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Optokinetic reflex in squirrel monkeys after long-term monocular deprivation

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Abstract

Horizontal optokinetic nystagmus (OKN) as well as neuronal response properties in the nucleus of the optic tract and the dorsal terminal nucleus of the accessory optic system (NOT-DTN) were investigated in three monocularly deprived squirrel monkeys. In two monkeys occlusion of one eye was performed at birth (early) and in the third after 7 weeks (late). In adulthood, in early deprived monkeys monocular horizontal OKN tested through the non-deprived eye was symmetrical and in no way different from normal, i.e. stimulation in the temporonasal and nasotemporal direction elicited equal and robust responses. OKN through the early occluded eye, however, was grossly abnormal with low gain and great variability in the consistency of nasotemporal and temporonasal slow phase eye movements. When in the late deprived monkey the non-deprived eye was occluded a strong spontaneous nystagmus developed despite the deprived eye viewing a stationary pattern. The slow phases were directed from nasal to temporal for the deprived eye. When tested through the non-deprived eye all neuronal responses of the NOT-DTN were normal. The deprived eye's influence on NOT-DTN neurons was extremely weak. No neuron with a moderate or even dominant input from the deprived eye was found after early deprivation. In the late deprived case the deficit was not as severe but still the non-deprived eye was clearly dominating the responses in all neurons tested. Velocity tuning of neurons tested through the non-deprived eye was normal and qualitatively corresponded well to slow phase eye velocity in response to equivalent retinal slip during OKN. Through the early deprived eye, however, velocity tuning was extremely poor. It was somewhat better through the late deprived eye. We suggest that the dramatic deterioration in the optokinetic reflex found after long-term monocular deprivation for the amblyopic eye is probably caused by the almost complete loss of retinal and cortical input driven by that eye to the NOT-DTN. These results are discussed in relation to our previous results in cats and reports in the literature for humans with occlusion amblyopia.

Introduction

Horizontal optokinetic nystagmus (OKN) when tested with one eye closed is stronger with temporonasal than with nasotemporal stimulus movement, i.e. is asymmetrical for the seeing eye in young infants (e.g. Atkinson, 1979; Naegele & Held, 1982) and kittens (Van Hof-Van Duin, 1978; Malach *et al*., 1981). In baby monkeys (Atkinson, 1979; Sireteanu *et al*., 1992; Distler *et al*., 1996) this asymmetry is very mild and highly variable. Monocular OKN becomes symmetrical, i.e. robust in both horizontal directions provided visual development is normal in these species. However, asymmetry exists throughout life following a number of early developmental abnormalities. Such abnormal conditions can be early monocular or binocular lid closure in animal experiments or dense cataracts from birth in one or both eyes in children, artificial or congenital strabismus and amblyopia (Malach *et al*., 1984; Markner & Hoffmann, 1985; Sparks *et al*., 1986; Behrens & Grüsser, 1988; Lewis *et al*., 1989; Reed *et al*., 1991; Aiello *et al*., 1994; Shawkat *et al*., 1995; Distler, 1996; Hoffmann *et al*., 1996).

The neuronal mechanisms underlying normal and abnormal development of monocular horizontal OKN are well understood for the cat. The pretectal nucleus of the optic tract and the dorsal terminal nucleus of the accessory optic system (NOT-DTN) contain the neurons which provide direction selective visual information from the retina and visual cortex to the oculomotor system (see Fig. 8). It has been shown that binocularly balanced responses of direction selective neurons in the NOT-DTN are critical for symmetrical OKN (Hoffmann, 1979, 1982; Cynader & Hoffmann, 1981; Grasse & Cynader, 1984, 1986, 1987; Hoffmann *et al*., 1996). Because each NOT-DTN in the cat codes only ipsiversive stimulus movement and at birth is primarily served by retinal fibres from the contralateral eye binocularity in the cortical projection is a prerequisite for the development of binocularity in the NOT-DTN and consequently for symmetry of OKN (Distler & Hoffmann, 1993). A failure in the development or a breakdown of binocular connections in the cortex is believed to be the primary cause for the loss of binocularity in the

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NOT-DTN and, following from it, for asymmetry in OKN. Monocular deprivation or large angle early onset strabismus maintain contralateral eye dominance in the NOT-DTN and therefore asymmetrical OKN in both eyes in the cat (Cynader & Harris, 1980; Cynader & Hoffmann, 1981; Hoffmann, 1983; Malach *et al*., 1984; Markner & Hoffmann, 1985; Grasse & Cynader, 1987; Distler & Hoffmann, 1996; Hoffmann *et al*., 1996).

In humans a high variability in the quality and quantity of the effects of deprivation and strabismus make a simple interpretation impossible (Schor, 1993). Children with dense cataracts in one eye from birth (Lewis *et al*., 1989) show asymmetrical OKN in both eyes similar to the results in monocularly deprived cats. In a recent study, Shawkat *et al*. (1995) could show, however, that only children with a non-profound monocular deprivation (MD) after early removed cataracts or corneal problems still allowing some though strongly impaired vision developed naso-to-temporal asymmetry and latent nystagmus for both eyes whereas children with profound MD due to unilateral congenital cataracts associated with hyperplastic primary vitreous or severe microphthalmus had a symmetric OKN for the intact eye and no OKN in the profoundly amblyopic (or blind) eye. The effects of early MD on OKN have been studied in macaque monkeys by Sparks *et al*. (1986) and in squirrel monkeys by Behrens & Grüsser (1988). In macaques, short-term early MD (7–14 days, onset 8–14 days after birth) leads to an asymmetrical OKN in the deprived but not in the non-deprived eye. Also long-term deprivation (18–26 months) leaves the non-deprived eye normal but renders the deprived eye totally unresponsive to optokinetic stimulation. In squirrel monkeys, long-term MD (1.5–9 years) also leaves the non-deprived eye normal, i.e. a symmetrical OKN is present in the adult, whereas the deprived eye shows lower gain and a high variability in response strength to the two directions of horizontal stimulus movement, i.e. OKN tested through the deprived eye remains immature and is sometimes symmetrical (Fig. 2A, B; Behrens, 1990). Thus, MD in subhuman primates leads to similar effects on OKN as profound MD in humans. These results also clearly demonstrate differences in the effects of MD by lid closure on development of the OKN system in cats and primates. In an attempt to find out whether these species differences are reflected at the neuronal level we measured the OKN and recorded from neurons in the NOT-DTN of three monocularly deprived squirrel monkeys and compared the results with our previous findings in cats. Results from both monkeys and cats will be related to findings in humans.

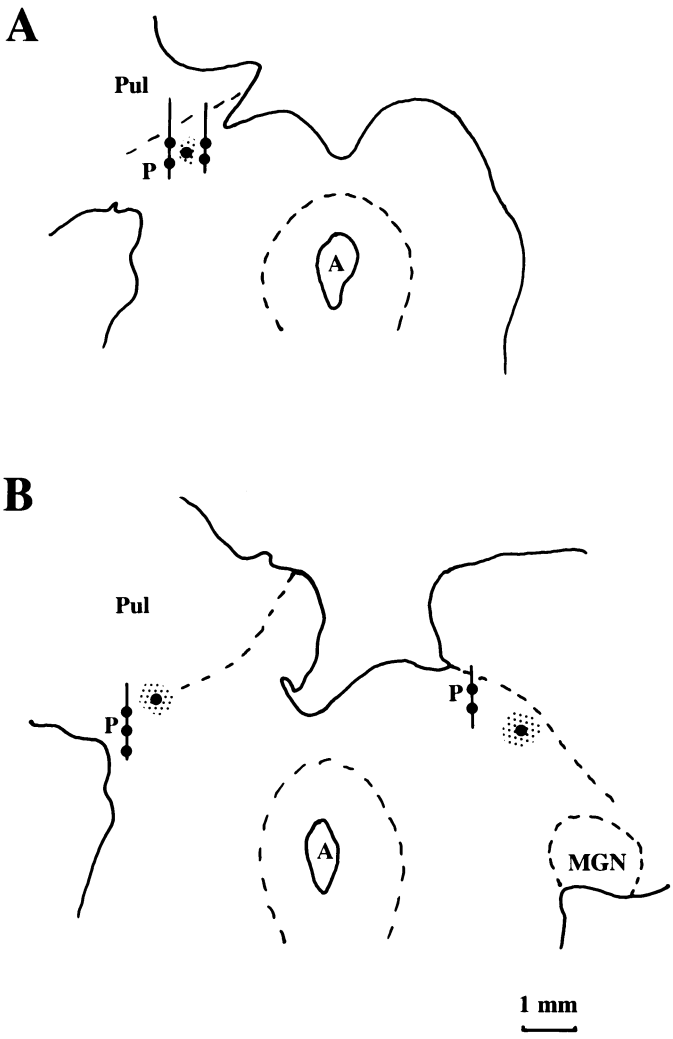

FIG. 1. Reconstruction of frontal sections through the pretectum of one of the early deprived monkeys (A) and of the late deprived monkey (B) demonstrating recording sites of retinal slip neurons in the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system. The straight lines are histologically identified penetration tracks. Black dots are recording sites of direction selective cells along these tracks as estimated from the depth reading on the microdrive. Shaded areas indicate the centres of physiologically controlled injection sites of neuronal tracers. A: aquaeductus cerebri, MGN: medial geniculate nucleus, P: penetration track, Pul: pulvinar. The scale bar represents 1 mm.

Materials and methods

Animals

Three squirrel monkeys, two females and one male were included in the present study. In two of the animals the lids of one eye were sutured on the day of birth under ketamine anaesthesia (25 mg/kg), in the third MD was introduced at the age of 7 weeks. After weaning from their mothers, the animals lived in a colony at the Freie Universität Berlin where the females produced several offspring during the next 12–16 years at which age the physiological experiments were conducted. The physiological data were compared with data from three normal squirrel monkeys in part published by Hoffmann & Distler (1986).

Behaviour

Approximately 1 week before the behavioural tests the lids of the deprived eye were opened under ketamine anaesthesia (25 mg/kg). Afterwards the eyes were treated with antibiotic ointment until the wounds were completely healed. For eye movement measurements the monkeys were seated in a primate chair with the head unfixed. As the animals were not chronically implanted the head could not be rigidly fixed. However, head movements were largely restricted by a padded collar. Eventually occurring head movements could be observed via an infra-red sensitive video camera. Measurements including any observable pursuit head movements were excluded from further analysis.

Optokinetic eye movements were recorded using electrooculography (EOG). During the measurements, the animals were placed in the centre of a circular arena 170 cm in diameter. The visual stimulus consisted of bright dots created by a planetarium projector mounted above the animal's head. The dots could move in clockwise and counterclockwise direction at velocities between 10°/s and 120°/s. EOG signals were recorded during 20-s periods via subcutaneous

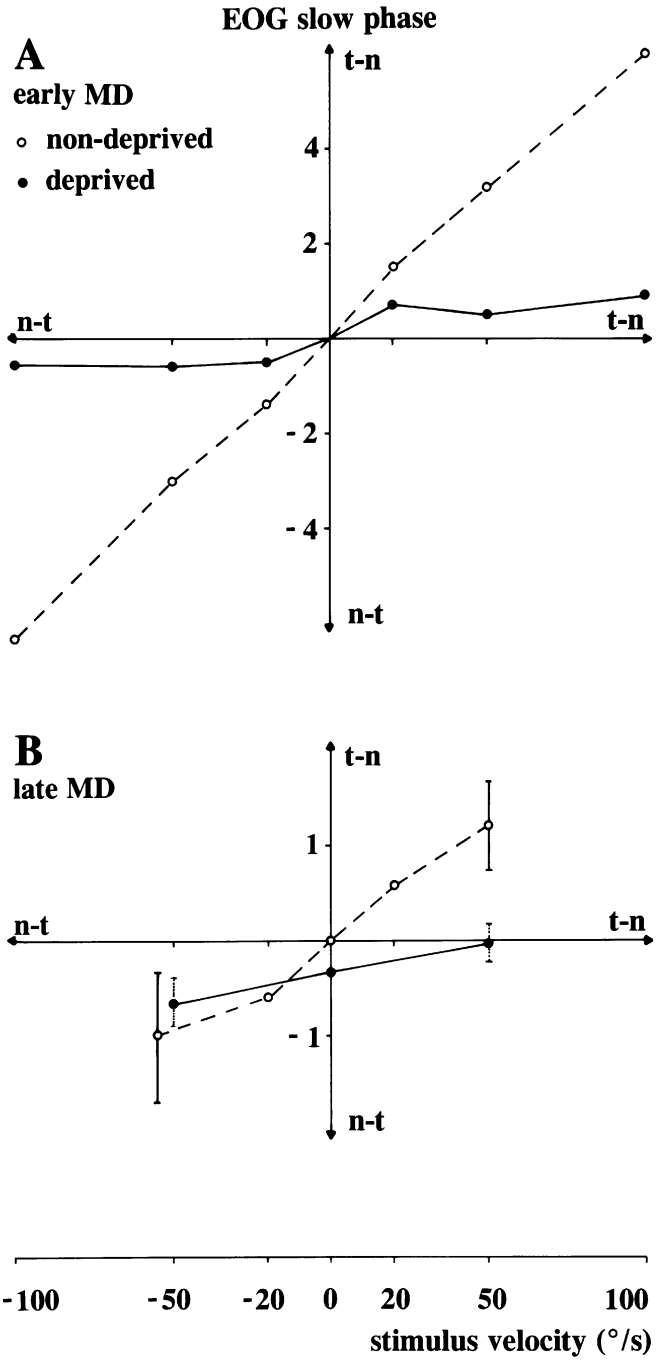

FIG. 2. Quality of slow phase eye movements during optokinetic stimulation in an early deprived (A) and a late deprived squirrel monkey (B). Stimulus velocity in temporonasal (t-n) direction is plotted to the right, in nasotemporal (n-t) direction to the left. Slow phases in t-n direction are given by positive electrooculography (EOG) voltage values plotted upwards, slow phases in the n-t direction by negative EOG voltage values plotted downwards. Abscissa: stimulus velocity (degrees per second), ordinate: EOG voltage signal during the slow phase of optokinetic nystagmus. Open circles and dashed lines represent data from the non-deprived eye, filled circles and continuous lines represent data from the deprived eye. Vertical solid lines in B indicate one standard deviation of measurements through the non-deprived eye, vertical dotted lines one standard deviation of measurements through the deprived eye. Values at 0 velocity correspond to eye movements with a stationary pattern. Note the spontaneous nystagmus with slow phases in the n-t direction while the non-deprived eye was covered in B.

bare chlorided tips of varnish-coated silver wires inserted bilaterally at the outer canthi of the eyes and connected to a DC-coupled EOG amplifier. This signal is valid only if eye movements are conjugate. We convinced ourselves of conjugacy during extensive observations of compensatory and saccadic eye movements during free head movements after opening the deprived eye. In our hands this method produced very stable recordings without significant drifts. In fact, even the signal amplitude from session to session was astonishingly stable. The amplified EOG voltage signals were fed into an interface board of a PC for on-line display of uncalibrated eye position and off-line differentiation for a qualitative estimate of eye velocity to be compared for different velocities of visual stimulation. We calculated the median of the distribution of slopes of the EOG voltage in the direction of stimulus movement in 10 ms time windows as an equivalent of eye velocity during the slow phases of OKN.

Electrophysiology

For single cell recordings the monkeys were initially anaesthetized with ketamine, intubated and fixed in a stereotaxic head holder. They were artificially ventilated with a 2 : 1 mixture of N_2O and carbogen (95% O_2, 5% CO_2) including 0.2–0.5% fluorane to maintain a sufficient level of anaesthesia. After additional local anaesthesia with prilocainhydrochloride (Xylonest^R) the skin overlying the skull was cut and a craniotomy performed to allow access to the midbrain and pretectum. After surgery the animals were paralysed with alcuronium chloride (Alloferin^R). Body temperature and end-tidal CO_2 were monitored and kept within physiological ranges. In addition, the state of anaesthesia was controlled with electrocardiography. If the heart rate raised upon strong somatosensory stimulation the level of fluorane was increased. Because the monkeys displayed large angle esotropia after lid-opening (see also Tusa *et al.*, 1991), the deviating deprived eye was pulled into a roughly normal position by a string attached to the temporal corner of the conjunctiva. Corneae were protected and refractive errors were corrected by contact lenses chosen with a refractrometer (Rodenstock, Munich, Germany).

Single cell activity was recorded with tungsten-in-glass microelectrodes. Spikes were conventionally processed and their rates analysed from peri-stimulus–time histograms (PSTHs) representing the activity during at least five to 10 repetitions of the stimulus. As in other mammals, the NOT-DTN in squirrel monkeys lies lateral and anterior to the foveal representation in the superior colliculus. Figure 1 presents recording sites as well as injection sites of neuronal tracers placed in the NOT-DTN under physiological control. Retinal slip neurons were recorded over a large proportion of the nucleus' posterolateral to anteromedial extent. As in macaques, no regional differences in the response properties of retinal slip cells in the NOT-DTN to the stimuli used were found (Hoffmann *et al.*, 1988; Hoffmann & Distler, 1989). Visual stimulation consisted of large area random dot patterns which could be moved via an *X–Y* double mirror system at various velocities along a linear horizontal path or along a circular path thus covering 360° of stimulus direction in one cycle. This latter method allows to measure a continuous directional tuning (DT) curve in a single measurement instead of reconstructing the DT from several PSTHs during linear stimulus movement in different directions (Schoppmann & Hoffmann, 1976; Hoffmann & Distler, 1989). Several response parameters were analysed (Table 1).

Ocular dominance (OD)

The influence of the two eyes upon individual NOT-DTN cells was investigated by quantitative comparison of the neuronal response during monocular stimulation of the contra- (c) and the ipsilateral (i)

TABLE 1. Summary of cells and parameters tested

	Early MD	Late MD	
	contra	contra	ipsi
No. recorded	47	22	18
OD	43	21	16
v-tune	13	5	8
DS	46	22	18
DT	4	3	–

OD: ocular dominance, v-tune: velocity tuning, DS: direction selectivity, DT: directional tuning.

eye: OD = (*c*–*i*)/*m*, with *m* being the maximal response. Based on these OD values, the cells were split into five OD groups. Group 1 cells are exclusively activated by the contralateral (OD > 0.9), group 5 cells by the ipsilateral eye (OD < – 0.9). Group 2 (group 4) cells are dominated by the contralateral (ipsilateral) eye, but receive an additional weaker input from the ipsilateral (contralateral) eye (0.3 < OD < 0.9 and – 0.9 < OD < – 0.3, respectively). Group 3 cells receive balanced input from both eyes (– 0.3 < OD < 0.3). The OD was generally determined at a stimulus velocity of 12.8°/s. Of 80 neurons tested, in seven cells OD varied with stimulus velocity. In these cases, OD values were averaged and then entered in the OD groups defined above.

Velocity tuning

To assess the neuron's response to various stimulus velocities, we plotted the activity during stimulation in the preferred, opposite to the preferred (null) direction, plus the neuronal modulation, i.e. the difference of neuronal activity during stimulus movement in the preferred and the null direction derived from individual PSTHs vs. stimulus velocity.

Direction selectivity

The direction selectivity (DS) was estimated by comparing the neuronal response to linear stimulation in the preferred (*p*) and the null (*n*) direction: DS = 1–*n*/*p*. Highly direction selective cells are characterized by DS values close to 1, totally non-selective neurons are indicated by a DS index of 0.

Directional tuning

The neurons' preferred direction was determined by finding the maximum in a Gaussian distribution fitted to the discharge frequency histogram. The sharpness of the DT of the cells was further estimated by calculating the range around the preferred direction in which 50% of the overall discharged spikes occurred (50% range).

Results

Optokinetic nystagmus

Prior to neurophysiological recordings a qualitative assessment of the OKN in one monkey with early onset MD revealed a symmetrical OKN through the non-deprived eye (Fig. 2A) resembling control data from Behrens & Grüsser (1988) and, compared with that, an extremely weak but also rather symmetrical OKN through the deprived eye. Another monkey had a later onset lid closure (7 weeks after birth). The OKN in this animal again appeared normal in the non-deprived eye. When only the deprived eye was open a strong spontaneous nystagmus with nasotemporal slow phases for this eye developed

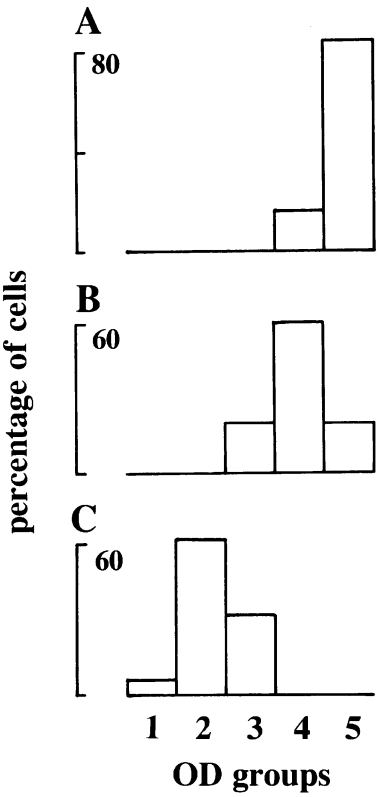

FIG. 3. (A) Ocular dominance distribution of retinal slip cells in the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN) contralateral to the early deprived eye in two squirrel monkeys, (B) in the NOT-DTN contralateral and (C) ipsilateral to the late deprived eye in one squirrel monkey. Ordinate: percentage of cells, abscissa: ocular dominance groups (OD) 1–5. OD1 = only input from the contralateral eye, OD2 = stronger input from the contralateral than from the ipsilateral eye, OD3 = equally strong input from the contralateral and the ipsilateral eye, OD4 = stronger input from the ipsilateral than from the contralateral eye, OD5 = only input from the ipsilateral eye.

even with a stationary pattern present. A stimulus driven OKN with slow phases in a temporonasal direction could not be elicited. Instead it was overridden by the spontaneous nystagmus (Fig. 2B). At a stimulus velocity of about 50°/s the spontaneous nystagmus was counterbalanced and no consistent slow phases appeared in any direction. Higher velocities were less effective and spontaneous nystagmus could again develop. With the uncalibrated EOG measurements employed in this study we cannot provide information about possibly occurring reductions in gain when the non-deprived eye is stimulated as compared with normal animals.

Ocular dominance

The most striking result of the neurophysiological study in the two early deprived animals was the almost complete loss of connections from the deprived eye to the neurons in the NOT-DTN. This result becomes very obvious when the OD distribution of neurons in the NOT-DTN contralateral to the deprived eye (Fig. 3A) is observed. Normally in primates the two eyes are more or less equally effective in driving NOT-DTN cells with a high preponderance of binocular cells in OD groups 2 and 3 (own unpublished qualitative observations in three normal squirrel monkeys and published quantitative assessment in macaques, Hoffmann & Distler, 1989). After its deprivation only a weak input from the normally slightly more effective contralat-

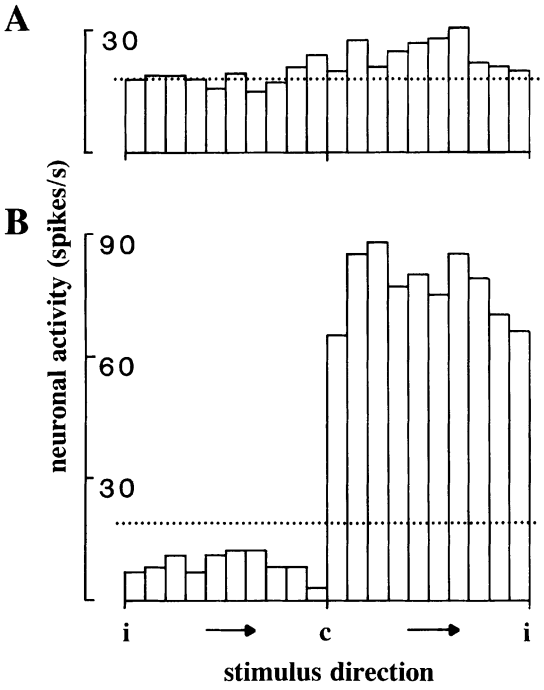

FIG. 4. Peri-stimulus-time-histograms of the responses of a retinal slip neuron in an early deprived animal during monocular stimulation of the deprived (A) and the non-deprived eye (B) by a whole field random dot pattern. Ordinate: neuronal activity (spikes/s), abscissa: stimulus direction from ipsilateral (i) towards contralateral (c) to the recording site and (second half) back to ipsilateral. Dotted lines indicate the spontaneous activity of the neuron.

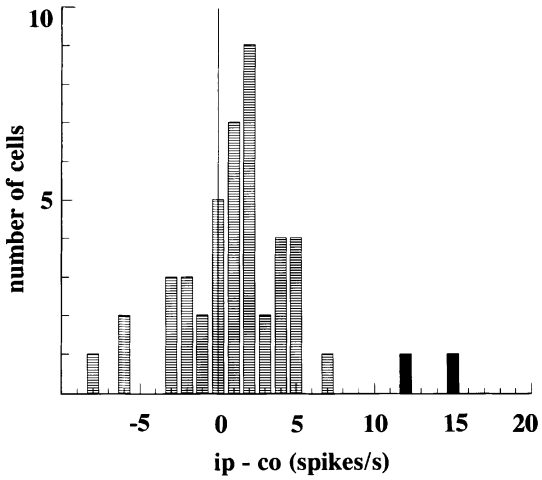

FIG. 5. Frequency distribution of the difference in the mean discharge rate during stimulation of the deprived eye in the ipsiversive (ip) and contraversive direction (co) of 45 nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system cells in early deprived monkeys. Solid black bars represent binocular neurons (OD4). Ordinate: number of cells, abscissa: activity difference (spikes/s).

eral eye was maintained in 16% of the cells (OD group 4). No binocularly balanced (OD group 3) or contralaterally dominated (OD groups 1 and 2) neurons existed. By contrast, 84% of the neurons were exclusively driven by the non-deprived, ipsilateral eye (OD group 5). This is completely different from our earlier results in cats (see below, Hoffmann, 1983).

Also the animal with late onset MD exhibited a significant shift in OD towards the non-deprived eye (Fig. 3B,C). Starting the deprivation not before 7 weeks after birth spared part of the connections of the deprived eye in the contralateral (Fig. 3B) as well as ipsilateral NOT-DTN (Fig. 3C). Binocularly balanced neurons (group 3) were still a minority. Cells dominated by the deprived eye similarly did not exist after late onset deprivation.

Direction selectivity

If a neuron in the NOT-DTN of the early deprived monkeys was direction selective through the non-deprived eye and could be modulated appreciably through the deprived eye it was selective for the ipsiversive direction through either eye (to the left in the left NOT-DTN and to the right in the right NOT-DTN). The DS indices for the non-deprived eye typically ranged from 0.3 to 1.0. There was no significant difference between these values in early or late deprived animals (early: DS = 0.628 ± 0.187, $n = 44$; late: DS = 0.695 ± 0.212, $n = 40$). These values correspond well to data from normal squirrel monkeys (DS = 0.76 ± 0.23, $n = 4$) and normal macaques (DS = 0.744 ± 0.209, $n = 94$). The weakness of direction selective responses elicited through the early deprived eye by a random dot pattern moving horizontally first contraversively and then ipsiversively is shown for one neuron in Fig. 4(A) in comparison with the response to the same test in the same neuron through the non-deprived eye (Fig. 4B). This was one of the rare cells in OD group 4 (Fig. 3A). In order to get a measure of the ability of the population of neurons in the NOT-DTN to code the direction of stimulus movement when stimulated through the contralateral deprived eye we calculated the population response difference for the two horizontal stimulus directions. The activity increase in the ipsiversive (preferred) against the contraversive direction of the population of NOT-DTN neurons is on average only 2 spikes/s which is nevertheless significantly different from 0 (t-test; $P < 0.02$). In the frequency distribution of these differences (ip-co; Fig. 5) measured in 45 direction selective NOT-DTN neurons (as classified by stimulating the non-deprived eye) it becomes apparent that some neurons seem to respond even stronger in the contraversive (normally null direction). These neurons belonged, however, to OD group 5 indicating that this 'response' was within the fluctuations of spontaneous activity. Only two of the neurons included in this analysis belonged to OD group 4 (filled bars in Fig. 5).

An assessment of the DT of NOT-DTN neurons through the deprived eye was unachievable due to low response strength and high variability. The tuning width through the non-deprived eye seemed to be in the normal range as determined by circular stimulus movement (see Methods) in seven cells (50% range 60°–163°, mean 108.8° ± 38.2; normal macaques: 50% range 74°–120°, mean 89.8° ± 17.6). Neither in the early nor in the late deprived monkeys did we find NOT-DTN neurons with clearly inverted (contraversive) direction specificity.

Velocity tuning

The velocity tuning of NOT-DTN cells when tested through the early deprived eye was again quite abnormal. The neuronal modulation between preferred and null direction at the optimal velocity at the population level, i.e. averaged over all cells, was less than 10% of the maximal activity whereas when tested through the non-deprived eye it was mostly above 50% which is comparable with normal (compare Fig. 6A,B and E). Following deprivation onset at 7 weeks after birth the velocity tuning of NOT-DTN neurons driven by the deprived eye was somewhat better than after deprivation onset at

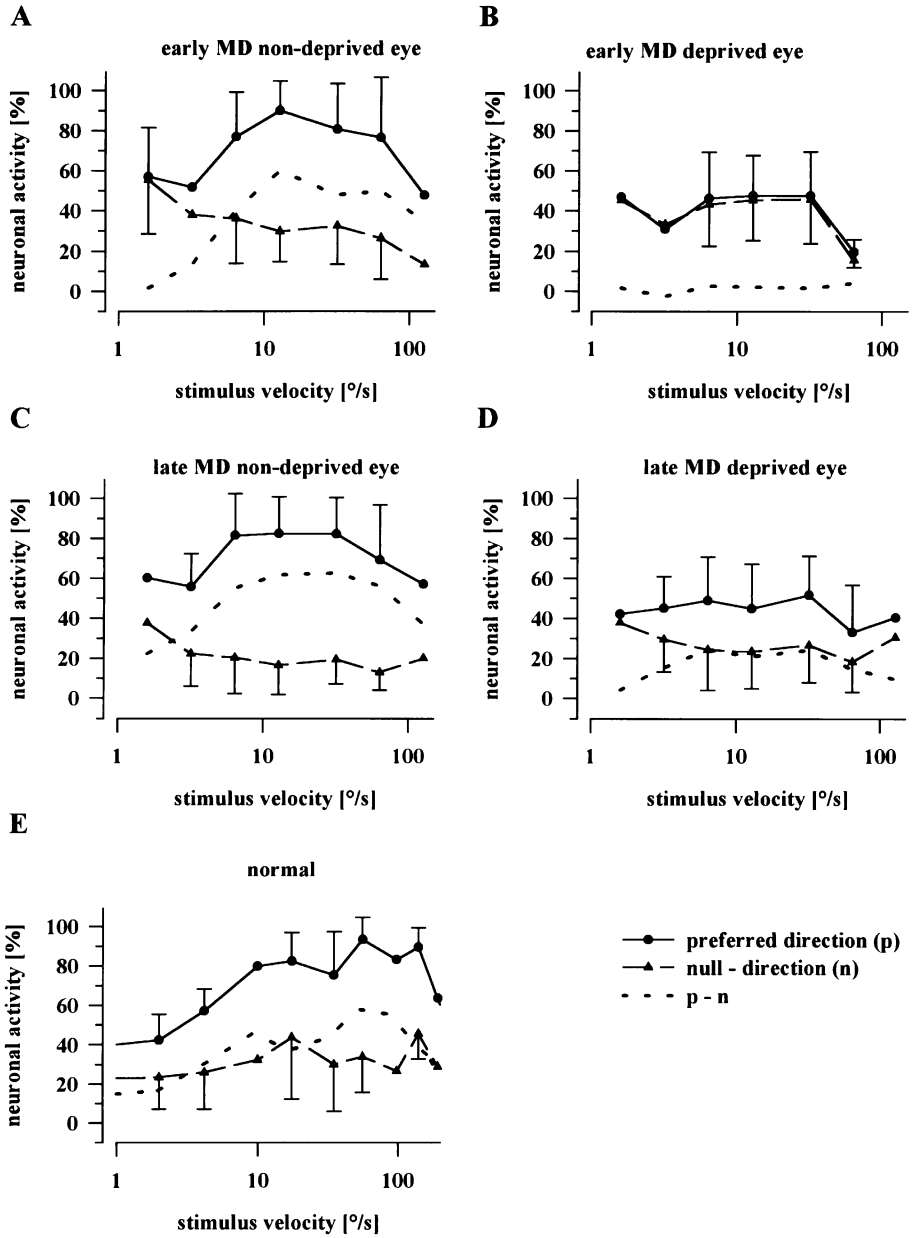

FIG. 6. Average velocity tuning curves measured through the non-deprived (A, C) and the deprived eye (B, D) of early (A, B) and late deprived monkeys (C, D) compared with data from normal squirrel monkeys (E). Filled circles and continuous lines: response to stimulation in preferred direction (p), filled triangles and broken lines: response to stimulation in null direction (n), dotted lines: neuronal modulation (p-n). Vertical bars indicate one standard deviation. Ordinate: mean relative neuronal activity in percentage (maximal activity of each neuron was normalized to 100% before pooling), abscissa: stimulus velocity (degrees per second).

birth. Over most of the velocity range tested the modulation between preferred and null direction was about 20% whereas for the non-deprived eye it was again clearly above 50% (Fig. 6C,D). Thus, also the tuning of the velocity response was less deteriorated after late onset MD in comparison with early onset MD (compare Fig. 6B,D).

Discussion

Long-term MD in squirrel monkeys leads to severe deficits in the optokinetic reflex and to an almost complete loss of input from the deprived eye to the NOT-DTN. Surprisingly, the deprivation effects on the neuronal responses in the NOT-DTN and on symmetry of monocularly elicited horizontal OKN through the non-deprived eye are negligible. In the animals we tested, OKN elicited through the deprived eye was extremely weak but symmetrical in one animal and completely biased in the nasotemporal direction by a strong spontaneous nystagmus in the other. From the same group of deprived animals Behrens & Grüsser (1988) reported for another animal OKN of the deprived eye to be stronger during temporonasal than nasotemporal stimulus movement like in MD cats and humans with unilateral cataracts. However, Behrens (1990) reports in his unpublished thesis that another three monocularly deprived squirrel monkeys tested had weak symmetrical OKN or OKN even stronger in the nasotemporal direction (Behrens, 1990). He also observed

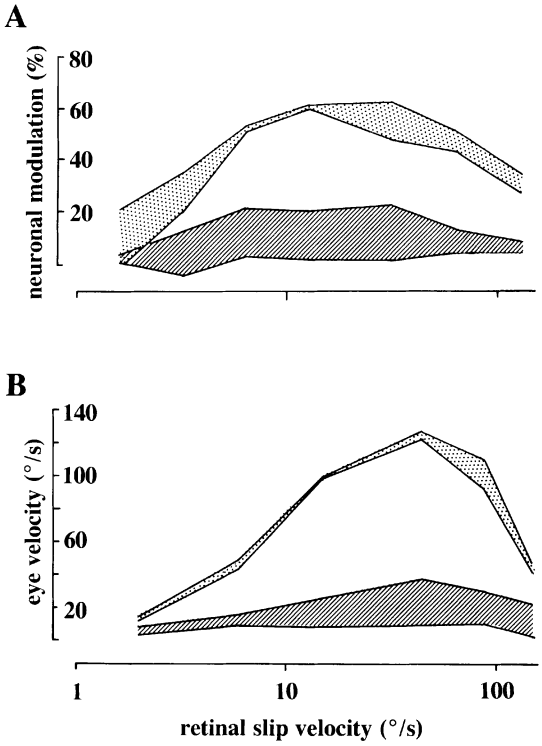

FIG. 7. (A) Range of neuronal modulation (%) (ordinate) plotted vs. retinal slip velocity (degrees per second) (abscissa) during stimulation of the non-deprived (dotted area) and the deprived (hatched area) eye. Data from early and late deprived animals are combined. (B) Range of eye velocity (degrees per second) (ordinate) plotted over retinal slip velocity (degrees per second) (abscissa) during stimulation of the non-deprived (dotted area) and deprived eye (hatched area). Data are taken from the study by Behrens & Grüsser (1988).

spontaneous nystagmus and nystagmus opposite to the stimulus direction in one animal comparable with our late deprived animal. Thus, MD has strong but highly variable effects on the OKN elicited through the deprived eye.

Can we attempt to relate the neurophysiologically derived directional and velocity tuning curves of neurons in the NOT-DTN to the slow phase eye velocity during optokinetic stimulation in MD squirrel monkeys? Comparing the quantitative OKN slow phase velocity measured with the search coil method as published by Behrens & Grüsser (1988) with the neuronal modulation of the NOT-DTN population of our early and late MD cases we can observe a corresponding drop in eye velocity and in neuronal modulation for the deprived eye compared with the non-deprived eye over the retinal slip range tested (Fig. 7). The two curves do not peak at the same velocities which may be explained by the fact that retinal slip during OKN was assessed from the difference between stimulus and eye velocities in closed loop measurements while the neuronal modulation was measured in anaesthetized animals with the eyes paralysed. The OKN testing by Behrens & Grüsser (1988) had been done in 1.5–9 year old animals deprived within the first 2 weeks after birth whereas we recorded from animals deprived at birth or 7 weeks after birth at the age of 12–16 years. Nothing is known so far about the effects of different lengths of visual experience before eye closure during the first 2 months after birth or different durations of deprivation (1.5 vs. 12–16 years) on OKN and the response properties of NOT-DTN neurons in monkeys. Despite these open questions we suggest that the observed abnormalities of OKN are to a large extent a consequence of the deteriorated neuronal responses elicited through the deprived eye in the NOT-DTN. Unfortunately, we have no neurophysiological data to explain the spontaneous nystagmus in the late deprived case. We did not observe an inversion of the preferred directions or an activity bias towards the right NOT-DTN to drive OKN slow phases from left to right even against the stimulus direction presented to the deprived eye. The correct but too weak directional output of the NOT-DTN seems to be just added to the ongoing nystagmus. Therefore, we have to assume that the cause for spontaneous nystagmus is downstream from the NOT-DTN in this animal.

If we compare the results from MD monkeys with those from MD cats quite a difference emerges. In MD cats there is a marked asymmetry in the OKN of the non-deprived eye (Van Hof-Van Duin, 1978; Malach *et al*., 1984; Markner & Hoffmann, 1985), which did not exist in squirrel monkeys (this study; Behrens & Grüsser, 1988) or in macaque monkeys (Sparks *et al*., 1986). This asymmetry in MD cats corresponds to a non-functional cortical input of the non-deprived eye to the ipsilateral NOT-DTN (Hoffmann, 1983; Grasse & Cynader, 1987). We suggest that the major difference in the effects of MD on the monkeys' and cats' optokinetic system lies in the loss of functional connections of the non-deprived eye to the ipsilateral NOT-DTN in MD cats, whereas in primates, these connections seem unaffected and highly dominant. In the cat, each eye establishes its connections to the ipsilateral NOT-DTN almost exclusively via the cortex (Distler & Hoffmann, 1993). This development is disrupted in MD cats for both eyes (loss of cortical connections driven by the deprived eye and failure of the corticofugal axons to establish connections in the ipsilateral NOT-DTN for the non-deprived eye) whereas in monkeys a stronger (compared with cats) direct ipsilateral retinal projection to the NOT-DTN exists at birth (Kourouyan & Horton, 1997) and may help the non-deprived eye to establish its cortical projection to the ipsilateral NOT-DTN (Fig. 8; see also figure 10 in Hoffmann, 1983). Thus there clearly is a species difference between cats and primates in the functional organization of the visual pathway leading to OKN.

Data from the study of children with dense cataracts from birth by Lewis *et al.* (1989) as well as the data of the non-profoundly deprived group of patients described by Shawkat *et al.* (1995) demonstrate very clearly that after removal of the cataract the pattern deprived eye shows a stronger OKN to temporonasal stimulus movement and, more importantly, the non-deprived eye did so all the time. These results differ from the observations in MD monkeys whose OKN instead resembles OKN of patients in the profound group of Shawkat *et al*. (1995). In these patients, OKN was mostly absent when tested through the deprived eye but symmetrical when elicited via the unaffected eye.

Figure 8 summarizes what we know about the connectivity in the optokinetic system of normal monkeys and the modifications caused by MD. Contrary to the cat, the retinal input to the NOT-DTN in the monkey includes a substantial though still inferior ipsilateral retinal projection (Ballas *et al*., 1981; Hutchins & Weber, 1985; Kourouyan & Horton, 1997). It is generally accepted that at sites of binocular competition MD puts the deprived eye's functional projections at a disadvantage. In the case of the cat, the almost totally crossed retinal projection to the NOT-DTN can survive deprivation because it does not have to compete in an early stage of development with a potent ipsilateral input at the same postsynaptic site. The deprived eye may even prevent proper functional connections between the visual cortex and NOT-DTN cells by creating a retinal driven spontaneous postsynaptic activity not matching the visually modulated activity in the corticofugal fibres driven via the ipsilateral non-deprived eye (Hoffmann, 1987). In the monkey, the ipsilateral retinal input to the NOT-DTN, although weaker at birth, could be strong enough to win against the input from the contralateral eye if the latter is deprived

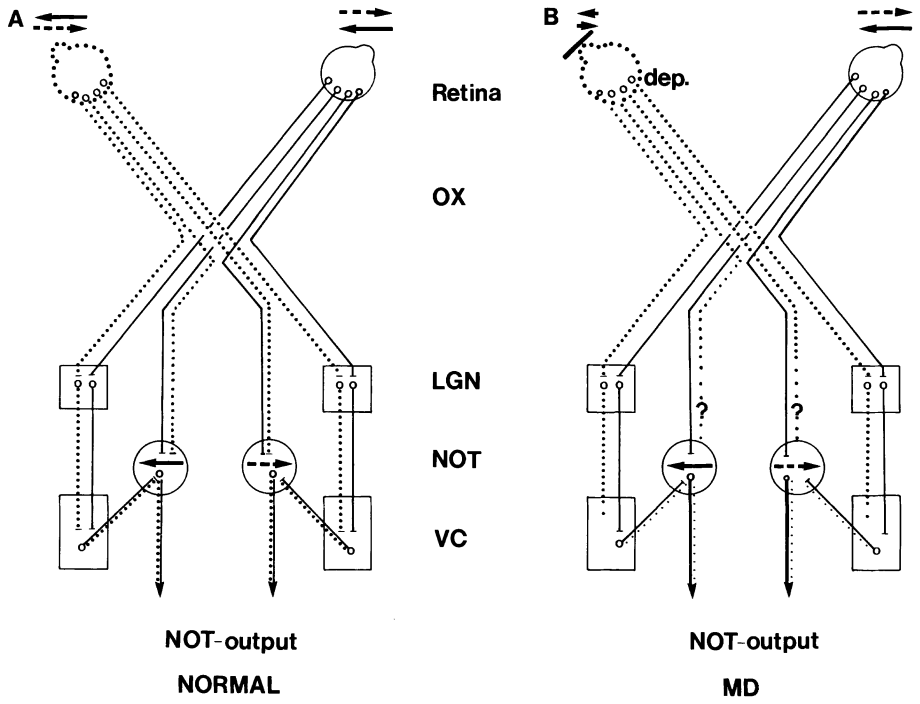

FIG. 8. Diagrams of the visual input to the optokinetic system in normal (A) and monocularly deprived (MD) monkeys (B). Input from the left eye is presented by dotted lines, input from the right eye by continuous lines. The left eye in (B) was deprived (dep). We assume retinal input from each eye and strong binocular cortical input to reach either nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN) in normal animals. In the deprived animal both the retinal as well as the cortical input driven by the deprived eye are strongly reduced (?between deprived retina and NOT, thin dotted line between cortex and NOT). This leads to a very weak NOT-output signal to drive optokinetic nystagmus (OKN) by the deprived eye (thin dotted line). Slow phases during OKN to the left (continuous arrows) and to the right (interrupted arrows) as indicated by the arrows in front of the eyes are coded by the left and right NOT-DTN, respectively. Short arrows in front of the deprived eye indicate low gain nystagmus.

of visual stimulation from birth onwards. It follows that the cortical input driven by the ipsilateral non-deprived eye then matches the retinal input from the same eye and can also connect to the NOT-DTN neurons. Owing to the competitive pressure from the non-deprived cortical and retinal terminals the deprived retinal terminals in both NOT-DTNs are strongly reduced as they are in the geniculo-cortical system. This would explain why in monkeys after long-term deprivation OKN cannot be elicited at all or shows extremely low gain and variable symmetry through the deprived eye. We nevertheless could anatomically demonstrate the retinal input from the deprived eye to the ipsilateral and contralateral pretectum by anterograde transport of horseradish peroxidase (Brockmann, Distler and Hoffmann, unpublished). The functional connections of the non-deprived eye to the contralateral as well as the ipsilateral NOT-DTN lead to symmetrical OKN through this eye. This situation would correspond to the findings in humans with profound deprivation (Shawkat *et al*., 1995). The retinal input to the NOT-DTN in monkeys is already much weaker than in the cat (Hoffmann *et al*., 1988). This trend may be even more manifested in humans so that in adulthood the OKN system would be under almost exclusive cortical control (Braddick *et al*., 1992; Braddick, 1996; Tychsen, 1996). The question, however, remains why in the human group with non-profound deprivation an asymmetrical OKN develops in the unaffected eye. Such non-profound deprivation conditions have not been defined for monkeys yet but we would expect the outcome of such conditions to be a breakdown of binocularity bilaterally in the NOT-DTNs previously reported for strabismic cats (Cynader & Hoffmann, 1981) and monkeys (Distler, 1996).

Conclusions

First, there is a species difference between monkeys and cats in the effects of early lid closure on the optokinetic system. In most cats ipsilateral functional connections of both eyes to the optokinetic system are impaired. In monkeys, the functional connections of only the deprived eye are severely impaired whereas those of the non-deprived eye remain normal.

Second, our findings in MD squirrel monkeys can explain the changes in OKN described for humans with profound MD.

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Abbreviations

DS	direction selectivity
DT	directional tuning
EOG	electrooculography
m	maximal response
MD	monocular deprivation
MGN	medial geniculate nucleus
n	null-direction
NOT-DTN	nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system
OD	ocular dominance
OKN	optokinetic nystagmus

p	preferred direction
P	penetration track
PSTH	peri-stimulus-time-histogram

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