Research report

Asymmetric adaptive gain changes of the vertical vestibulo-ocular reflex in cats

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Abstract

The present study was conducted to examine adaptive gain changes of vertical vestibulo-ocular reflex (VOR) after exposure to a vertical visual–vestibular mismatch in cats. The visual–vestibular mismatch was induced by oscillating the animals for an hour about an inter-aural axis at frequencies of 0.16 and 0.32 Hz with the peak velocity of 20°/s, coupled with either in-phase ("gain decrease" conditioning) or out-of-phase ("gain increase" conditioning) sinusoidal rotation of a random-dot pattern. Eye movements were measured with a magnetic search coil system. Before conditioning, vertical VOR showed up–down asymmetric responses. That is, upward slow phase eye velocity (SPV) in response to downward head rotation was significantly larger than downward SPV in response to upward head rotation. After adaptation to "gain increase" conditioning, VOR gain increased in both stimulus directions. The increase in VOR gain was significantly larger for upward SPV than for downward SPV. After adaptation to "gain decrease" conditioning, VOR gain decreased in both stimulus directions. The decrease in VOR gain was, however, significantly larger for downward SPV than for upward SPV. Our results indicate that VOR in the vertical plane adaptively changes but that the gain change shows a directional asymmetry. This asymmetry was dependent on the direction of the slip of visual image rather than the direction of head rotation, and the gain change was smaller when the retinal slip was generated downward. Possible explanations for the asymmetry are discussed on a physiological and anatomical basis.
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1. Introduction

The vestibular system functions to maintain clear vision during head movements: The vestibulo-ocular reflex (VOR) minimizes slip of visual image on the retina (retinal slip) by generating eye rotation opposite to the direction of the head rotation. If the eye counter-rotation is inappropriate to stabilize vision and retinal slip is produced over an extended period, VOR adaptively changes so that eye velocity more closely equals head velocity during head movements (VOR adaptation). The adaptive change of VOR gain (a ratio of eye velocity to head velocity) has been experimentally observed

in several species by employing reversing prisms, magnifying or reducing lenses, and sinusoidal rotation of the animal with in-phase or out-of-phase visual surround rotation (e.g., cat [13,19,32], monkey [23,27,28], human [5,12,14,15,29]). While most of these studies of VOR adaptation have primarily examined the head-horizontal plane, several studies have also been conducted on the head-vertical plane. For example, the adaptability of vertical VOR was examined with visual–vestibular stimuli at orthogonal axes (cross-axis adaptation); after exposure to pitch vestibular rotation coupled with horizontal visual stimuli, the VOR adapts so that the eyes move obliquely in response to vertical head rotation in darkness [1,2,30,35]. Vertical VOR adaptation has also been examined with visual–vestibular stimuli at parallel axes while the animal lay on its side. After exposure

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to sinusoidal rotation about an earth-vertical axis coupled with in-phase or out-of-phase visual surround rotation, the gain of the vertical VOR was modified in such a way as to reduce the slip of retinal images during head movements [4,38]. Consequently, several studies have demonstrated adaptive changes of VOR during vertical head rotation. What seems to still be lacking, however, is data on vertical VOR adaptation during upright pitch rotation in animals.

The on-side pitch motion is a non-physiological condition in which the vertical semicircular canals are stimulated without any change of head position with respect to gravity. Most natural head movements in the head-vertical plane activate not only the semicircular canals but also the otoliths. The VOR responses during rotation about an earth-horizontal axis are different from those during rotation about an earth-vertical axis [33,40]. For example, the vertical VOR gain of animals during upright pitch is higher by an effect of gravity than that of animals on their side [40]. Another important issue for vertical reflexive eye movements is that of up–down asymmetry in their responses. VOR responses have been shown to be greater for downward head rotation than for upward head rotation [9,40]. Ocular responses to visual slip known as the optokinetic reflex (OKR) also show an asymmetry. OKR is greater for the upward direction than for downward direction (e.g., cat [20], monkey [7], human [41]). Taking these asymmetric responses of VOR and OKR into account, it is possible that the gain change of vertical VOR induced by a visual–vestibular mismatch could show a directional asymmetry. Curiously, asymmetric gain of VOR adaptation was not observed in cats when the vertical VOR was examined during on-side pitch [38]. Yakushin et al. [42] have recently shown an asymmetric decrease of vertical VOR adaptation in typical data obtained from monkeys, but they have not analyzed it quantitatively.

The particular interest of this study was to investigate the question of whether or not vertical VOR shows an asymmetric gain change after adaptation. Given such asymmetric gain change, we wanted to determine which is the predominant influence on the asymmetry: the direction of head rotation or the direction of visual slip.

2. Methods

2.1. Animal preparation

Six docile adult cats, weighing 2.0–3.5 kg, were used in this study. The animals were anesthetized with pentobarbital sodium (Nembutal, 35 mg/kg, ip) and placed on a stereotaxic apparatus. Under sterile operating conditions, head restraining screws were implanted using two inverted, stainless-steel screws anchored to the calvarium with smaller stainless-steel screws and dental cement placed peripherally. Two weeks later, a scleral search coil was chronically implanted in the frontal plane of the eye beneath the conjunctiva and around

the cornea. Under pentobarbital sodium anesthesia and local anesthetic eye drops, a circular incision was made in the conjunctiva. The prefabricated coil, consisting of three loops of Teflon-coated stainless-steel wire, was then placed on the eye, between the sclera and the conjunctiva. After the coil was in place, the conjunctiva incision was sutured together with three or four stitches. The free end of the coil leads were then fed under the skin to a small electric connector imbedded in the dental cement that also held the head restraining screws. The animals were given 2 weeks to recover from the surgery before being exposed to vestibular stimulation. All surgical and experimental procedures were approved by the Animal Care and Use Committee of Toyama Medical and Pharmaceutical University (TMPU) of Japan, and performed in accordance with the TMPU guidelines for the Care and Use of Laboratory Animals. Each cat was given antibiotics during and after surgery.

2.2. Procedure for VOR adaptation

The cat's body was gently wrapped in a cloth bag. The head was then fixed by the implanted larger head screws to a restraining bar attached to a stereotaxic frame, which was mounted on the inner table of a three-axis turntable (Daiichi Medical, FAV-100S). The restraining bar held the head rigidly in the turntable's center of rotation. The inner table also includes the magnetic fields for measuring eye movements and a plastic restraining box that held animal's body [43]. The animal's body was secured by strapping it into the restraining box. Foam rubber was added to the box to further restrict body movement.

Before conditioning, VOR gains were measured during sinusoidal rotation at frequencies of 0.16 and 0.32 Hz with the peak velocity of 20°/s in total darkness. For VOR conditioning, a random-dot pattern (a diameter of 1 dot 0.2–2.0° of visual angle) was projected through a fisheye lens to the inner surface of a half-cylindrical dome at a distance of 80 cm from the animal's eyes (Fig. 1). The stimulus pattern subtended 52° in the horizontal and 152° in the vertical direction. The random-dot pattern rotation was synchronized with either out-of-phase ("gain increase" conditioning) sinusoidal head–body rotation or in-phase ("gain decrease" conditioning) head–body rotation for 1 h under the control of a PC. After conditioning, VOR gains were measured again during sinusoidal rotation at frequencies of 0.16 and 0.32 Hz with the peak velocity of 20°/s in total darkness.

Some animals showed a tendency to fall asleep during the experiments. Alertness was maintained by making a variety of noises around the animals. If animals showed signs of discomfort, they were immediately released. No cat was ever sick or showed any signs of nausea.

2.3. Eye movement recording and data analysis

Eye movements were measured using a magnetic search coil system [31]. Eye position and table position were

A. "gain increase" conditioning

A random-dot pattern rotation

Cat rotation

B. "gain decrease" conditioning
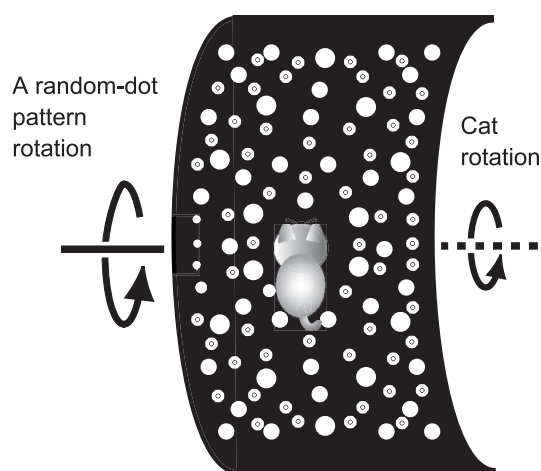

A random-dot pattern rotation
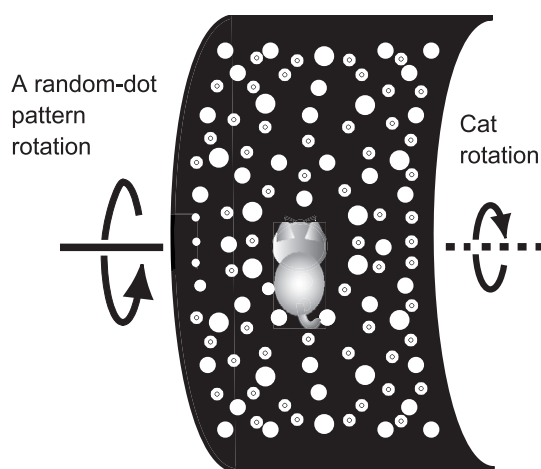
Cat rotation

Fig. 1. A schematic diagram showing the experimental situation. For induction of VOR adaptation, sinusoidal head–body rotation at frequencies of 0.16 and 0.32 Hz with a peak velocity of 20°/s was synchronized with a random-dot pattern rotation. (A) Out-of-phase rotation of visual pattern ("gain increase" conditioning). (B) In-phase rotation of visual pattern ("gain decrease" conditioning).

sampled at 100 Hz using a CED 1401-plus AD-converter with a CED spike2 program (Cambridge Electronic Design, Cambridge, UK), run on a PC. Calibrations for horizontal and vertical eye position were performed in two ways. First, the horizontal 0° and vertical 0° in the eye position were determined by evaluating eye-position recordings while the animal watched a target moving along the vertical and horizontal meridians on the screen, respectively. Then, the horizontal positions of $\pm 10°$ and $\pm 20°$ and the vertical positions of $\pm 10°$ and $\pm 20°$ were evaluated by measuring the amplitudes of the horizontal and vertical eye displacements while the animal was coaxed to look at a target positioned from $-20°$ to $+20°$ vertically and horizontally (in 10° increments). Second, the eye movements were calibrated before each session by submitting the animal to sinusoidal rotations at 0.25

Hz $\pm 20°$ directly in front of a stationary random-dot pattern, under the assumption that compensatory eye movement gain was 1.0 during this condition [19,25]. In the present study, the value of downward SPV in response to upward rotation was slightly but significantly smaller than that of upward SPV in response to downward rotation (downward SPV/upward SPV: Mean 0.90, S.D. ± 0.06, $n=6$). We took the average value of upward SPV for vertical calibration. There was no difference in the results between the two ways of calibration.

Data analysis was performed with user-written programs. The fast phases of nystagmus and saccadic eye movements were removed to obtain slow phase eye velocity (SPV) records. The gain and phase values of the VOR were determined by fitting the SPV records with a sinusoidal function using a nonlinear least squares algorithm (Levenberg–Marquardt methods): $y=A\sin(x+B)+C$, where A is the amplitude of SPV, B is the phase, and C is the bias level of the sinusoidal fit. VOR gain was separately measured during upward and downward head rotation. VOR gain during upward SPV (VOR gain during downward SPV) was defined as: upward peak SPV/peak head velocity (downward peak SPV/peak head velocity). The phase of VOR was expressed as the time difference (in degrees) between the peaks of the SPV and head velocity. Ten to twenty cycles were used for gain and phase estimation.

The statistical evaluations for the "before-and-after adaptation" and "up-and-down" factors were performed using the paired Student t tests. A difference was considered statistically significant at $p<0.05$.

In addition to the main protocol, two animals were also tested with the paradigms in which the visual stimulus velocity for VOR adaptation was adjusted so as to equalize the value of retinal slip velocity in the upward and downward directions. In each conditioning, the downward visual stimulation was modified by the amount of the difference (in °/s) between the pre-adaptive value of upward peak-SPV and the pre-adaptive value of downward peak-SPV.

3. Results

Fig. 2 shows an example of a waveform obtained from one animal while it was rotated with a peak velocity of 20°/s at a frequency of 0.16 Hz. Before conditioning, upward SPV in response to downward head rotation was larger than downward SPV in response to upward head rotation. After adaptation to "gain increase" conditioning, SPV increased in both stimulus directions (Fig. 2A). Similarly, after adaptation to "gain decrease" conditioning, SPV decreased in both stimulus directions (Fig. 2B).

Before adaptation, mean VOR gain at a frequency of 0.16 Hz for the six cats was significantly higher during upward SPV than during downward SPV (Fig. 3). After adaptation to "gain increase" conditioning at 0.16 Hz,
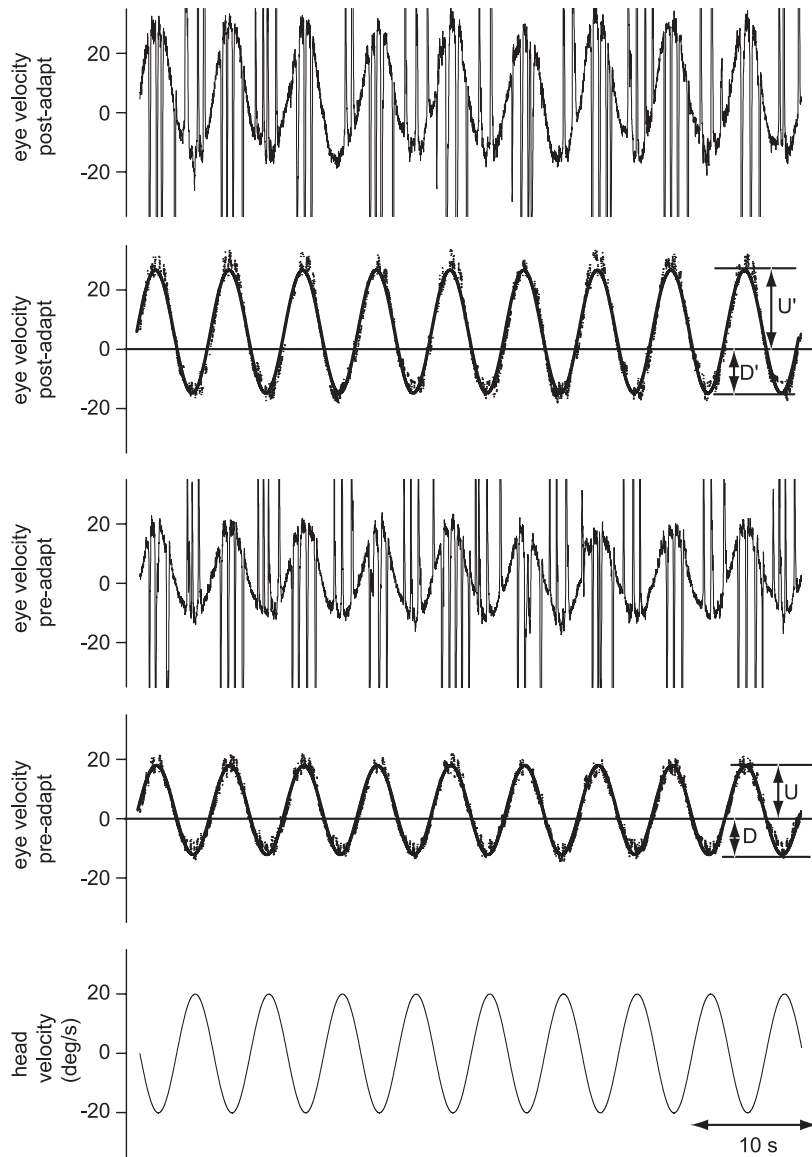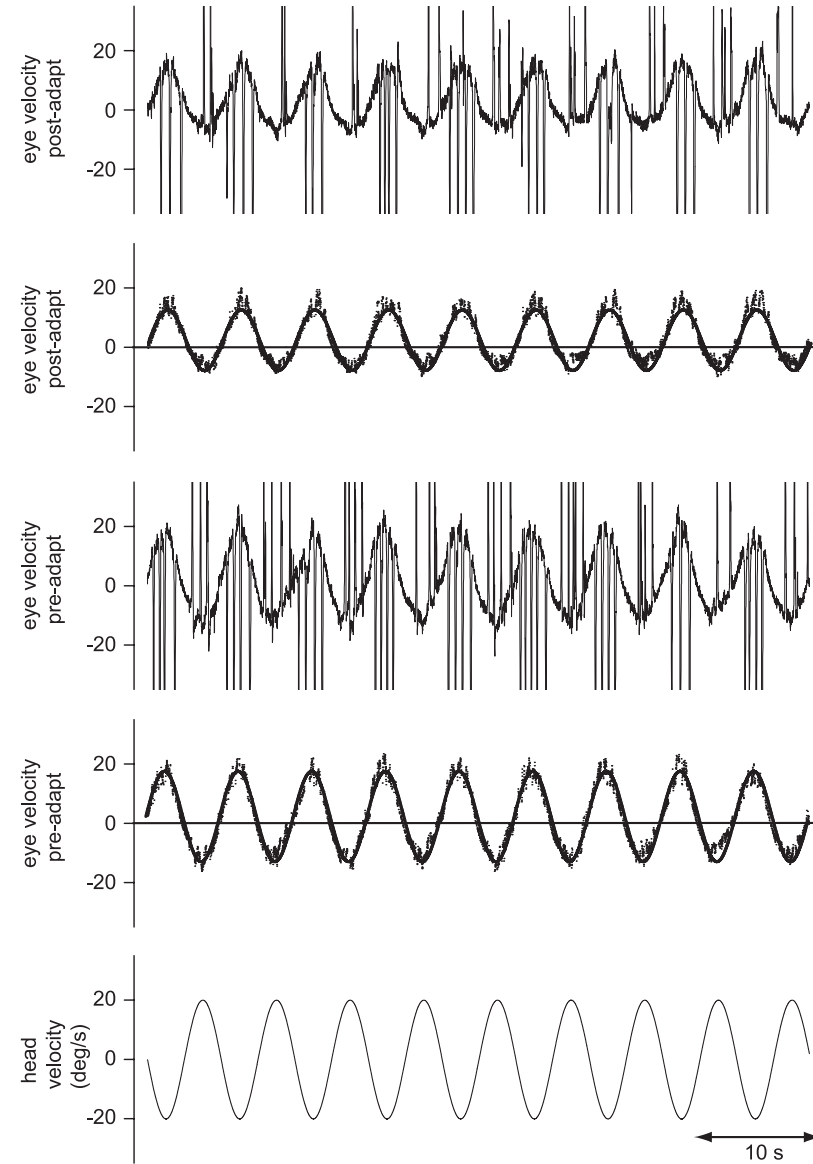
Fig. 2. An example of data obtained from one animal while it was rotated about an inter-aural axis at 0.16 Hz with a peak velocity of 20°/s. Slow phase eye velocity (SPV) increased after adaptation to the "gain increase" conditioning (A). On the other hand, SPV decreased after adaptation to the "gain decrease" conditioning (B). From top to bottom, each trace shows post-adaptive eye velocity, post-adaptive desaccade eye velocity fitted with sinusoids, pre-adaptive eye velocity, pre-adaptive desaccade eye velocity fitted with sinusoids, and head velocity. U and D respectively indicate upward peak-SPV and downward peak-SPV in response to head rotation in darkness before adaptation. U′ and D′ indicate upward peak-SPV and downward peak-SPV in response to head rotation in darkness after adaptation.
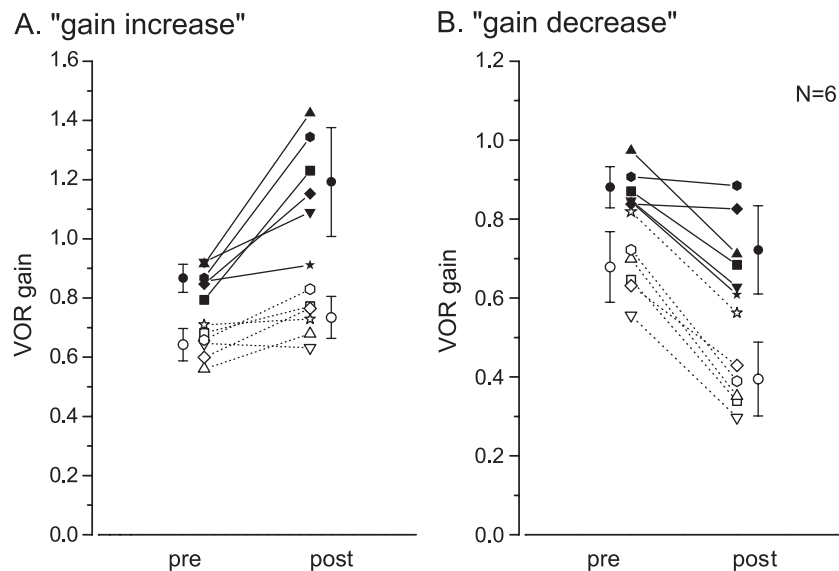
Fig. 3. VOR gains before and after conditioning at 0.16 Hz for each of the six cats. VOR gain increased significantly after adaptation to the "gain increase" conditioning (A), and the increase in the VOR gain was significantly larger for upward SPV than for downward SPV. On the other hand, VOR gain decreased significantly after adaptation to the "gain decrease" conditioning (B), but the decrease in the VOR gain was significantly smaller for upward SPV than for downward SPV. Filled and open symbols represent VOR gain with upward SPV and with downward SPV, respectively. The vertical bars represent the standard deviation of the mean (●) of six cats. Each symbol corresponds to an individual cat.

VOR gain increased significantly for both upward and downward SPV, but the increase in the VOR gain was significantly smaller for downward SPV than for upward SPV (Fig. 3A). The mean gain changes (post-adaptive gain/pre-adaptive gain) of the upward and downward SPV for the six cats were 137.7±21.3% and 114.7±12.4%, respectively. Conversely, after adaptation to "gain decrease" conditioning at 0.16 Hz, VOR gain decreased significantly for both upward and downward SPV, but the decrease in the VOR gain was significantly smaller for upward SPV than for downward SPV (Fig. 3B). The mean gain changes of the upward and downward SPV were 82.1±12.6% and 57.8±8.3%, respectively. Significant up–down asymmetric gain changes were also observed at a frequency of 0.32 Hz. After adaptation to "gain increase" conditioning at 0.32 Hz, the mean gain changes of the upward and downward SPV for the six cats were 133.1±15.8% and 120.4±7.6%, respectively. After adaptation to "gain decrease" conditioning at 0.32 Hz, the mean gain changes of the upward and downward SPV for the six cats were 83.4±9.1% and 63.5±9.5%, respectively.

In addition to the main protocol, two animals were also tested with the paradigms in which the visual stimulus velocity was adjusted so as to equalize the value of retinal slip velocity in the two directions. Under these conditions, asymmetric VOR gain changes were observed. After adaptation to "gain decrease" conditioning at 0.16 Hz, the mean gain changes of the upward and downward SPV were 138.2% and 116.8%, respectively. After adaptation to "gain decrease" conditioning at 0.16 Hz, the mean gain changes of the upward and downward SPV were 79.5% and 52.9%, respectively.

There were no significant differences in the phase before and after adaptation.

4. Discussion

The present study was set up to examine how the vertical VOR adapts during upright pitch rotation in cats. After 1 h of adaptation to simultaneous upright pitch head-oscillation combined with vertical optokinetic stimulation, the gain of the vertical VOR was modified in such a way as to reduce the retinal slip. VOR gain increased significantly after adaptation to "gain increase" conditioning, and decreased significantly after adaptation to "gain decrease" conditioning. In addition, we observed that the gain change was directionally asymmetric in both conditions.

An up–down asymmetry in the number of nystagmus beats and velocity of VOR has been previously reported in cats [9,40]. In the present study, VOR gain also showed an up–down asymmetry before adaptation. The average value for VOR gain with downward SPV in response to upward head rotation was 65% smaller than that with upward SPV in response to downward head rotation. One possible explanation is that the asymmetric gain change of VOR adaptation may correlate with the direction of the head rotation. If so, the gain change in response to downward head rotation should be greater than that to upward head rotation in both "gain increase" and "gain decrease" conditions. However, the gain change was significantly less for downward head rotation than for upward head rotation after "gain decrease" conditioning. Rather, vertical VOR

gain was greater when the retinal slip was generated upward (VOR gain with upward SPV after "gain increase" conditioning, VOR gain with downward SPV after "gain decrease" conditioning). Unlike the VOR in cats, the VOR in monkeys is symmetric [8]. However, an asymmetry can be induced by using adaptive optokinetic stimulation [42], suggesting a retinal origin of the effect.

The cerebellar flocculus is likely involved in VOR adaptation. Retinal-slip information reaches the flocculus through brain stem circuitry [18,24,32,44]. The retinal-slip information that induces adaptive VOR gain changes is conveyed from the retina through the accessory optic system (AOS) and the lateral pretectum to the dorsal cap (DC) of the inferior olive, which, in turn, is conveyed to the cerebellar flocculus via climbing fibers [10,36]. The neurons involved in the vertical visual system are direction-selective in their responses (AOS [17,37], DC [22], Purkinje cell of flocculus [11,16,39]). For example, the complex spikes of Purkinje vertical-type cells in the flocculus have been shown to increase during upward visual stimuli. A monosynaptic inhibitory projection from the flocculus to the vestibular y group, a structure that responds to upward retinal slip, may facilitate upward eye movements [34]. Structurally homologous circuitry for the downward VOR has not been yet found. Electrical stimulation of the flocculus induces depression of the reflexive electrical activity recorded in extraocular muscles following electrical stimulation of the anterior and lateral, but not posterior semicircular canal ampullae [18]. Thus, the present findings that gain changes are smaller when retinal-slip error signals are generated in the downward direction, correlate well with this physiological and anatomical evidence.

In the present study, the pre-adaptive value of downward SPV in response to upward head rotation was slightly but significantly smaller than that of upward SPV in response to downward head rotation. It follows that, in "gain increase" conditioning, retinal slip velocity is slightly faster for upward head rotation than for downward head rotation. Conversely, in the "gain decrease" conditioning, retinal slip velocity is slightly faster for downward head rotation than for upward head rotation. One might thus think that the differences in the absolute value of the retinal slip velocity might be responsible for the asymmetric gain changes. In order to rule out this possibility, we examined adaptive VOR gain changes in two animals with a paradigm in which the visual stimulus velocity was adjusted to equalize the value of retinal slip in the two directions. Under these conditions, asymmetric VOR gain changes were also observed.

Contrary to our results, Snyder and King [38] have reported symmetric gain change in cats, when the vertical VOR adaptation was induced during on-side pitch. However, these data are not directly comparable to our results. First, the vertical VOR responses under these conditions reflect the canal-mediated reflex. During upright pitch rotation, there is an additional effect by the dynamic otolith

stimulation. The peak-to-peak VOR gain is 14.5% higher during upright pitch oscillation than during on-side pitch oscillation [40]. Also, vertical OKR responses are also affected by gravity [6,21,26]. Consequently, adaptive responses during upright pitch are different from those during on-side pitch, when the visual–vestibular mismatch is induced in the head-vertical plane. Second, they calculated VOR gain from initial peak eye velocities in response to velocity-step rotation, although adaptation was induced by sinusoidal vestibular stimulation coupled with either in-phase or out-of-phase sinusoidal visual stimulation (0.2 Hz, $\pm 15°/s$).

We could not determine from our experiments the relative contribution of the dynamic otolithic component to the adaptive gain changes. We can speculate, however. We found that the vertical VOR gain adaptively changed at a lower stimulus frequency of 0.02 Hz (personal communications), at which the vertical VOR depends largely on the otolith-mediated reflex [3]. This finding suggests that the otolithic component of the VOR gain could be modified. It would be of value to obtain an estimate of the otolithic component of the VOR by finding, in the same animals, the adaptive gain changes during on-side pitch rotation (semicircular canal signal) and the adaptive gain changes during upright pitch rotation (present results: semicircular canal signal+otolith signal), and subtracting one from the other. Recent studies in monkeys have shown a static otolith contribution to the vertical VOR adaptation [42]. Maximal gain changes of the vertical VOR occur when the animals are tested in the head orientation in which the adaptation occurred; these changes decrease continuously as the head is deviated from this orientation.

In conclusion, our results indicate a non-linear interaction of the vestibular and visual signals in the vertical VOR adaptation of cats. The gain change is smaller when the retinal slip is generated downward. The asymmetry may be due to asymmetric neuronal circuitry in the central visual–vestibular system.

Acknowledgments

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