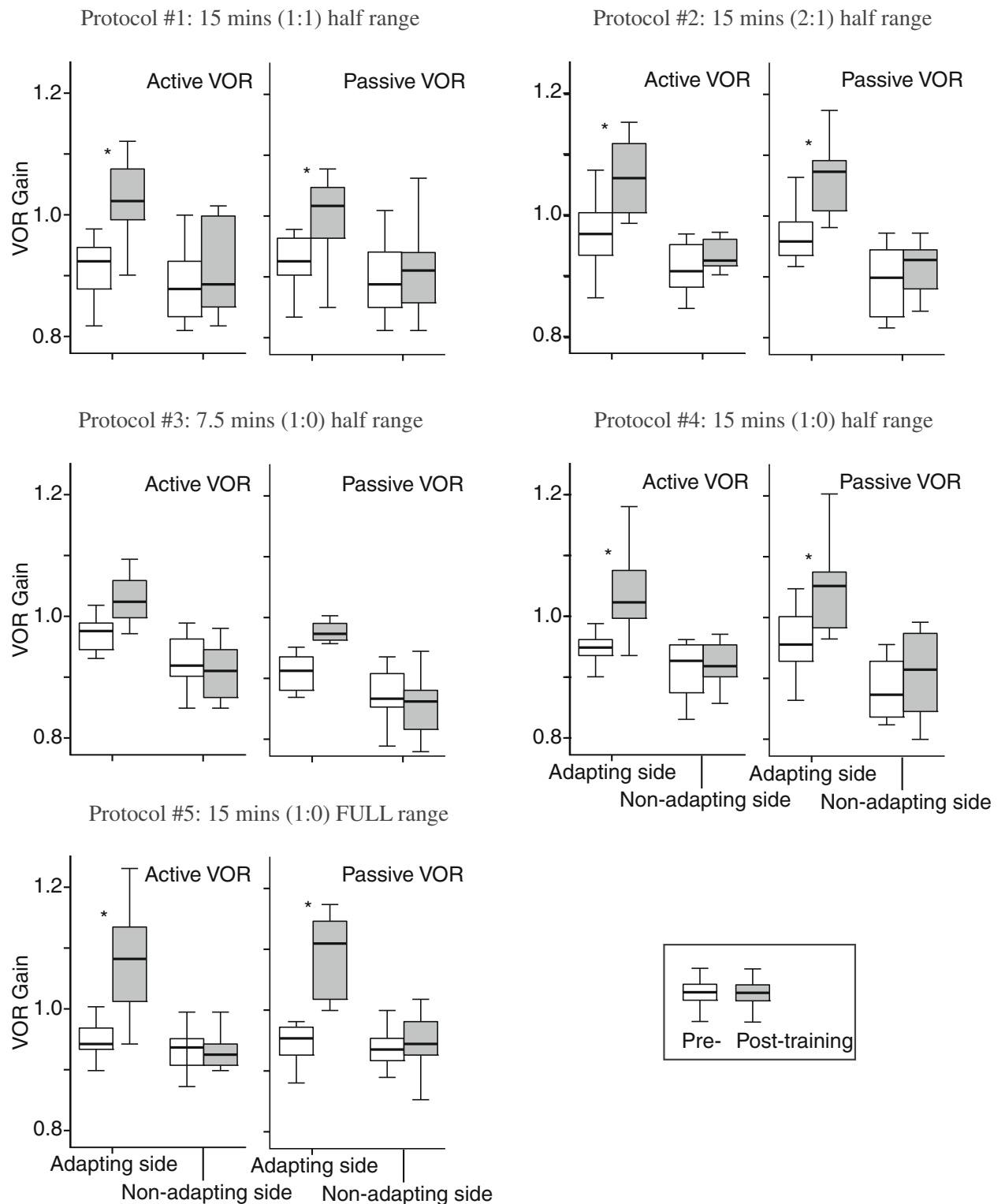


FIG. 2. VOR gain data from training protocols one (top-left panel), two (top-right panel), three (middle-left panel), four (middle-right panel) and five (bottom-left panel). For each protocol (i.e. panel), the active (left graph) and passive (right graph) VOR gain pre-training (white boxplot) and post-training (grey boxplot) are shown for head

impulses towards the adapting (left side of graph) and non-adapting (right side of graph) sides. The boxplots show the median with second and third quartiles and whiskers showing the minimum and maximum gains. An asterisk (*) denotes a significant (t test $P < 0.05$) increase in gain as a result of the training

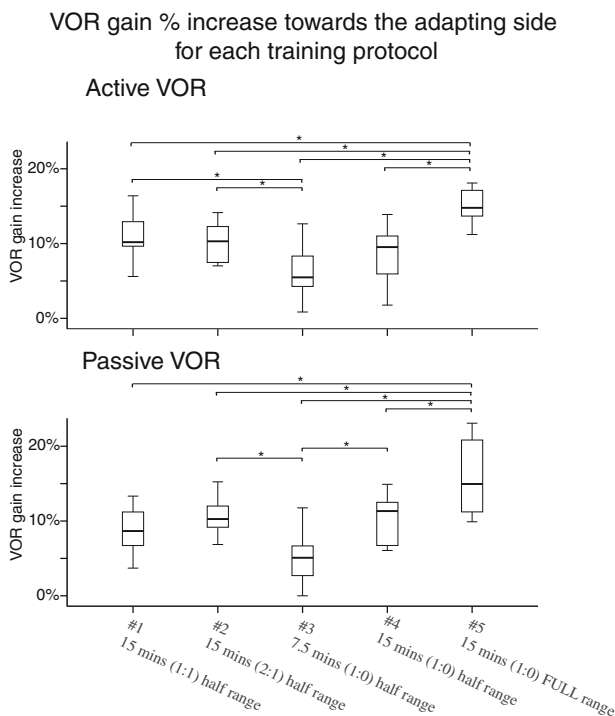


Fig. 3. Normalised active (top panel) and passive (bottom panel) VOR gain percentage increases towards the adapting side only for each training protocol. An asterisk (*) denotes a significant (t test $P < 0.05$) difference in mean percentage increase between the two protocols being compared

in active and passive VOR gains (See Table 2). The mean protocol three gain increase is $\sim 5\%$, whereas the mean protocol five increase is $\sim 16\%$ (Table 2).

Taken together, the data suggest that the number of head impulses does not affect the VOR gain increase; at least once the number of head impulses is above ~ 200 . Protocols one and three had the same number of head impulses towards the adapting side, yet the VOR gain increase for protocol one was about double that of protocol three. Also, protocol four had about double the number of head impulses towards the adapting side compared to protocol one, and the number of head impulses for protocol two was in between them both, yet the VOR gain increase was the same for protocols one, two and four. On the other hand, the training duration had a significant effect on the VOR gain increase.

TABLE 2

Mean and SD of the active and passive percentage gain increases due to adaptation training for each training protocol

Protocol	Active VOR gain increase	Passive VOR gain increase
1	$11.1 \pm 3.4\%$	$8.9 \pm 3.2\%$
2	$10.3 \pm 2.9\%$	$11.1 \pm 5.4\%$
3	$6.2 \pm 3.8\%$	$5.2 \pm 3.9\%$
4	$8.5 \pm 3.6\%$	$9.4 \pm 5.3\%$
5	$16.2 \pm 5.4\%$	$16.1 \pm 5.2\%$

Training protocols three and four were identical except that the total training time for protocol three was half that of protocol four, resulting in protocol three having about half the gain increase of protocol four. Also, increased exposure to the visual target during each head impulse had a significant effect on the VOR gain increase. Training protocols four and five were identical except that exposure to the visual target during each head impulse for protocol four was half (i.e. from head impulse onset to peak-head velocity) that of protocol five (i.e. from head impulse onset to peak-head amplitude), resulting in protocol five having an $\sim 50\%$ larger increase in gain than protocol four.

DISCUSSION

This proof of concept study suggests that the training parameters that most affected VOR adaptation towards the adapting side were the duration of exposure to the visual-vestibular mismatch stimulus during each head impulse and the total training time. The number of head impulses, i.e. training stimulus repetitions, had no significant effect on VOR adaptation, at least once the number of head impulses was above ~ 200 . Therefore, the repetition rate of head impulses towards the adapting side, which is equal to the total number of head impulse repetitions divided by the total training time, did not significantly affect VOR adaptation. There was no difference in the active and passive VOR gain increases towards the adapting side due to adaptation training, and there was no gain increase towards the non-adapting side as a result of the adaptation training.

Unilateral Adaptation Training Effects Towards the Non-adapting Side

In the first unilateral incremental VOR adaptation study, head rotations towards the non-adapting side were performed in the absence of a visual target, i.e. the laser target was turned off at the onset of head rotation (Migliaccio and Schubert 2013). In that study, a significant increase in the active VOR gain towards the non-adapting side, albeit $\sim 70\%$ smaller than the adapting side, was noted. This increase was attributed to changes in the commissural vestibular pathways from the adapting side, which contribute to the non-adapting side response (McCrea et al. 1981; Shimazu and Precht 1966). In order to prevent adaptation on the non-adapting side, a second unilateral adaptation study used a visual laser target that was stationary during rotations towards the non-adapting side, so that the VOR gain was maintained at unity (Migliaccio and Schubert 2014), as was the case

in protocols one and two in the present study. In that second study, VOR adaptation no longer occurred on the non-adapting side. It was thought that the presence of visual feedback during head rotations to the non-adapting side prevented ‘crossover’ adaptation from the commissural-vestibular (adapting side) pathways during head rotations towards the adapting side and associated retinal slip error signal. In the present study, however, subjects did not perform any head rotations towards the non-adapting sides and return of head rotation to the start position similarly offered no visual target during training protocols 3–5. If commissural pathways were responsible for ‘crossover’ adaptation, then there should have been a significant increase in the VOR gain towards the non-adapting side for training protocols 3–5. The fact that this was not observed, coupled with the fact that the increase towards the non-adapting side has only ever occurred in the active VOR, suggests that ‘crossover’ adaptation is due to changes in the predictive modelling component of the VOR response and not the commissural pathways. We hypothesise that leftward and rightward VOR gains are independently controlled, as per the models of Minor et al. (1999; Clendaniel et al. 2001), so that if a vestibular stimulus is: (1) *not* provided to one side, then the gain to that side is not modified, (2) provided to one side *without* a visual stimulus, then the gain to that side is affected by the contralateral gain and (3) provided to one side *with* a visual stimulus, then the gain to that side is independently modified. The simplest model for this would be one that includes the addition of a contralateral-sourced weighted input to gain during training that is gated depending on whether there is visual feedback during rotations to that side.

Extending the Visual-Vestibular Stimulus to the Second Half of the Head Impulse

In prior studies that have used the incremental VOR adaptation technique, significant differences between active and passive VOR gain increases were detected (Migliaccio and Schubert 2013; Fadaee and Migliaccio 2016). In those studies, the VOR gain to passive head impulses after active training increased by ~10%, which doubled for active head impulses. In contrast, later studies reported similar passive and active VOR gain increases of ~10% (Mahfuz et al. 2018). The main difference between those studies was the duration of the visual-vestibular mismatch stimulus during each head impulse. In the earlier studies, the visual stimulus was extinguished once head peak-amplitude (end of impulse) was detected, whereas in the later study, it was extinguished once head peak-velocity (middle of impulse) was detected. In the present study, we determined the effect of visual-vestibular stimulus duration

on VOR adaptation by comparing protocols four and five, which were identical except that protocol five had double the exposure to the visual stimulus per head impulse, resulting in ~50% greater active and passive VOR gain increases. This result suggests that visual feedback during the latter half of the head impulse also contributes to VOR adaptation. The fact that in earlier studies the active VOR gain increased more than the passive VOR, but not so in this study, could depend on how much of the increased VOR response is due to the contribution of volitional versus reflexive non-vestibular vision stabilising systems. Presumably, a reflexive non-vestibular response, e.g. optokinetic, would affect both the active and passive VOR, whereas a volitional non-vestibular response, e.g. smooth pursuit, which requires priming due to its long open-loop latency (Bahill and McDonald 1983a, b; Barnes et al. 1995; Kettner et al. 1996; McHugh and Bahill 1985), would mostly affect the active VOR. Another explanation is that during a head impulse there are two acceleration peaks (one positive, one negative) at which the VOR is maximally stimulated. When the target is extinguished at the middle of the head impulse, the VOR receives visual feedback at only one of these peaks, thereby missing exposure to feedback at an influential point. It is also possible that under this condition, a strong gaze position error feedback signal is provided at the end of the head impulse further driving VOR adaptation (Fadaee and Migliaccio 2016). Another possible explanation is that because the VOR gain demand is changing in small increments, the retinal image velocity error is small. Therefore, there is less need for corrective saccades, which can only be generated during the second half of the head impulse due to their long latency. Fewer corrective saccades result in less interruption of the retinal velocity error signal driving VOR adaptation, thus increasing the amount of feedback driving VOR adaptation.

Implications for VOR Rehabilitation

Although the present study only tested subjects with normal VOR function, the findings reveal aspects of VOR adaptation/motor learning that have implications for VOR rehabilitation in patients with peripheral hypofunction, i.e. incomplete damage to the peripheral vestibular end-organ or eighth cranial nerve resulting in VOR gains less than ~0.75. One of the two parameters that most affected VOR adaptation was the total training time, suggesting that the vestibular, and possibly optokinetic and smooth pursuit, neural pathways require time to consolidate changes. However, the number of training stimulus presentations (i.e. the number of head impulses) did not affect VOR adaptation—at least once the number of head impulses was above 200, which over 15 min is

a slow rate of one impulse per 4.5 s. Increasing the training stimulus repetition rate and halving the training time so that the number of head impulses was the same resulted in decreased VOR adaptation in the present study. Applying the principles of motor learning, this finding suggests that the practice amount (number of trials per session, i.e. small vs. large) or practice variability (training to one side vs. both sides in differing ratios) does not improve VOR motor learning as much as increased practice distribution (fixed number of trials over more or less time, i.e. massed vs. distributed). Instead, practice duration and duration of exposure to the visual-vestibular training target during each head impulse were the most critical components for VOR motor learning in our study. This suggests that increased target complexity (tracking throughout the entire head impulse rather than just during the first half could be considered a more complex target) and increased time both improve VOR motor learning. This finding emphasises the importance of encouraging patients to keep their eyes open and focused during activities, including gaze stabilisation exercises, which involve head movement. Finally, the data from this study show that focusing the VOR training only towards one side, i.e. block training towards the ipsilesional side in patients with unilateral vestibular hypofunction, does not result in undesirable crossover adaptation towards the other side.

Funding Information A.A. Migliaccio was supported by The Garnett Passe and Rodney Williams Memorial Foundation, Senior/Principal Research Fellowship in Otorhinolaryngology and Project Grant (2013-15) and NHMRC Development Grant APP105550.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical Approval Participation in this study was voluntary and subjects gave written informed consent before participating as approved by the University of New South Wales, Human Ethics Committee.

REFERENCES

- BAHILL AT, McDONALD JD (1983A) Model emulates human smooth pursuit system producing zero-latency target tracking. *Biol Cybern* 48:213–222
- BAHILL AT, McDONALD JD (1983B) Smooth pursuit eye movements in response to predictable target motions. *Vis Res* 23:1573–1583
- BARNES GR, GOODBODY S, COLLINS S (1995) Volitional control of anticipatory ocular pursuit responses under stabilised image conditions in humans. *Exp Brain Res* 106:301–317
- BARTL K, LEHNEN N, KOHLBECHER S, SCHNEIDER E (2009) Head impulse testing using video-oculography. *Ann N Y Acad Sci* 1164:331–333
- CARCAUD J, FRANÇA DE BARROS F, IDOUX E, EUGÈNE D, REVERET L, MOORE LE, VIDAL PP, BERANECK M (2017) Long-lasting visuo-vestibular mismatch in freely-behaving mice reduces the vestibulo-ocular reflex and leads to neural changes in the direct vestibular pathway. *eNeuro* 4:1
- CAREY JP, MINOR LB, PENG GC, DELLA SANTINA CC, CREMER PD, HASLWANTER T. CHANGES IN THE THREE-DIMENSIONAL ANGULAR VESTIBULO-OCULAR REFLEX FOLLOWING INTRATYMPANIC GENTAMICIN FOR MÉNIÈRE'S DISEASE. *J ASSOC RES OTOLARYNGOL* 3:430-443, 2002
- CARRIOT J, JAMALI M, BROOKS JX, CULLEN KE. INTEGRATION OF CANAL AND OTOLITH INPUTS BY CENTRAL VESTIBULAR NEURONS IS SUBADDITIVE FOR BOTH ACTIVE AND PASSIVE SELF-MOTION: IMPLICATION FOR PERCEPTION. *J NEUROSCI* 35: 3555–3565, 2015
- CLENDANIEL RA, LASKER DM, MINOR LB (2001) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. IV. Responses after spectacle-induced adaptation. *J Neurophysiol* 86:1594–1611
- FADAE SB, MIGLIACCIO AA (2016) The effect of retinal image error update rate on human vestibulo-ocular reflex gain adaptation. *Exp Brain Res* 234:1085–1094
- GAUTHIER GM, ROBINSON DA (1975) Adaptation of human's vestibulo-ocular reflex to magnifying glasses. *Brain Res* 92:331–335
- GONSHOR A, MELVILL JONES G (1976A) Short-term adaptive changes in the human vestibulo-ocular reflex arc. *J Physiol* 256:361–379
- GONSHOR A, MELVILL JONES G (1976B) Extreme vestibulo-ocular adaptation induced by prolonged optical reversal of vision. *J Physiol* 256:381–414
- GROSSMAN GE, LEIGH RJ, ABEL LA, LANSKA DJ, THURSTON SE (1988) Frequency and velocity of rotational head perturbations during locomotion. *Exp Brain Res* 70:470–476
- HALMAGYI GM, CURTHOYS IS (1988) A clinical sign of canal paresis. *Arch Neurol* 45:737–739
- HÜBNER PP, KHAN SI, MIGLIACCIO AA (2014) Velocity-selective adaptation of the horizontal and cross-axis vestibulo-ocular reflex in the mouse. *Exp Brain Res* 232:3035–3046
- HÜBNER PP, KHAN SI, MIGLIACCIO AA (2015) The mammalian efferent vestibular system plays a crucial role in the high-frequency response and short-term adaptation of the vestibuloocular reflex. *J Neurophysiol* 114:3154–3165
- KAGERER FA, CONTRERAS-VIDAL JL, STELMACH GE (1997) Adaptation to gradual as compared with sudden visuo-motor distortions. *Exp Brain Res* 115(3):557–561
- KETTNER RE, LEUNG HC, PETERSON BW (1996) Predictive smooth pursuit of complex two-dimensional trajectories in monkey: component interactions. *Exp Brain Res* 108:221–235
- KHAN SI, HÜBNER PP, BRICHTA AM, SMITH DW, MIGLIACCIO AA (2017) Aging reduces the high-frequency and short-term adaptation of the vestibulo-ocular reflex in mice. *Neurobiol Aging* 51:122–131
- KILGARD MP, MERZENICH MM (2002) Order-sensitive plasticity in adult primary auditory cortex. *Proc Natl Acad Sci U S A* 99:3205–3209
- KÖRDING KP, TENENBAUM JB, SHADMEHR R (2007) The dynamics of memory as a consequence of optimal adaptation to a changing body. *Nat Neurosci* 10:779–786
- KRAUZLIS RJ, LISBERGER SG (1994) Temporal properties of visual motion signals for the initiation of smooth pursuit eye movements in monkeys. *J Neurophysiol* 72:150–162
- LISBERGER SG, PAVELKO TA, BROUSSARD DM (1994A) Neural basis for motor learning in the vestibuloocular reflex of primates. I. Changes in the responses of brain stem neurons. *J Neurophysiol* 72:928–953
- LISBERGER SG, PAVELKO TA, BRONTE-STEWART HM, STONE LS (1994B) Neural basis for motor learning in the vestibuloocular reflex of primates. II. Changes in the responses of horizontal gaze velocity Purkinje cells in the cerebellar flocculus and ventral paraflocculus. *J Neurophysiol* 72:954–973
- MAHFUZ MM, SCHUBERT MC, TODD CJ, FIGTREE WVC, KHAN SI, MIGLIACCIO AA (2018) The effect of visual contrast on human vestibulo-ocular reflex training. *J Assoc Res Otolaryngol* 19:113–122

- MCCREA RA, YOSHIDA K, EVINGER C, BERTHOZ A (1981) The location, axonal arborization and termination sites of eye-movement related secondary vestibular neurons demonstrated by intraaxonal HRP injection in the alert cat. In: Fuchs A, Becker W (eds) *Progress in oculomotor research*. Elsevier, North Holland, Amsterdam, pp 379–386
- McHUGH DE, BAHILL AT (1985) Learning to track predictable target waveforms without a time delay. *Invest Ophthalmol Vis Sci* 26:932–937
- MIGLIACCIO AA, SCHUBERT MC (2013) Unilateral adaptation of the human angular vestibulo-ocular reflex. *J Assoc Res Otolaryngol* 14:29–36
- MIGLIACCIO AA, SCHUBERT MC (2014) Pilot study of a new rehabilitation tool: improved unilateral short-term adaptation of the human angular vestibulo-ocular reflex. *Otol Neurotol* 35:310–316
- MINOR LB, LASKER DM, BACKOUS DD, HULLAR TE (1999) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. I. Normal responses. *J Neurophysiol* 82:1254–1270
- MITCHELL DE, DELLA SANTINA CC, CULLEN KE (2017) Plasticity within excitatory and inhibitory pathways of the vestibulo-spinal circuitry guides changes in motor performance. *Sci Rep* 7(853):853
- NAGARAJAN SS, BLAKE DT, WRIGHT BA, BYL N, MERZENICH MM (1998) Practice-related improvements in somatosensory interval discrimination are temporally specific but generalize across skin location, hemisphere, and modality. *J Neurosci* 18:1559–1570
- PAIGE GD, SARGENT EW (1991) Visually-induced adaptive plasticity in the human vestibulo-ocular reflex. *Exp Brain Res* 84:25–34
- SADEGHI SG, MINOR LB, CULLEN KE (2011) Multimodal integration after unilateral labyrinthine lesion: single vestibular nuclei neuron responses and implications for postural compensation. *J Neurophysiol* 105:661–673
- SCHUBERT MC, DELLA SANTINA CC, SHELHAMER M (2008) Incremental angular vestibulo-ocular reflex adaptation to active head rotation. *Exp Brain Res* 191:435–446
- SHELHAMER M, ROBINSON DA, TAN HS (1992) Context-specific adaptation of the gain of the vestibulo-ocular reflex in humans. *J Vestib Res* 2:89–96
- SHELHAMER M, TILIKET C, ROBERTS D, KRAMER PD, ZEE DS (1994) Short-term vestibulo-ocular reflex adaptation in humans. II. Error signals. *Exp Brain Res* 100:328–336
- SHIMAZU H, PRECHT W (1966) Inhibition of central vestibular neurons from the contralateral labyrinth and its mediating pathway. *J Neurophysiol* 29:467–492