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Role of the Flocculus and Paraflocculus in Optokinetic Nystagmus and Visual-Vestibular Interactions: Effects of Lesions*

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Summary. 1. Optokinetic nystagmus (OKN), optokinetic after-nystagmus (OKAN), vestibular nystagmus and visual-vestibular interactions were studied in monkeys after surgical ablation of the flocculus and paraflocculus. After bilateral flocculectomy the initial rapid rise in slow phase eye velocity of horizontal and vertical OKN was severely attenuated, and maximum velocities fell to the preoperative saturation level of OKAN. There is generally little or no upward OKAN in the normal monkey, and upward OKN was lost after bilateral lesions. Unilateral flocculectomy affected the rapid rise in horizontal velocity to both sides.

2. Consistent with the absence of a rapid response to steps of surround velocity, animals were unable to follow acceleration of the visual field with eye accelerations faster than about 3–5°/s^2.

3. The slow rise in OKN slow phase velocity to a steady state level was prolonged after operation. However, rates of rise were approximately equal for the same initial retinal slips before and after operation. The similarity in the time course of OKN when adjusted for initial retinal slip, and in the gain, saturation level and time course of OKAN before and after flocculectomy indicates that the lesions had not significantly altered the coupling of the visual system to the velocity storage integrator or its associated time constant.

4. When animals were rotated in a subject-stationary visual surround after flocculectomy, they could not suppress the initial jump in eye velocity at the onset of the step. Despite this, they could readily suppress the subsequent nystagmus. The time constant of decline in the conflict situations was almost as short as in the normal monkey and was in the range of the peripheral vestibular time constant. This suggests that although the animals were unable to suppress rapid changes in eye velocity due to activation of direct vestibulo-oculomotor pathways, they had retained their ability to discharge activity from the velocity storage mechanism. Consistent with this, animals had no difficulty in suppressing OKAN after flocculectomy.

5. Visual-vestibular interactions utilizing the velocity storage mechanism were normal after flocculectomy, as was nystagmus induced by rotation about a vertical axis or about axes tilted from the vertical. Also unaffected were the discharge of nystagmus caused by tilting the head out of the plane of the response and visual suppression of nystagmus induced by off-vertical axis rotation. The flocculus does not appear to play an important role in mediating these responses.

6. The data before and after flocculectomy were simulated by a model which is homeomorphic to that presented previously. The model has direct pathways from the vestibular and visual systems. The visual and vestibular systems couple to a common velocity storage integrator. There is also a dump mechanism which shortens the time constant of the integrator when eye velocity exceeds surround velocity. An important element in the model is a nonlinearity that couples the visual system to the integrator. Approximate closed form relationships were established between the parameters of the nonlinearity and the dynamics of OKN and OKAN. The nonlinear element is assumed to receive a central representation

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of retinal slip as its input. Its output drives the velocity storage integrator. The model predicts the normal responses, and by removal of the direct pathway it simulates the data after flocculectomy. The nonlinearity explains why the storage integrator charges more slowly for larger initial retinal slips both in the normal animal and after flocculectomy. The model also predicts that surround velocity would be followed better during deceleration than acceleration. This is a result of activation of the dump mechanism which shortens the time constant of the velocity storage integrator, effectively discharging it. Activation of the dump mechanism is independent of the flocculus.

7. Although the flocculus is closely linked to the vestibular system, its function in the monkey appears closely related to production of rapid changes in eye velocity from the visual system, either during slow phases of nystagmus or during ocular pursuit (Zee et al. 1981). It does not appear to cancel the horizontal VOR at the level of the vestibular nuclei, nor does it directly affect the dynamics of vestibular nystagmus, OKAN or the velocity storage mechanism.

Key words: Flocculus – Optokinetic nystagmus – Visual-vestibular interactions – Slow phase eye velocity – Velocity storage mechanism – Modelling

Introduction

Optokinetic nystagmus (OKN) is composed of two processes: a rapid initial change in slow phase eye velocity followed by a slower rise to a steady state level (Cohen et al. 1977). The fast rise is believed to be due to activation of pathways from the visual to the oculomotor system which are capable of rapidly exciting the oculomotor system. We refer to these as the "direct" visual-oculomotor pathways although they are neither monosynaptic nor oligosynaptic. There are also pathways that produce slower changes in eye velocity during OKN as well as optokinetic after-nystagmus (OKAN). These are referred to as "indirect" pathways. A key element in the indirect pathways is a velocity storage mechanism that is shared in common with the vestibular system; it contributes significantly to the low frequency characteristics of the vestibulo-ocular reflex (VOR) (Raphan et al. 1979).

Single cell and lesion studies indicate that the flocculus, and possibly the paraflocculus, play an important role in the enhancement of OKN and the suppression of vestibular nystagmus. Some floccular Purkinje cells are modulated during OKN (Waespe and Henn 1981). They rapidly increase their firing rates at the onset of OKN with slow phases to the ipsilateral side, but this activity is maintained only if steady state eye velocity is above 30–60°/s; there is no modulation in the activity of Purkinje cells during OKAN. Similar increases in firing rate are associated with suppression of contralateral slow phases of vestibular nystagmus during visual-vestibular conflict at high accelerations. At low accelerations, however, firing rates of Purkinje cells are not modified. This suggests that the flocculus may be part of the direct visual-oculomotor pathways that mediate rapid changes in slow phase eye velocity. Slow changes in eye velocity which involve the velocity storage mechanism are probably processed elsewhere.

In accord with this, lesions of the flocculus and paraflocculus reduce the ability of monkeys to make rapid changes in slow phase eye velocity during OKN (Zee et al. 1981). Bilateral flocculectomy also impairs the ability to reduce slow phase velocity during caloric nystagmus, although OKAN and spontaneous nystagmus can still be suppressed (Takemori and Cohen 1974; Zee et al. 1981). The latter indicates that the visual system can utilize extra-floccular mechanisms to counter inappropriate nystagmus. The relative contribution of floccular and extrafloccular mechanisms to suppression of nystagmus has not been fully studied.

In this study we determined how direct and indirect visual-oculomotor pathways for horizontal and vertical OKN are affected by unilateral and bilateral lesions of the flocculus and paraflocculus. We also modeled OKN, OKAN and visual-vestibular interactions before and after flocculectomy to determine which parameters of the model were affected by flocculectomy. The purpose was to show how the flocculus participates in producing slow phases of nystagmus.

Methods

Experiments were performed on three rhesus (M. mulatta) and two cynomolgus (M. fascicularis) monkeys. Under anesthesia, silver-silver chloride electrodes (Bond and Ho 1970) were placed in the bone around the eyes. Screws were implanted on the skull for immobilizing the head. A well that accepts a microelectrode carrier was fixed to the skull for subsequent unit recordings in the vestibular nuclei after flocculectomy (Waespe and Cohen 1983). The bone overlying the cerebellum was removed and the cerebello-pontine angle was visualized. Under an operating

microscope, the flocculus, ventral paraflocculus and adjacent parts of the dorsal paraflocculus were removed by suction-ablation. Blood vessels that connect the brainstem and cerebellum, especially the posterior inferior cerebellar artery, were left intact. In order to preserve the vasculature, posterior portions of the flocculus were not completely removed in some monkeys.[1]

Animals were allowed to recover for several days after operation before testing began. Eye movements were recorded with DC-electrooculography (EOG). The EOG's were differentiated and rectified to obtain slow phase velocity. During testing monkeys sat in a primate chair under an optokinetic drum. They were given steps of angular velocity or angular acceleration about vertical and off-vertical axes, or were given steps or ramps of surround velocity. In order to test the response to conflict stimulation, the OKN drum was mechanically coupled to the primate chair so that when the animal was rotated in light, the visual environment rotated with it. We refer to this as rotation in a subject-stationary, visual surround. The characteristics of the drum and chair have been described elsewhere (Raphan et al. 1981). Voltages representing eye position, eye velocity and the various stimuli were recorded on FM magnetic tape. To calibrate the EOG animals were rotated at a constant velocity about a vertical axis in an earth-stationary lighted surround while either upright or on their sides. The response to rotation in light at 30°/s was used for calibrating the EOG. The gain of nystagmus (peak slow phase eye velocity/angular velocity) at this velocity is close to unity in the normal (Skavenski and Robinson 1973; Raphan et al. 1979; Miles and Eighmy 1980) and in the flocculectomized monkey (Zee et al. 1981). Values recorded during testing were normalized with regard to the calibration velocity. As a result each unit on the ordinate of the graphs represents approximately 30°/s.

Time constants of velocity declines were obtained by dividing the area under the velocity envelopes by the peak slow phase eye velocity (Cohen et al. 1977). The same technique was used to calculate the time constant of the slow rise in slow phase velocity during OKN except that the steady state velocity was used as the baseline. The peak velocity of the initial jump was taken 1 s after the stimulus was delivered, or if there was a decline in velocity, as the average of the first two beats. When measuring the time constant of the approximate exponential change in eye position during gaze nystagmus, the first 200 ms after the eccentric saccade was disregarded (Zee et al. 1981). Measurements in the figures and tables are averages of four to ten trials.

At the conclusion of single cell recordings animals were anesthetized and perfused through the heart with saline and buffered 10% formalin. After fixation the brains were removed, and the extent of the lesions was drawn and photographed from the gross specimens. Celloidin was embedded in the brains with high frequency sound. Serial sections were cut and stained with cresyl violet and Weil stain to determine the extent of lesions.

1 The critical and most difficult part of the operation is to ablate rostral-most lobules of the flocculus without extending the lesion into the middle cerebellar peduncle. If this occurs, there is a much more profound effect on the oculomotor system than after flocculectomy alone. Two animals (M6 and M7) had such lesions. Afterward these animals were unable to maintain eccentric positions of gaze. On making lateral saccades their eyes drifted back with a short time constant (< 900 ms) in light or in darkness. They were unable to maintain constant velocity slow phases and had no OKN or nystagmus during rotation about off-vertical axes. The gain of their vestibular nystagmus (eye velocity/stimulus velocity) was low, and time constants of decline after velocity steps were below 6 s. These animals were excluded from further consideration

Results

Description and General Effects of Lesions

The flocculus was totally removed on both sides in two monkeys (M1 and M2, Fig. 1). In monkey M3 (not shown) parts of folium 8 on the right side and parts of folia 9 and 10 on both sides were preserved. Unilateral (left) flocculectomy was performed in two monkeys (M4 and M5). In M4 parts of the flocculus were intact (Fig. 1, Sections 265, 330, arrows). Flocculectomy was complete on the left in M5. It should be noted that when we refer to effects of "flocculectomy", this term is used for convenience; the ventral paraflocculus and parts of the dorsal paraflocculus were also removed in all monkeys. Monkeys 1 and 2 had hydrocephalus at the time of sacrifice 46 and 84 days after operation (Fig. 1). There was no hydrocephalus in the other animals. In all monkeys there was some demyelination of the middle cerebellar peduncle. Microlesions of the vestibular nerve could not be excluded, but there was no obvious degeneration in ventral portions of the lateral vestibular nucleus that accompanies vestibular nerve lesions (Walberg et al. 1958).

Monkeys 1, 4 and 5 had few ill effects of surgery and they were able to move about normally in their cages soon after operation. Monkeys 2 and 3 vomited repeatedly, but they recovered quickly and could be tested after one week. M2 initially had a slight head tremor but this disappeared. Monkeys were extensively tested at least twice after operation. In this report we will concentrate on the eye movements induced by optokinetic and vestibular stimulation 2–7 weeks after operation, immediately before single cell recordings were begun.

Eye Movements: Gaze Paretic and Spontaneous Nystagmus

Monkeys with bilateral flocculectomy had nystagmus on lateral gaze in both directions (gaze nystagmus). Animals with unilateral flocculectomy had gaze nystagmus only when looking to the side of the lesion. When attempting to hold eccentric eye positions, there was a slow, approximately exponential drift of the eyes towards the midline. It was not possible to correlate the amount of gaze nystagmus with the extent of the lesion except, as noted, when the lesions extended into the middle cerebellar peduncle. The time constants of the gaze nystagmus in darkness ranged from 1–3 s. All monkeys but one (M5) had a slow upward drift of the eyes and downward nystagmus in darkness. This was most conspicuous in M1 in

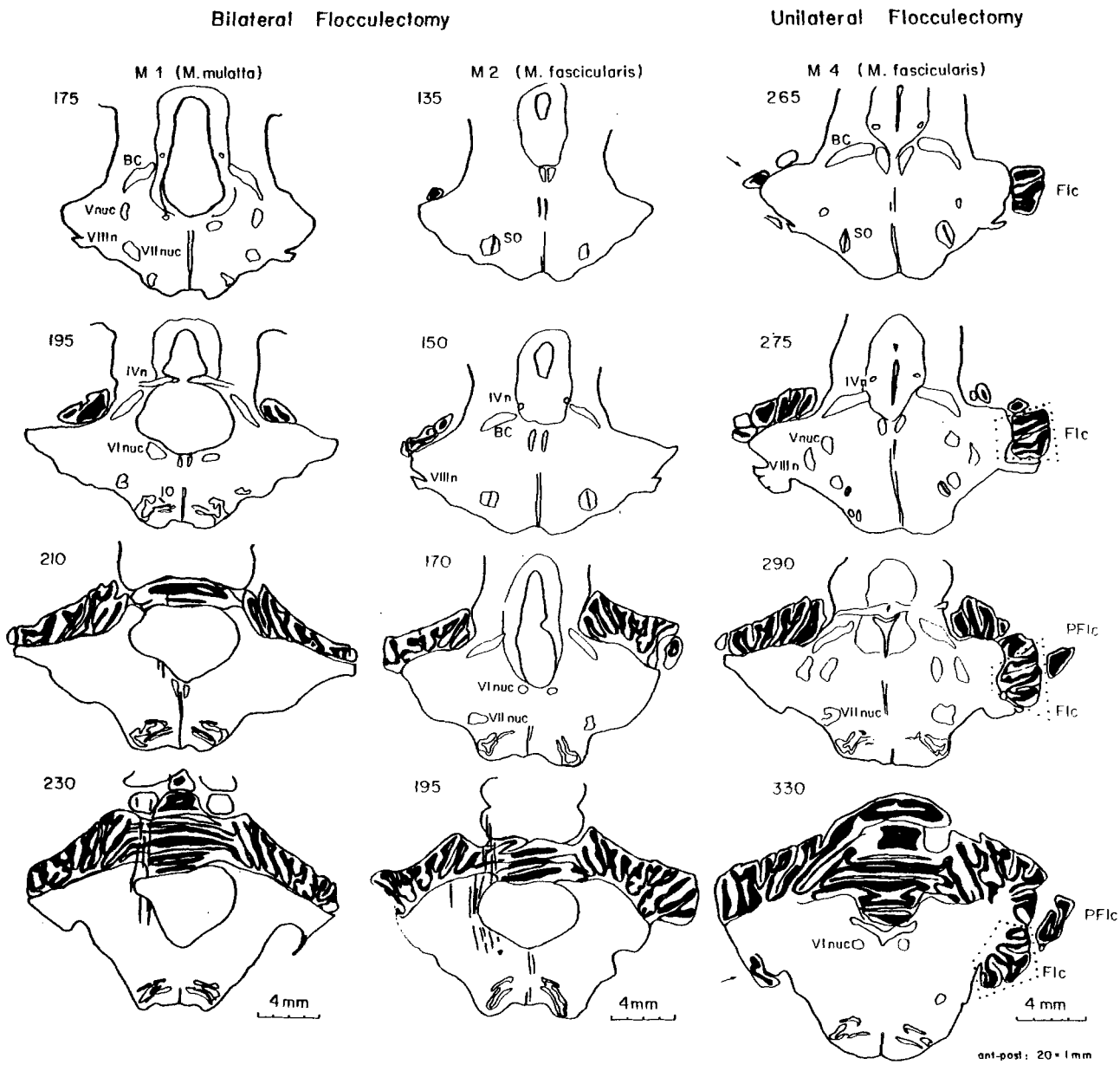


Fig. 1. Diagrams of lesions in three of the five animals. Coronal sections of the brainstem in the vertical stereotaxic plane. The flocculus, the ventral paraflocculus and parts of the dorsal paraflocculus were removed on both sides in M1 and M2, and on one side in M4. Remaining parts of the flocculus in M4 are shown by *arrows*. The normal flocculus on the opposite side in M4 is outlined by the *dotted lines*. Sections were cut serially (20 sections/mm). Electrode tracks through the vestibular nuclei are shown in sections 210 and 230 of M1 and 195 of M2. The results of single cell recording in the vestibular nuclei are described in another paper (Waespe and Cohen 1983). The anatomy of the lesion in M5 is also presented in that paper. *Abbreviations: BC* brachium conjunctivum, *SO* superior olive, *IO* inferior olive, *Flc* flocculus, *PFlc* paraflocculus, *Vnuc* trigeminal nuclei, *VInuc* abducens nucleus, *VIInuc* facial nucleus, *IVn* trochlear nerve, *VIIIn* eighth nerve

whom slow phase velocities were 10–15°/s. There was also horizontal spontaneous nystagmus of between 5 and 10°/s in darkness in M2. M4 had strong transient horizontal nystagmus of 100°/s to the side of flocculectomy for a week after operation.

Vestibular Nystagmus: Steps of Velocity About a Vertical Axis in Darkness

Qualitatively, there was little change in nystagmus induced by steps of angular velocity after operation

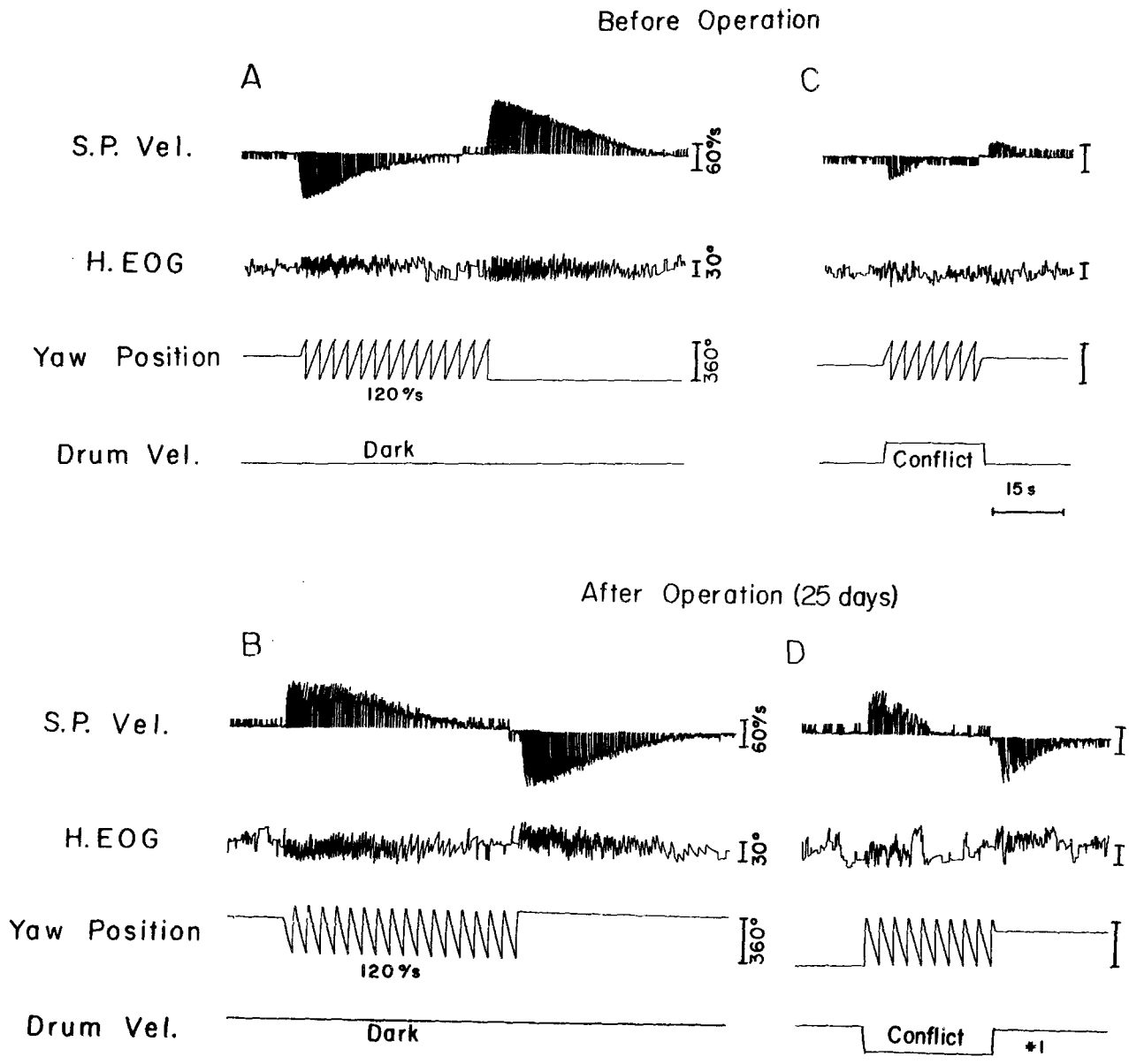


Fig. 2A–D. Nystagmus induced by steps of angular velocity of 120 deg/s about a vertical axis in darkness (**A, B**) and in a subject-stationary lighted surround (**C, D**) before and after operation in M1. Top trace, horizontal slow phase eye velocity; second trace, horizontal eye position; third trace, chair position about vertical axis (potentiometer resets each 360°); fourth trace, drum velocity. The angular velocity reached during the conflict situation in **C** and **D** was 120°/s. Velocities in the SP Vel trace due to saccades have been manually removed or reduced to allow clearer observation of slow phase velocities. Note the similarity of vestibular nystagmus in darkness before (**A**) and after (**B**) operation. The peak velocity of nystagmus in the conflict situation was greater after flocculectomy (**D**), but the time constant was shorter in light (**D**) than in darkness (**B**) and was only slightly longer than before operation (**C**)

(Fig. 2A, B). There were small asymmetries in the responses, but these were negligible. The gain of the initial jump in eye velocity induced by a step of angular velocity of 120°/s varied. It was unchanged in M1 and M4, but was lower in M2, M3 and M5 (Table 1). Unilateral flocculectomy in M5 affected the gain to both sides. The time constant of the nystagmus induced by steps of velocity in darkness was either unaffected or was somewhat reduced after operation (Table 1). The reductions were within the range of time constants in normal monkeys that have been tested repeatedly (Raphan et al. 1979). These results show that direct vestibulo-oculomotor pathways and the contribution of the velocity storage mechanism to vestibular nystagmus are little affected by flocculectomy.

Table 1.

A. Gain and time constant of vestibular nystagmus

	M1[a]		M2[a]		M3[a]		M4[b]				M5[b]			
	Before	After	Before	After	Before	After	Before		After		Before		After	
									Lesion	Normal			Lesion	Normal
Gain	0.92	0.93	0.87	0.77	0.84	0.69	0.93	0.98	0.92	0.95	0.98	0.93	0.63	0.76
T_c s	17	18	39	24	30	18	34	35	29	30	19	22	15	16

[a] Values for right and left nystagmus combined
[b] Direction according to slow phase

B. Velocity of slow phases of off-vertical nystagmus

	M1[a]		M2[a]		M3[a]		M4[b]				M5[b]			
Stimulus velocity	Before	After	Before	After	Before	After	Before		After		Before		After	
									Lesion	Normal			Lesion	Normal
60 deg/s	48	50	49	41	33	27	47	43	47	56	52	47	26	39
120 deg/s	40	50	66	51	39	10	50	57	50	64	67	59	32	53

[a] Values for right and left nystagmus combined
[b] Direction according to slow phase

Optokinetic Nystagmus (OKN) and After-Nystagmus (OKAN): Velocity Steps

OKN induced by a step in surround velocity is characterized by an initial fast increase in velocity within the first second followed by a slower increase to a steady state level (Fig. 3A, B; Cohen et al. 1977). For stimulus velocities up to 120°/s the initial rise is about 40–80% of the steady state level. Flocculectomy had a profound effect in reducing the initial fast rise in velocity in the monkeys with bilateral flocculectomy (Table 2). In M1 the initial jump in velocity was less than 10°/s (Fig. 4C), and in M2 and M3 it was 20°/s or less at all velocities (Fig. 3C, D; Table 2).

After unilateral flocculectomy the initial fast rise in slow phase velocity was reduced during OKN to either side (Fig. 5C). During ipsilateral slow phases of OKN, the initial jump was on average about 30 to 50% of the value before operation; during contralateral slow phases it was about 35 to 70% of the preoperative level (Table 2). This shows that the flocculi work together to produce the initial jump in eye velocity.

Zee et al. (1981) noted that the time course of the increase in slow phase eye velocity was longer after bilateral flocculectomy than in normal animals in response to a step of optokinetic stimulation at 60°/s. The same was true in our animals at lower velocities (Fig. 3C). However, time constants were only slightly longer at higher velocities (Fig. 3D). The long time constant after operation could be related to the increase in initial retinal slip due to the reduction in the fast rise in OKN. If time constants of the slow rise in OKN were compared for stimulus velocities that produced the same amounts of initial retinal slip before and after operation, the rise times were approximately equal (Fig. 4D). These findings show that the dynamics of the charge of the velocity storage mechanism by the visual system were not modified by flocculectomy. The same was true in one of the animals with unilateral flocculectomy for nystagmus with slow phases to the lesion but not to the contralateral side (Fig. 5D). The other animal (M5) had similar rise times before and after operation.

Steady state values of eye velocity during OKN before and after operation were approximately equal for stimulus velocities up to 60°/s (Fig. 4A, B; Table 2). At this velocity we found the same gain of 0.86 as Zee et al. (1981). Above about 60°/s, OKN saturated in animals with bilateral flocculectomy (Fig. 4B). The saturation value was approximately the same as the preoperative saturation level of OKAN (Fig. 4A). In the unilateral flocculectomized animals, maximum slow phase velocities of OKN to the ipsilateral side

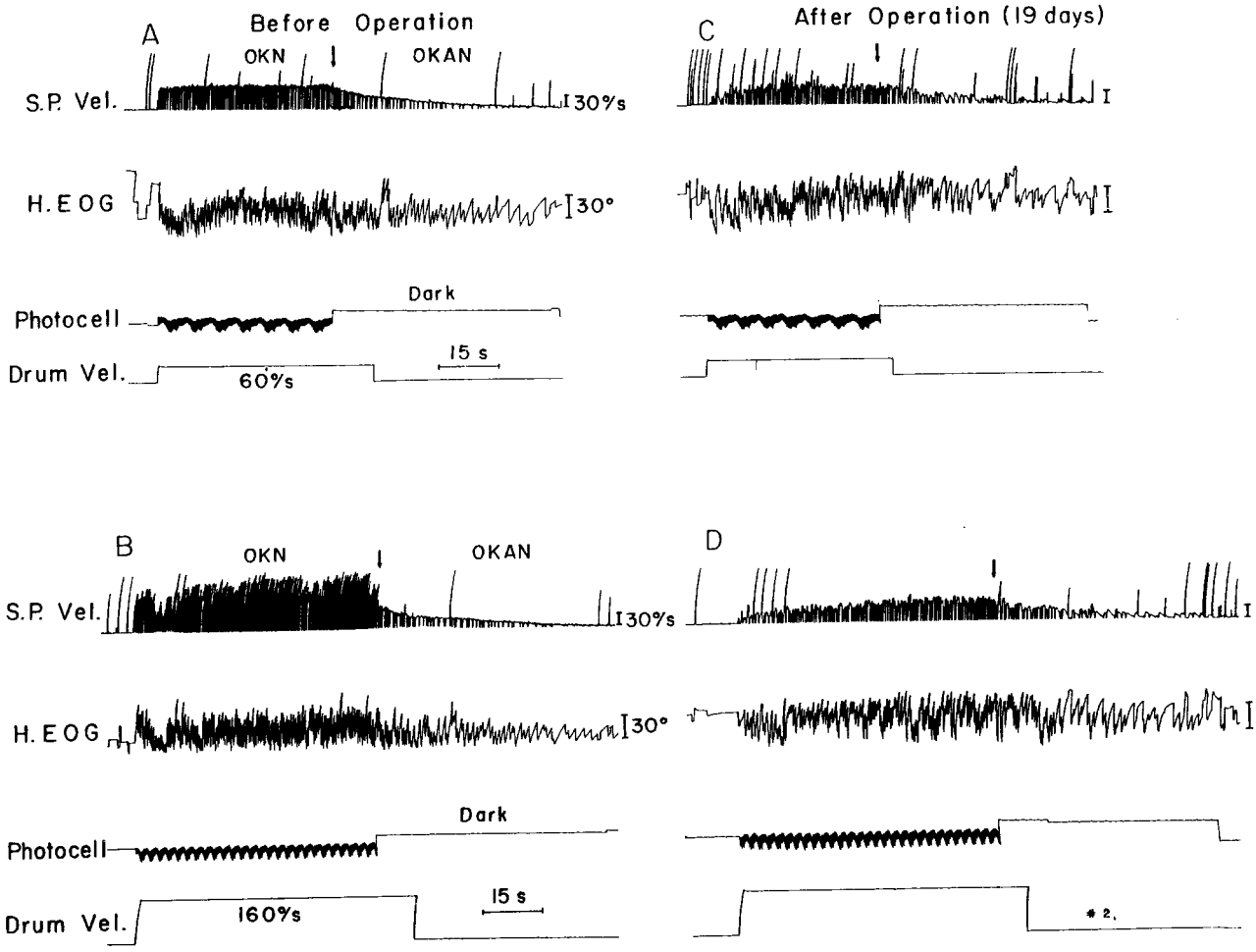


Fig. 3. OKN and OKAN in M2 induced by stimulus velocities of 60 and 160°/s before (**A, B**) and after (**C, D**) flocculectomy. *Downward arrows* indicate lights out. The photocell responds to stripe passage and to lights on and off. Because of the relatively slow time base individual deflections are not readily seen in the photocell trace, but an envelope is formed that shifts in phase with each full revolution of the drum (360°). The initial rapid rise in slow phase velocity at the onset of OKN in the normal animal was reduced after flocculectomy, and the saturation velocity of OKN fell to the preoperative saturation velocity of OKAN. The slow rise in OKN to a steady state level was slower after than before operation. OKAN was unaffected by flocculectomy. There was an interaction of gaze nystagmus and OKN when the beating field of the nystagmus was on the right or left side

Table 2. OKN and OKAN

Stimulus velocity		Parameter	M1		M2		M3				M4				M5	
			Before	After	Before	After	Before	After	Before		After		Before		After	
											Lesion	Normal			Lesion	Normal
60 deg/s	OKN	Init. jump[a]	25	3	42	13	22	20	45	41	20	20	44	42	21	28
		Steady state[a]	54	54	60	48	56	55	57	55	53	51	59	53	52	55
		T_c[b]	10	15	4	11	–	–	9	15	16	13	5	7	6	6
	OKAN	Velocity[a]	50	53	49	47	48	50	48	47	49	48	57	52	40	51
		T_c[b]	14	13	15	15	30	18	27	41	26	30	28	19	11	12
120 deg/s	OKN	Init. jump[a]	37	6	82	15	39	12	76	82	24	29	62	74	23	36
		Steady state[a]	98	63	109	51	97	51	93	97	59	84	101	103	54	98
		T_c[b]	17	23	16	18	–	–	15	23	34	31	12	17	12	19
	OKAN	Velocity[a]	66	59	59	42	59	39	47	57	43	66	74	77	35	63
		T_c[b]	11	11	16	17	29	16	30	32	20	25	21	20	10	9

[a] deg/s; [b] s

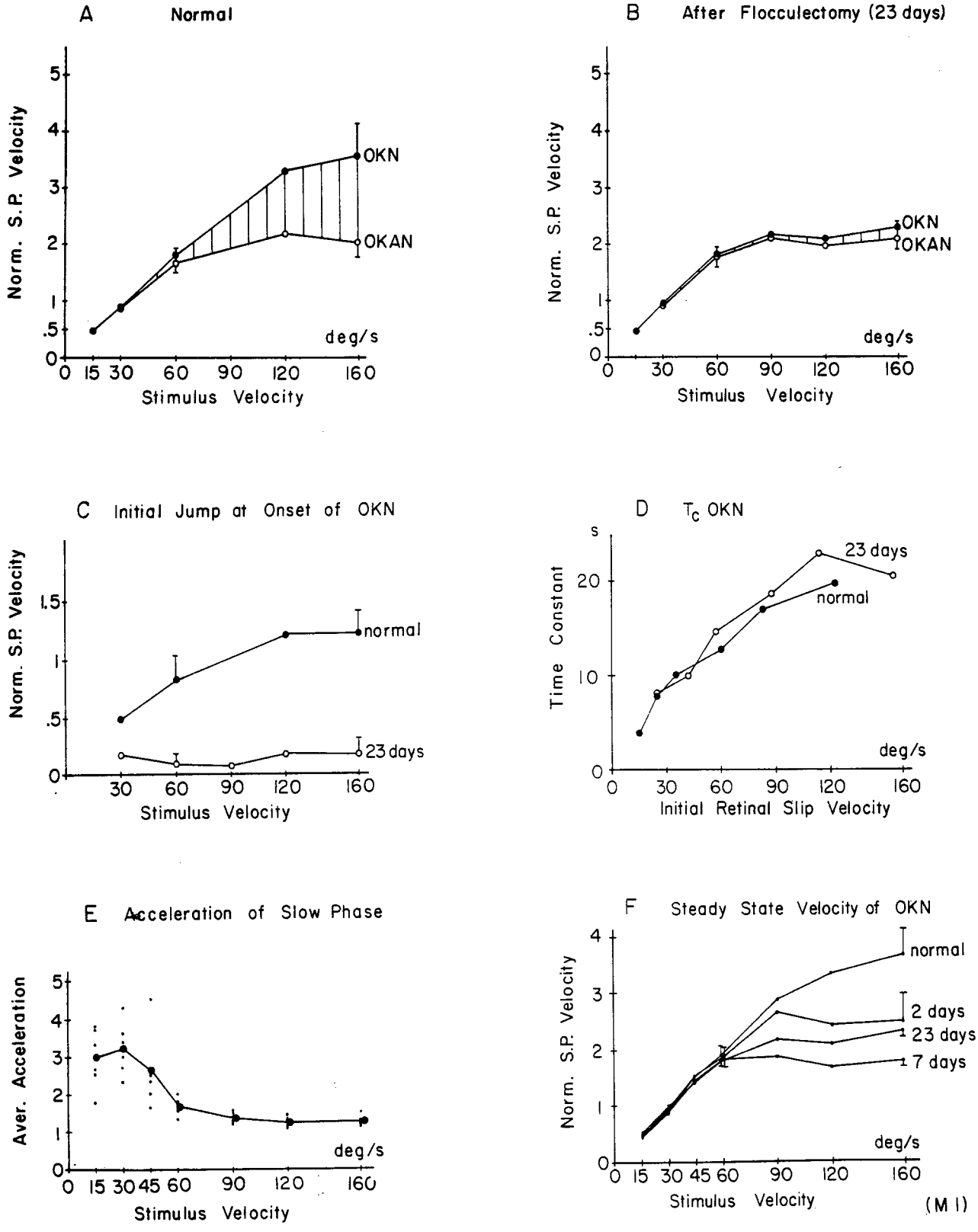

A Normal
Norm. S.P. Velocity
OKN
OKAN
deg/s
Stimulus Velocity
B After Flocculectomy (23 days)
Norm. S.P. Velocity
OKN
OKAN
deg/s
Stimulus Velocity
C Initial Jump at Onset of OKN
Norm. S.P. Velocity
normal
23 days
Stimulus Velocity
D T_c OKN
Time Constant
23 days
normal
deg/s
Initial Retinal Slip Velocity
E Acceleration of Slow Phase
Aver. Acceleration
deg/s
Stimulus Velocity
F Steady State Velocity of OKN
Norm. S.P. Velocity
normal
2 days
23 days
7 days
deg/s
Stimulus Velocity
(M I)

Fig. 4A–F

were reduced to about 60°/s (Fig. 5B, lesion side), as in the bilateral animals. Contralateral slow phases reached velocities of 90–100°/s, a reduction of 15–25% from the preoperative value (Fig. 5B, normal side).

Optokinetic after-nystagmus (OKAN) in the normal animal is characterized by a sudden drop in eye velocity when animals are put in darkness, followed by a slower decline to zero. After bilateral flocculectomy the transition from OKN to OKAN was smooth, and there was little or no fast decay in eye velocity (Fig. 3C, D, downward arrows). Occasionally, OKAN had a more rapid initial decay in M2 and M3, but this appeared related to a change in eye position that evoked gaze nystagmus. In the unilateral flocculectomized animals there was a drop in eye velocity at the end of OKN; it was greater for nystagmus with contralateral than ipsilateral slow phases. Up to stimulus velocities of 60°/s, OKAN velocities were approximately equal before and after flocculectomy in all monkeys (Table 2). Time constants of OKAN were unchanged in M1 and M2 but were shorter in M3, M4 and M5.

After flocculectomy monkeys retained their ability to use velocity information stored during OKN to counteract post-rotatory nystagmus. This was evaluated by giving steps of velocity in light and measuring the post-rotatory nystagmus in darkness. Findings were the same as in normal animals: there was little or no post-rotatory nystagmus after steps of velocity up to the saturation velocity of OKAN (Raphan et al. 1979). In these animals this velocity was 60°/s. This shows that visual-vestibular interactions that utilize the velocity storage mechanism are unaffected by flocculectomy. It also shows that there was no mismatch between the gain of vestibular nystagmus and of OKAN after operation.

Acceleration and Deceleration of OKN

OKN was also tested using accelerations and decelerations of 5, 10 and 40°/s^2 to an end velocity of about 120°/s (Fig. 6). The vertical dashed lines in Fig. 6 show the end of the periods of acceleration and deceleration. Eye velocities of a normal animal (M1, before flocculectomy) are shown by the solid lines. Normal animals tracked OKN stimulus velocities accurately at low accelerations (5°/s^2) up to 100°/s (Fig. 6C). At higher accelerations (10 and 40°/s^2) eye velocity fell behind stimulus velocity after reaching 70 and 60°/s, respectively (Fig. 6B, A). The same end velocity (100°/s) was reached at each acceleration, however. During deceleration normal animals tracked the stimulus velocity closely, although there was a lag in eye velocity at 40°/s^2 (Fig. 6A). This is shown by the presence of eye velocity after the stimulus had gone to zero.

The effect of bilateral flocculectomy on the response to acceleration was similar in all monkeys: they lost the ability to track the velocity of the stimulus at accelerations of 5°/s^2 and above (Fig. 6, dash – dotted lines). Although their eye velocity increased at an approximately constant acceleration, this acceleration was always less than that of the stimulus. In M1 the maximum acceleration of the eyes was between 1.3 and 1.9°/s^2. Average accelerations determined from steps of surround velocity, were slightly higher at lower stimulus velocities (15 and 30°/s, Fig. 4E), and fell for higher stimulus velocities. The decreasing acceleration with increasing stimulus velocities indicates the inherent nonlinear characteristics of the optokinetic response after flocculectomy. Peak velocities for steps of acceleration after flocculectomy were limited to about 60°/s (Fig. 6), which was the same as the steady state value achieved during steps of velocity (Fig. 4B). It was a general finding that the eyes could decelerate faster than they could accelerate. After operation animals were able to follow the decline in stimulus velocity accurately at 5°/s^2 although they could not accelerate at this rate (Fig. 6C). Eye velocity lagged decelerations at 10 and 40°/s^2 (Fig. 6B, A); the maximum deceleration in M1 was about 6.5°/s^2 in response to a stimulus deceleration of 10°/s^2.

Fig. 4. A, B Graphs showing OKN (*closed circles*) and OKAN (*open circles*) before (**A**) and after (**B**) flocculectomy. Stimulus velocity is on the abscissa and slow phase velocity, normalized with regard to an eye velocity of 30°/s, is shown on the ordinate. Therefore, each unit in this and other graphs represents approximately 30°/s. Note that OKN steady state velocities fell after flocculectomy (**B**) to approximately the value of OKAN, which was unaffected by the lesions. The *vertical lines* indicate the rapid drop in eye velocity at the end of OKN and the onset of OKAN. **C** Changes in the initial jump in slow phase eye velocity at the onset of a step in surround velocity before and after flocculectomy. **D** Time constants of the slow rise in OKN before and after lesion in relation to initial retinal slip velocity. The rapid rise at the onset of OKN was subtracted from the OKN stimulus velocity to obtain the value of retinal slip at the onset of the slow rise in OKN (abscissa). Since the initial rapid rise was markedly attenuated after flocculectomy, the retinal slip at the onset of the slow rise was close to the stimulus velocity. **E** Acceleration of the eyes (ordinate) after the initial step induced by steps of OKN at different stimulus velocities after flocculectomy. The *solid line* is the average value. This gives the approximate shape of the nonlinearity assumed to exist in indirect visual pathways. **F** Peak OKN velocity (ordinate) induced by OKN stimulus velocities (abscissa) before and 2, 7 and 23 days after operation. Note the fall off in peak velocity of OKN between the 2nd and 7th day and its subsequent recovery. All data are from M1

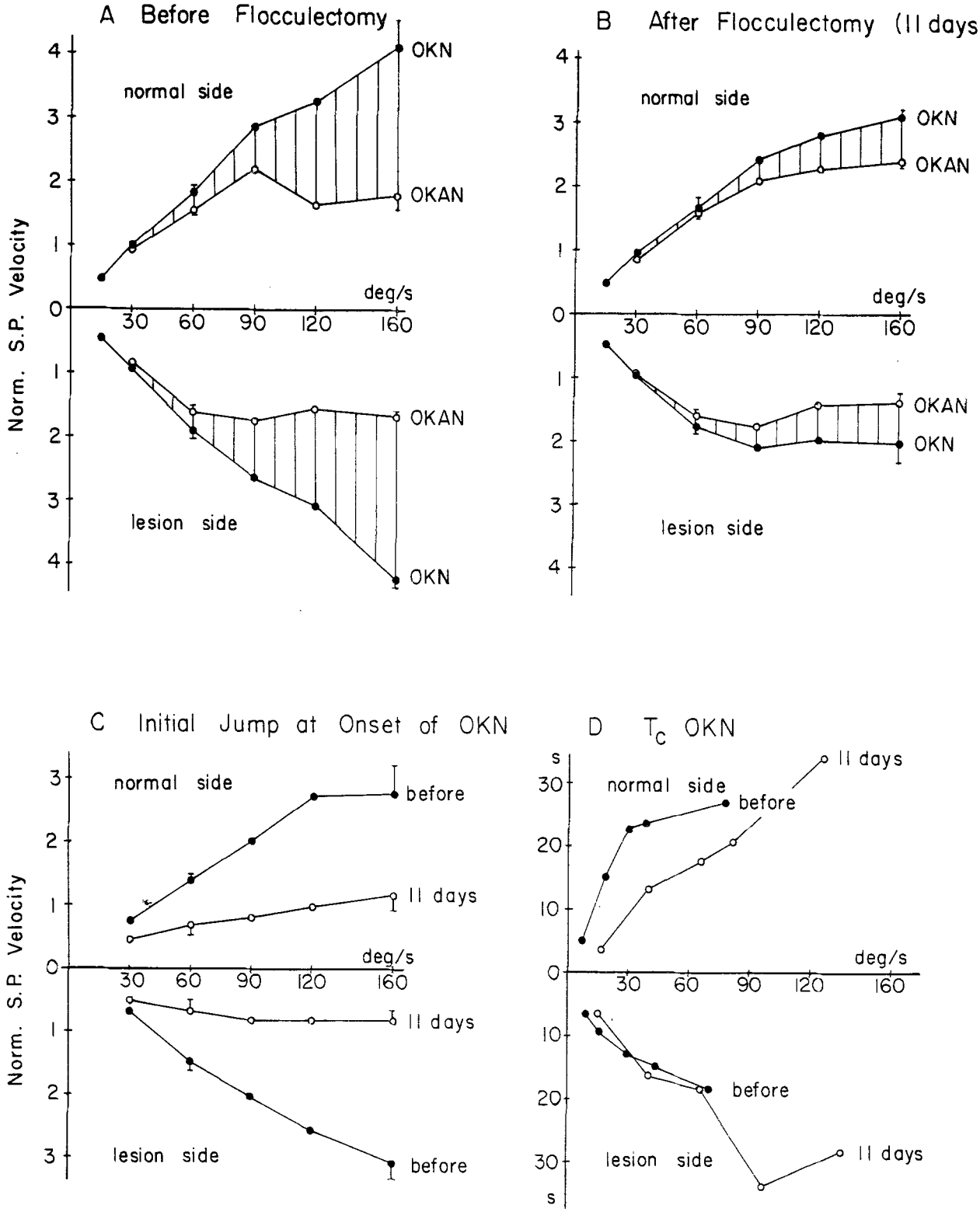


Fig. 5. A, B Steady state eye velocity of OKN and peak velocity of OKAN before (**A**) and after (**B**) unilateral flocculectomy in M4. Slow phase eye velocities above the abscissa are to the normal side and below the abscissa are to the lesion side. The scheme is otherwise similar to that used in Fig. 4A–D. **C** Velocity of initial jump at onset of OKN before and 11 days after operation. Note that the rapid rise was reduced to both sides. **D** Time constant (ordinate) of the slow rise in OKN in relation to initial retinal slip velocity (abscissa). Eleven days after flocculectomy there was no spontaneous nystagmus in darkness

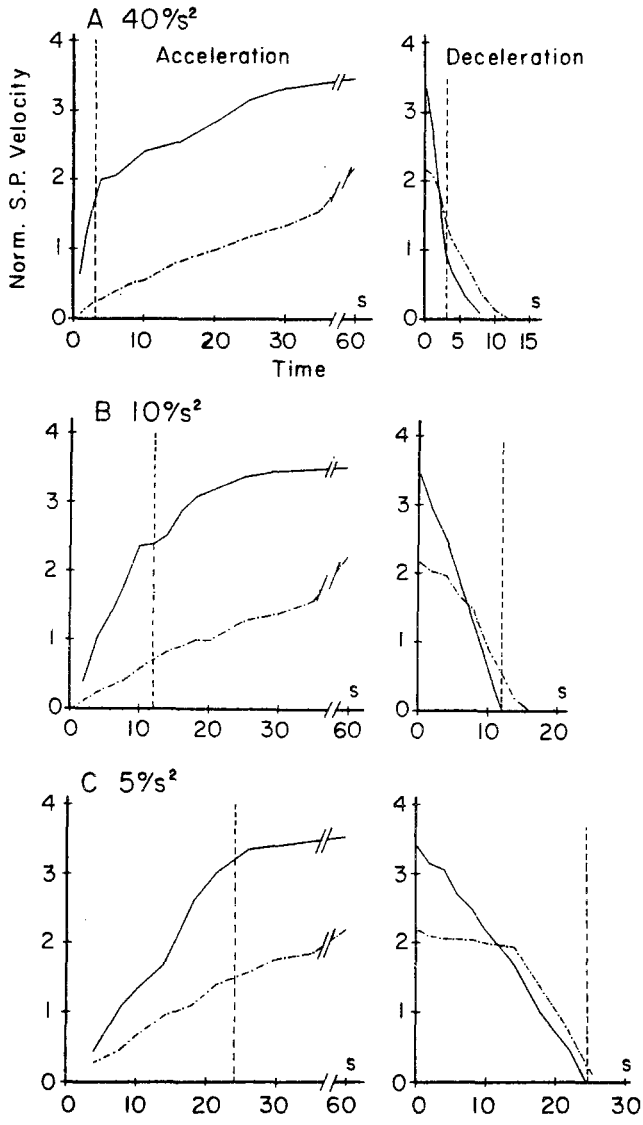


Fig. 6. Changes in eye velocity of M1 during constant acceleration of the visual surround at 40°/s² (**A**), 10°/s² (**B**) and 5°/s² (**C**). Acceleration is shown on the left and deceleration on the right. The abscissa is time after onset of stimulation, the ordinate is normalized slow phase velocity with regard to a 30°/s normalizing velocity. *Vertical dashed lines* indicate end of acceleration at peak stimulus velocity of 120°/s and end of deceleration at zero velocity. *Solid lines* show values in the animal before operation; dot-dashed lines show values after bilateral flocculectomy

In summary, the major changes in OKN induced by step stimuli were an attenuation of the initial rapid rise of slow phase eye velocity and a reduction in maximum OKN velocities which fell to the pre-operative saturation level of OKAN. The similarity in the rate of the slow rise in OKN when adjusted for retinal slip, and in the gain, saturation level and time course of OKAN before and after flocculectomy indicates that the lesions had not significantly altered the charge or discharge characteristics of the velocity storage mechanism. In addition, stored velocity information could be used to counteract post-rotatory nystagmus. We conclude that after flocculectomy, OKN is produced primarily by activation of the velocity storage mechanism which then interacts with the vestibular system in a normal fashion.

Visual Suppression of Vestibular Nystagmus and OKAN

After flocculectomy there is a relative inability to suppress caloric nystagmus (Takemori and Cohen 1974; Zee et al. 1981). However, all types of fixation suppression are not lost, and animals can suppress OKAN and spontaneous nystagmus induced by labyrinthectomy (Takemori and Cohen 1974). Animals were tested in a subject-stationary visual surround by rotating them at 120°/s in light with the OKN drum coupled to the primate chair. Before flocculectomy the peak velocity of post-rotatory nystagmus in the conflict situation was reduced to 44% (± 11) of the response in darkness in M1 (Fig. 2C) and to 28% (± 6) in M2. The time constant of the response was much shorter in the conflict situation than in darkness. Mean values in the normal animals were 4.1 and 4.0 s in light and 16.0 and 39 s in darkness in M1 and M2, respectively.

A major effect of flocculectomy was to limit the animal's ability to reduce the initial jump in eye velocity at the beginning of rotation during conflict stimulation. There were usually one to several beats at the onset of nystagmus whose amplitude and velocity were as large as when the animal was in darkness (Fig. 2D). This was followed by a rapid decline in eye velocity. As a result, the peak eye velocity of the initial step in the conflict situation was considerably greater after than before operation (cf. Fig. 2C, D). After operation in M1 the gain of the initial jump was about the same in the conflict situation as it was in darkness (Figs. 2B, D and 7A). In M2 the response in light after operation was 78% (± 10) of the response in darkness, which was also greater than before operation.

There was also a diminished ability to suppress the initial jump in eye velocity during vestibular nystagmus after unilateral flocculectomy. The reduction in eye velocity was bilateral, but it was more pronounced during suppression of contralateral than ipsilateral slow phases. For example, before operation during steps of angular velocity of 120°/s the peak velocity of contralateral slow phases in the conflict situation was about 30% of the response in darkness in M4 and M5. After operation it was about 80%. Both monkeys could suppress the velocity of ipsi-

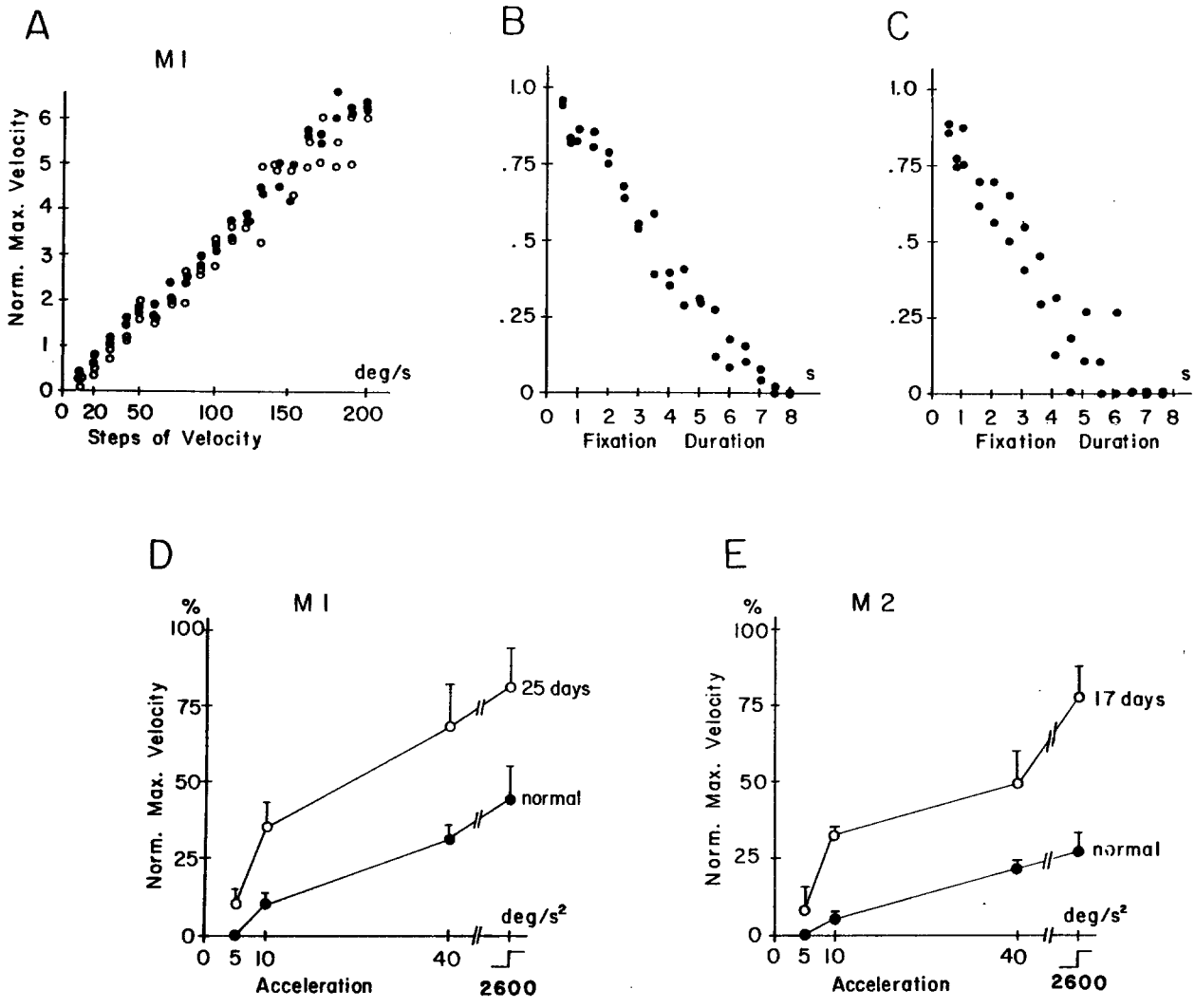


Fig. 7. **A** Peak value of slow phase eye velocity (ordinate) induced by steps of velocity in darkness (*filled circles*) and in the conflict situation (*open circles*) in M1 after operation. **B** and **C** *Ordinate:* ratio of slow phase eye velocity in M1 after periods of visual suppression to value just before exposure to stationary visual surround. *Abscissa,* duration of fixation. Suppression during post-rotatory nystagmus (**B**) and OKAN (**C**) was similar to that in normal monkeys. **D, E** Ratio of peak eye velocity during steps of acceleration during conflict stimulation, relative to peak eye velocity during rotation in darkness (set to 100%) before (*filled circles*) and after (*open circles*) bilateral flocculectomy. The vertical bars show 1 standard deviation. The animals were not able to suppress vestibular nystagmus as well after operation, especially at higher accelerations

lateral slow phases by more than 50% after operation during visual-vestibular conflict.

Despite the inability to suppress the initial jump in eye velocity, animals could reduce or "dump" post-rotatory nystagmus and OKAN after flocculectomy by shortening the time constant of the responses. An example is shown in Fig. 2D. Time constants of post-rotatory nystagmus were 6.4 (±0.7) and 5.0 s (±0.6) during conflict stimulation in M1 and M2. This is close to the time constant of activity of semicircular canal afferents (Goldberg and Fernandez 1971). Time constants of per- and post-rotatory nystagmus in darkness were 18.5 s (±2.2) and 19.5 s (±7.4) in these two animals. "Dumping" of post-rotatory nystagmus and OKAN was also tested by giving brief periods of exposure to a subject-stationary visual surround. The ratio of the slow phase velocities before and after the period of exposure was used as the index of suppression (Cohen et al. 1977; Raphan et al. 1979). The time constant of the discharge of post-rotatory nystagmus after flocculectomy in M1 was 3.5 s (Fig. 7B) and of OKAN was 2.8 s (Fig. 7C). These values are within the normal range (Cohen et al. 1977; Raphan et al. 1979). The ability to shorten the time constant of nystagmus in conflict situations indicates that animals

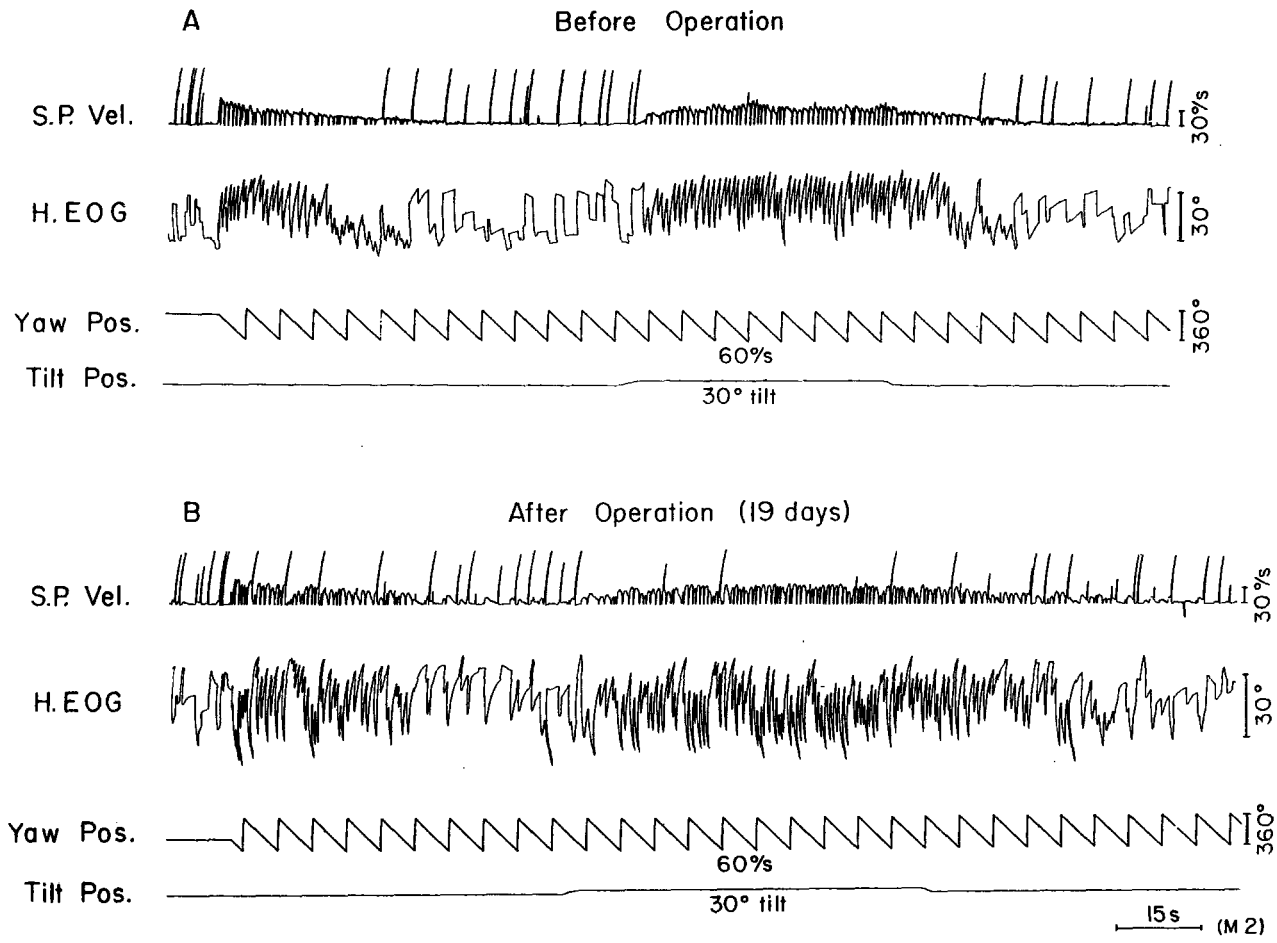


Fig. 8. A, B Nystagmus induced by rotation in darkness about an axis tilted from the vertical (off-vertical axis nystagmus) before (**A**) and after (**B**) bilateral flocculectomy in M2. The animal was first rotated about a vertical axis in darkness at 60°/s until the nystagmus disappeared (left). Then, as rotation continued, the axis was tilted 30° (center) and nystagmus reappeared. Moving the axis back to the vertical caused the nystagmus to disappear once again. The time course of the appearance and decline of the nystagmus and the gain were similar before and after operation

had retained their ability to discharge activity from the velocity storage mechanism after bilateral flocculectomy. After unilateral flocculectomy time constants of the attenuated nystagmus in the conflict situation were essentially the same as before operation, being less than 4 s in M5 and less than 10 s in M4. Here too, the ability to discharge stored activity was preserved after lesion.

VOR suppression was also tested by giving monkeys M1 and M2 steps of angular acceleration while in a subject-stationary visual surround (Fig. 7D, E). The ability to suppress nystagmus during accelerations of 5°/s^2 after bilateral flocculectomy was similar to that before operation. Both animals could attenuate or suppress nystagmus so that normalized maximum velocities were less than 10% of the value in darkness (Fig. 7D, E). During accelerations of 10°/s^2 they could also reduce nystagmus after operation so that it was about 30–35% of the response in darkness. During larger accelerations, however, significant nystagmus appeared when animals were in light. Thus, after flocculectomy monkeys were unable to suppress or attenuate nystagmus at higher accelerations. This is consistent with the response to step stimuli.

Generation and Visual Suppression of Nystagmus During Off-Vertical Axis Rotation; Tilt Suppression

Rotation about axes which are tilted from the vertical results in continuous nystagmus due to activation of otolith-ocular reflexes (Guedry 1965; Young and Henn 1975; Raphan et al. 1981). Animals were tested by rotating them at constant velocities of 30–120°/s about an axis tilted 30° from the vertical. In M1 and M4 the pre- and post-operative nystagmus were similar. In the three other animals (M2, M3 and M5) the steady state eye velocities were less after opera-

tion at most stimulus velocities (Table 1). The gain of vestibular nystagmus and the saturation velocity of OKAN was also reduced in these animals.

Charge characteristics of the velocity storage mechanism in response to otolith activation were determined by rotating the animals in darkness about a space-vertical axis until nystagmus had declined to zero. Then the axis of rotation was tilted as rotation continued. Nystagmus built up with a time constant of about 8–11 s (Fig. 8A). The time constant of the rise in velocity was unchanged by operation (Fig. 8B). This indicates that the velocity storage mechanism is charged normally by the otolith organs after flocculectomy.

Consistent with the finding that the visual system was capable of suppressing vestibular nystagmus elicited by low accelerations (Fig. 7D, E), monkeys could readily suppress nystagmus elicited by rotation about an off-vertical axis when exposed to a subject-stationary visual surround. Suppression was elicited by turning on the lights after nystagmus had reached a steady state level. Eye velocity fell to zero within 8 s. This time course is only slightly longer than before operation.

If animals are tilted during post-rotatory nystagmus induced by angular rotation about a space-vertical axis in darkness, there is a rapid decline in slow phase velocity due to a loss or "dump" of activity from the velocity storage mechanism (Raphan et al. 1981). Characteristics of "tilt" dumps were determined by tilting animals 90° at a velocity of 30°/s during post-rotatory nystagmus induced by a step of velocity of 60°/s. Nystagmus was reduced by the same amount and over a similar time course before and after operation. This demonstrates that vestibulo-vestibular interactions that cause suppression of nystagmus are unaffected by flocculectomy.

Vertical OKN and OKAN

Vertical OKN and OKAN was tested in M1 after bilateral flocculectomy and in M4 and M5 before and after unilateral flocculectomy. During testing monkeys were on their right side receiving steps of surround velocity about a vertical axis. In the normal monkey peak velocities of upward OKN (slow phases down) are about 40–60°/s while downward OKN (slow phases up) saturates at about 80–100°/s (Matsuo et al. 1979). There is little or no upward OKAN. Downward OKAN in the lateral position is much stronger, saturating at about 40°/s.

Sustained upward OKN could not be induced after bilateral flocculectomy (Fig. 9B). Downward OKN was present but it saturated at about 40°/s (Fig. 9A). The initial fast increase in eye velocity at the onset of downward OKN was lost, and there was no fast decay in eye velocity at the transition of OKN to OKAN (downward arrow, Fig. 9A). OKAN was present in the downward direction and absent in the upward direction, as in the normal animal (Matsuo et al. 1979). Visual-vestibular interactions in the sagittal plane were tested by eliciting per-rotatory nystagmus in light followed by a step in darkness. The level of the post-rotatory velocity was consistent with the presence or absence of OKAN. Thus, there was only weak upward post-rotatory nystagmus in darkness following rotation that elicited downward nystagmus in light, up to the saturation velocity of OKAN (Fig. 9C). In contrast, as there was no upward OKAN, downward post-rotatory nystagmus was as vigorous after rotation that induced upward nystagmus in light as after such rotation in darkness (Fig. 9D; Matsuo et al. 1979). This shows that flocculectomy had affected the direct visual-oculmotor pathways for vertical as for horizontal nystagmus, but had left the indirect pathways intact.

In the animals with unilateral flocculectomy the findings varied. M5 with total removal of the left flocculus had no change in any of the parameters of vertical OKN. In M4 the initial fast rise of upward and downward OKN was reduced by about half. Maximum velocities of downward OKN were the same before and after operation, but the maximum velocity downward of OKAN increased. Maximum velocities of upward OKN were about 35°/s before and 20°/s after operation. Upward OKAN, which had a maximum velocity of 8°/s in this animal, was lost after operation.

In summary, upward OKN was lost after bilateral flocculectomy. Downward OKN was present, but with animals in the lateral position its saturation velocity fell to the pre-operative saturation velocity of downward OKAN. The loss of upward OKN and of the initial fast rise in downward OKN after bilateral flocculectomy indicates that direct visual-oculomotor pathways for vertical as well as for horizontal nystagmus are mediated through the flocculus. Presumably upward OKN is lost because there is little or no upward OKAN, i.e. no indirect pathways, and the direct visual-oculomotor pathways have been interrupted. Both flocculi appear to contribute to generation of OKN slow phases in the upward and downward directions.

Responses Just After Operation

In the first week after operation OKN and OKAN velocities were lower in all monkeys compared to

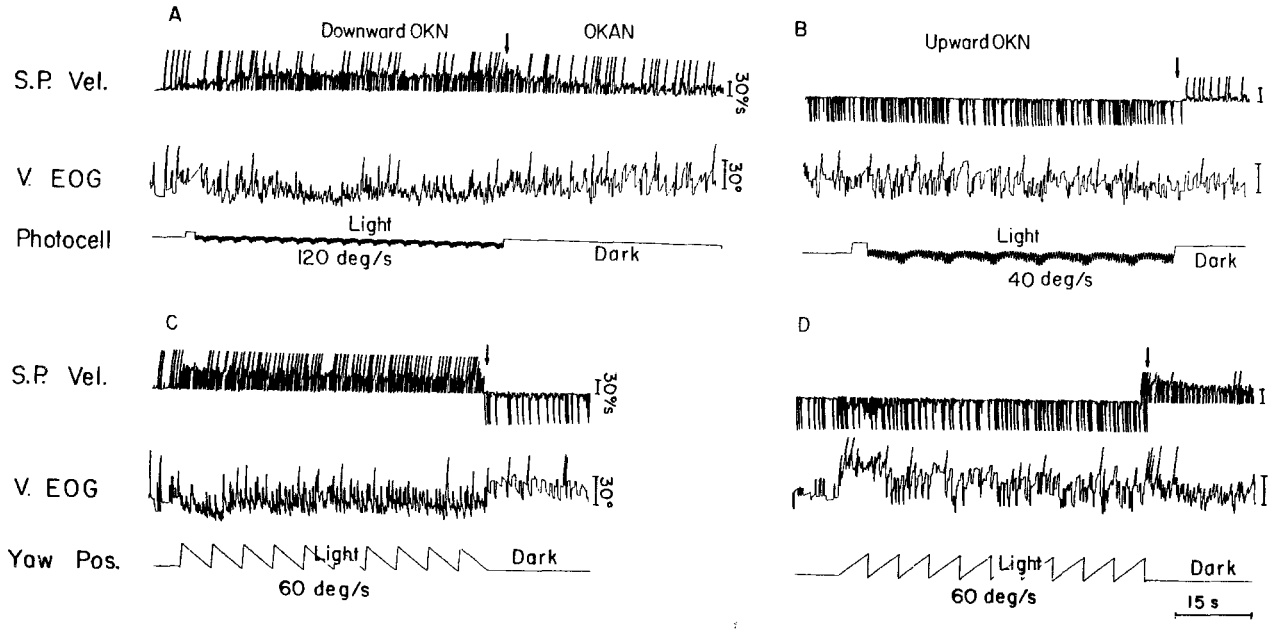


Fig. 9. **A** Downward OKN and OKAN induced after bilateral flocculectomy in M1 by movement of the entire visual surround in the animal's sagittal plane while it lay on its right side. The velocity of the stimulus was 120°/s. There was no initial rapid rise in slow phase velocity at the onset of downward OKN. **B** The response to surround movement of 40°/s in the opposite direction. No upward OKN or OKAN was induced. **C, D** Response to rotation at 60°/s about a vertical axis in a lighted earth-stationary visual surround. As before, the animal was lying on its right side. **C** Downward nystagmus in light was followed by very weak upward nystagmus when the animal was stopped in darkness. **D** In contrast, there was active downward nystagmus in darkness after upward nystagmus had been elicited by rotation in light

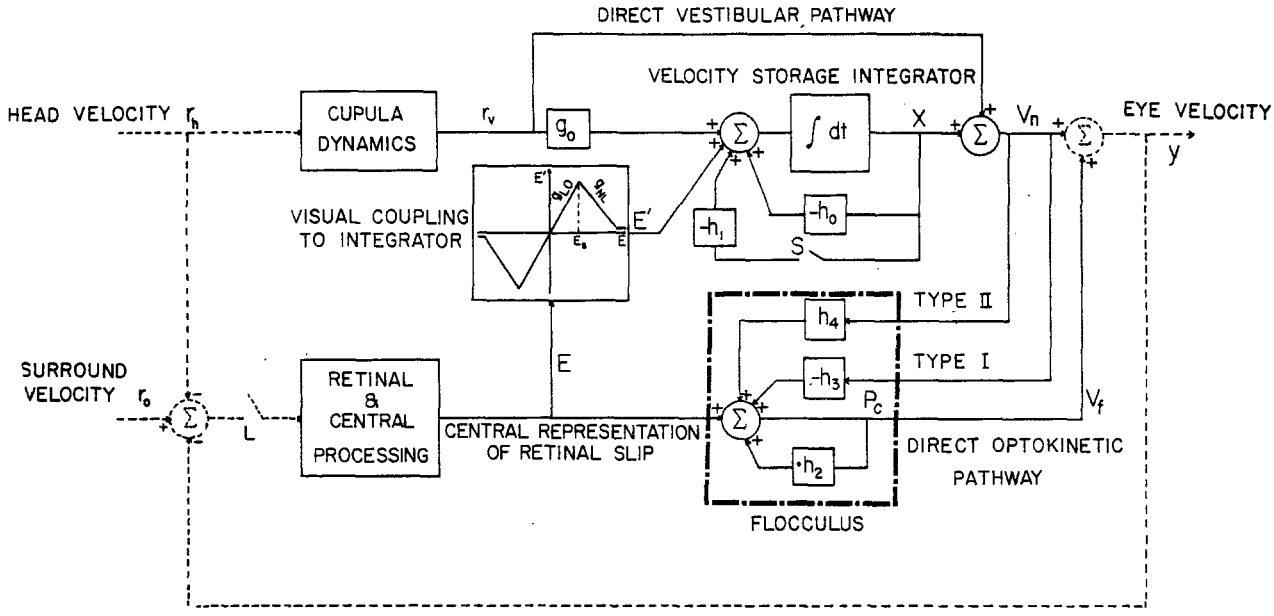
values recorded several weeks later. It was of interest that OKN steady state gains fell gradually over 7 days in the one monkey who was tested immediately after operation (Fig. 4F). Time constants of OKAN were shorter, sometimes by more than half when compared to the responses 1–3 weeks later. OKAN saturation velocities typically reached their maximal values at stimulus velocities of 60°/s and declined at higher stimulus velocities. In each of the three monkeys the reduction in the initial fast rise in OKN and the inability to suppress the initial jump in slow phase velocity of vestibular nystagmus were the same just after lesion as later. The major changes that occurred after the first week were an increase in OKN steady state velocity together with a similar recovery of OKAN velocity and duration.

Unilateral flocculectomy had a similar effect on eye movements as bilateral flocculectomy, but the effects were asymmetrical, being more pronounced when stimulation caused the eyes to move in slow phases to the lesion side. There was ipsilateral spontaneous and gaze nystagmus, and OKN steady state velocities and the gain of vestibular nystagmus with slow phases to the lesion side were strongly reduced. OKAN velocities were below 15°/s and the duration of OKAN was less than 6 s. OKN steady state velocities, maximal OKAN velocities, OKAN duration and the gain of vestibular nystagmus improved rapidly. However, there was no recovery in the initial fast rise of OKN and in the ability of animals to attenuate peak velocities of vestibular nystagmus during conflict stimulation.

Modelling of Vestibular Nystagmus, OKN, OKAN and Visual-Vestibular Interaction in the Flocculectomized Monkey: Conceptual Basis for the Model

Models that have been developed over the past few years can simulate the dominant aspects of OKN, OKAN and visual-vestibular interactions (Raphan et al. 1977; Robinson 1977; Raphan et al. 1979; Robinson 1980; Buizza and Schmid 1982). The models are behaviorally homeomorphic, although they emphasize different aspects. There is general agreement that both the VOR and OKN are mediated via direct as well as indirect pathways. The direct pathways can be represented simply as a gain element. They mediate rapid responses while the indirect pathways respond more slowly. The indirect pathways can be represented as a mathematical integrator whose purpose is to store velocity information (cf. Raphan and Cohen 1981).

The model's realization can be restructured to reflect physiological variables such as the firing frequency of neurons in the brainstem and flocculus



$$\dot{x} = -(h_0 + s\cdot h_1)x + g_{LO}E + g_0 r_v \qquad |E| < E_s \qquad (1)$$

$$\dot{x} = -(h_0 + s\cdot h_1)x - g_{NL}E + g_0 r_v + (g_{LO} + g_{NL})E_s \qquad |E| \geq E_s \qquad (2)$$

$$v_f = g_1 E + g_1(h_4 - h_3)(x + r_v) \qquad g_1 = \frac{1}{1 - h_2} \qquad |v_f| \leq d_s \qquad (3)$$

$$E = (r_0 - r_h - v_f - x - r_v)\cdot L \qquad (4)$$

$$x = x_s \operatorname{sgn}(x) \quad |x| > x_s \qquad v_f = d_s \operatorname{sgn}(v_f) \quad |v_f| > d_s \qquad (5)$$

$$V_n = X + r_v \qquad (6)$$

$$y = V_n + V_f \qquad (7)$$

Fig. 10. Model of OKN, OKAN, vestibular nystagmus and visual-vestibular interactions. *Solid lines* represent neural signals, *dotted lines* represent mechanical variables. The parameters used for the simulations in Figs. 11 and 12 were $h_o = 0.075$; $g_{LO} = 0.25$; $g_{NL} = 0.025$; $E_s = 24°/s$; $g_o = 0.3$. The cupula dynamics were represented by a system with a dominant time constant of 4 s. The velocity saturation of the integrator's output was chosen as $x_s = 60°/s$. The velocity saturation of the direct pathway was chosen as $d_s = 35°/s$. These were based on the experimental observations in monkey M1 before and after flocculectomy

to explain the dominant behavioral responses after bilateral flocculectomy. The signal in the vestibular nuclei represents a summation of the direct input from semicircular canal afferents and the velocity storage integrator (Raphan and Cohen 1981). The visual system couples to the vestibular nuclei mainly through the velocity storage mechanism, and the direct visual-oculomotor pathways do not project directly to the vestibular nuclei (cf. Raphan and Cohen 1981 for further elaboration). From recordings in the flocculus during ocular pursuit and fixation-suppression, it has been suggested that head and eye velocity signals project to floccular Purkinje cells where they summate with a representation of retinal slip to produce the velocity command signal during ocular pursuit and suppression of the VOR (Miles

and Fuller 1975; Lisberger and Fuchs 1978). In this scheme it assumed that the head velocity signal comes primarily from the eighth nerve, and the retinal signal slip from the visual system. The origin of the eye velocity signal is unclear.

While mossy fibers that input to the flocculus have an eye velocity component in their firing frequency during pursuit, eye position and saccadic eye movements are also reflected in their firing rates (Lisberger and Fuchs 1978; Miles et al. 1980; Noda and Warabi 1982). As yet, no input mossy fibers solely related to eye velocity have been found during pursuit, or during OKN, OKAN or visual-vestibular interactions. Moreover, mossy fiber inputs with activity, characteristic of eighth nerve afferents, were not encountered in the flocculus (Waespe et al. 1981).

Unit recordings from the vestibular nuclei (Waespe and Henn 1977a, b, 1978, 1979) and flocculus (Waespe and Henn 1981) indicate that there is complementary processing of activity in these structures during OKN, OKAN, and visual-vestibular interaction. Floccular Purkinje cells have characteristic firing rates related to the output of the direct visual-oculomotor pathways (Waespe and Henn 1981). Frequencies of some input neurons to the flocculus are related to full field retinal slip (Noda 1981; Waespe et al. 1981). Other classes of mossy fibers which input to the flocculus have the same characteristics as cells in the vestibular nuclei (Waespe et al. 1981). We assume, therefore, that eye velocity alone is not a predominant input to the flocculus, that the major input from the vestibular system to the flocculus is from the vestibular nuclei, and that a representation of eye velocity is realized in the flocculus by summing signals from the vestibular nuclei and the direct pathway.

Model Description

A modified realization of the model presented by Raphan et al. (1979) with explicit variables related to unit activity is shown in Fig. 10. The model has two inputs: r_h corresponding to head velocity and r_o representing environmental velocity. The model representation of the vestibular system responds to the mechanical variable head velocity (r_h) and generates an eighth nerve signal represented by r_v dependent on the cupula dynamics (Goldberg and Fernandez 1971). The signal r_v couples to the integrator via the parameter g_o as well as having a direct pathway around it. The state of the integrator x and the direct pathway around it summate to form the velocity signal V_n that reflects the activity of "horizontal" second order neurons in the vestibular nuclei. The output of the integrator has been saturated to explain the data in this study and previous data on OKAN (Cohen et al. 1977). The model representation of the visual system has retinal slip as its input, formed by subtracting head velocity and eye velocity from surround velocity. This signal is transformed into a central representation of retinal slip by visual system processing. When the lights are off, visual system processing is inactivated; this is represented by opening switch L. The signal E, which is the central representation of retinal slip, couples to the velocity storage integrator through a nonlinear element. The structure of the nonlinearity accounts for many of the characteristics observed during OKN, OKAN and the visual-vestibular interaction. It is also important for explaining the effects of flocculectomy on nystagmus.

The direct pathway output of the visual system is assumed to be realized by the flocculus which is represented in the portion of the model enclosed by the heavy dashed lines. A central representation of retinal slip E is summed with parallel out-of-phase signals from V_n and a self loop that feeds back from the direct pathway. The out-of-phase signals from V_n are represented by the gain elements h_4 and h_3. This could represent input to the flocculus from Type 1 and Type 2 vestibular nuclei neurons. Feedback from the direct pathway is shown as the loop containing h_2 and could be realized by axon collaterals of Purkinje cells (Eccles et al. 1967; Marr 1969). While data in this report do not bear directly on the structure of the direct pathways that was chosen, the formulation is consistent with the firing frequency of neurons recorded in the flocculus during OKN, OKAN and visual-vestibular interactions (Waespe and Henn 1981; Waespe et al. 1981).

As noted above, the time constant of the frequency of input mossy fibers in the flocculus is related to that of cells in the vestibular nuclei, not to activity of fibers in the vestibular nerve (Waespe et al. 1981). Therefore, for present purposes it is assumed that the head velocity signal comes from the vestibular nuclei as a representation of activity in Type 1 neurons. It is further assumed that input neurons to the flocculus are not present whose firing rates are related to eye velocity ($V_n + V_f$). Instead, efference feedback of eye velocity is realized by separately feeding back velocity command signals from V_n and the output from the direct pathway V_f. This has the effect of producing out-of-phase signals from the vestibular nuclei. Under normal conditions h_4 and h_3 are equal to each other, and their contribution is not apparent, but they change separately in adapted conditions. This could account for the

change in firing rates of floccular Purkinje cells found in some circumstances (Miles et al. 1980).

An important part of the model which enables simulation of the effects of flocculectomy on OKN, OKAN and visual-vestibular interaction is a nonlinear element in the indirect pathway that couples the visual system to the velocity storage integrator (Fig. 10). While this nonlinearity has been noted before (Young 1971; Collewijn 1972; Simpson et al. 1979; Hoffman 1981; Demer 1981; Buizza and Schmid 1982), quantitative relationship have not been established between the parameters of the nonlinearity and the dynamics of OKN. In order to accomplish this, the nonlinearity has been approximated as piecewise linear having a positive incremental gain for $E < E_s$ and a negative incremental gain for $E \geq E_s$.

Model Parameter Identification

The equations describing the behavior of the system are shown below in Fig. 10. These equations describe the rate of change of the state of the storage integrator as a function of the surround velocity r_o, head velocity r_h, the semicircular canal afferent input r_v, and the states of the light and suppression switches L and S, respectively. When the lights are off, L = 0 the response is governed by the integrator and vestibular input r_v. For a step in surround velocity r_o with the light swith on, i.e. L = 1, there is a step in the variables V_f, the direct visual pathway, and y, eye velocity. This is because when the head is stationary, the input signals r_h and r_v are equal to zero giving an initial value of $V_n = 0$. If it is further assumed that $h_4 = h_3$, then parameter g_1 determines the gain of the direct visual pathway and the rapid jump in eye velocity (Substitute Eqs 4 and 6 into Eq 3 and solve for V_f). This gives:

$$V_f = g_1 r_o/(1+g_1) \tag{8}$$

The direct visual pathway gain was about 0.6 in our previous study (Cohen et al. 1977). However, the monkey (M1) used to simulate the data had an average direct pathway gain of approximately 0.35. This fixes the parameter $g_1 = 0.55$ ($h_2 = 0.8$) and the initial value of eye velocity, V_f.

Parameter estimates for the nonlinearity can be obtained by examining the optokinetic response in light before and after flocculectomy. The magnitude of the initial value of $(r_o - V_f)$ determines the region of the nonlinearity, i.e. $E < E_s$ or $E \geq E_s$ where the system will find itself at the start of stimulation. Thus, the gain of the direct pathway has a profound effect on the initial drive on the system which in turn affects the dynamics of charging the integrator. After flocculectomy, it is assumed that $g_1 = 0$. Thus, the initial value of the surround velocity r_o determines the initial point on the nonlinearity for the system. By substituting Eq 3 into Eq 4, solving for E and substituting it into Eqs 1 and 2, the rate of charge of the integrator or its time constant before and after flocculectomy is determined. It is obtained from the elements in the parentheses of Eqs 1 and 2 multiplying the state x after the substitutions are made (cf. Raphan and Cohen 1981 for explanation). It is assumed that S = 0 since the system is not suppressing.

Before flocculectomy, if the system is initially in the positive incremental gain region ($E < E_s$) then the time constant of rise is

$$T_{RB} = 1/[h_o + g_{LO}/(1+g_1)] \tag{9}$$

where $1/h_o$ is the time constant of the integrator (time constant of OKAN) and g_{LO} is the positive incremental gain of the nonlinearity. After flocculectomy $g_1 = 0$ and the rising time constant is

$$T_{RA} = 1(h_o + g_{LO}) \tag{10}$$

Since $g_1 > 0$, it indicates that the removal of the direct pathway decreases the charging time constant in the positive incremental gain region although the time constant of the integrator is unchanged. The steady state value of the integrator response before flocculectomy is given by

$$x_{ss} = [g_{LO}/(1+g_1)] \cdot r_o/[h_o + g_{LO}/(1+g_1)] \tag{11}$$

After flocculectomy

$$x_{ss} = g_{LO} \cdot r_o/(h_o + g_{LO}) \tag{12}$$

Although the model predicts a difference between the steady state integrator response before and after flocculectomy, the difference is small since $g_{LO} \gg h_o$.

Before flocculectomy if the system is initially in the negative incremental gain region ($E \geq E_s$), Equation 2 is applicable and the rising time constant is

$$T_{RB} = 1/[h_o - g_{NL}/(1+g_1)] \tag{13}$$

After flocculectomy the rising time constant is

$$T_{RB} = 1/(h_o - g_{NL}) \tag{14}$$

It is interesting to note that if g_{NL}, which is the slope of the negative incremental gain, is made equal to h_o, the inverse of the time constant of the integrator, i.e. $g_{NL} = h_o$, then the rising time constant is infinite after flocculectomy, and the integrator looks as if it is ideal. If h_o is close to g_{NL}, the integrator time constant is large and also looks almost ideal (cf. Raphan and Cohen 1981). Under these conditions the integrator's response would be an approximately linear increase in velocity while the system is in the negative incremental gain region. For $g_{NL} > h_o$ the time constant is negative and the response characteristic changes to a convex function as long as $E \geq E_s$. This behavior is observed in rabbits, which have a negligible direct pathway gain when they are subjected to large velocities of drum rotation (Collewijn 1972). In the normal monkey with an intact direct pathway, g_{NL} would have to be much larger in order to produce a convex response. This analysis shows that the gain of the direct pathway not only affects the rapid rise in slow phase eye velocity, but by interacting with the nonlinear coupling from the visual system to the integrator affects the dynamics of the integrator's response characteristics.

To obtain numerical estimates of the parameters, the response of M1 was analyzed at 160°/s after flocculectomy. At this velocity the system is confined to the negative incremental gain region ($E \geq E_s$) since the steady state retinal slip E is approximately 100°/s. The time constant of the rise was approximately 20 s. Therefore,

$$h_o - g_{NL} = 1/20 = 0.05 \tag{15}$$

However, the time constant of OKAN was about 13 s giving $h_o = 0.075$. Therefore, the slope of the negative incremental gain region $g_{NL} = 0.025$. The parameter g_{LO}, the slope of the positive incremental gain, was estimated from the rising time constant at low velocities after flocculectomy. Under these conditions

$$T_{RA} = 1/(h_o + g_{LO}) \tag{16}$$

For $T_{RA} = 3$ s, $g_{LO} = 0.25$. When the direct pathway is present, the time constant of rise is 4 s. Thus, the range of rising time constants will be from 4–20 s before flocculectomy and from 3–20 s after flocculectomy. The time constant will increase if the system spends more time in the negative incremental region as would occur at higher velocities. This explains the dependence of rise time on stimulus velocity both before and after flocculectomy that was observed in this and a previous study (Cohen et al. 1977).

Once approximate values for g_{LO} and g_{NL} are obtained it is only necessary to find a point on the negative incremental gain line to determine where it intersects the positive incremental gain line. This is approximated from the response at 160°/s. As shown in the Appendix the initial acceleration of the rise of OKN that would be predicted from the model is twice the average acceleration of the data when approximated by a straight line (Fig. 13). For a stimulus velocity of 160°/s the average acceleration of the eyes was approximately 1.25°/s^2 after flocculectomy (Fig. 4E). From the model equations the initial acceleration a_I is given by:

$$a_I = (g_{LO} + g_{NL})\, E_s - g_{NL}\, r_o \tag{17}$$

$$a_I = 2(1.25) = 2.5 \quad \text{(from Appendix)}$$

Therefore,

$$2.5 = (0.25 + 0.025)\, E_s - 0.025(160)$$

This gives an approximate value for $E_s = 24$°/s. Thus, the parameters for the model to simulate the response in M1 have been determined. They are given in the legend of Fig. 10.

Model Simulations Before and After Flocculectomy

Utilizing the parameters found above, OKN and OKAN of M1 were simulated (Fig. 11, solid lines). The simulations are consistent with experimental data obtained during four to six trials before and after flocculectomy (Fig. 11, dots). Normal OKN before flocculectomy has both a rapid and slow rise (Fig. 11A, B). The time constant of the slow rise is longer at 160 (Fig. 11A) than at 60°/s (Fig. 11B). For a stimulus of 160°/s the integrator is saturated at 60°/s and the direct pathway gain is saturated at 35°/s. This gives a steady state slip velocity of 65°/s that is greater than E_s. Hence at 160°/s the system never comes into the positive incremental gain region and the rising time constant is always very long. In contrast when the stimulus is 60°/s the system crosses over into the positive incremental gain region. This is characterized by an approximately linear rise while the system is in the negative incremental gain region due to its long time constant and the large velocity to which it is driving. At the arrow in Fig. 11B, it shifts to the positive incremental gain region, and the rising time constant becomes shorter and reaches the steady state according to Eq. 1. The model also fits the data for OKAN in both instances. Thus, the model simulates the normal data of M1 over a wide range of velocities.

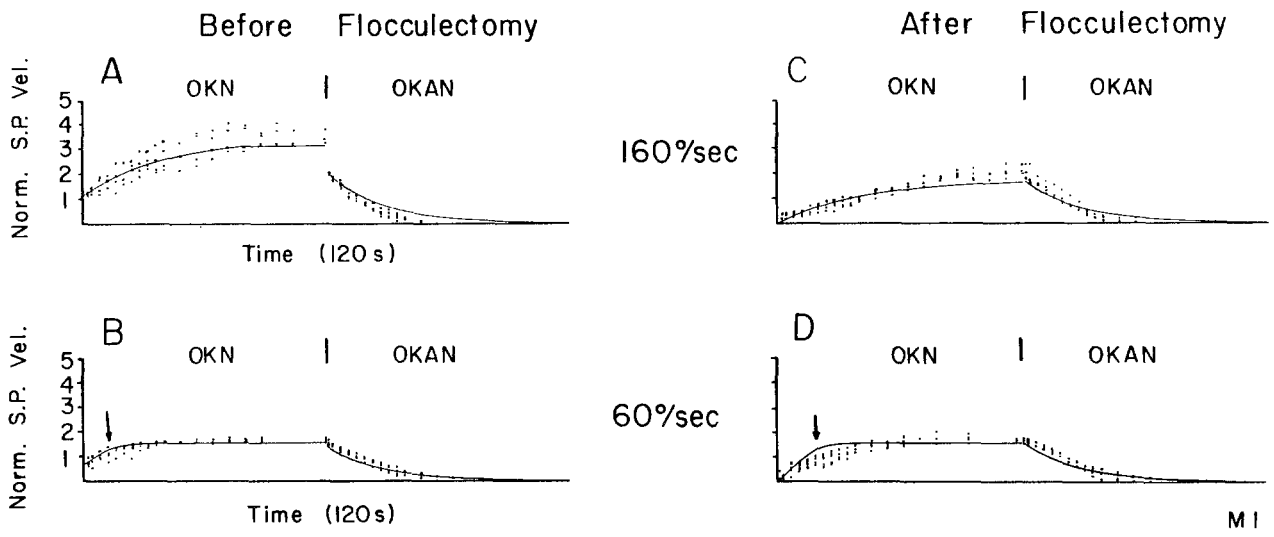


Fig. 11. A–D Comparison of simulation of slow phase velocity of OKN and OKAN (*solid lines*) before (**A, B**) and after (**C, D**) the direct visual pathways were removed from the model with actual data from M1 obtained during OKN and OKAN. The input velocity to the model was 160°/s in **A** and **C** and 60°/s in **B** and **D**. The *dots* represent actual values for OKN and OKAN taken from four to six experiments in M1. The *downward arrows* in **B** and **D** show the transition point from positive to negative incremental gain regions

After flocculectomy the gain of the direct pathway is set to zero. At 160°/s the system is always in the negative incremental gain region, and it rises with a long time constant (Fig. 11C). The model predicts that for this velocity the integrator would not saturate but would only reach 50°/s. For a stimulus velocity of 60°/s (Fig. 11D) the model again predicts an approximately linear rise followed by a rise with a faster time constant when the system crosses into the positive incremental gain region at the arrow.

For a step in head velocity in the dark r_h, the model behaves as described in Raphan et al. (1979). It is assumed that flocculectomy does not affect the direct vestibular pathways or the coupling to the integrator from the vestibular system g_o. Thus, there is no difference in the model response to a step in head velocity in darkness with and without the direct visual pathway. The only difference is that the present model has an output-saturated integrator which modifies the dynamics for high stimulus velocities. The simulated response to a 120°/s step in angular velocity of the head in darkness is shown in Fig. 12A. The model predicts that before and after flocculectomy there is a rapid rise in slow phase eye velocity (SP Vel) due to activation of the direct vestibular pathway. There is a plateau in velocity due to a summation of the output of the integrator and the direct vestibular pathway (Raphan et al. 1979). This is followed by a brief decline with the cupula time constant since the output of the integrator (Int) has been saturated at 60°/s. When the eighth nerve signal (Cupula) has fallen so that the integrator comes out of saturation, slow phase velocity declines more slowly. The effects of the saturation cause a decrease in the duration of the plateau and a sharper decline thereafter at higher velocities. This is consistent with general characteristics of nystagmus observed in this and a previous study (Raphan et al. 1979). The simulated response is also consistent with data that shows that flocculectomy does not affect the general characteristics of nystagmus in response to a step in head velocity in darkness (Zee et al. 1981).

The visual-vestibular interaction predicted by the model in various conflict situations is shown in Fig. 12B–D. A step of head velocity that causes the cupula to deflect maximally would drive the eyes with a gain of 1 over the direct vestibular pathway. However, in a subject-stationary visual surround before flocculectomy (Fig. 12B), it is opposed by the direct visual pathway (Dir Vis Pathway) which reduces slow phase eye velocity (SP Vel). The integrator is driven by the cupula deflection, but this is opposed by the visual coupling to the integrator and by the activation of the suppression switch. This causes the integrator to discharge and decay more rapidly than in darkness (cf. Int in 12A and 12B). This is consistent with data on conflict stimulation before flocculectomy (Fig. 2C).

After flocculectomy (Fig. 12C) the direct visual pathway response is zero. Therefore, slow phase eye velocity (SP Vel) jumps unopposed to the level determined by cupula deflection. The integrator is only partially charged as before because the coupling of retinal slip to the integrator is maintained and the

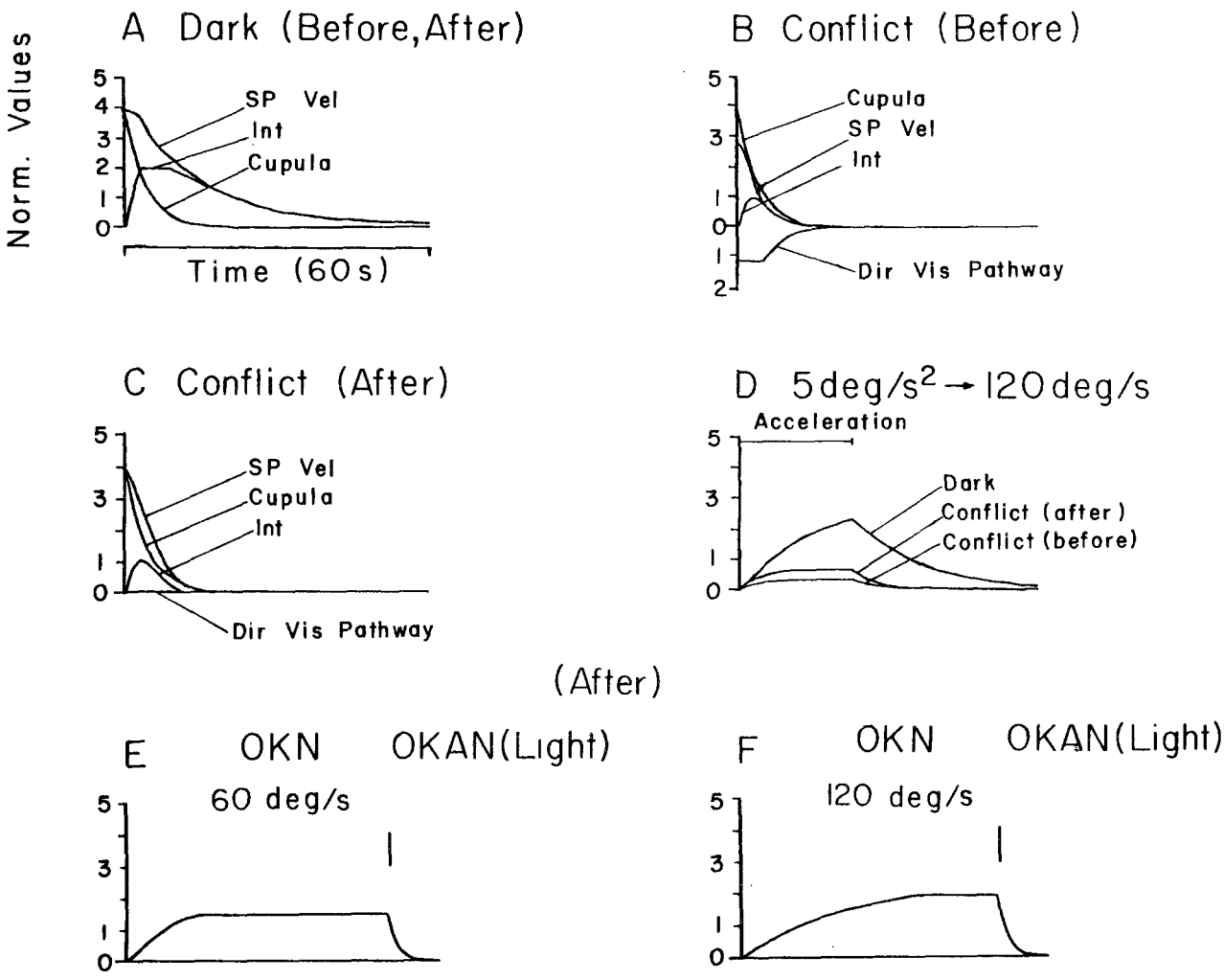


Fig. 12. Model simulations of cupula deflection, integrator activity (*Int*) and slow phase velocity (*SP Vel*) before and after flocculectomy. Cupula deflection is assumed to produce activity in the eighth nerve with the same characteristics. Activity in the direct visual pathway (Dir Vis Pathway) is also shown in **B** and **C**. The conflict situation in **B** to **D** is equivalent to that produced by rotating the animal in a lighted, subject-stationary surround. **E, F** OKN and OKAN in light after removal of the direct visual pathway which simulates effects of flocculectomy. This causes conflict during OKAN, since the nystagmus is occurring in the presence of a subject-stationary surround, and the model suppresses OKAN. Note the short OKAN in this condition despite the absence of the direct visual pathway

suppression mechanism is intact (cf. Int of Fig. 12B, C). This causes slow phase velocity to decay more rapidly than in darkness (Fig. 12A), but slightly slower after than before flocculectomy in the conflict situation (Fig. 12C, B). The predicted values of the time constants of decline of slow phase velocity before and after operation are 4.5 and 5.6 s, respectively; the actual data values from M1 were 4.1 and 6.4 s (see above). The model also predicts visual-vestibular interaction in the conflict situation, i.e. in a subject-stationary visual surround during angular acceleration. An example at $5°/s^2$ is shown in Fig. 12D. In the dark there is no difference in development of slow phase velocity before and after flocculectomy. In the conflict situation slow phase velocity is reduced in both cases, but the reduction is slightly greater before than after operation. This is consistent with the findings shown in Fig. 7D, E.

The effects of visual suppression of OKAN after flocculectomy at 60 and 120°/s are shown in Fig. 12E, F. (Conflict, here, is produced by leaving on the lights, i.e. by setting L = 1, at the end of OKN.) After flocculectomy the model predicts that nystagmus would be suppressed with a time constant of about 3 s. In M1 suppression of OKAN in light had a time constant of 2.8 s (Fig. 7C).

The model does not fit the data perfectly. It predicts a faster rise during OKN at 60°/s after flocculectomy than is present in the data (Fig. 11D). The saturation of OKN after flocculectomy is slightly higher than predicted by the model (Fig. 11C). In addition, the gain of the direct pathway in M1 is

assumed to be 0.35, but in M2 it was as high as 0.6 or 0.7. Differences between the model and the data could be due to several factors. The nonlinearity is approximated by straight lines for ease of mathematical manipulation, but it may have another configuration (Fig. 4E). Secondly, the storage mechanism has been approximated by a single integrator, but it is likely that it is of higher order. This could change the response dynamics, slowing down the rise characteristics. Finally, the model is a deterministic model, and the parameters are constant, but the nervous system is stochastic in nature. Even with these shortcomings, however, the model is able to approximate the data closely, and explicate the detailed effects of flocculectomy.

Discussion

This study indicates that a major role of the flocculus is to mediate signals in the direct visual-oculomotor pathways that are responsible for rapid changes in slow phase eye velocity for both horizontal and vertical OKN. Evidence for this is the reduction in the rapid change in slow phase velocity at the onset and end of OKN, and the inability of animals to attenuate the rapid jump in eye velocity during a step in head rotation in a subject-stationary visual surround. Support for this also comes from the simulation of OKN, OKAN and visual-vestibular interactions after flocculectomy by removal of the direct visual-oculomotor pathway from the model shown in Fig. 10. The dynamics of slow phase generation mediated through the velocity storage mechanism and the direct vestibular pathways were largely unaffected by flocculectomy. While the lesions appeared to modify the charge characteristics of OKN, so that the rising time constant was longer after than before operation for the same stimulus velocities (Fig. 11C, D and Zee et al. 1981), this could be attributed to increased initial retinal slip that accompanied the reduction of gain in direct visual-oculomotor pathways.

Although the data were simulated with the direct visual-oculomotor pathways removed from the model, there was indication that they were not lost entirely. Small rapid changes in eye velocity were present during OKN after complete bilateral lesions (Fig. 4C). This indicates that there are weak extraflocculer direct pathways, either in the cerebellum or brainstem, that are utilized in producing the rapid rise in OKN. It seems clear, however, that most activity for the initial jump in velocity is probably processed through the areas which were ablated. Unilateral flocculectomy also attenuated the rapid rise in OKN slow phase velocity in both directions and affected vertical OKN. This indicates that each flocculus contributes to rapid changes in slow phase eye velocity during OKN in any direction.

Zee et al. (1981) found reductions in pursuit capability in monkeys after bilateral flocculectomy. These animals also had difficulty in cancelling the VOR in a conflict situation when fixating a point source. Therefore, the flocculus appears to play a role in producing rapid changes in eye velocity during pursuit as well as during OKN. In support of this, Purkinje cells are known to respond to ocular pursuit of small moving targets and fire during cancellation of the VOR while viewing a head-fixed target during rotation (Miles and Fuller 1975; Lisberger and Fuchs 1978). However, the precise relationship between the neural mechanisms responsible for pursuit and for rapid changes in eye velocity during OKN is not clear (cf. Henn et al. 1980, pgs. 542–543 for further discussion).

In order to simulate OKN after removal of the direct visual-oculomotor pathways, it was necessary to include nonlinear coupling of the visual system to the integrator in the indirect pathways. Similar nonlinearities have been found in OKN of rabbits (Collewijn 1972), cats (Hoffman 1981) and humans (Young 1971). The nonlinearity is such that up to a certain threshold its output increases with increasing retinal slips (positive incremental gain) while above this threshold the output decreases (negative incremental gain). The point at which the system switches from positive to negative incremental gain varies. In the rabbit and cat the transition occurs at 1–2°/s (Collewijn 1972) and about 10°/s (Hoffman 1981). For the monkey whose data was simulated (M1) this transition has been inferred to occur at about 24°/s. In the intact monkey the direct pathways tend to keep the system in the positive incremental gain region, and the characteristics of the negative gain region of the indirect pathway are obscured. In the rabbit and cat direct pathways are much weaker and OKN is generated primarily through the velocity storage mechanism. Hence, in these animals the presence of a negative incremental gain region is easier to detect.

The nonlinear behavior of OKN in the rabbit has been related to the velocity characteristics of retinal ganglion cells (Barlow et al. 1964; Oyster et al. 1972; Collewijn 1972). A similar type of nonlinearity is also present in the relationship between stimulus velocity and firing rates of cells in the nucleus of the optic tract (NOT) in both rabbit (Collewijn 1975) and cat (Hoffman and Schoppman 1981). NOT receives direct retinal projections and appears to lie in optokinetic pathways (Precht 1981). Cells that respond to moving fields have also been reported in

the vicinity of nucleus reticularis tegmenti pontis (NRTP) of the monkey (Keller and Crandall 1981), but they saturate at velocities that are lower than those predicted for the monkey from the present results. Hence they do not appear to have the kind of nonlinear response that would be required to fit the data.

In the rabbit convergence of activity in NOT changes and shapes the nonlinearity (Collewijn 1975). This suggests that central structures play an important role in its realization. The same is probably true in other species (Hoffman 1981). Since the nonlinearity was unmodified after flocculectomy in the monkey, the flocculus does not appear to play an important role in its realization in this animal. In the rabbit climbing fibers to the flocculus from the inferior olive have similar nonlinear behavior as do cells in NOT (Simpson and Alley 1974). As rabbits have virtually no direct visual-oculomotor pathways, this may indicate that the flocculus is important in coupling the visual system to the velocity storage mechanism in this animal.

The ability to study indirect pathways for OKN in relative isolation after flocculectomy has revealed new aspects of organization of the mechanism for suppression of nystagmus. It was initially assumed from data on caloric nystagmus that activity responsible for visual suppression of the VOR primarily arose in the flocculus, although it was clear that OKAN and spontaneous nystagmus could be suppressed after flocculectomy (Takemori and Cohen 1974). Results of this study have shown that there are at least two extrafloccular mechanisms for suppression of nystagmus in the indirect pathways. One is related to visual feedback of retinal slip, the other to activation of the dump mechanism that changes the time constant of the velocity storage mechanism, causing it to discharge more rapidly. Thus, while floccular Purkinje cells oppose rapid changes in slow phase eye velocity produced by the vestibular system in conflict situations (Miles and Fuller 1975; Lisberger and Fuchs 1978), testing after flocculectomy shows that these Purkinje cells are not solely responsible for opposing slower changes in eye velocity, nor does loss of their activity change the monkey's ability to modify the time constant of the velocity storage mechanism. Tilting animals out of the plane of nystagmus also caused suppression of post-rotatory nystagmus and OKAN after flocculectomy as in normal animals (Raphan et al. 1981). This shows that nystagmus suppression mechanisms can be activated from the vestibular as well as from the visual system in the absence of the flocculus. It seems likely that a common dump mechanism is utilized in adapting the time constant of the velocity storage mechanism in both visual-vestibular and in canal-otolith conflict situations, and that the flocculus is involved neither in the realization of the dump mechanism nor in its activation.

There have been a number of studies of effects of flocculectomy in various animals, but for a variety of reasons it is difficult to compare results from one species to another. In many species the gain of vestibular nystagmus and OKN was reduced after flocculectomy (Hassul et al. 1976; Keller and Precht 1979; Ito et al. 1982) although this happened inconsistently in the monkey (Zee et al. 1981). In most studies, the anatomy of the lesions has not been presented, so it is difficult to determine whether the lesions involved the same structures. Keller and Precht (1979) showed that post-rotatory nystagmus was cancelled in the cat after rotation in light. This is similar to findings in the monkey and implies that the velocity storage mechanism was intact in the cat after flocculectomy. However, the relative contribution of the direct and indirect pathways to the production of OKN and OKAN have not been studied in the cat either before or after flocculectomy. In the rabbit only low velocities, within the range of the initial rapid rise of OKN, were used to test the animals (Ito et al. 1982); these stimulus velocities would not excite the velocity storage integrator (Collewijn 1969, 1972). Hence, the effects of flocculectomy on the storage integrator and on OKAN must still be determined in this animal.

There is a more basic problem with cross-species comparisons, however. In the monkey the flocculus is strongly related to generation of pursuit eye movements (Zee et al. 1981) and the initial rapid rise in OKN. The rabbit has no independent ocular pursuit and only a minimal rapid rise in OKN, although it has a well developed flocculus. Thus, while the flocculus appears to be a part of the motor pathway for ocular pursuit and for the direct pathways for OKN in the monkey, its function in the rabbit is as yet unknown.

In contrast to rabbits which have little or no rapid rise in OKN, humans have OKN that is produced primarily by activation of direct pathways, and the velocity storage mechanism contributes much less to its generation (Cohen et al. 1981; Koenig and Dichgans 1981). Based on results in the monkey, one would predict that lesions of the flocculus would severely affect OKN in humans. In accord with this, there is a relative inability to generate ipsilateral slow phases of OKN and pursuit movements after unilateral lesions in the region of the flocculus (Dichgans et al. 1978). Moreover, OKN and ocular pursuit are lost in patients with diffuse cerebellar cortical lesions (Dichgans et al. 1978). It seems likely, therefore, that

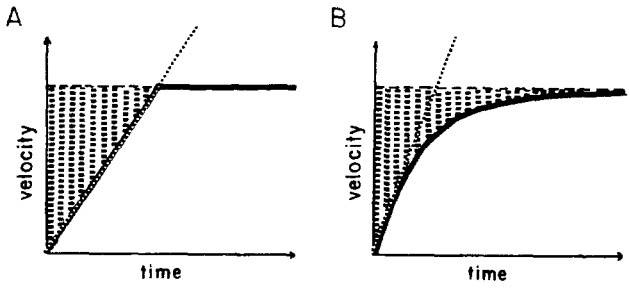


Fig. 13. Relationship between initial slope of linearly (**A**) and exponentially (**B**) rising velocity (*dotted lines*) given that the areas encompassed by the two envelopes are equal and their steady state values are the same. By our definition systems having these characteristics have the same time constant (Cohen et al. 1977). The slope in **B** is twice that in **A**. This relationship makes it possible to find the approximate value of E_s in the model which best simulates the data. E_s is the retinal slip velocity at which the system changes from positive to negative incremental gain

in humans as in monkeys, a major portion of the direct visual-oculomotor pathways mediating the rapid rise in OKN as well as pursuit are mediated through the flocculus and probably paraflocculus. Vestibular nystagmus is unaffected in humans with cerebellar cortical degeneration (Baloh et al. 1975).

In conclusion, although the flocculus is closely linked to the vestibular system, in the monkey its function is quite specific and appears related to production of rapid changes in eye velocity either during slow phases of OKN or pursuit. It probably also helps maintain the time constant of the final velocity to position integrator (Zee et al. 1981). It does not appear to cancel the VOR at the level of the vestibular nuclei, nor does it directly affect the dynamics of the velocity storage mechanism.

Appendix

In simulating OKN after flocculectomy, the model predicts an exponential rise in velocity to the steady state value x_{ss} with a time constant T_{RA}. Therefore:

$$x(t) = x_{ss}(1 - \exp -(t/T_{RA})) \quad \text{(A1)}$$

The initial acceleration a_I is given by:

$$a_I = \dot{x}|_{t=0} = x_{ss}/T_{RA} \quad \text{(A2)}$$

But using the definition of time constant derived in Cohen et al. (1977), the time constant T_{RA} of a function with an approximately linear rise from zero velocity to a steady state value is given by:

$$T_{RA} = \text{Total eye deviation}/x_{ss} = \tfrac{1}{2} x_{ss} D/x_{ss} \quad \text{(A3)}$$

$$T_{RA} = D/2 \quad \text{(A4)}$$

Substituting Eq A4 into A2 gives

$$a_I = 2 x_{ss}/D \quad \text{(A5)}$$

But the average acceleration a_A when the data are approximated by a straight line is given by:

$$a_A = x_{ss}/D \quad \text{(A6)}$$

Therefore, the initial acceleration a_I of an exponential having the same time constant as a linear function with acceleration a_A is given by:

$$a_I = 2 a_A \quad \text{(A7)}$$

In short, if the rising velocity profile of the data is linear as shown in Fig. 13A and the model response is exponential as shown in Fig. 13B, and both have the same shaded area and steady state velocity, then the initial slope, in B, i.e. the initial acceleration predicted by the model (dotted line), is twice that of the observed acceleration in A (dotted line).

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