Cerebellum
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Role of Cerebellum in Motion Perception and Vestibulo-ocular Reflex—Similarities and Disparities

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Abstract Vestibular velocity storage enhances the efficacy of the angular vestibulo-ocular reflex (VOR) during relatively low-frequency head rotations. This function is modulated by GABA-mediated inhibitory cerebellar projections. Velocity storage also exists in perceptual pathway and has similar functional principles as VOR. However, it is not known whether the neural substrate for perception and VOR overlap. We propose two possibilities. First, there is the same velocity storage for both VOR and perception; second, there are nonoverlapping neural networks: one might be involved in perception and the other for the VOR. We investigated these possibilities by measuring VOR and perceptual responses in healthy human subjects during whole-body, constant-velocity rotation steps about all three dimensions (yaw, pitch, and roll) before and after 10 mg of 4-aminopyridine (4-AP). 4-AP, a selective blocker of inward rectifier potassium conductance, can lead to increased synchronization and precision of Purkinje neuron discharge and possibly enhance the GABAergic action. Hence 4-AP could reduce the decay time constant of the perceived angular velocity and VOR. We found that 4-AP reduced the decay time constant, but the amount of reduction in the two processes, perception and VOR, was not the same, suggesting the possibility of nonoverlapping or partially overlapping neural substrates for VOR and perception. We also noted that, unlike the VOR, the perceived angular velocity gradually built up and plateau prior to decay. Hence, the perception pathway may have additional mechanism that changes the dynamics of perceived angular velocity beyond the velocity storage. 4-AP had no effects on the duration of build-up of perceived angular velocity, suggesting that the higher order processing of perception, beyond the velocity storage, might not occur under the influence of mechanism that could be influenced by 4-AP.

Keywords Vestibular · Eye movements · GABA · Brainstem · Velocity storage · Cerebellum

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Introduction

Stabilization of images on the fovea is the fundamental requirement for clear vision. In order to stabilize gaze during natural behavior, the brain computes an estimate of head movement and ensures an appropriate reflexive eye movement [the vestibulo-ocular reflex (VOR)]. Perception of self-motion and spatial orientation is also critical to assure appropriate reflexive and volitional behavior. It is possible that motion perception and VOR might share fundamental neural strategies. The neural mechanisms for the VOR are relatively well known. Angular motion sensors (the semicircular canals) respond to head *acceleration*, but the eyes must rotate to a new orbital *position*. Mathematical integration of the angular velocity from the labyrinthine sensors is therefore required for the eye movement to be equal and opposite to the head movement [1–4]. The first integration is performed in the labyrinth by the mechanical properties of

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the endolymph and cupula. As a result, the afferents from the semicircular canals discharge in proportion to head *velocity*. The premotor neurons within the brainstem or deep cerebellar nuclei further integrate the velocity signal into a position signal that is encoded in the activity of ocular motor neurons [5]. This network is called the common oculomotor integrator as it provides necessary position signal for the conjugate eye movements of all types.

Upstream from the common oculomotor integrator is the velocity storage, the integrator more specific to the vestibular system. The velocity storage extends the bandwidth over which the angular VOR is compensatory for head movement and improves the VOR response during relatively low-frequency head rotations. In response to a head-velocity step, the velocity storage prolongs the decay of compensatory eye movements beyond that of activity of the vestibular afferents. The velocity storage is not perfect, but its output decays exponentially [1]. The time constant of this decay, the velocity-storage time constant, is affected by GABA-mediated inhibitory projections from the cerebellar cortex (nodulus and ventral uvula) [1, 5–10]. The $GABA_B$ receptor agonist, baclofen, reduces the velocity-storage time constant in human subjects, while focal lesions of the macaque nodulus and ventral uvula prolong it [6, 8].

The perception of self-motion also outlasts the semicircular canal output, suggesting a velocity-storage mechanism in motion perception [11, 12]. The dynamics of motion perception and of the VOR during angular velocity steps are same in the sense that both processes feature relatively prolonged exponential decays. The key difference between the two processes is that motion perception gradually rises to its peak followed by a plateau, suggesting a transient, but steady percept of angular motion before the perceived angular velocity begins to decay [13, 14]. In contrast, slow-phase eye velocity of rotational VOR abruptly increases and instantaneously begins to decay [13, 14]. It was recently proposed that differences between the dynamics of motion perception and those of the VOR during angular velocity steps can be described by the same principle of velocity storage processing, but with minimal contribution from the direct pathway in case of perception [14]. The latter study, however, was not equipped to assess whether the neural substrate for perception and VOR is anatomically the same [14]. Some indirect evidence comes from macaque experiments [15]. Single neuron responses of macaque dorsolateral thalamic neurons had similar dynamic properties as recorded from the deep cerebellar and vestibular neurons [2, 15–17]. Retrograde tracer injections in dorsolateral thalamic neurons revealed their anatomical origin in rostral contralateral anterior interposed and fastigial nuclei, and anterograde tracer injections in deep cerebellar and vestibular nuclei revealed their projections within the thalamic terminal zones [15]. Therefore, it was speculated that vestibular signal that was recorded from the thalamus might be received from the vestibular and deep cerebellar nuclei, and transmitted to the cerebral cortex [15]. Other studies in humans showed that the outcomes of the vestibular processing for VOR and perception are separate [18–21]. For example, in a patient with transient ophthalmoplegia, a disease model of visuo-vestibular adaptation, the perceptual measures of vestibular function had a different amount of attenuation compared to the eye movements [18]. The amount of habituation to the repeated vestibular stimuli in healthy subjects was different for perceived motion and VOR [19].

Taken together, these studies showed different VOR and perceptual responses to the same rotational stimulus, thus suggested two possibilities. One, there is identical low order vestibular pathway (putatively in the brainstem or deep cerebellar nuclei) with additional higher order processing exclusively in case of perception (hypothesis A, Fig. 1). The second possibility is that there are nonoverlapping or partially overlapping networks; one might be primarily involved in perception and the other for the VOR (hypothesis B, Fig. 1). We predict that the same manipulation of these networks would have different amounts of effects on the VOR and perception if the perception and VOR velocity-storage have non-overlapping or partially overlapping elements.

We assessed these hypotheses by measuring VOR and perception of angular motion in humans during whole-body, constant-velocity rotations about an earth-vertical axis,

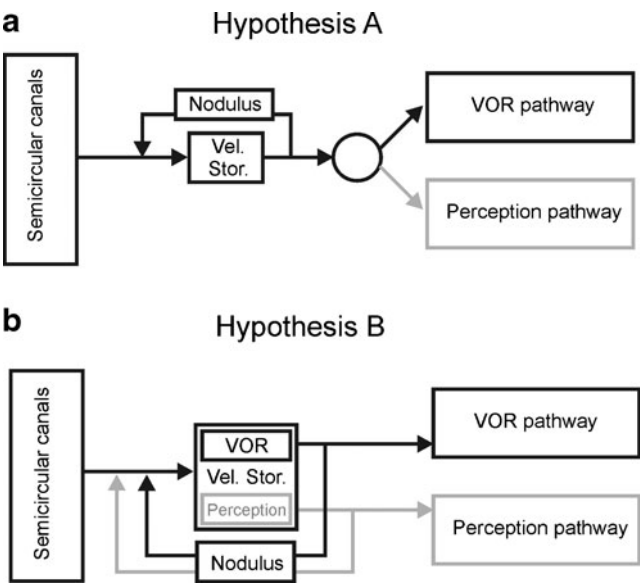

Fig. 1 Summary of two hypotheses. **a** Hypothesis A predicts that the same group of neurons performs the velocity storage function in the perception and VOR pathways. **b** Hypothesis B predicts that the groups of neurons responsible for velocity storage in the perceptual and VOR pathways are functionally and computationally identical, but anatomically discrete

before and after 10 mg of 4-aminopyridine (4-AP). 4-AP blocks inward rectifier potassium conductances (I_A and I_D) that regulate the intrinsic membrane properties of secondary vestibular neurons [22–24]. 4-AP improves synchronization and precision of the Purkinje neurons and possibly increases the synaptic concentration of GABA [25–27]. 4-AP should reduce the decay time constant of perceived angular velocity if indeed perceptual velocity storage is under the influence of GABAergic cerebellar projections. We predict that if the hypothesis A is true, but further processing of perceptual signal beyond velocity storage is not dependent upon cerebellar Purkinje neurons or other 4-AP dependent mechanisms, the extent of reduction in the decay time constant of VOR and perceived angular velocity must be the same. However, if hypothesis B is true, the time constants of the decay in VOR and perception both may decrease, but by different amounts.

We recorded VOR and perception of angular velocity during on-axis whole-body velocity steps of rotations in all three planes. We know that humans have strong VOR velocity storage for yaw rotations (i.e., rotations on earth vertical axis when the subject is sitting upright), but velocity storage during pitch (i.e., rotations on earth vertical axis when subject's ear faces the ground) or roll (i.e., rotations on earth vertical axis when subject is supine) rotations is weak [28]. We also assessed the perceptual velocity storage during yaw, pitch, and roll rotations.

Methods

Six healthy subjects (two women and four men; age range, 30–45) enrolled in the study. The experimental protocol was approved by an ethics committee of the Canton of Zurich and adhered to the Declaration of Helsinki for research involving human subjects. The subjects were naive to the outcome of the experiments.

Experimental Setup

The subjects were seated upright on a three-axis motor-driven turntable (Acutronic, Jona, Switzerland) with the head restrained by an individually molded thermoplastic mask (Sinmed BV, Reeuwijk, The Netherlands). Subjects first were rotated on an earth-vertical axis while seated upright, in which case the angular vestibular response is primarily through stimulation of the lateral semicircular canals, (yaw rotation, schematic inset in Fig. 2a). Subjects were then rotated on an earth-vertical axis while supine (roll-rotation, schematic inset in Fig. 2c) or on the side with their left-ear down (pitch-rotation, schematic inset in Fig. 2e). In these cases, the vertical semicircular canals are primarily stimulated. The gravity vector with respect to the head remained constant during these rotation stimuli. The rotations were delivered in both directions (e.g., relative to head-fixed coordinates, right or left during yaw, up or down during pitch, and clockwise or counterclockwise during roll). Thus, each subject had at least six sets of velocity-step rotations.

Before each trial, subjects looked at a laser dot (diameter, 0.1°) projected onto a sphere with a radius of 1.4 m by two mirror-galvanometers fixed to the rotating chair. The laser and room lights were then extinguished, and rotations began at an initial acceleration at 90°/s^2 to a final speed of 100°/s. One and a half minutes later, the rotations were stopped by a 90°/s^2 deceleration. The eye movements and perceived angular velocity were measured during and after rotations for 90 s.

Eye movement Recordings

The eye movements were recorded from each eye using dual search coils (Skalar Instruments, Delft, The Netherlands). Search coil annuli were calibrated and then placed sclera of the right or left eye after local anesthesia with oxybuprocaine 0.4 % [29]. The coil frame around the head (side length, 0.5 m) generated three orthogonal, digitally synchronized magnetic wave field signals of 80, 96, and 120 kHz. A digital signal processor computed a fast Fourier transform in real time on the digitized search coil signal to determine the voltage induced on the coil by each magnetic field (Primelec, Regensdorf, Switzerland). Coil orientation was determined with an error of <7 % over a range of ±30°, and with a noise level <0.05° (root mean squared deviation). Eye position signals were digitized at 1,000 Hz per channel with 12-bit resolution.

Perception Recordings

Subjects reported their perception of angular motion by turning a lever attached to a potentiometer. Subjects were instructed to match the perceived motion with the rate at which they spun the lever. The potentiometer signals were sampled at 1,000 Hz. This method for assessing the perception of angular velocity permits the comparison of *relative* magnitudes during the time course of a single response [11]. This technique investigates whether perceived angular velocity is sensed as constant, increasing, or decreasing. Without training, this method cannot estimate the absolute magnitude of perceived angular velocity. We did not train the subjects with an intention to keep them naïve and avoid the influence of vestibular habituation.

The experiments were performed on the same subjects with and without 4-AP. The sequence of control and 4-AP experiment sessions was randomly determined, and both experiments were done at least 4 days apart to allow adequate time for washout (if subjects

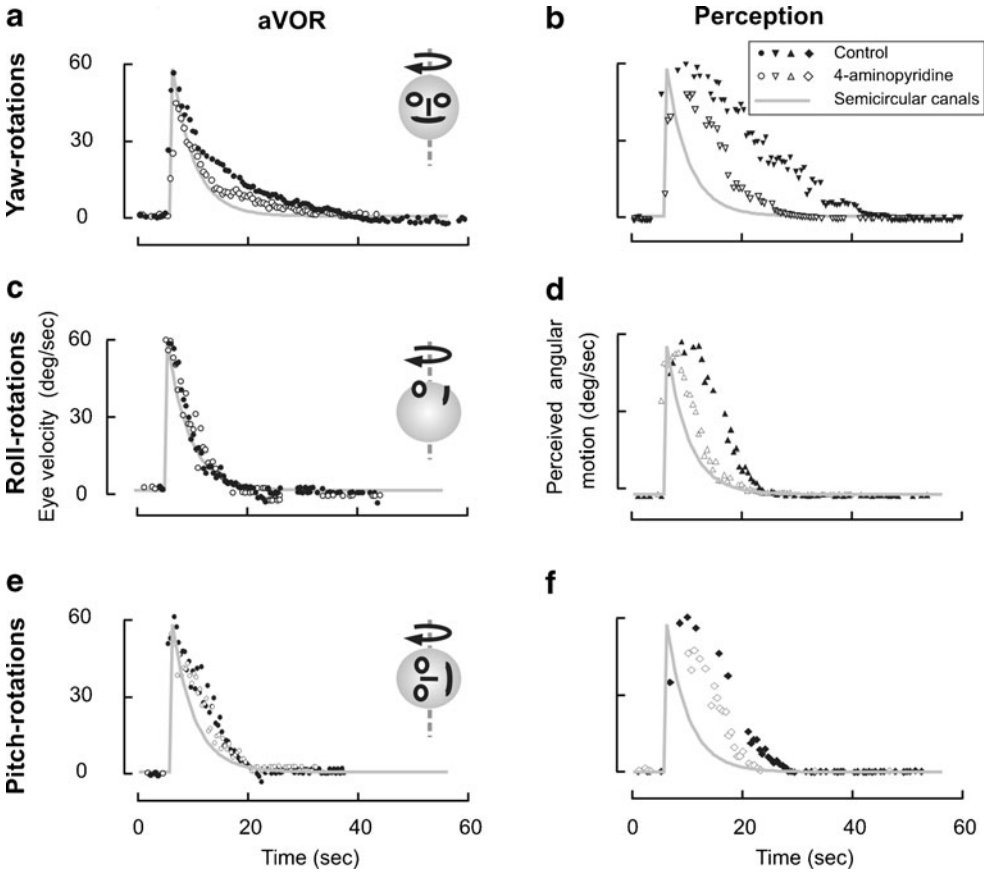

Fig. 2 Slow-phase eye velocity during VOR and perceived angular motion during constant angular velocity rotations. **a** Constant-velocity rotations, when the subject was seated upright evoked the horizontal VOR. The slow-phase velocity (*filled circles*) of the horizontal VOR had a rapid rise followed by an exponential decay. 4-Aminopyridine reduced the time constant of the slow-phase velocity (*open circles*). Perceived angular motion during constant-velocity rotations when subjects were seated upright [yaw rotations, **b** supine (roll rotations, **d**) or on their left side (left ear facing the floor—pitch rotations, **f**] is illustrated by *filled symbols*. Perceived angular motion had a slow rise and gradual decay. 4-Aminopyridine did not alter the time constant of decay of the VOR evoked during pitch, and roll-rotations (**c**, **e**)

took 4-AP during the first session). The 4-day-period also allows sufficient time to recover from the effects of any possible vestibular habituation [30].

Data Analysis

Calibrated eye position signals from the search coils and perceived angular position signals from the potentiometer were processed to compute slow-phase velocity and perceived angular velocity using interactive programs written in MatLab® (The Mathworks, Natick, MA, USA). Eye positions were represented as 3D rotation vectors in a head-fixed coordinate system. Rotation vectors were smoothed, and angular eye velocity was computed as described previously [31]. The eye velocity and perceived angular motion traces were divided into intervals of different lengths at the zero-crossings from negative to positive values. All data points were sorted in an ascending order in each interval. The value at the least slope represented the slow-phase velocity or perceived angular velocity for the given processed interval. Spline interpolation between the representative points of all intervals resulted in an envelope describing the slow-phase velocity or perceived angular velocity over time. The time constant was computed when the eye velocity and the perceived velocity began to decay. The slow-phase velocity data was first processed with a Skavinsky–Golay smoothing filter. Smoothed data was then fitted by an exponential function with parameters estimated in the MatLab® least-square fitting algorithm (MatLab®, Mathworks, Optimization Toolbox).

Results

Figure 2a illustrates the rapid rise in the slow-phase velocity of the horizontal VOR followed by the immediate exponential decay during yaw-rotation in one subject. The time constant of the decay of the slow-phase velocity was 10 s (Fig. 2a, filled circles), larger than expected from the mechanical properties of the semicircular canal cupula (about 4 s, gray trace drawn for reference) [32]. The open circles in Fig. 2a illustrate slow-phase velocity of the horizontal VOR during yaw-rotation in the same subject 30 min after taking 10 mg 4-AP by mouth. Slow-phase velocity now decayed more rapidly with a time constant of 6.0 s. A quantitative estimate of the perception of horizontal angular velocity during yaw rotation in the same subject is shown by the filled triangle symbols in Fig. 2b. There was an exponential decay in perceived angular velocity with a time constant of 13.7 s (Fig. 2b, filled triangles). The time constant of decay was reduced to 8.6 s after 10 mg 4-AP (Fig. 2b, open triangles).

Figure 2c depicts an example of slow-phase velocity of the vertical VOR in the same subject during pitch rotations.

Prior to 4-AP, the time constant of the decay of slow-phase velocity during pitch rotations was 8.0 s. The time constant reduced to 7.5 s after 10 mg 4-AP. Perceived angular velocity during pitch rotations is illustrated in Fig. 2d. The decay time constant of perceived velocity during pitch rotations was 6.3 s. Thirty minutes after 10 mg 4-AP, the time constant reduced to 5.0 s.

Figure 2e depicts an example of slow-phase velocity of the torsional VOR in the same subject during roll rotations. The decay time constant of slow-phase velocity during roll rotations was 5.5 s. In the same subject, the time constant was reduced to 5.1 s after 10 mg 4-AP. Figure 2f illustrates the perceived angular velocity during roll rotations. The decay time constant of perceived velocity during roll rotations was 5.6 s. Thirty minutes after 10 mg 4-AP, the time constant reduced 4.0 s.

The slow-phase velocity of the VOR rapidly peaked and began to decay immediately. In contrast, the perceived angular velocity had a gradual growth to its peak value (introducing a delay to peak), and there was a delay before the perception of angular motion began to decay, appearing as a "plateau" (Fig. 2b, d, and f).

Figure 3a summarizes the effects of 4-AP on the VOR time constant in six subjects. The decay time constant of the VOR with 4-AP is plotted along the ordinate, and the control value is plotted on the abscissa. Each symbol represents one rotation trial, each symbol type represents one subject, and the symbol color represents the rotation plane (black, yaw; blue, roll; red, pitch). All black-colored data points in Fig. 3a are below the equality line, suggesting a consistent and statistically significant reduction of the decay time constant of the horizontal VOR during yaw rotations (one-way ANOVA, $p<0.01$). In Fig. 3a, blue and red-colored data points scattered on the both sides of the dashed equality line, suggesting no consistent effect of 4-AP on the VOR time constant during roll (blue symbols) and pitch rotations (red symbols) (one-way ANOVA, $p>0.05$).

Figure 3b summarizes the effects of 4-AP on the decay time constant of perceived angular velocity in six healthy subjects. Black and red data points, illustrating perceived angular velocity during yaw and pitch rotations, respectively, are below the equality line, suggesting a consistent reduction in the perceived angular velocity by 4-AP (one-way ANOVA, $p<0.03$). However, the effects of 4-AP on the decay time constant of the perceived angular velocity during roll rotations was not consistent (blue symbols in Fig. 3b, one-way ANOVA, $p>0.05$).

During both the control and the 4-AP conditions, the time constants of the VOR and of perceived angular velocity were poorly correlated (Fig. 3c). The r^2 coefficients for yaw, pitch, and roll rotations were 0.09, 0.04, and 0.001, respectively. Figure 3d compares the delay in the peak slow-phase velocity during the VOR and the delay in the peak perceived angular velocity in all three rotation planes for all experimental trials, before and after 4-AP. The delay to peak

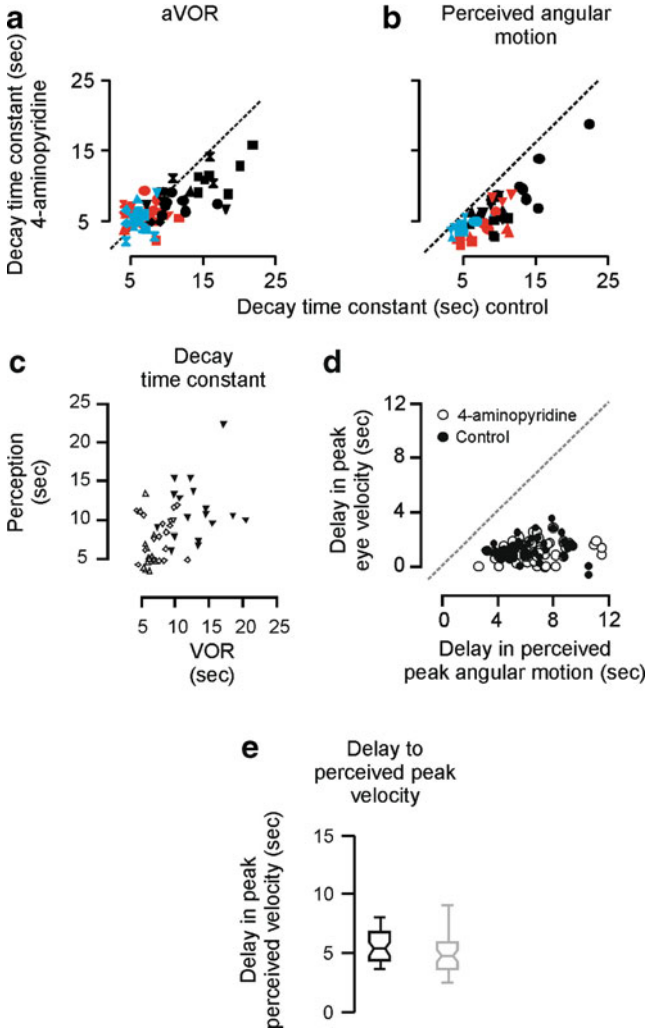

Fig. 3 Summary of results from all subjects: 4-aminopyridine significantly reduced the time constant of the exponential decay of horizontal VOR during yaw-rotations (**a**) as well as the perceived angular velocity during yaw and pitch-rotations (one-way ANOVA, $p<0.03$) (**b**). The exponential decay of the VOR during roll and pitch rotations and the perceived angular velocity during roll rotations was not consistently affected when subjects took 4-aminopyridine (**a**, **b**). In **a** and **b**, each data point represents one trial, each symbol color represents the type of rotational stimulus, and each symbol type represents one subject. *Black symbols* represent yaw rotations; *blue symbols*, roll rotations; and *red symbols*, pitch rotations. **c** The time constant of decay of the perceived angular velocity did not correlate with that of the VOR. Different stimulus conditions are represented by the symbol types. The r^2 coefficients for yaw, pitch and roll rotations were 0.09, 0.04, and 0.001, respectively. Inverted *triangles* represent yaw rotations; *upright triangles* represent roll rotations; *diamond-shaped symbols* represent pitch rotations. **d** All subjects (before and after 4-aminopyridine) had a relatively longer delay in perceived peak angular motion. Such a delay was larger than the one observed for peak slow-phase velocity of the VOR. **e** 4-AP did not affect the delay of the peak perceived angular velocity (median delay control, 5.3 s; median delay 4-AP, 4.7 s; one-way ANOVA, $p>0.05$)

eye velocity after the onset of rotation is plotted on the ordinate, and the delay to the peak of perceived angular velocity is plotted on the abscissa. All data points fall below the dashed equality line, indicating that the delay in the perception of peak angular motion was larger than the delay to peak slow-phase velocity of the VOR. The box and whisker plots in Fig. 3e illustrate that the delay to peak perceived angular velocity during control rotations was not significantly different from the value after taking 4-AP (median delay control, 5.3 s; median delay 4-AP, 4.7 s; one-way ANOVA, $p>0.05$, Fig. 3e).

The VOR time constant was greater during yaw rotations as compared to pitch and roll. The decay time constant of perceived angular velocity during yaw rotations was significantly larger than roll rotations (Fig. 4). 4-AP significantly decreased the decay time constants of the VOR during yaw rotations and perception during yaw and pitch rotations (Fig. 4, Table 1, one-way ANOVA, $p<0.05$).

We next investigated whether the reduction in the time constant of decay induced by 4-AP was similar in a given subject for the pair of complementary rotation stimuli that produce identically directed nystagmus (for example, per-rotatory decay time constant during rightward yaw rotations and postrotatory during leftward yaw rotations). Figure 5a illustrates the summary of the reduction in the time constant of the horizontal VOR (circular symbols) and of the perceived angular velocity (square, upright triangle, inverted triangle for horizontal, coronal, and sagittal planes, respectively) induced by 4-AP using the complementary rotational stimuli. The data points in Figure 5a were restricted along the dashed equality line and the changes in the time constant of decay induced by 4-AP during the two complementary conditions strongly correlated (r^2, 0.92). These results suggest that 4-AP had a consistent effect on the time constant of velocity storage related both to perceived angular velocity and to the VOR and the drug equally affected per- and postrotational responses.

Then, we asked whether the change in the time constant of decay of the VOR induced by 4-AP correlated with the change in the time constant of the decay of perceived angular velocity during the same rotational condition. The reduction in the decay time constant of the VOR is plotted along the abscissa and that of the perceived angular velocity is plotted along the ordinate in Fig. 5b. Each data point represents a single trial. Dark blue circles represent yaw, light blue circles are roll, and magenta circles are pitch rotations. The wide scatter of the data points suggests that the magnitude of the reduction in the velocity-storage time constants of perceived angular velocity and of the VOR induced by 4-AP were not correlated ($r^2=0.05$).

In summary, we learned that (1) 4-AP reduces the decay time constant of horizontal VOR during yaw rotations, (2) 4-AP reduces the decay time constant of perceived angular velocity during yaw and pitch rotations, (3) the amount of reduction in the decay time constant of perceived angular velocity and horizontal VOR induced by 4-AP is different, and (4) 4-AP does not affect the build-up duration of the perceived peak velocity. These results suggest that the velocity storage for perception abide the same principle as the VOR. Both networks are influenced by the inhibitory GABAergic projections from the cerebellar Purkinje neurons. However, it is possible that non- or partially overlapping neural substrates independently serve the velocity storage for VOR and perception. Furthermore, higher order processing of motion perception, beyond velocity storage, might not be affected by 4-AP-dependent mechanism.

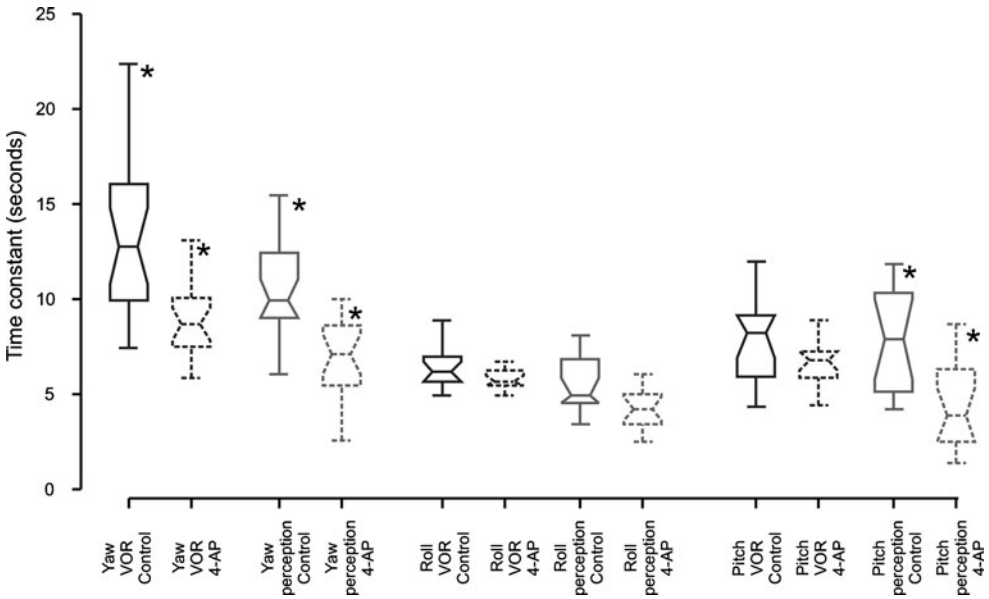

Fig. 4 The time constants of decay of the VOR and perceived angular velocity before and after 4-AP during all three planes of rotations are summarized as *box* and *whisker plots*. *Black data* represent time constant of decay of the VOR, and *gray* represent that of perceived angular velocity. *Horizontal line at the center of the box* represents median, while *notches* are 95 % confidence intervals around the median. If notches from two box–whisker plots do not overlap, the difference between the median in the two populations is statistically significant. The *asterisks above the box–whisker plot* indicate statistically significant difference

Table 1 Summary of time constants

Condition	Mean (seconds)	Variance (seconds)
Yaw VOR control	13.4	16.6
Yaw VOR 4AP	9.1	5.7
Yaw perception control	10.6	12.8
Yaw perception 4AP	7.5	11.9
Roll VOR control	6.3	1.0
Roll VOR 4AP	5.8	1.7
Roll perception control	6.1	8.0
Roll perception 4AP	4.2	1.0
Pitch VOR control	7.8	4.8
Pitch VOR 4AP	5.9	2.8
Pitch perception control	7.9	7.2
Pitch perception 4AP	4.5	5.3

Discussion

We measured the effects of 4-AP on VOR and perceived angular velocity during constant velocity yaw, pitch, and roll rotations about an earth-vertical axis. 4-AP is a rapidly acting drug that blocks inward rectifier potassium currents (I_A and I_D) [22–24, 26, 27, 33] and improves synchronization and precision of the cerebellar Purkinje neurons to possibly increase the synaptic concentrations of GABA at their projection sites [23, 25–27].

Velocity storage is inferred because the slow phases of the VOR and the perception of self-motion outlasts the duration of the response originating from the semicircular canals [11, 12, 34, 35] (Fig. 2). Like horizontal VOR, the prolonged time constant of the perceived angular velocity during yaw rotations suggests velocity storage [35]. Consistent with the earlier studies, we found the weak of VOR velocity storage during pitch and roll rotations [28]. Also consistent with the prior studies, we found an evidence of velocity storage for perception during pitch rotations but not during roll [34]. We also found that the perceptual response was delayed and smoothed relative to the VOR. This delay and smoothing was not altered by 4-AP, for all three axes (Fig. 2b, d, and f). Thus, the perceptual response might be altered by another mechanism further downstream from the velocity storage. This "downstream" mechanism might not be responsive to 4-AP; hence, it may not be under GABA mediated cerebellar control.

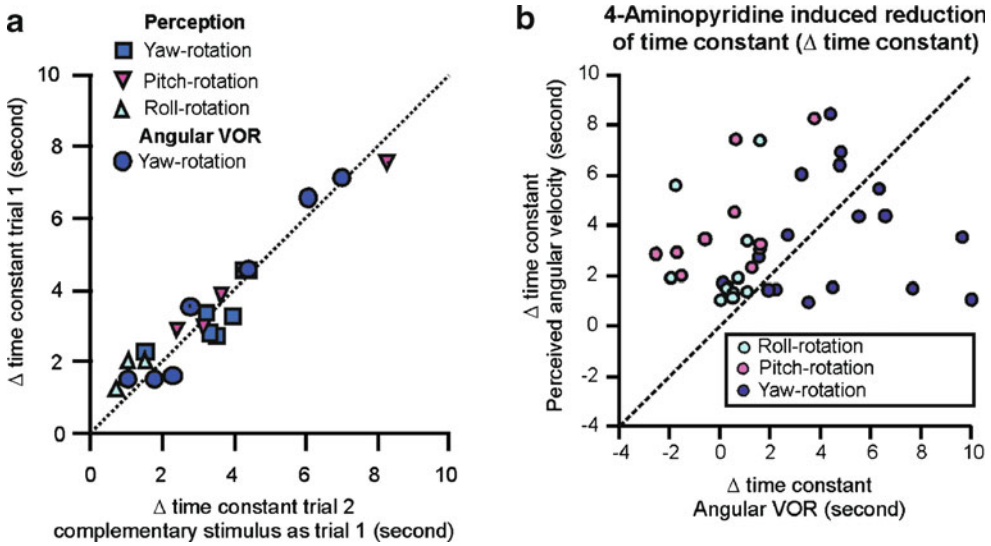

Fig. 5 **a** 4-AP induced change in the time constant of the VOR or perceptual responses during two complementary stimulus conditions are compared. The decrease in the time constant induced by 4-AP during one trial is plotted along the *ordinate*, while the same during the second trial (with identical stimulus) is plotted along *abscissa*. Each data point represents one pair of complementary stimulus trials. The decrease in the perceptual time constant for stimulus pairs during yaw, roll, and pitch rotations are plotted as *squares*, *upright triangles*, and *inverted triangles*, respectively. Decreases in the time constant of the horizontal VOR during identical stimulus pairs are plotted as *round symbols*. The responses during two complementary stimulus pairs strongly correlated (r^2=0.92). All data points fall along the unity line (slope of the regression line is 0.98). **b** The magnitude of the reduction in the time constant of perceived angular velocity and the VOR induced by 4-AP is compared. The reduction in the time constant of decay of the VOR (*abscissa*) is plotted against the perceived angular velocity (*ordinate*). Each data point represents a single trial. Color coding represents the plane of rotation. The *blue circles* are widely scattered with a regression coefficient of 0.05. Therefore, 4-AP significantly reduced the time constant of perceived angular velocity and the horizontal VOR during yaw rotation, the magnitude of the effects were not equal. All *light blue and magenta circles*, representing roll and pitch rotations, fell above the dashed equality line. This suggests that during roll and pitch rotations, 4-AP did not significantly affect the time constant of VOR. However, it significantly reduced the time constant of perceived angular velocity during pitch rotations. In the case of yaw rotations, 4-AP reduced the time constants of the VOR and perceived angular velocity though the magnitude of its effect on the two was different

Differences Between Velocity Storage for the VOR and for the Perception of Angular Velocity

Differences in the velocity storage for the VOR and perceived angular velocity can be inferred from the decay time constant longer than 4 s and in a drop of that time constant in response to 4-AP. The VOR shows longer decay time constants for all three axes, although only slightly better than 4 s for the roll rotations. Perceived angular velocity shows a delayed and smoothed response for all axes, but only a longer time constant for yaw and pitch rotations. 4-AP reduces the time constants in yaw for both systems, in pitch for the perceptual system, but in neither for roll. These results suggest a weak (or absent) perceptual velocity storage for roll rotations and weak (or absent) VOR velocity storage for pitch and roll rotations. Perhaps, the absence of a changing gravity cue associated with stimulation of the vertical canals during this unnatural motion pattern is the reason for the absence of VOR velocity storage during pitch and roll rotations. Indeed, the time constant of the torsional VOR is higher (as reflected in less phase lead at low frequencies of oscillation) when subjects are sinusoidally oscillated around roll axis with the head upright (with a changing gravity vector) than in the supine position (with an unchanging gravity vector) [36]. The perception pathway, however, seems to use an integrated velocity signal even during rotation without a changing gravity vector.

Although 4-AP significantly reduced both the time constant of the VOR and of perceived angular velocity during yaw rotations, the *amount* of its effect on the two was different (Fig. 5b). Furthermore, 4-AP did not affect the build-up time for perceived angular velocity. All together, our results supports hypothesis B that nonoverlapping or partially overlapping neural networks might exist, one serving the velocity storage in the VOR pathway, the other in the perceptual pathway (Fig. 1). One more possibility that could explain our results is hypothesis A but, additionally, in perception pathway, the "downstream" processing not only introduces the build-up delay but also changes the decay time constant. In this scenario, to explain our results, 4-AP should only affect decay time constant but not the delay in build-up of perceived velocity, the process that hypothetically takes place at the level of (additional) "downstream" processing. Such selective effect of 4-AP on the same process is less likely. In this regards, hypothesis B is more feasible. Our results and results and hypothesis B also explain the basis for severe vertigo but without spontaneous nystagmus among occasional sufferers of rare cerebellar strokes [37].

In What Other Ways Might 4-AP Influence Perception?

Ion channels sensitive to 4-AP such as those conducting I_A and I_D as well as GABA-mediated inhibitory neurotransmission are found throughout the central nervous system [38]. Therefore, it can be claimed that 4-AP might have altered the perception of angular velocity by affecting the cognition, alertness, attention, or other aspects of motor behavior and that the effect is not confined to the velocity storage. It is known, however, that 4-AP chronically administered at a dose three times higher than used in our study does not worsen cognitive function measured with conventional neuropsychological tests in patients with multiple sclerosis [39, 40]. In fact, long-term treatment with 4-AP had improved cognitive function in multiple sclerosis patients who had cognitive decline prior to treatment [40]. Likewise, we also found that 4-AP given once in small amounts does not have any effect on baseline cognitive and attention functions or natural motor behavior in normal subjects (authors' observations). We emphasize that the subject's ability to perceive and report the change in motion could reflect their cognitive state. As illustrated in Fig. 3d and e, 4-AP did not alter the delay to reach peak perceived velocity (i.e., the decision that motion has begun or has reached its peak). This result serves as an internal control for each subject and suggests that 4-AP did not affect their general motor behavior, attention, or cognitive ability to perceive and report the motion of their body. We also noticed that 4-AP only affected the decay time constant of perceived angular velocity in yaw and pitch rotations. 4-AP did not affect the decay time constant of perceived velocity in roll rotations. If the observed effects of 4-AP were secondary to changed alertness, cognition, or peripheral motor function, we would expect a similar decrease in decay time constant in all three planes of rotation. This was not the case and further supports the likelihood that 4-AP did not affect cognition, alertness, and peripheral motor function in our subjects.

Our results suggest the possibility that the effect of 4-AP on perceived angular velocity were secondary to its effects on the velocity storage. The effect is similar to that of baclofen (a GABA mimetic agent), which also reduces the dominant time constant of VOR velocity storage in humans [8]. Baclofen increases the synaptic GABA levels in neurons subserving velocity storage and reduces the dominant time constant of the horizontal VOR but does not alter other dynamic features of the VOR (e.g., the rise time and plateau of velocity are unchanged with baclofen; see Fig. 2 in Dai et al. [8]). Our perceptual results are comparable to the VOR findings reported by Dai and colleagues [8].

Differences Between the Dynamic Characteristics of the Early Response of Perceived Angular Velocity and the VOR

Why did the dynamic response of the perceived velocity show a delay and a plateau that were much longer than that for the VOR? One possibility is that the delay in the perception pathway simply reflects the latency in using

the hand and the potentiometer to reflect perception. The relatively larger mass of the hand moving the lever attached to the potentiometer and the mechanical time constants associated with limb movement and potentiometer could cause a delay in reaching the maximum rotation velocity as reflected by the movement of the potentiometer. While this might explain the delay in peak perceived velocity, it does not explain the sustained value of perceived velocity (plateau) before it starts decaying. In a separate study, the perception of constant velocity rotation in the horizontal plane was compared using three ways of reporting sensation: first with a potentiometer as in the present study; second, by pushing a button when rotation was first sensed, when velocity reached a peak, when velocity began to decrease, and when velocity reached zero; and third by changing the static position of the dial such that a bigger change in the angular position of the dial correlated with a larger perceived velocity [13]. During all three tasks, there was a delay in the time at which peak velocity of rotation was perceived relative to the beginning or end of the rotation as well as the presence of a plateau before perceived angular velocity started to decay [13]. In another study of vestibular perception, using a similar experimental setup to ours, the lever spinning task to report perception was performed with auditory tones instead of vestibular stimuli [14]. There was a good correlation between the time of initiation, peak, and cessation of the auditory stimulus and the velocity of lever spinning, but there was no plateau. When the same subjects reported their perception of angular rotation, however, there was a plateau.

There may be more fundamental reasons for the delay and the plateau in perception of motion, and we will consider several theoretical constructs to interpret these findings. First is the influence of prediction in perception [41, 42]. Predictive behavior relies on the memory of the preceding sensations and the influence of the reaction (or percept) to the ongoing sensory input. In other words, the reaction (or percept) of the ongoing sensory signal could represent the average of the predicted and the current sensory signals [43, 44]. This signal processing could include the weighted averaging of the prospective estimate of the future movement and the current signal (in this case received from the velocity storage mechanism). Thus, during impoverished conditions, such as constant velocity rotation in darkness, the predictive component of the motion cues might have a stronger influence on the computation of perceived motion [43]. Such a mechanism might blunt the perceptual response to rapidly changing, unexpected movements.

Another way to look at this idea is based on the *probability* that the interpretation by the brain of a change in the sensory inputs to perception is correct [45]. Normally, there is a strict concordance among the various sensory inputs, e.g., vision, labyrinthine, and somatosensory, that contribute to motion perception. In an impoverished sensory environment, however, such as rotation in the dark while sitting in a chair, or in a conflicting sensory environment, when labyrinthine and visual sensations are at odds, the perceptual mechanisms may be reticent to assume immediately that the signal from one source or another is the correct one. Only as corroborating information becomes available, or when no conflicting information emerges, can the perceptual mechanism begin to "believe" that the initial stimulus actually reflects what the body is doing in the environment. An example of this is the delay in the onset of circularvection (the illusion of rotation) when a normal subject sits in a stationary chair and a surrounding optokinetic drum is rotated [46]. Regardless of the interpretation—prediction or sensory conflict—the sluggishness of the response can be described mathematically by low-pass filtering, which delays and blunts the response to an abrupt change in the input.

In conclusion, our results suggest that the perception and VOR both processes rely on a velocity-storage mechanism. 4-AP, presumably by increasing the precision and synchronicity of cerebellar Purkinje neurons and enhancing GABAergic inhibition of secondary vestibular neurons, influences both motion perception and the horizontal VOR. The results also suggest that the neural substrate comprising velocity storage for perception and VOR may not entirely overlap. There is also an evidence of further "downstream" processing in the perception pathway. Finally, it is observed that the velocity storage for the VOR and the perception of angular velocity is strong in yaw, is weak in pitch, and is weak if not absent in roll. We must emphasize that, although our results are in support of the possibility of nonoverlapping or partially overlapping neural circuits for perception and VOR, further anatomical lesion studies, structural lesion models in humans, or behavioral and electrophysiology experiments in nonhuman primates trained for psychophysical tasks to report perceived motion are justified.

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Conflict of Interest Authors do not have any conflict of interest.

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