Development of the Optokinetic Response in Macaques

A Comparison with Cat and Man

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ABSTRACT: In macaque monkeys, an optokinetic response (OKR) can be elicited monocularly both in temporonasal and, albeit weaker, in nasotemporal direction very early after birth. The further maturation of equal strengths of OKR in both directions depends on stimulus velocity: at low-stimulus velocities (10–20°/s) symmetry is reached at 3–4 weeks of age, at higher-stimulus velocities (40–80°/s) it is reached only at 4–5 months of age. Retinal slip neurons in the NOT-DTN are direction selective for ipsiversive stimulus movement shortly after birth. Most of these neurons receive input from both eyes; many are dominated by the contralateral eye. Electrophysiological and neuroanatomical evidence suggests that the cortical input to the NOT-DTN starts to become functional by postnatal day 14, at the latest. Based on these behavioral and physiological data, as well as on comparison with data from kittens and human infants, we hypothesize that the very early monocularly elicited bidirectional optokinetic response is due to the direct retinal input from both eyes to the NOT-DTN. As the cortical projection matures, it gains more and more influence upon the response properties of retinal slip neurons in the NOT-DTN, and the retinal influence gradually decreases.

KEYWORDS: optokinetic nystagmus; monkey; cat; man; cortical input; NOT-DTN

NEURONAL SUBSTRATE OF THE OPTOKINETIC REFLEX

In all mammals investigated thus far, the neuronal substrate underlying the optokinetic response is very similar (FIG. 1). The visuomotor interface for this stabilizing reflex is formed by neurons in the nucleus of the optic tract and the dorsal terminal nucleus of the accessory optic system, which form a functional entity, the NOT-DTN. These retinal slip neurons in the NOT-DTN code for the retinal velocity error signal, i.e., the difference between stimulus and eye velocity. The retinal slip neurons are characterized by their strong selectivity for ipsiversive stimulus movement; i.e., neurons in the left NOT-DTN prefer movement to the left and vice versa. In non-

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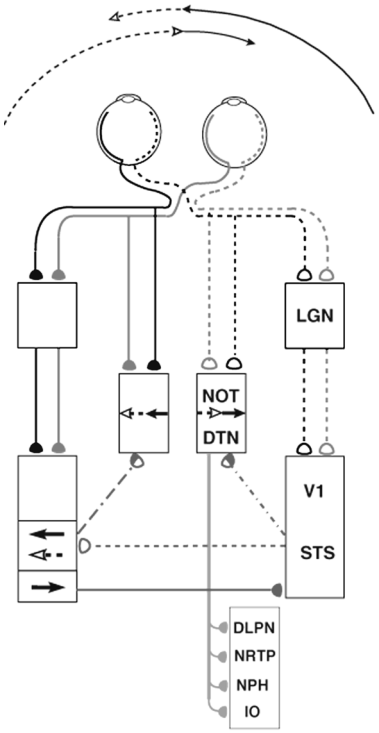

FIGURE 1. Depicted is the neuronal pathway underlying the horizontal optokinetic reaction in mammals, especially in primates. Projections of the left eye are shown in *black*; those of the right eye in *light grey*. Presumably binocular callosal and corticofugal projections are shown in *dark grey*. *Continuous lines* indicate the representation of the right, and *broken lines* the representation of the left visual hemifield. *Arrows* indicate the direction of stimulus movement represented in the various areas of the pathway. For further explanation see text. DLPN: dorsolateral pontine nucleus; IO: inferior olive; LGN: lateral geniculate nucleus; NOT-DTN: nucleus of the optic tract and dorsal terminal nucleus; NPH: nucleus prepositus hypoglossi; NRTP: nucleus reticularis tegmenti pontis; STS: motion sensitive areas in the superior temporal sulcus; V1: primary visual cortex.

primates, the NOT-DTN receives direct retinal input predominantly from the contralateral eye. Due to the distinct retinal decussation pattern, in primates this retinal projection is much more bilateral, the ipsilateral projection reaching about 40% of the contralateral projection.[1] This bilateral retinal projection is present at birth.[2] Experiments in wallabies strongly indicate that the retina imprints the behaviorally relevant direction selectivity on the retinal slip neurons: rotation of the anlage of the eye causes a corresponding rotation of the preferred direction of retinal slip neurons. Consequently, horizontal OKR can then best be elicited by the "old" temporonasal direction, i.e., downward stimulation after a 90° counterclockwise rotation of the anlage.[3] In all animals investigated (turtle,[4] rabbit,[5] cat[6]), it was shown that the retinal input to the accessory optic system is derived from direction-selective ganglion cells and, even though it has yet to be shown, it is assumed that this is also true for primates.

In addition to the retinal input, retinal slip neurons receive input from various cortical areas (e.g., rat,[7] guinea pig,[8] cat,[9] monkey[10,11]). In monkey, the main cortical input originates from area MT followed by V1, V2, and V3.[12] Lesion studies indicate that the cortical input to the NOT-DTN is responsible for the binocularity and response to high-stimulus velocities in retinal slip neurons at least in non-primates and for symmetry of OKR in both non-primates and primates (e.g., Refs. 13–17).

Retinal slip neurons project to the dorsal cap of the inferior olive, to the nucleus prepositus hypoglossi, the nucleus reticularis tegmenti pontis, and the dorsolateral

pontine nucleus. The information is then transmitted to the vestibular nuclei and via climbing fibers to the flocculus of the cerebellum. Projections of the above structures to the nucleus oculomotorius, nucleus abducens, and nucleus trochlearis innervating the extraocular muscles close the loop.[18–21]

DEVELOPMENT OF THE OPTOKINETIC SYSTEM IN CAT

In cat, OKR can first be elicited reliably at around postnatal day P18 (FIG. 2). During monocular stimulation, only temporonasal stimulus movement is efficient in driving stabilizing eye movements. Only at about 4 weeks of age (P30) OKR can be elicited for the first time also in the nasotemporal direction. During further maturation, nasotemporal OKR becomes stronger so that in the adult cat OKR is almost symmetrical. [22,23]

Electrophysiological recordings in the NOT-DTN of kittens of various ages revealed that in 3-week-old animals retinal slip neurons are already direction selective for ipsiversive stimulus movement, but their stimulus-driven as well as their spontaneous activity is significantly lower than in adults. When tested at different stimulus velocities, the velocity-tuning curve is relatively flat with an optimum around 10°/s. Most important perhaps is the fact that almost all retinal slip neurons (83%) are ex-

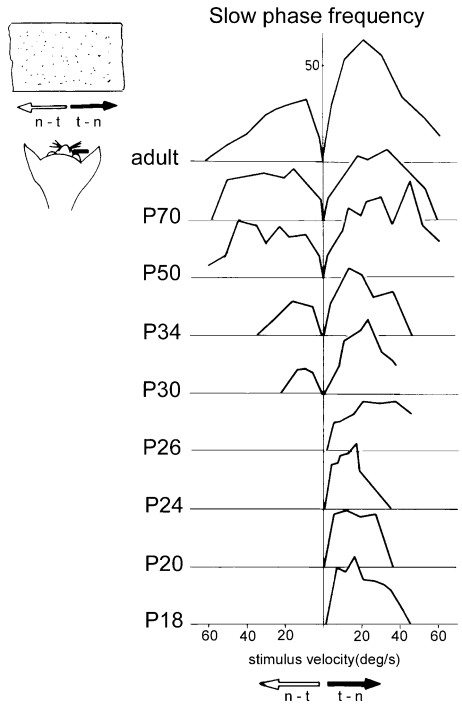

FIGURE 2. Slow-phase frequency of monocular horizontal OKR (*ordinate*) during stimulation in temporonasal (*right*) and nasotemporal (*left*) direction at various stimulus velocities (*abscissa*). The graphs represent the optokinetic reaction at various ages ranging from postnatal day 18 (P18) to adulthood (Meyer-Koll and Hoffmann, unpublished observation).

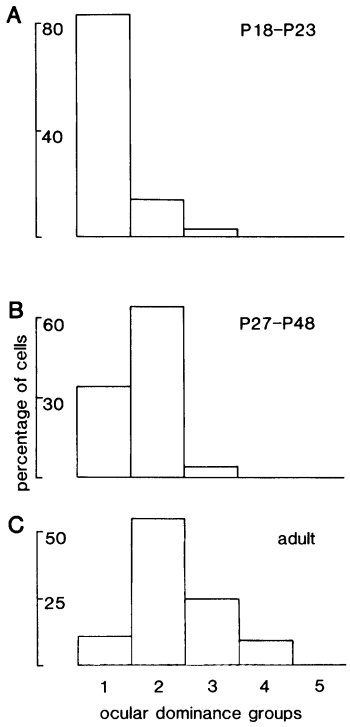

FIGURE 3. Ocular dominance distribution of retinal slip neurons in P18–P23 kittens (**A**), in P27–P48 kittens (**B**), and adult cats (**C**). *Ordinate*: percentage of cells; *abscissa*: ocular dominance groups. Neurons in group 1 (5) are exclusively activated by the contralateral (ipsilateral) eye; neurons in group 2 (4) are dominated by the contralateral (ipsilateral) eye but receive additional input from the ipsilateral (contralateral) eye; and neurons in group 3 are equally influenced by both eyes.

clusively activated by the contralateral eye; only few neurons receive an additional but weaker input from the ipsilateral eye (FIG. 3).

At 4 weeks of age, sudden changes occur in numerous response properties of retinal slip neurons. Stimulus-driven and spontaneous activity as well as neuronal modulation, that is, the difference in firing rate during stimulation in the preferred and non-preferred direction, become adultlike. The neurons begin to respond to a wider range of stimulus velocities, including also higher velocities. At this developmental stage, the influence of the ipsilateral eye suddenly increases significantly so that now most retinal slip cells receive an additional though weaker input from the ipsilateral eye, the proportion of neurons exclusively activated by the contralateral eye is reduced. During further maturation, the ipsilateral input becomes even stronger, and the velocity tuning of retinal slip neurons broadens toward lower-stimulus velocities.

In an attempt to reveal the cause for these developmental changes, we electrically stimulated the area 17/18 border representing the central visual field in order to elicit orthodromic potentials at retinal slip neurons in the NOT-DTN. At 3 weeks of age, no orthodromic potentials could be elicited at retinal slip cells, even though such responses could be elicited in the central visual field representation of the superior colliculus. At 4 weeks of age, orthodromic potentials could also be elicited at retinal slip cells confirming earlier results.[9] During further maturation, orthodromic latencies shorten significantly. These electrophysiological results are supported by anatomical studies in the literature, indicating that the cortico-subcortical projections to

the superior colliculus (and the pretectum?) in neonatal cats consist mainly of fibers and growth cones but only few boutons. At around 4 weeks of age, this projection consists mainly of boutons, and only few growth cones are left (for references see Distler and Hoffmann[24]).

Thus, in the cat the beginning symmetry of monocular OKR can be linked to the increase of the input of the ipsilateral eye onto retinal slip cells. Because the direct retinal input in the cat comes almost exclusively from the contralateral retina, this ipsilateral influence most likely is transmitted via the cortical input becoming functional at the same developmental stage as the binocularity in the NOT-DTN, and bidirectionality of OKR is first observed.

DEVELOPMENT OF THE OPTOKINETIC SYSTEM IN MONKEY

In order to investigate whether a similar developmental sequence is present in monkeys, we undertook a longitudinal study using EOG recordings to measure horizontal optokinetic eye movements in infant monkeys ranging in age from 2 days to about 6 months.[25] In the 2-day-old animal, monocular OKR could already be elicited both in temporonasal and, albeit more weakly, in nasotemporal direction. During further maturation, especially the nasotemporal component grew stronger so that eventually symmetry was reached. The age when symmetry was reached depended on the velocity of the stimulus (FIG. 4). To quantify this we calculated an asymmetry

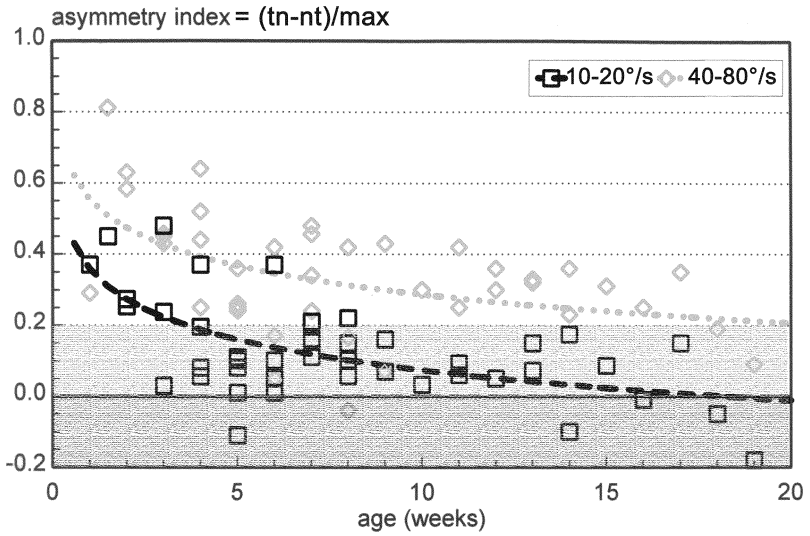

FIGURE 4. Development of monocular horizontal OKR in infant macaques. *Ordinate*: asymmetry index of OKR (difference between the OKR in temporonasal and nasotemporal direction, normalized to the larger of the two); *abscissa*: postnatal age in weeks. *Shaded area* indicates symmetry of OKR. *Black line and symbols*: asymmetry index during stimulation at low-stimulus velocities (10–20°/s); *grey line and symbols*: asymmetry index during stimulation at high-stimulus velocities (40–80°/s).

index, that is, the difference between the reaction to temporonasal and nasotemporal stimulation divided by the larger of the two. An index of ± 0.2 was regarded as symmetry. In FIGURE 3 we segregated the data according to stimulus velocity in a low-velocity (10–20°/s, black symbols and line) and in a high-velocity group (40–80°/s, grey symbols and line). For low-stimulus velocities, symmetry of monocular OKR was reached between 3 and 4 weeks of age; for higher-stimulus velocity OKR symmetry was reached only between 4 and 5 months of age. At the highest velocity tested (120°/s) symmetry was not reached during our period of observation.

Electrophysiological recordings were performed in a P9 and a P14 infant monkey under deep anesthesia and paralysis. As seen in kitten, retinal slip neurons were already strongly direction selective for ipsiversive stimulus movement in the P9 animal. When tested at various stimulus velocities, the resulting tuning curve was very narrow, with an optimal stimulus velocity around 10°/s. By contrast, in adults stimulus velocities yielding very good reactions range from about 1°/s to several 100°/s.[26] In contrast to cat, most retinal slip neurons in the NOT-DTN already received input from both eyes in the P9 animal (FIG. 5). In both infant monkeys, about half of the neurons received equal input from both eyes, and the other half was dominated by the contralateral eye. During further maturation, the influence of the ipsilateral eye strengthens so that in the adult the majority of neurons receives equal input from the contralateral and the ipsilateral eye.[26]

In order to find out whether the binocularity in the NOT-DTN can be attributed to the presence of a cortical input, we electrically stimulated the central visual field representation of V1. In the P9 infant, we were unable to elicit orthodromic responses in the NOT-DTN. In the P14 animal, however, orthodromic responses could be elicited after stimulation in V1 in the SC as well as in about 40% of the retinal slip

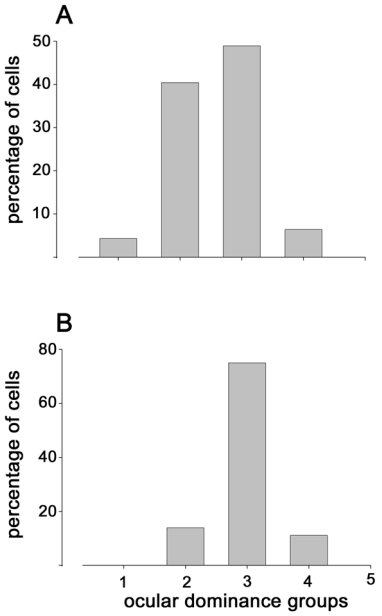

FIGURE 5. Ocular dominance distribution of retinal slip neurons in infant (P9 and P14, **A**) and adult (**B**) macaques. *Ordinate*: percentage of cells; *abscissa*: ocular dominance groups.

neurons tested. This is a considerably smaller proportion than in the adult where 97% of the neurons tested could be activated by electrical stimulation in V1.[27] In addition, the orthodromic latencies were significantly longer in the infant than in the adult.

Thus, bidirectionality of monocular OKR can be linked to binocularity in the NOT-DTN also in monkey. However, due to the bilateral direct retinal input to the NOT-DTN in primates, it is difficult to decide whether the binocularity present shortly after birth is caused by the bilateral retinal or by a cortical input. In the present study, we were unable to demonstrate a cortical input to the NOT-DTN prior to two weeks of age. Although we cannot completely rule out that a weak projection may be present even earlier, we propose that the early binocularity and the bidirectionality of monocular OKR at low-stimulus velocities shortly after birth is indeed mediated by the direct retinal input from both eyes to the NOT-DTN. As the cortical input starts to mature, it gradually dominates the NOT-DTN and the retinal input loses much of its influence so that after cortical lesion it is unable to maintain a normal performance of OKR.

COMPARISON TO MAN

Can these results be extrapolated to humans? Monocular OKR in human infants becomes symmetrical at around 4–5 months of age, thus closely resembling the monkey data.[28,29] Obviously, the optokinetic system seems to be an example where the "weeks to months" rule (one week in monkey development corresponds to one month in human) does not apply.

It can be safely assumed that the neuronal substrate for the optokinetic reflex in man corresponds to that found in other mammals. It has been shown that man has a complete accessory optic system,[30] and a nystagmogenic region, presumably the NOT-DTN, has been identified by electrical stimulation.[31] Further clues come from lesion studies in children.[32] Hemispherectomized infants younger than about 10 months of age perform bidirectional, albeit quite asymmetric, OKR during monocular and binocular viewing condition. However, toward the damaged side OKR gets weaker and finally is completely lost during further development, that is, the children are optokinetically blind during stimulation toward the lesioned hemisphere.

These data can be explained by assuming that in man as in other primate and subprimate species the retinal input to the NOT-DTN is responsible for imprinting the system and for the optokinetic response shortly after birth. As the cortex and/or the corticofugal projections during normal development become functional and mature, the system is taken over completely by the cortical input. The retina then loses its influence to a degree that it cannot drive the system at all, even if the cortical input is lost.

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