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# Stimulation of the nodulus and uvula discharges velocity storage in the vestibulo-ocular reflex

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**Abstract** The nodulus and sublobule d of the uvula of rhesus and cynomolgus monkeys were electrically stimulated with short trains of pulses to study changes in horizontal slow-phase eye velocity. Nodulus and uvula stimulation produced a rapid decline in horizontal slow phase velocity, one aspect of the spatial reorientation of the axis of eye rotation that occurs when the head is tilted with regard to gravity during per- and post-rotatory nystagmus and optokinetic after-nystagmus (OKAN). Nodulus and uvula stimulation also reproduced the reduction of the horizontal time constant of post-rotatory nystagmus and OKAN that occurs during visual suppression. The brief electric stimuli (4–5 s) induced little slow-phase velocity and had no effect on the initial jump in eye velocity at the onset or the end of angular rotation. Effects of stimulation were unilateral, suggesting specificity of the output pathways. Activation of more caudal sites in the uvula produced nystagmus with a rapid rise in eye velocity, but the effects did not outlast the stimulus and did not affect VOR or OKAN time constants. Thus, stimulation of caudal parts of the uvula did not affect eye velocity produced by velocity storage. We postulate that the nodulus and sublobule d of the uvula control the time constant of the yaw axis (horizontal) component of slow-phase eye velocity produced by velocity storage.

**Key words** Nodulus · Uvula · Velocity storage
Vestibulo-ocular reflex · Monkey

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## Introduction

Gravity has a profound effect on the spatial orientation of the vestibulo-ocular reflex (VOR). When monkeys are upright and receive optokinetic stimulation about their yaw axis, the induced nystagmus (OKN) and after-nystagmus (OKAN) are purely horizontal. When the animals are tilted and receive the same yaw axis stimulus, a vertical component appears during OKN that shifts the axis of eye rotation toward the spatial vertical (Dai et al. 1991). At the end of OKN, the horizontal, OKAN slow-phase velocity declines more rapidly than if the animals had been upright, and additional vertical and/or torsional velocities appear that shift the axis of eye rotation further towards alignment with gravity (Raphan and Cohen 1988; Dai et al. 1991).

A similar reorientation occurs when humans, cats or monkeys are stopped in side down positions after rotating about axes tilted from the vertical (off-vertical axis rotation, OVAR; Harris and Barnes 1987; Harris 1987; Raphan et al. 1992). The slow component of vestibular nystagmus also tends to align with the combined gravito-inertial acceleration (GIA) vector during centrifugation (Merfeld et al. 1991; Raphan et al. 1994). In each instance, the reorientation entails a reduction in the time constant of the horizontal component of the nystagmus and the appearance of vertical and/or torsional components. Since the rapid components of the angular VOR are oriented purely in a semicircular canal, i.e., a head frame of reference (see Cohen and Henn 1988, for review), it is the slow component of the VOR, termed "velocity storage", that is responsive to gravitational orientation (Raphan and Sturm 1991; Raphan et al. 1992). Spatial orientation of velocity storage is also probably responsible for the recently discovered gravitational dependence of human OKN (Gizzi et al. 1994).

The time constant of post-rotatory nystagmus or OKAN also becomes shorter when the head is tilted during post-rotatory nystagmus or OKAN (Benson 1974; Schrader 1985; Waespe et al. 1985a; Cohen et al. 1992a; Fetter et al. 1992; Angelaki and Hess 1994;

Raphan et al. 1994). The loss of slow phase velocity in this condition has been called, "tilt-dumping", because events initiated by the tilt rapidly discharge or "dump" activity from velocity storage (Raphan et al. 1981; Cohen et al. 1992a). Whether there is also an associated increase in pitch and/or roll eye velocity during tilt dumping is in dispute. It occurs in monkeys (Raphan et al. 1992; Merfeld et al. 1993a, b; Angelaki and Hess 1994; Raphan et al. 1994), but was not found in humans (Fetter et al. 1992). Regardless, it seems clear that head tilt during post-rotatory nystagmus or OKAN induces one component of spatial re-orientation of velocity storage, a reduction of the horizontal or yaw axis time constant.

Slow-phase eye velocity generated by velocity storage during either per- or post-rotatory nystagmus or OKAN can also be suppressed by exposure to a subject-stationary visual surround (Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983; Waespe et al. 1985a).[1] This has been termed, "visual suppression", and it comprises both a rapid fall in eye velocity, dependent on activity processed in the flocculus (Lisberger and Fuchs 1978; Zee et al. 1981; Waespe et al. 1983; Waespe et al. 1985b), and a slower discharge of activity from velocity storage (Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983; Waespe et al. 1985a). When modelled, a key part of this mechanism has been represented by a feedback parameter ($h_o$), that is the inverse of the time constant of the velocity storage integrator. It critically affects the charging and falling time constants, as well as the steady state velocity of velocity storage (Cohen et al. 1977; Raphan et al. 1979; Cohen et al. 1987; Raphan et al. 1994). This parameter is of interest because, when it was replaced with a three-dimensional matrix, the previous models reproduced the spatial characteristics of velocity storage with regard to gravity (Raphan et al. 1979; Waespe et al. 1983; Raphan and Cohen 1988; Raphan and Sturm 1991).

The neural basis for the loss of activity that leads to a reduction in the horizontal time constant of velocity storage during these paradigms is not well understood. Lesion studies implicate the nodulus and uvula of the vestibulo-cerebellum. After nodulo-uvulectomy, there was an increase in the dominant time constant of the VOR and of OKAN (Waespe et al. 1985a; Cohen et al. 1992b, for review), along with a failure of the nystagmus to re-orient when the head was statically (Cohen et al. 1994) or actively tilted (Waespe et al. 1985a). There is also loss of habituation (Cohen et al. 1992b, for review). Animals were capable of rapidly suppressing eye velocity in a relative stationary visual surround, but eye velocity promptly returned when the lights were extinguished, indicating that activity had not been discharged from the velocity storage integrator (Waespe et al. 1985a). The implication is that the nodulus and ventral uvula control spatial orientation of velocity storage and the discharge of activity from the velocity storage integrator produced by visual suppression. More specifically, that these structures mediate the activity that controls the cross-coupling parameter $h_o$.

The present experiments were carried out to determine if electrical stimulation of the nodulus and uvula could shorten the time constant of the horizontal component of nystagmus induced by velocity storage, thereby reproducing one of the effects of active or passive head tilt or exposure to a relative stationary surround. While this study was in preparation, a study by Heinen et al. (1992) appeared on nodulus and uvula stimulation. Similarities and differences between these studies will be considered. Some of the results have been reported in preliminary form (Solomon et al. 1985).

## Materials and methods

Experiments were performed on three rhesus monkeys (*Macaca mulatta* M1151, M1164; M1166) and one cynomolgus monkey (*Macaca fascicularis* M1169). The experiments conformed to the Principles of Laboratory Animal Care (NIH Publication 85–23, revised 1985), and were approved by the Institutional Animal Care and Use Committee (IACUC). Findings were the same in both species, and are combined. Under anesthesia (6 mg/kg ketamine, 1.6 mg/kg xylazine intravenously; maintenance doses as required) using surgical conditions, scleral search coils were fixed to one eye to record horizontal and vertical eye position. Bolts were fixed to the skull with acrylic resin cement for painless head restraint during experiments. Analgesics (morphine sulfate 2 mg, intramuscular $\times 2$) and antibiotics (cephalothin 100 mg, intramuscular, daily $\times 5$) were given after surgery to reduce post-operative pain and infection.

Vestibular stimulation was produced by rotating the animals in darkness in a three-axis vestibular stimulator about a vertical axis with steps of constant velocity. The stimulus velocities ranged from 30 to 180°/s with accelerations and decelerations of $>500°/s^2$. This produced per-and post-rotatory nystagmus. OKN was induced by moving the shell of the stimulator, which was 89 cm in diameter, 61 cm high, with 10° black and white stripes, at a constant velocity of 60°/s about the animal's yaw axis for 30 s. At the end of OKN, the lights were extinguished, and OKAN was recorded in darkness. The animals could also be tilted with regard to gravity around a separate pitch-roll axis (see Raphan et al. 1992; Reisine and Raphan 1992, for a description of the apparatus).

Effects of head tilts on velocity storage and tilt-dumps were determined during post-rotatory nystagmus. Animals were first rotated in darkness about a vertical axis producing per-rotatorynystagmus. Rotation was continued until nystagmus velocity had declined to zero. Then rotation was stopped, inducing post-rotatory nystagmus. Ten seconds later, the animal was pitched back about an interaural axis at angles from 15 to 90°. This caused a reduction in the falling time constant of horizontal slow phase velocity. The animal was brought back to the upright position in light after the nystagmus had disappeared.

To test visual suppression, per- and post-rotatory nystagmus were induced. Ten seconds after the onset of post-rotatory nystagmus, the lights were turned on for variable periods of 1–10 s,

[1] In this paradigm, the visual surround moves at the same velocity as the head. It is frequently produced by restraining the head and moving the visual surround and the subject at the same velocity and in the same direction. The vestibular system signals that the head is moving, but the visual system signals that no movement has occurred relative to the surround. In these circumstances, nystagmus is suppressed, and eye velocity quickly falls to zero. Similar suppression is observed when an earth-stationary background is exposed during post-rotatory nystagmus or OKAN (Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983)

exposing the animal to a structured, subject-stationary visual surround. The lights were then extinguished, and the recovery eye velocity, if any, was measured. Effects of visual suppression were tested on OKAN in a similar fashion: the stationary visual surround was exposed 2 s after the end of OKN for variable periods. (A description of the techniques for inducing and measuring eye velocities using these experimental paradigms is given in Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983).

To stimulate the nodulus and uvula electrically, a tungsten microelectrode of 0.1–0.5 MΩ impedance (measured at 1 KHz) was introduced into the cerebellum at an angle of 11° tilted backward or 45° tilted forward from a vertical stereotaxic plane. Advantages of the 45° tracking were that it was not necessary to traverse as much brain before encountering the nodulus and uvula, and the presence of the fourth ventricle and brainstem gave positive identification of the location of the stimulating electrode. Stimulus trains were composed of monopolar, 0.5 ms, constant current pulses (electrode tip referenced to the barrel of the guide tube). Pulse trains were of variable duration and frequency. Most commonly, constant currents of 20–60 μA, frequencies of 100–400 Hz and train durations of 2–10 s were used. In general, the effects of stimulation was tested every 500 μm in each track.

In the figures, the periods of stimulation are shown by the horizontal bars under the traces. Eye movements to the right and up are associated with upward trace deflections in the position and velocity traces. In one animal, a second stimulating microelectrode was introduced into the nucleus of the optic tract (NOT) to elicit nystagmus and after-nystagmus through velocity storage in the VOR (Schiff et al. 1988).

Voltages related to eye movement and stimulus parameters were recorded using amplifiers with a bandwidth of DC to 35 Hz (Beckman Dynograph) and stored on FM magnetic tape. Eye position was differentiated electronically (time constant 38 ms) and rectified to remove quick phases and obtain slow phase velocity. We concentrate only on horizontal eye movements in this report. Eye velocity was calibrated by rotating the animal about a vertical axis with short steps of velocity of 30°/s in light. It was assumed that the gain of the VOR was close to unity under these conditions. Animals received amphetamine sulfate (0.3 mg/kg) 30 min before the start of experiments to maintain a constant level of alertness.

Data analysis was based on the paper records. Per- and post-rotatory (vestibular) nystagmus were characterized by the step gain and the dominant time constant of the decline in slow-phase eye velocity. The step gain was defined as the maximum slow phase velocity measured 1–2 s after the onset or end of rotation divided by the stimulus velocity. The dominant time constant was the time constant of a falling exponential whose area was the same as the area under the slow phase velocity envelope. It was obtained by dividing the integral of the slow phase velocity envelope by the initial velocity (Raphan et al. 1979). The gain and dominant time constant of OKAN were obtained in a similar fashion (Cohen et al. 1977). Dump ratios, which reflect the loss of activity from velocity storage due to visual suppression, were calculated by dividing slow phase eye velocity just prior to the period in light by the value just afterward (Cohen et al. 1977). The points of measurement are marked by downward arrows in Figs. 3, 5 and 6 to facilitate comparison. For statistical analysis, paired *t*-tests were used to compare the step gain of the VOR with and without nodulus stimulation in the same animal. A test of normality on the pooled controls ($n=20$) rejected the hypothesis that the distribution was not normal ($P=0.28$). We also determined slopes with linear least squares regression analyses.

Small electrolytic lesions were made at the bottom of some tracks for identification by passing 100 μA of DC current for 30 s. At the conclusion of the experiments, animals were deeply anesthetized and perfused through the heart with saline and 10% formalin. After fixation, the brain was removed and serially sectioned in sagittal planes at 40 μm intervals. Nissl (cresyl violet) stained sections were used to identify the location of sites of stimulation. The atlas of Madigan and Carpenter (1971) was used as an aid for plotting the location of the stimulus sites.

## Results

### Sites of stimulation

Stimulation sites, from which nystagmus was either induced or modified (positive sites), were found throughout lobules IX and X of the posterior vermis in the cerebellar cortex and adjacent white matter. In M1164, the microelectrode well was angled 45° rostrally, and the area explored was 3.5 mm to either side of the midline and 5.5 mm in an AP direction. Nine of 18 separate tracks were positive, in that they produced nystagmus or a reduction in nystagmus. The positive stimulation sites in this animal are shown in Fig. 1A on a parasagittal section of the cerebellum 1 mm from the midline.

Filled circles represent sites where slow-phase velocity of nystagmus developed slowly and changes in time constant of the response outlasted the stimulus (slow responses). Such sites were present rostrally in the region of the nodulus, in sublobule d of the uvula, and in the surrounding white matter. Open circles represent sites where substantial nystagmus was generated during stimulation (rapid responses), but where there was little or no effect on the time course of per- or post-rotatory nystagmus or OKAN. The dashed line represents the limits of the cerebellar white matter and nuclei that was explored. Stimulus sites that appear to be in ventral portions of lobules V and VI in Fig. 1A were actually lateral in the white matter or in the cortex of the vermis, which is more dorsal in lateral sections. In agreement with Heinen et al. (1992), rapid response sites were located in sublobules a and b of the dorsal uvula.

The results were generally similar in the other three animals. Thirteen tracks were positive in M1166, 12 in M1151 and 5 in M1169. A single track from M1151 at an 11° angle from the stereotaxic vertical, demonstrating positive sites in the folia of sublobule d, is shown in Fig. 1B. Both slow and rapid responses were produced from a stimulus site in this track. Data from this site are presented in Figs. 3E–G and 5E.

### Slow responses from nodulus and sublobule d of the uvula

Typically, little or no nystagmus or after-nystagmus was produced when the nodulus or rostral uvula were stimulated with brief (4–5 s) trains of pulses while the animals were stationary and in darkness (Fig. 2C). When the stimulus was combined with per-rotatory nystagmus that produced rightward slow phases, however, eye velocity fell rapidly after a brief (2.5 s) latency (Fig. 2B, left). This decline in eye velocity can be compared to the slower fall in velocity of the control response (Fig. 2A, left). As a result, when the nodulus was stimulated, the duration of the per-rotatory response was shorter (10 s vs 21 s, control response). Using the point of onset of the rapid decline in slow-phase velocity in Fig. 2B, left, as the time of onset for measurement, the falling time con-

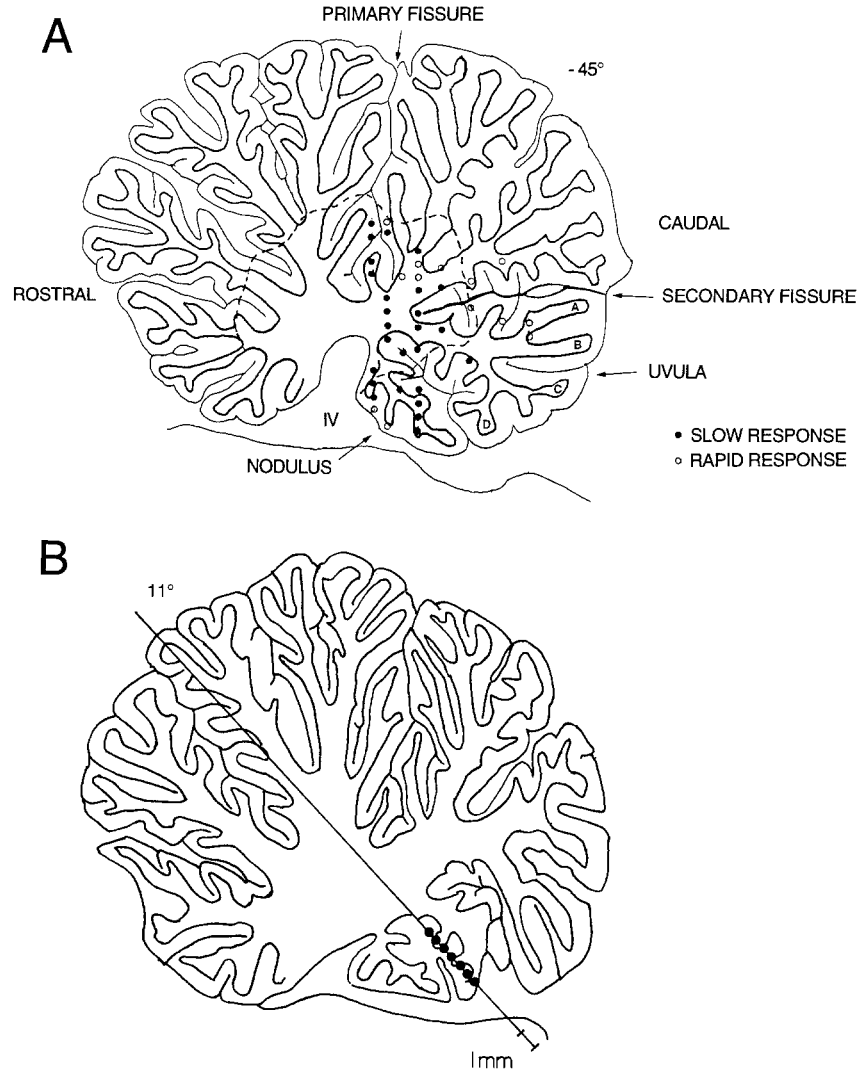



**Fig. 1** **A** Parasagittal section of cerebellum from monkey M1164 near the midline with effective stimulation sites superimposed, regardless of laterality. Electrodes were tilted forward at a 45° angle from the stereotaxic vertical. *Filled circles* represent "slow response" sites, which when stimulated outlasted the stimulus in inhibiting the slow component of the VOR. *Open circles* are "rapid response sites", where slow-phase velocities were generated during stimulation with little or no effect on the time course of post-rotatory nystagmus or OKAN. The dashed line represents the border of the central white matter on a section taken through the most lateral track which had effective sites. **B** Electrode track in sublobule d of the uvula with effective stimulus sites from M1151. This track was tilted back at an 11° angle from the stereotaxic vertical

stant was 1.8 s for the response with stimulation; the time constant of the control response from the same point was 9 s.

For nystagmus with slow-phases to the left (Fig. 2B, right), the stimulus had the reverse effect, i.e., it extended the plateau of slow-phase velocity for an extra 3 s. As a result of the added slow-phase velocity, the duration of nystagmus with nodulus stimulation was 33 s (Fig. 2B, right) versus a control value of 31 s (Fig. 2A, right). Time constants of decline from comparable points following stimulation were 13 s after nodulus stimulation versus 10 s for the control response. Generally, the enhancing effects of nodulus stimulation were weaker than those shown in Fig. 2B, right, and caused only minimal increases in time constant. Therefore, we concentrated on inhibitory effects of stimulation, i.e., on the reduction in time constant.

Effects of nodulus and sublobule d stimulation were the same for OKAN as for per- and post-rotatory nystagmus: the time course of OKAN was shortened (compare Fig. 3E,F to control response Fig. 3D). Stimulation effects were unilateral, in that they produced or altered nystagmus in only one direction; for example, the stimulus in Fig. 2B was on the right and inhibited slow-phase velocities to the right. Since most sites were close to midline, it was not certain whether ipsilateral or contralateral slow-phase velocities were inhibited. For stimulation sites farther from the midline, it was more common for ipsilateral eye velocity to be affected, although there were lateral sites that produced inhibition of contralateral slow-phase velocity.

Although the stimulus began at the time the animal accelerated or decelerated in Fig. 2B, there was no effect on the initial jump in eye velocity. When the electrical stimulus immediatedly preceded or was concurrent with the velocity step, the mean peak right slow-phase eye velocity was $62 \pm 5°/s$ ($n=7$) as against a control value of $62 \pm 5°/s$ ($n=7$). For left slow-phase eye velocity, the means were $63 \pm 4°/s$ ($n=7$) versus $64 \pm 3°/s$ ($n=7$), with and without stimulation. The means were not significantly different ($P=0.75$ right, $P=0.66$ left).

Thus, stimulation of the nodulus and of sublobule d of the uvula primarily altered the characteristics of the slow component of the VOR and of OKN, causing a

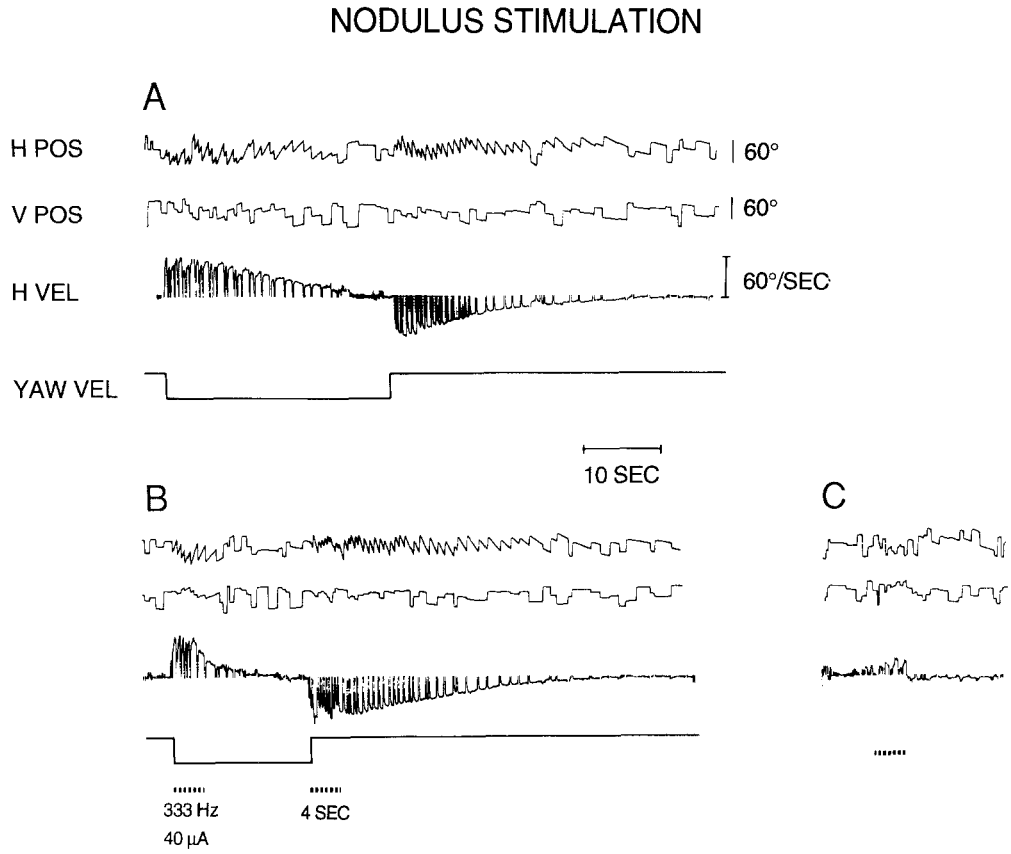



**Fig. 2** **A** Control per- and post-rotatory nystagmus induced by rotation at 60°/s in darkness. **B** Per- and post-rotatory nystagmus as in **A**. At the points noted by the *bar* beneath the yaw velocity trace in **B**, a site in the right nodulus was electrically stimulated with a 4 s train of 0.5 ms pulses at 333 Hz with a constant current of 40 μA. Although stimulation concurrent with the onset or end of the step had no effect on the initial jump in eye velocity, it reduced the duration of nystagmus to the right and enhanced the response to the left. **C** Stimulation delivered with the animal in darkness in the absence of ongoing nystagmus generated only weak slow-phase velocity and after-nystagmus. *H POS* Horizontal eye position, *V POS* vertical eye position, *H VEL* horizontal slow-phase eye velocity, *YAW VEL* angular velocity about an earth vertical axis with monkey upright. In this and subsequent figures, *upward traces* represent velocity or position to the right and up

reduction in the time constant of ongoing per- or post-rotatory nystagmus. This is consistent with the absence of a rapid rise in slow-phase velocity of nystagmus when the site was stimulated with the eyes stationary (Fig. 2C). It is also in agreement with the findings of Precht et al. (1976) that nodulus stimulation does not affect vestibulo-ocular pathways that produce rapid changes in slow-phase eye velocity.

## Rapid changes in eye velocity from caudal uvula and mixed responses

The foregoing can be contrasted to the response from a site located in the caudal dorsal uvula. Electrical stimulation with the animal stationary in darkness caused nystagmus which was associated with a shift in eye position toward the quick-phase side (Fig. 3C, top traces). At stimulus frequencies of 100 and 200 Hz, there was a rapid rise in slow-phase eye velocity of about 50°/s (Fig. 3C, bottom traces) and no after-nystagmus (Fig. 3C, top traces). The latency of the responses were under 100 ms, and the rise times were substantially faster than after nodulus stimulation (Fig. 2C). At the end of stimulation, slow-phase eye velocity fell quickly back to zero. Nystagmus with similar characteristics has been reported after uvula stimulation by Heinen et al. (1992).

Increasing the frequency of stimulation from 100 to 200 Hz at 30 μA caused the quick phases to be more frequent and have a smaller amplitude (Fig. 3C, right). As a result, the nystagmus became shimmering. However, the slow-phase velocities were approximately the same at both frequencies of stimulation, and there was no after-nystagmus. There was a positive relationship between frequency of stimulation and frequency of nystagmus ($r=0.59$; $n=8$), whereas there was no relationship between frequency of stimulation and slow-phase velocity ($r=0.08$, $n=8$).

When the caudal uvula site was stimulated during per- and post-rotatory nystagmus (Fig. 3B), leftward slow-phase velocities were generated, regardless of the direction of the ongoing nystagmus. Slow-phase velocity came rapidly back to the predicted envelope at the end of stimulation. The durations of the per- and post-rotatory responses were approximately the same before and after stimulation (27 s versus 32 s, left; 30 s versus 32 s, right). This suggested summation of the two responses without interaction. The same lack of interaction was found for OKAN.

Occasionally sites were encountered where both slow and rapid effects were produced, i.e., where there was a rapid increase or decrease in slow-phase velocity at the onset and end of stimulation, and where the recovery velocity and time constant of the after-response were significantly decreased after the end of stimulation. An example from stimulation of sublobule d (Fig. 1B) is shown in Fig. 3E,F. When this site was activated (Fig. 3G), both nystagmus and after-nystagmus were induced, similar to responses elicited induced from the

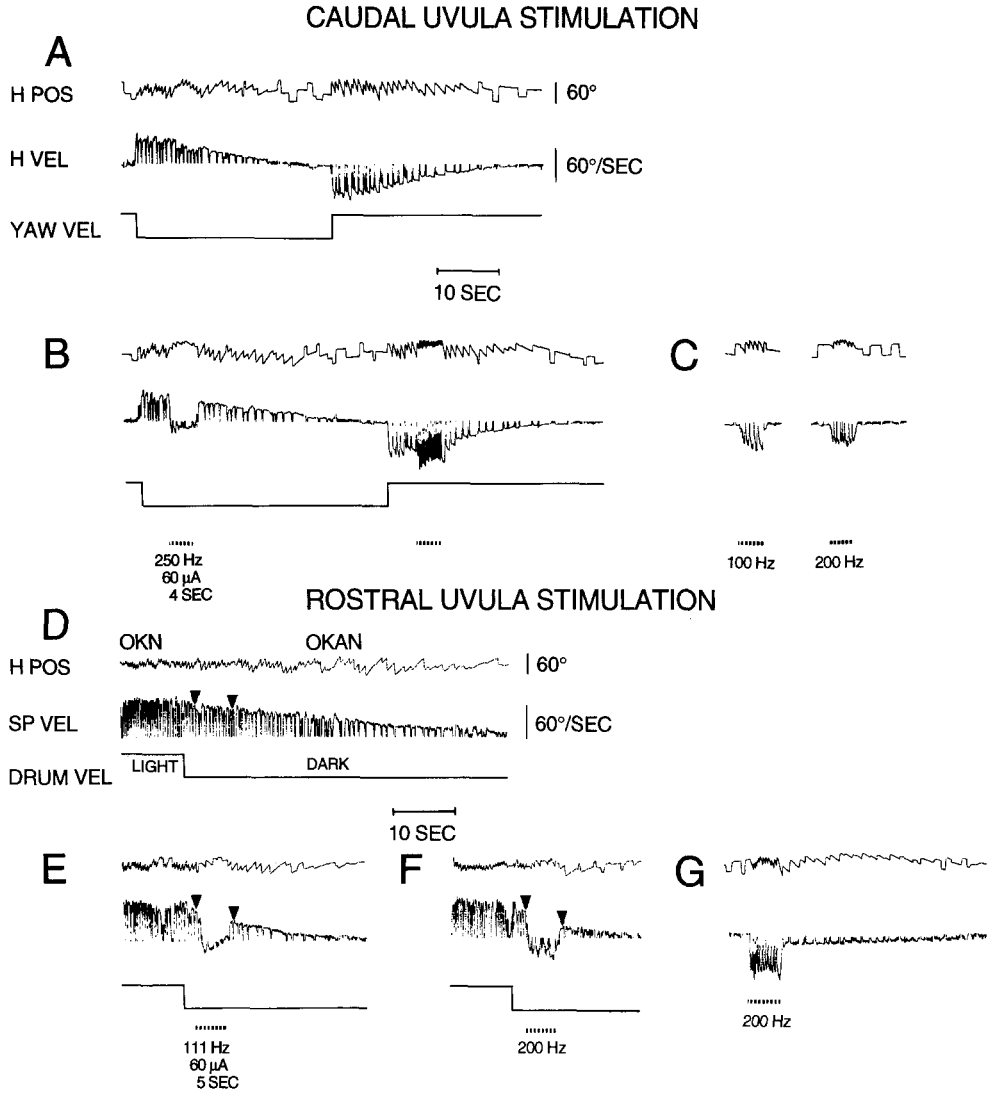



**Fig. 3** **A** Control per- and post rotatory response. **B** Stimulation of a dorsal-caudal site in the left uvula (250 Hz, 60 μA, 4 s duration) transiently decreased slow-phase velocity to the right (*left side*) or increased slow-phase velocity to the left (*right side*). **C** The same stimulus, given with the animal stationary, caused nystagmus with a peak velocity of about 50°/s. The rising and falling time constants were short, and there was no after-nystagmus. Doubling the stimulus rate from 100 to 200 Hz caused an increase in frequency of the nystagmus, but did not affect the induced slow-phase velocity. **D** Control OKN and OKAN with slow-phases to the right generated by surround rotation of 60°/s. **E,F** Stimulation of sublobule d of the rostral uvula on the right for 5 s at 60 μA caused eye velocity to the left, followed by inhibition of the OKAN slow-phase velocity to the right. The frequency was 111 Hz in **E** and 200 Hz in **F**. *Downward arrows* in **D–F** indicate similar points of slow-phase velocity in the control OKAN (*D*) and uvula stimulations (**E,F**). These were used for measuring dump ratios in Fig. 6E,F. **G** Control stimulation at 200 Hz with the eyes stationary caused a mixed response, with eye velocity to the left during and after stimulation

same area by Heinen et al. (1992). When the stimulus was given during OKAN with slow-phases to the right, however, eye velocity fell rapidly (Fig. 3E,F). The recovery velocity of the nystagmus was reduced, and the time course of the after-nystagmus was shortened. The duration of the OKAN from the end of stimulation was 21 s and 12 s in Fig. 3E,F, respectively, whereas the duration measured from the same point in the control response was 46 s (Fig. 3D). Combining effects of stimulus frequencies of 100 Hz and above, the OKAN time constant fell from a control value of $19.0 \pm 1.8$ s ($n=4$) to a post-stimulus value of $7.9 \pm 3.1$ s ($n=10$).

## Stimulation of the nucleus of the optic tract (nOT) and the nodulus

Electrical stimulation of the nucleus of the optic tract (NOT) produces relatively pure excitation of velocity storage, and there is little or no activation of direct optokinetic or pursuit pathways (Schiff et al. 1988). After the onset of NOT stimulation, there is a slow rise in slow-phase velocity to a level of about 60°/s, followed by stimulus after-nystagmus (Fig. 4A). The saturation velocity of the stimulus-induced nystagmus and the falling time constant of the after-nystagmus matched those of OKAN in this, as in other animals (Schiff et al. 1988).

When a 2 s nodulus stimulus was given after the end of NOT stimulation (Fig. 4B), it caused a rapid decline in the stimulus after-nystagmus, similar to the effect of nodulus and uvula stimulation on the VOR and OKAN time constants (Figs. 2B, 3E,F). The falling time constant of the NOT-induced nystagmus was 3 s after nodulus stimulation (Fig. 4B) and 14 s without stimulation (Fig. 4A). A 5 s nodulus stimulus, just after the onset of the NOT stimulus, caused the peak velocity of the NOT-induced nystagmus to reach only 28°/s (Fig. 4C), vs 60°/s for the control response (Fig. 4A). The time constant at the stimulus after-nystagmus was also reduced (9 s for Fig. 4C vs 14 s for Fig. 4A). Similar effects have been produced by baclofen, a $GABA_B$ agonist, and modelled as a sustained reduction in the time constant

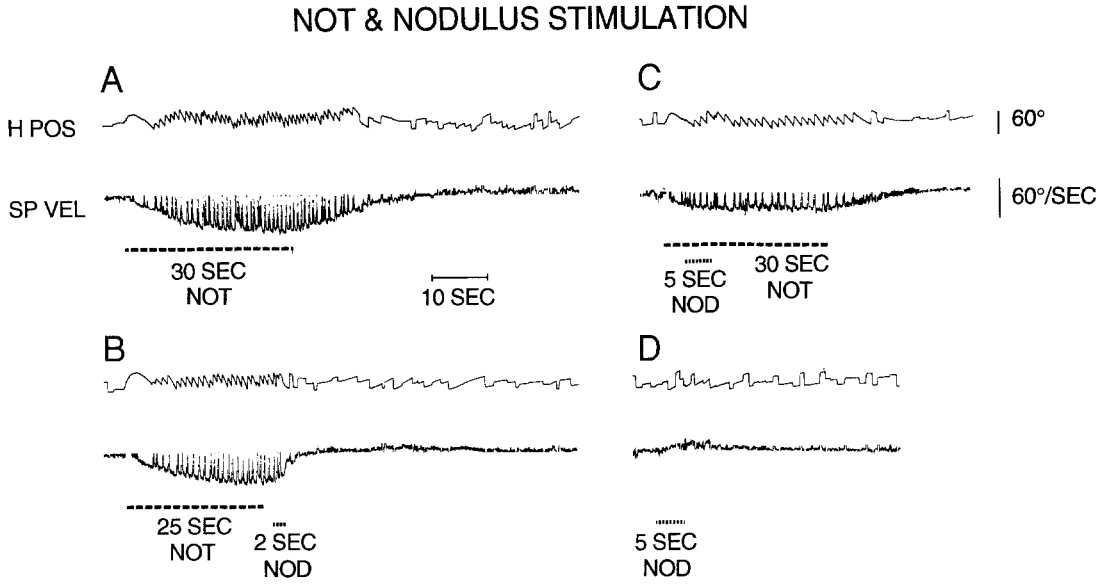



**Fig. 4** **A** Electrical stimulation of the nucleus of the optic tract (NOT) for 30 s at 60 μA and 250 Hz in an alert rhesus monkey (M1164) in darkness. **B** Stimulation of the nodulus (NOD) for 2 s caused a rapid decline in the NOT-induced after-nystagmus. **C** Nodulus stimulation at 333 Hz, 60 μA and 5 s duration, 4 s after the NOT stimulus had begun, truncated the rise in slow-phase velocity, reduced the peak velocity, and shortened the stimulus after-nystagmus. **D** Nodulus stimulation alone for 5 s generated little nystagmus, indicating that the responses in **B** and **C** were not an algebraic combination of the control and stimulus responses (**A**,**D**).

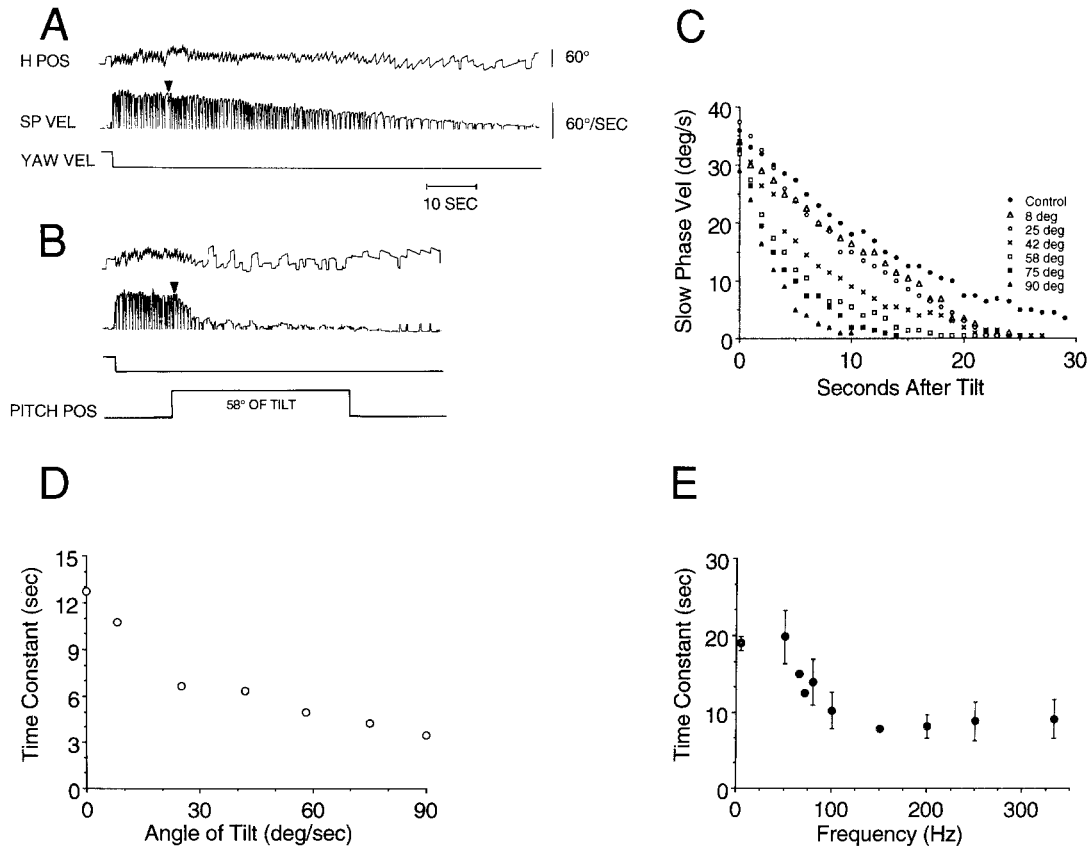
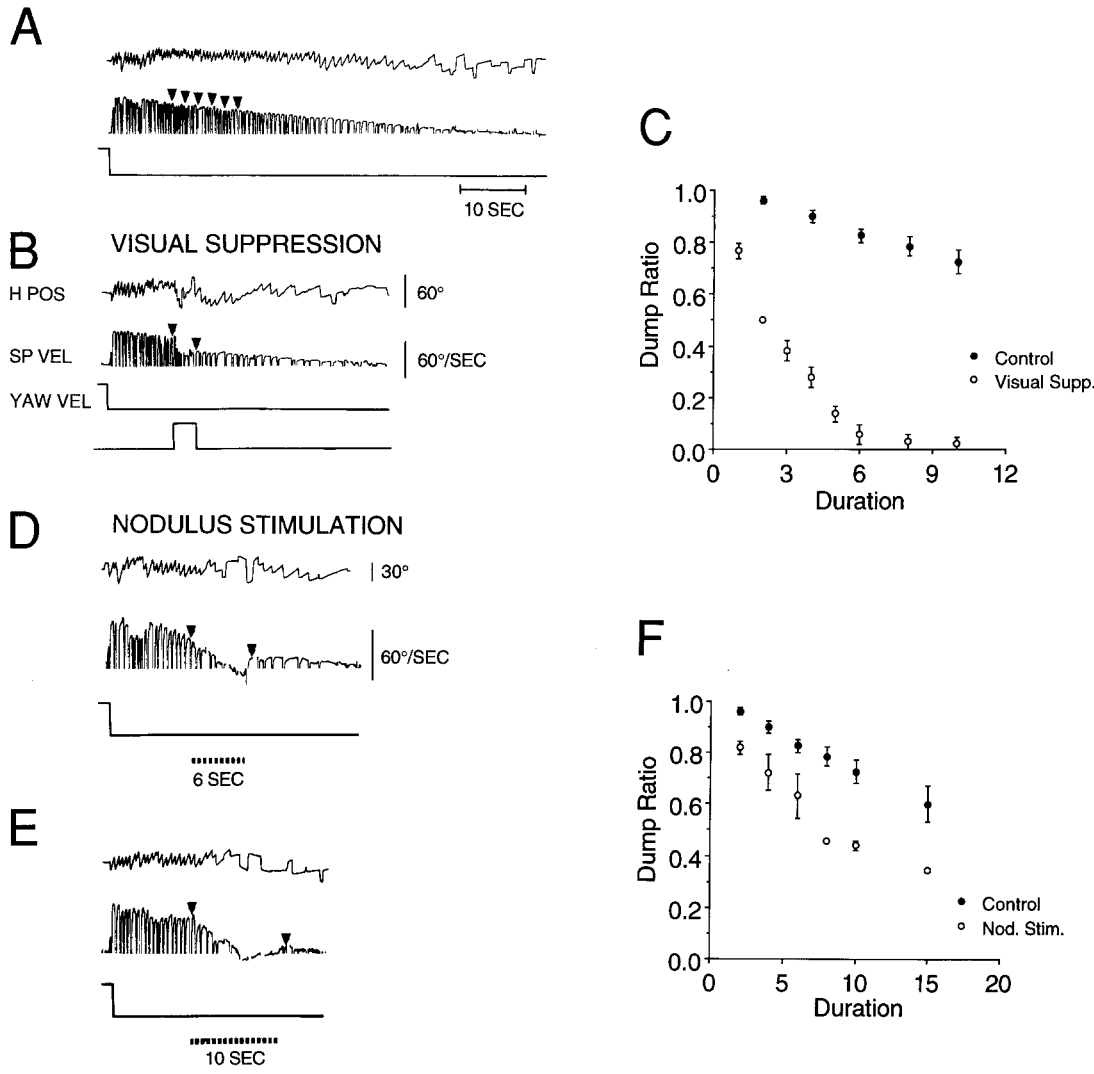



**Fig. 5** **A** Post-rotatory response of monkey M1169 following the termination of constant velocity rotation to the right at 60°/s. The *downward arrow* shows the point of onset of the measurement of time constant for this data and that of **B**,**C**. **B** Ten seconds after the onset of the post-rotatory nystagmus, the animal was pitched upward (Pitch Position), rotating 58° about an interaural axis toward the supine position. Eye velocity fell with a reduced time constant. **C** Slow-phase velocity, measured at 1 s intervals following tilts about the naso-occipital axis from 8° to 90°. Each point is the average of eight trials. **D** Time constant (ordinate) as a function of tilt angle (abscissa) for the data of C. The time constant fell from an initial value of 13 s for the upright condition to 3.5 s for 90° of pitch tilt. **E** Time constant as a function of increase in frequency of electrical stimulation. The data were taken from the experiment shown in Fig. 3E,F. The time constant fell from about 20 s to 8 s between frequencies of stimulation of 50 and 150 Hz




of the velocity storage integrator caused by an increase in the value of $h_o$ (Cohen et al. 1987). At this stimulus location in the nodulus, the 5 s train of pulses produced weak nystagmus and some after-nystagmus (Fig. 4D), but the responses in Figs. 4B and 4C were not an algebraic combination of the control (Fig. 4A) and stimulus responses (Fig. 4D).

The latency of response from some rostral sites was difficult to determine, because the decline in slow-phase velocity was frequently obscured by a transient increase in velocity during stimulation. In Figs. 2B and 4B, however, nodulus stimulation caused little initial change in eye velocity, so that the decrease in the time constant of the NOT-induced after-nystagmus could be attributed solely to a loss of activity in velocity storage. The latency of the decrease in slow-phase eye velocity during the stimulus after-nystagmus ranged between 1 and 2.5 s. This is similar to the latency of the reduction in slow-phase velocity of post-rotatory nystagmus during tilt (Fig 5B: Raphan et al. 1981; Waespe et al. 1985a; Cohen et al. 1992a).

**Fig. 6** **A** Post-rotatory nystagmus in monkey M1166 following the end of rotation to the right of 60°/s. *Arrows* indicate times when measurements were taken for control curve in **C**. **B** The animal was exposed to a stationary visual surround for 3 s, 10 s after the post-rotatory response had begun. This caused a reduction in the "recovery" velocity of nystagmus when the animal was once again in darkness. Bottom trace indicates period of exposure to visual surround. **C** Graph of dump ratio versus duration. There was greater suppression of eye velocity (*circles*) for longer periods of exposure to the stationary surround. Error bars in **C** and **E** represent ± SEM. **D,E** Effects of 6 s and 10 s of nodulus stimulation, respectively, with trains of 40 μA at 80 Hz on post-rotatory nystagmus. *Arrows* in **D** and **E** indicate the beginning and end of the stimuli. **F** Dump ratio of slow-phase velocity from a similar experiment in the same animal at another site in the nodulus. More activity was lost after stimulation for longer durations

## Spatial reorientation, tilt dumps and visual suppression

Horizontal slow-phase velocity is reduced when subjects are tilted during post-rotatory nystagmus (Benson 1974; Schrader 1985; Waespe et al. 1985a; Cohen et al. 1992a; Fetter et al. 1992; Angelaki and Hess 1994; Raphan et al. 1994). Tilt dumps were studied by pitching

an animal backward (feet up) during post-rotatory nystagmus (Fig. 5 A,B). From the point of tilt (downward arrow), the envelope of horizontal slow-phase eye velocity was reduced from a time constant of 17 s when upright (Fig. 5A) to 6 s following a backward pitch of 58° (Fig. 5B). Increasing angles of tilt caused slow-phase velocity to decay more rapidly (Fig. 5C), with a concomitant reduction in the falling time constant (Fig. 5D). Similar results have been reported by Shrader et al. (1985) and Angelaki and Hess (1994).

The effects of stimulating sublobule d of the uvula on the slow-phase velocity of post-rotatory nystagmus are shown in Fig. 5E. We held stimulus duration and current constant (5 s and 60 μA, respectively) and varied stimulus frequency between 50 and 400 Hz. For stimulus frequencies between 50 to 150 Hz, there was a decline in the post-rotatory time constant from about 20 s to 7.5 s. In this range, the shape of the curve was similar to the shape of the time constant versus tilt angle curve (Fig. 5D).

The velocity of per- or post-rotatory nystagmus or OKAN is reduced by exposure to a relative stationary visual surround (visual suppression, Fig. 6A–C: Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983). After a 2 s period of suppression, the recovery velocity of the OKAN was reduced by about half, and the duration of the response was substantially reduced (Fig. 6B; compare with Fig. 6A, control). About 6 s of exposure to a stationary surround were necessary to reduce the recovery velocity to less than 10% of its initial value (Fig. 6C). The effects of different durations of electrical stimulation were tested at a rostral site in this animal, while holding the current (40 μA), frequency (80 Hz) and latency after the end of rotation (10 s) constant (Fig. 6D,E). Both stimuli were effective in reducing the recovery velocity of post-rotatory nystagmus, but larger decreases were produced by longer periods of stimulation (Fig. 6E). Similar results were obtained by stimulation at a different site (Fig. 6F). Thus, by changing the frequency or duration of stimulation, it was possible to reproduce aspects of tilt dumping or visual suppression on post-rotatory nystagmus and OKAN.

## Discussion

We have shown that the time course of the yaw axis (horizontal) component of per- or post-rotatory nystagmus and OKAN is reduced when the nodulus and rostral ventral uvula are electrically stimulated. The reduction in horizontal slow-phase eye velocity produced by electrical stimuation was similar to that found when post-rotatory nystagmus was elicited with subjects in tilted positions (Harris and Barnes 1987; Harris 1987; Raphan and Cohen 1988; Dai et al. 1991; Raphan and Sturm 1991; Raphan et al. 1992), or when the gravito-inertial acceleration vector was shifted by centrifugation (Merfeld et al. 1991; Raphan et al. 1994). It was also similar to the more rapid decline in eye velocity when the head was tilted during post-rotatory nystagmus (tilt dumping: Benson 1974; Raphan et al. 1981; Schrader 1985; Waespe et al. 1985a; Cohen et al. 1992; Fetter et al. 1992; Angelaki and Hess 1994; Raphan et al. 1994), or when animals were exposed to a relative stationary visual surround during OKAN or vestibular nystagmus (visual suppression: Cohen et al. 1977; Waespe et al. 1983, 1985a). The latency to onset of the decrease in activity was about 1–2.5 s, similar to the latency during tilt dumps (Raphan et al. 1981; Cohen et al. 1992a).[2]

These findings support the hypothesis that activity responsible for the reduction in the time constant of the yaw axis (horizontal) component of the VOR during spatial reorientation of velocity storage originates in the nodulus and sublobule d of the uvula. It is consistent with the finding that this function is lost after nodulo-uvulectomy (Waespe et al. 1985a; Cohen et al. 1994). Concurrently, pitch and roll components of eye velocity appear that realign the axis of eye rotation to the spatial vertical (Merfeld et al. 1993a). Whether the appropriate vertical velocities could be generated by nodulus stimulation is not known, but would be predicted. Habituation of velocity storage, which is associated with a reduction in the time constant of the VOR or of OKAN, is also under control of the nodulus and rostral uvula (Cohen et al. 1992b).

Our study concentrated on the inhibitory effects of nodulus and rostral ventral uvula stimulation, whereas Heinen et al. (1992) focussed on nystagmus produced by stimulation of the caudal uvula and only briefly considered nystagmus induced by stimulation of the nodulus and rostral uvula. Nevertheless, they found that both nystagmus and after-nystagmus were induced when the nodulus and rostral uvula were stimulated. We also observed this buildup at some stimulation sites (Fig. 3G). In both studies, slow-phase eye velocity built slowly during nodulus and rostral uvula stimulation, and it was weak for the brief stimuli that we used. The enhancing effects of nodulus stimulation are of interest. It is not unlikely that the nodulus and rostral uvula can both decrease and increase the time constant of yaw axis eye velocity, possibly by inhibition and disinhibition of cells producing this velocity in the vestibular nuclei. In agreement with Heinen et al. (1992), electrical stimulation at caudal uvular sites, in sublobules a to c, elicited nystagmus with rapid changes in eye velocity. Such stimulation had no effect on the time constant of ongoing nystagmus.

Visual dumps produce a rapid decrease in slow-phase velocity when the eyes are moving relative to the visual field (Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983; Cohen et al. 1987). Triggered by a difference signal between eye velocity and surround velocity (Raphan et al. 1979; Waespe et al. 1983), at least three

[2]The latency to the onset of the reduction in eye velocity associated with visual suppression cannot be determined easily, because there is a contribution of both the rapid and slow pathways (Raphan et al. 1979; Waespe et al. 1983)

mechanisms bring the eyes to the velocity of the visual surround: (1) a rapid change, utilizing either the fast optokinetic pathway or ocular pursuit tends to stabilize the eyes; (2) a rapid discharge (dump) of activity in velocity storage reduces the drive on slow-phase eye velocity; and (3) optokinetic stimulation due to residual eye movement tends to bring the velocity of the eyes toward the velocity of the surround.

Nodulus stimulation alone did not entirely reproduce this response. For example, eye velocity fell more slowly after nodulus stimulation (Fig. 6D,E) than during natural visual suppression (Fig. 6B). Presumably, the flocculus is involved in producing the rapid component of suppression (Lisberger and Fuchs 1978; Zee et al. 1981; Waespe et al. 1983; Waespe et al. 1985b), although activity from the caudal uvula, similar to that in Fig. 3C,G, could contribute to the rapid changes in eye velocity.

The nodulus and uvula are organized in microzones (Oscarsson 1969; Groenewegen and Voogd 1977; Kano et al. 1990), that are related to semicircular canal and optokinetic input in different spatial planes (Barmack and Shojaku 1992). There is mossy fiber input from NOT, reflecting horizontal or yaw axis optokinetic activation, via nucleus reticularis tegmenti pontis (Maekawa et al. 1984) and the prepositus hypoglossi nuclei (Belknap and McCrea 1988). Mossy fiber input also comes from the medial, superior and descending vestibular nuclei (Epema et al. 1990; Barmack et al. 1992; Tan and Gerrits 1992) and from the labyrinth (Korte and Mugnaini 1979; Gerrits et al. 1989). This includes otolith information that could signal a sense of the upright (Marini et al. 1975). Climbing fiber activity from NOT comes through the dorsal cap of Kooy (Takeda and Maekawa 1989; Kano et al. 1990; Shojaku, et al. 1991), and vestibular input from the vertical canals reaches these regions from the beta nucleus of the inferior olive (Shojaku et al. 1991; Barmack and Shojaku 1992; Barmack et al. 1993).

Efferents of the nodulus and ventral uvula terminate ipsilaterally in the dorsal and peripheral portions of SVN (Angaut and Brodal 1967), in regions which are part of the vertical VOR pathways, and which provide crossed oculomotor projections (Carpenter and Cowie 1985). There are also projections from the nodulus to MVN (Shojaku et al. 1987; Walberg and Dietrichs 1988) to areas where cells project head velocity information to eye muscle motor nuclei. Thus, the nodulus and ventral uvula have the appropriate anatomical connections to receive and transfer activity that could inhibit yaw axis velocity, and shift the axis of eye rotation from the yaw axis to axes related to gravity.

We were not able to detect the microzonal organization of the nodular or uvular cortex in our study. Presumably, this is because we stimulated both the cerebellar cortex and white matter and studied only horizontal eye movements. Nevertheless, it was clear that the nodulus/uvula output was specifically organized, because the direction of inhibition of velocity storage was either ipsi- or contralateral but never both. This is consistent with the finding that cells in microzones of the nodular or uvular cortex are unidirectionally activated during horizontal OKN and OKAN (Kano et al. 1990; Barmack and Shojaku 1992).

Given that the output of the nodulus and uvula is via Purkinje cells, that the major transmitter of these neurons is GABA, and that the time constant of velocity storage is reduced by administration of the $GABA_B$ agonist baclofen (Cohen et al. 1987), it is likely that nodulus and uvula control is mediated by activation of GABAergic receptors in the vestibular nuclei.

Activity of type 1, "vestibular-only" (VO) cells has been related to velocity storage (Reisine and Raphan 1992). Since there are direct projections from the nodulus to regions of the vestibular nuclei where VO neurons are found (Angaut and Brodal 1967; Shojaku et al. 1987; Walberg and Dietrichs 1988), a relatively simple explanation for the reduction in yaw axis time constant would be that the nodulus and sublobule d inhibit type 1, lateral canal-related VO neurons in MVN.

In terms of the one-dimensional model of the horizontal VOR proposed by Raphan et al. (1979), nodulus stimulation could be simulated by an increased negative feedback in the element $h_o$, causing a reduction in the time constant of the velocity storage integrator (Raphan et al. 1979; Cohen et al. 1987). In three dimensions, this would presumably cause a reorientation of the system matrix controlling velocity storage (Raphan and Sturm 1991; Dai et al. 1991). In the experiment utilizing stimulation of NOT, it was striking that the time constant of velocity storage could be modified for 20–30 s by a brief (5 s) nodulus stimulus (Fig. 4C). This is well beyond the time course of IPSP's produced by voltage-gated channels. It implies involvement of other mechanisms that may have a considerably longer time course.

In summary, we have demonstrated that stimulation of the nodulus and the adjacent sublobule d of the uvula causes shortening of the dominant time constant of the VOR and of OKAN, while caudal uvula stimulation causes rapid changes in eye velocity, but had little or no effect on velocity storage. We postulate that Purkinje cells in the nodulus and sublobule d control the yaw axis (horizontal) component of slow-phase velocity produced by velocity storage, and that these regions are responsible for the reduced vestibular and OKAN time constants of velocity storage during spatial reorientation, tilt dumping, and visual suppression of nystagmus.

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