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Functions of the nucleus of the optic tract (NOT):

II. Control of ocular pursuit

Sergei B. Yakushin

Department of Neurology, Box 1135, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029, USA e-mail: syakush@smtpLink.mssm.edu Tel.: +1-212-2417068, Fax: +1-212-8311610

Martin Gizzi

New Jersey Neuroscience Institute, Seton Hall University, JFK Medical Center, Edison, NJ 08818, USA

Harvey Reisine

Department of Neurology, Box 1135, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029, USA

Theodore Raphan

Department of Neurology, Box 1135, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029, USA

Department of Computer and Information Science, Brooklyn College of CUNY, Brooklyn, NY, USA

Jean Büttner-Ennever

Institute of Anatomy, University of Munich, 80366 Munich, Germany

Bernard Cohen

Department of Neurology, Box 1135, Mount Sinai School of Medicine, 1 East 100th Street, New York, NY 10029, USA

Department of Physiology and Biophysics, Mount Sinai School of Medicine, New York, NY, USA

Abstract

Ocular pursuit in monkeys, elicited by sinusoidal and triangular (constant velocity) stimuli, was studied before and after lesions of the nucleus of the optic tract (NOT). Before NOT lesions, pursuit gains (eye velocity/target velocity) were close to unity for sinusoidal and constant-velocity stimuli at frequencies up to 1 Hz. In this range, retinal slip was less than 2°. Electrode tracks made to identify the location of NOT caused deficits in ipsilateral pursuit, which later recovered. Small electrolytic lesions of NOT reduced ipsilateral pursuit gains to below 0.5 in all tested conditions. Pursuit was better, however, when the eyes moved from the contra-lateral side toward the center (centripetal pursuit) than from the center ipsilaterally (centrifugal pursuit), although the eyes remained in close proximity to the target with saccadic tracking. Effects of lesions on ipsilateral pursuit were not permanent, and pursuit gains had generally recovered to 60–80% of baseline after about 2 weeks. One animal had bilateral NOT lesions and lost pursuit for 4 days. Thereafter, it had a centrifugal pursuit deficit that lasted for more than 2 months. Vertical pursuit and visually guided saccades were not affected by the bilateral NOT lesions in this animal. We also compared effects of these and similar NOT lesions on opto-kinetic nystagmus (OKN) and optokinetic after-nystagmus (OKAN). Correlation of functional deficits with NOT lesions from this and previous studies showed that rostral lesions of NOT in and around the pretectal oli-vary nucleus, which interrupted cortical input through the brachium of the superior colliculus (BSC), affected both smooth pursuit and OKN. In two animals in which it was tested, NOT lesions that caused a deficit in pursuit also decreased the rapid and slow components of OKN slow-phase velocity and affected OKAN. It was previously shown that slightly more caudal NOT lesions were more effective in altering gain adaptation of the angular vestibulo-ocular reflex (aVOR). The present findings suggest that cortical pathways through rostral NOT play

an important role in maintenance of ipsilateral ocular pursuit. Since lesions that affected ocular pursuit had similar effects on ipsilateral OKN, processing for these two functions is probably closely linked in NOT, as it is elsewhere.

Keywords

Monkey; Smooth pursuit; Optokinetic nystagmus; Nucleus of the optic tract (NOT); Eye movement

Introduction

Ocular pursuit maintains the image of moving targets on the fovea in frontal-eyed animals. The gain of pursuit (eye velocity/target velocity) is a measure of how fast the eyes are moving relative to the target. If pursuit gain is less than unity, both a retinal slip velocity and a retinal error signal are produced. These errors are generally nulled by the saccadic system that brings the eyes back onto the target (Segraves and Goldberg 1988,1994), so that pursuit can continue with a small retinal error. Maintenance of pursuit should, therefore, depend on activity related to retinal slip. Such activity is found in the visual cortex (Maunsell and Van Essen 1983;Segraves and Goldberg 1987;Komatsu and Wurtz 1988;Gizzi et al. 1990). In particular, the macaque middle temporal area (MT) contains cells whose responses are related to image motion (Dubner and Zeki 1971;Van Essen et al. 1981;Albright 1984;Movshon et al. 1985). Using a step-ramp paradigm, Newsome et al. (1985) demonstrated that small electrolytic lesions in MT decreased initial pursuit velocity for targets presented in the related portion of the visual field (Newsome et al. 1985). Lesions of the medial superior temporal cortex (MST) have also resulted in a parallel loss of pursuit and of the rapid component of optokinetic nystagmus (OKN) (Yamasaki and Wurtz 1991). Activity in MST and MT falls if the target disappears (Newsome et al. 1988).

Subcortical pathways may also play a role in production of pursuit, since pursuit did not disappear in monkeys in whom the visual cortex was ablated (Zee et al. 1987). The nucleus of the optic tract (NOT) is a likely candidate for participation in either the initiation or the maintenance of horizontal ocular pursuit. It receives direct retinal input bilaterally, predominantly from the contralateral eye (Weber and Harting 1980;Hoffmann and Stone 1985;Zhang and Hoffmann 1993;Feig and Harting 1994) and a bilateral projection from the cortical areas MT and MST. Some NOT units have receptive fields less than $10 \times 10^\circ$. These units are modulated during smooth pursuit, and if the visual target is extinguished during ongoing pursuit, the relationship of unit activity to pursuit disappears (Mustari and Fuchs 1990), similar to the behavior of MST and MT units. A majority of NOT units are directionally related to the horizontal retinal-slip signal (Hoffmann and Schoppmann 1981;Hoffmann and Distler 1989;Mustari and Fuchs 1990), and some NOT units in the monkey follow retinal slip to velocities as high as $200^\circ/\text{s}$ and 5 Hz (Mustari and Fuchs 1990). Thus, cortical activity reaching NOT could provide the activity for coding high retinal-slip velocities. Mustari and Fuchs (1990) and Ilg and Hoffmann (1991) also found units with small receptive fields that had frequency characteristics over a low velocity range that was related to pursuit. The latency of these units was sufficient for involvement in the initiation of pursuit (Klauer et al. 1990; Mustari, personal communication). Ilg et al. (1993) demonstrated that pursuit became saccadic after a rather extensive lesion in the pretectal area in one monkey, and proposed that NOT supports ocular pursuit. There was no quantitative description of the pursuit deficit in this animal.

It is widely accepted that cortico-ponto-cerebellar pathways carry activity for the generation of smooth pursuit and the rapid component of OKN (Westheimer and Blair 1973,1974;Brodal 1978a,1978b,1982;Glickstein et al. 1980,1985,1994;Waespe et al. 1981,1983;Waespe and

Henn 1981;Zee et al. 1981). Cortical signals are transmitted to nucleus reticularis tegmenti pontis (NRTP) and the dorsolateral pontine nuclei (DLPN) (Brodal 1978a,1978b;Glickstein et al. 1980,1985), which in turn project to the flocculus via mossy-fiber input (Langer et al. 1985). From there, floccular Purkinje cells project to the vestibular nuclei and, thence, to the oculomotor nuclei. Output pathways from NOT also go to NRTP and DLPN (Mustari et al. 1994;Buettner-Ennever et al. 1996a).

At many locations, activity related to ocular pursuit and the rapid component of OKN slow-phase velocity are processed in the same nuclei and by the same neurons. NOT has been shown to be an important structure for production of OKN and optokinetic after-nystagmus (OKAN) (Collewyn 1975a,1975b;Hoffmann 1981,1989;Kato et al. 1986,1988;Schiff et al. 1988,1990) and, therefore, might be expected to play a role in modulation of pursuit. The gain of the initial jump in slow-phase velocity at the onset of OKN is reduced after NOT lesions in monkey (Schiff et al. 1990), and after some NOT lesions, both the rapid and slow components of OKN slow phase velocity were lost (Kato et al. 1986,1988;Schiff et al. 1990). Together, these studies suggested that both the direct and indirect optokinetic pathways are altered by activity that arose in NOT (Cohen et al. 1992).

In the present experiments, we studied the effects of lesions of NOT on smooth pursuit and on OKN and OKAN. We also studied saccadic eye movements and the effect of eye position on pursuit. The aim of this research was to determine if inactivation or lesions of NOT would cause changes in ocular pursuit and to characterize these deficits. We also questioned whether the lesions that caused changes in pursuit would also cause changes in OKN and OKAN.

Material and methods

Animal preparation

One cynomolgus (*Macaca fascicularis*, M8916) and two rhesus monkeys (*Macaca mulatta*, M9121 and M9314) were used to study smooth pursuit and saccades in chronic experiments. The experiments conformed to the Guide for the Care and Use of Laboratory Animals (Council 1996) and were approved by the Institutional Animal Care and Use Committee. The surgical procedures, the head implant, and the method of eye-movement recordings have been described in the preceding paper (Yakushin et al. 2000). Horizontal and vertical eye position was recorded with scleral search coils. Eye-position voltages and voltages related to OKN stimulus velocity or visual-target position were recorded with amplifiers with a bandpass of 0–100 Hz. Eye and target positions were sampled at a frequency of 500 samples/s and written to disk for subsequent analysis.

Behavioral training

Two weeks after the search coils were implanted, the monkeys were seated in a lucite chair with their heads restrained in the stereotaxic horizontal position at the center of a 120 cm translucent hemisphere. A three-axis OKN projector (Neurokinetics, Pittsburgh, Pa., USA) was positioned directly over the monkey's head. A red-laser target was projected onto the rear of the hemisphere using a two-axis mirror-galvanometer. Each monkey was water deprived for approximately 12 h prior to training sessions. A water reward was provided via a plastic tube attached to a solenoid-activated delivery system. The monkey's weight was controlled during the period of experiments and, if necessary, extra fruit was given at the end of each experimental day.

Monkeys were first trained to fixate a target at the primary position using the water reward. Rewards were initially given for short periods of gaze fixation (500 ms) on a target within a large window ($\pm 20^\circ$). As animals learned to watch the target, the required duration of fixation

was gradually increased. When fixation reached 2 s, the size of the window was gradually reduced to $\pm 3\text{--}5^\circ$. Monkeys were then trained to make saccades from central (primary) gaze position to eccentric targets chosen at random. If the monkey fixated the central target for 1 s, this target was shifted to an eccentric position. If the monkey made a saccade to the eccentric target within 500 ms and maintained fixation at this new position for 500 ms, it received a reward. If the monkey made a mistake, the fixation trial was repeated, starting from the primary target position after a 10-s delay.

Monkeys were next trained to pursue targets moving sinusoidally at low frequencies. The monkeys were rewarded for each 3 s of accurate tracking (window size $3\text{--}5^\circ$). A tone preceded the reward by 1 s. As the monkeys learned the task, the duration of tracking required for a water reward was gradually increased by 2 s up to 7–11 s of tracking. The tone signaling successful tracking sounded after each 2 s of accurate pursuit, serving as a conditioned reward. Once smooth pursuit was reliable, we increased the amplitude and frequency of the stimulus.

Testing protocol

Animals were tested with sinusoidally moving targets at various peak velocities and target amplitudes (Table 1). It should be noted that, for any specific peak velocity, the frequency increased as the target amplitude became smaller. For all conditions tested, the frequency was less than 1.0 Hz and within the capabilities of normal pursuit.

Optokinetic nystagmus was induced by stimulation about the yaw axis at $60^\circ/\text{s}$ for 60 s, and optokinetic after-nystagmus was recorded in the darkness. The direction of nystagmus was defined by the direction of the slow phase, as in previous publications (Raphan et al. 1979; Gizzi et al. 1994). Slow-phase eye velocity contraversive or ipsiversive to the side of the lesion was called contralateral or ipsilateral OKN, respectively. A similar nomenclature was used for pursuit. Sinusoidal and triangular pursuit were recorded for stimuli traversing from $\pm 5^\circ$ to $\pm 20^\circ$. Peak velocities from $3^\circ/\text{s}$ to $40^\circ/\text{s}$ were included, resulting in frequencies ranging from 0.02 Hz to 1 Hz. Both horizontal and vertical pursuit was recorded. At least ten successful pursuit cycles were recorded for each condition. Saccades were made to targets located $\pm 10^\circ$ horizontally and vertically, as well as $\pm 20^\circ$ horizontally. Recording began at the time the eccentric target appeared and continued for 1 s. At least 200 saccades were recorded for each target position before and after NOT lesions.

Lesions

Techniques for electrode placement and for making lesions were described in the preceding publication (Yakushin et al. 2000). We searched for NOT using 125 μm electrodes with tracks placed 4 mm laterally from the trochlear nucleus. The appropriate depth was determined by electrical stimulation using pulse trains of 40 μA , 0.4 ms pulse width, 250 Hz, and 10–30 s duration passed every 0.5 mm. In the region of NOT, nystagmus with ipsilateral slow phase velocity of $40\text{--}60^\circ/\text{s}$ followed by stimulus after-nystagmus was generated in darkness (Schiff et al. 1988). Two lesions were produced in the left NOT of M9121 and bilateral NOT lesions in M9314 (see Figs. 5A and 6 of Yakushin et al. 2000).

Morphology

At the end of the experiments, animals were deeply anesthetized and killed with pentobarbital ($>50\text{ mg/kg}$) and perfused through the heart with saline and 5% formalin. The brains were stored in 10% formalin. Sections were stained with cresyl violet for cell bodies, and the depth and extent of the lesions were reconstructed. Detail of morphology are summarized in Fig. 9.

General methods of data analysis

Each channel of eye position was smoothed by sequentially averaging four sampling intervals. The waveform signals were digitally differentiated by finding the slope of the least-squares linear fit to 11 data points. This corresponded to a filter that had a 3 db cutoff above 40 Hz. Saccades were then removed from the record using a maximum-likelihood detection criterion (Singh et al. 1981). The accuracy of the program's identification of saccades was confirmed by visual inspection on the computer monitor and edited regions could be deleted or added manually (generally in less than in 5% cases). Saccades were eliminated and a straight line added to connect the velocity before the saccade to the velocity following the saccade.

Target position was digitally differentiated and smoothed with the same filtering characteristics as described for eye position. In addition to desaccaded eye velocities, retinal slip (target velocity–eye velocity), retinal error (target position–eye position), and gain (desaccaded eye velocity/target velocity) were also calculated. All calculated data were additionally smoothed at 10 Hz and saved to data files as additional channels for later analysis.

Because NOT lesions only affected pursuit in one direction, a straightforward sinusoidal analysis, which averaged data over a full cycle was not appropriate. Instead, we analyzed the ratio of the eye velocity to stimulus velocity at each instant of time. We then represented this ratio as a temporal sequence, which was defined as the instantaneous gain, $G(t)$ (see Fig. 1). The instantaneous gain values were stable over the pursuit cycle, except at target turn-around where eye and stimulus velocity crossed zero. Values were averaged for each half cycle. Data from the periods of instability were not included. To obtain a grand mean (± 1 SD) for the gain of the half cycles, these averages were then averaged. After a bilateral lesion, pursuit was affected more when pursuing the target away from the center. This was called centrifugal pursuit, and to analyze it, we averaged the instantaneous gain over each quarter cycle.

Retinal slip and retinal error were measured in a similar way. Averages and standard deviations (SD) were calculated based on values obtained for more than five cycles. Average values and standard deviations were plotted as a function of peak-to-peak target amplitude for each peak velocity. Since retinal slip (E_s) is the difference between stimulus velocity (V_t) and eye velocity (V_e) at each instant of time:

$$E_s = V_t - V_e \quad (1)$$

then the retinal slip can be given in terms of the instantaneous gain, $G(t)$, as follows:

$$E_s = (1 - G(t)) V_t \quad (2)$$

Thus, the retinal slip can be easily obtained from the instantaneous gain and the stimulus velocity. Therefore, statistics regarding retinal slip have not been presented. When the features of the saccades were of interest, the amplitude, peak velocity, latency, and duration of saccades were measured.

Results

Normal pursuit

Eye position and eye velocity accurately matched target position and velocity during sinusoidal pursuit, within the limits of the capability of each monkey (limits: 12°/s in M8916 and 40°/s in M9121 and M9314). Typical data are shown in Fig. 1A. The instantaneous gain was close to unity, and retinal slip and retinal error were small. Pursuit of targets oscillating at constant velocity was not as accurate as pursuit of sinusoidally moving targets because of increases in retinal error as the animal anticipated or lagged the target at turnaround (Fig. 1B). At other

parts of the cycle, eye-velocity profiles accurately matched target velocity, retinal slip and retinal error were small, and the instantaneous gain on average was close to unity.

Average gains for sinusoidal pursuit for each animal before lesion are shown by the open circles in Figs. 2A-F (M9121), 4G-L (M8916), and 6A-F (M9314). Gains were close to unity for stimuli moving over amplitudes of $\pm 5^\circ$ to $\pm 20^\circ$ and frequencies of 0.08–0.64 Hz. For all three animals, the amplitude of eye excursion during smooth pursuit was equal to the amplitude of target excursion in all tested conditions ($P > 0.05$), as in Fig. 1A and B, and retinal error did not exceed 2° . Average gains of triangular pursuit were as high as gains of sinusoidal pursuit for frequencies below 1.0 Hz (M9121, see Fig. 3, open symbols; M9314, see Fig. 6G-L, open symbols).

Effects of unilateral NOT lesions

Unilateral lesions of NOT produced deficits in ocular pursuit when the eyes moved towards the side of the lesion. Following a lesion on the left side in M9121, sinusoidal tracking was defective when the eyes followed movement of the target to the left, and the animal tracked target position with a series of small saccades (Fig. 1C). Consequently, retinal slip increased when pursuing to the side of the lesion and instantaneous gain dropped below 0.5. Effects were solely unilateral and eye velocity matched target velocity well for contralateral target movement. As before lesion, retinal error stayed within 2° of the target (compare Fig. 1A and C).

Effects were similar for triangular pursuit. Ipsilateral pursuit was saccadic, and pursuit eye velocities as well as instantaneous gain were close to zero while tracking ipsilaterally moving targets (Fig. 1D). Consequently, retinal-slip velocities were high, but the retinal error was within the same bounds as the prelesion retinal error (compare Fig. 1B and D). However, the triangular pursuit exposed an additional deficit. Pursuit velocities decreased and tracking became more saccadic as animals followed targets moving into the field ipsilateral to the side of the lesion. Consequently, retinal-slip velocities increased and instantaneous gains decreased as a function of eye position (Fig. 1D).

Graphs of the decline in the gain of sinusoidal pursuit after an initial and subsequent NOT lesion on the left in M9121 are shown in Fig. 2. Gain to the left was reduced to below 0.5 ($P < 0.05$, Fig. 2A-C) on the first (filled triangles) and second (filled circles) days after the first lesion. By the 22nd day (filled squares), the gain had recovered to prelesion values. The second lesion, which extended more caudally (see below), caused a similar deficit in pursuit gain (Fig. 2G-L, filled triangles and circles). Changes in gain after the first and second lesions were not significantly different from each other ($P = 0.23$, ANOVA). Triangular pursuit of ipsilaterally moving target was affected in a similar fashion after both lesions (Fig. 3A-C, lesion 1; Fig. 3D-F, lesion 2). Pursuit to the contralateral side following lesion was normal in all conditions (Fig. 2D-F and J-L, Fig. 3A-F).

Microelectrode penetrations can cause mechanical damage to the brain structures that are being observed. This probably occurred in NOT since transient deficits in smooth pursuit were found after penetrations had been made through NOT to locate the area with the strongest nystagmic response to electrical stimulation (see Methods). When tested on the day after such penetrations, ipsilateral pursuit velocities were reduced and pursuit was saccadic, similar to the pursuit after NOT lesions (M9121, Fig. 4A-C; M8916, Fig. 4J-L). In both animals, average pursuit gains were below 0.5 for the first three days (Fig. 4A-F) and then recovered.

Effects of bilateral NOT lesions

The foregoing experiments indicate that NOT exerts control over ipsilateral pursuit, but has no discernible effect on the gain of pursuit in the contralateral direction. They further suggest that there is a greater deficit in pursuit when the eyes move from the midline to the ipsilateral side (centrifugal pursuit) than from the contralateral side to the midline (centripetal pursuit). To investigate the centrifugal pursuit deficit further, bilateral lesions of NOT were made in M9314. After these lesions, the animal was unable to track the moving visual target in either direction for 4 days. Over this time, its on-target saccades were normal, demonstrating that it was capable of fixating stationary target and that it was participating in the experiment. Thus, in contrast to the unilateral lesions, which caused a deficit in pursuit in one direction, bilateral NOT lesions abolished horizontal pursuit for some period.

When recorded five days after the bilateral lesions, there were deficits in both directions when the eyes followed the target from the midline laterally (centrifugal pursuit). When the monkey pursued the target moving from lateral positions toward midline (centripetal pursuit), the gain was normal. Similar centrifugal deficits were found both during sinusoidal (Fig. 5A) and constant-velocity pursuit (Fig. 5B). The deficits were greater when the eyes moved to the left and were more evident when the eyes moved at constant velocity across the entire field. The location of the lesions, which was different on the two sides, will be considered below.

Before the bilateral NOT lesions, M9314 was capable of accurately pursuing targets moving with sinusoidal or triangular at velocities up to 40°/s (Fig. 6, open symbols). Average gains for centrifugal sinusoidal pursuit on the 5th and 6th day and 2 months after lesions reflected the changes described above (Fig. 6A-C). The reduction in pursuit gain to the left (Fig. 6A-C) was greater than to the right (Fig. 6D-F; $P < 0.05$) for all target velocities tested. Sinusoidal pursuit at 40°/s had a low gain, but had begun to recover to the right by the 7th day after lesion (Fig. 6F, filled triangles). Changes in sinusoidal pursuit were significant for all conditions ($P < 0.05$) except for targets moving over a 5° amplitude at 10°/s peak velocity (Fig. 6D). The bilateral lesions also caused a significant decrease in gain for triangular centrifugal pursuit in both directions (Fig. 6G-L; $P < 0.05$, ANOVA). On the 5th day, the monkey was only able to pursue the target moving at 10°/s (Fig. 6G and J; filled circles). By the 6th day, the monkey was able to pursue at 20°/s (Fig. 6H and K, filled squares). It was never able to pursue a target moving at a constant velocity of 40°/s, even 2 months after lesion. Thus, the bilateral NOT lesions caused a complete loss of horizontal pursuit for 5 days, followed by a prolonged deficit in centrifugal pursuit.

Vertical pursuit was not as accurate as horizontal pursuit in any of the three animals, and the gain of the best vertical pursuit was, on average, lower than 0.8 (Fig. 7A). Nevertheless, there were no significant differences between vertical-pursuit gain before or after unilateral or bilateral NOT lesions (Fig. 7B). Average peak vertical sinusoidal-pursuit gains for a target moving $\pm 5^\circ$, $\pm 10^\circ$, and $\pm 15^\circ$ at 10°/s peak velocity before and after the bilateral NOT lesions in M9314 are shown in Fig. 7C. There was no difference between them when tested before and after the lesion. Therefore, the NOT lesions did not affect the animal's ability to pursue targets moving vertically.

Horizontal saccades made to targets $\pm 10^\circ$ and $\pm 20^\circ$ as well as vertical saccades to targets $\pm 10^\circ$ were analyzed before and after NOT lesions. Typical data are presented for M9314 in Table 2. The accuracy, peak velocity, duration, and latency of horizontal and vertical saccades was not affected by any of the NOT lesions. Therefore, the NOT lesions did not affect the animal's ability to find and fixate targets in its visual field.

Effect of NOT lesions on OKN and OKAN

Lesions of NOT cause a reduction in ipsilateral slow-phase velocities of OKN and eliminate ipsilateral OKAN, leaving contralateral OKN and OKAN intact (Kato et al. 1986,1988;Schiff et al. 1990). We considered whether the lesions that produced deficits in pursuit in these animals also caused changes in their OKN and OKAN.

One day after the first lesion in the left NOT of M9121, the maximal value for the steady-state slow-phase velocity of ipsilateral OKN elicited by a stimulus velocity of 60°/s was decreased to 30°/s (gain: 0.5), and the time constant of OKAN was reduced to less than 2 s (Fig. 8B, right). By the 23rd day after lesion, ipsilateral OKN had recovered and the OKAN time constant increased to 5 s, the prelesion value (Fig. 8C, right). After the second NOT lesion, ipsilateral OKAN was eliminated during all subsequent testing up to the 136th day (Fig. 8D-F, right). The gain of the initial jump of OKN was smaller than before lesion and there was a substantial reduction in steady-state eye velocity of OKN, which never recovered. Contralateral OKN was not affected by either the first or second lesion (Fig. 8A-F, left).

The bilateral lesions of NOT in M9314 caused a reduction in the gain of steady state OKN from 1.0 to 0.25 in both directions when tested on the first day after lesion, and there was only very weak OKAN to either side. OKN and OKAN to the right had fully recovered by day 98, but OKN and OKAN to the left only partially recovered. The OKN gain was about 0.5, and the initial velocity of OKAN in response to an OKN stimulus velocity of 60°/s was 22°/s (37% of prelesion value). Thus, OKN and OKAN were reduced more after the left than the right NOT lesion in this animal, similar to the effects observed during smooth pursuit to the left. After a right NOT lesion in M8916, caused by electrode identification of NOT (see above), the ipsilateral steady-state OKN gain fell 0.7 to 0.3 when tested on the 2nd day and OKAN was abolished. OKN steady-state gain recovered to 0.5 by the 29th day after lesion, and the initial OKAN velocity in response to the 60°/s OKN stimulus was 15°/s. There was no further recovery in OKN or OKAN parameters on the 55th day. Contralateral optokinetic responses were unaffected by the lesion. Thus, each of the animals that had a lesion in NOT which affected ocular pursuit also had associated deficits in OKN and OKAN.

Comparative morphology of NOT lesions

NOT extends from the rostral pretectum to the junction of the superior colliculus and the pulvinar (heavy dots, Fig. 9A). It is not a homogeneous structure and has several separate subnuclei (Büttner-Ennever et al. 1996a,1996b). The pretectal olivary nucleus (OLN) is a prominent structure within rostral NOT, whereas caudal NOT lies adjacent to the dorsal terminal nucleus (DTN). Input to NOT from the cortex comes in rostrally and laterally through the brachium of the superior colliculus (BSC) together with the cortical input to DLPN and NRTP, which also passes through NOT. There is also prominent input from the contralateral retina through the BSC, but it enters NOT caudally and laterally, whereas the projections to the lower brainstem leave NOT caudally from the medial border. The foregoing imply that lesions in different areas of NOT may have affected different structures and, in turn, different functions.

To address this question, we overlaid the lesions that affected pursuit (Fig. 9B), OKN and OKAN (Fig. 9C), and the vestibulo-ocular reflex (VOR)-gain adaptation (Fig. 9D) on a standard series of sections through NOT (Fig. 9A). Two animals (M9121; M9314) were tested in all three paradigms, and one monkey (M9221) was tested with gain adaptation and OKN/OKAN. We also added the lesions in animals M1176 and M1169, in which only OKN and OKAN were studied (Schiff et al. 1990). The first lesion in M9121 and the two lesions in M9314 caused changes in ocular pursuit. Each was centered in rostral dorsal NOT in and around the pretectal olivary nucleus (OLN; Fig. 9B). The second lesion in M9121 was not included

in this compilation because the changes in pursuit after the second lesion were essentially similar to those after the first lesion. The BSC, carrying input from the visual cortex, was partially interrupted by these lesions. Lesions that affected OKN and OKAN in M1176 and M1169 as well as the left lesion in M9314 and the second lesion in M9121, are shown in Fig. 9C. They were not strikingly different from those affecting smooth pursuit. BSC was partially damaged in all cases, in common with the lesions shown in Fig. 9B. The right lesion in M9314, the lesion in M9221, and the second lesion in M9121, represented in Fig. 9D, affected the ability to adapt the gain of the angular vestibulo-ocular reflex (aVOR). These lesions were, in general, more caudal in NOT than those involving smooth pursuit (Fig. 9B). In summary, lesions that affected smooth pursuit were located more rostral in NOT and frequently involved OLN and the cortical input to NOT. Lesions that affected OKN and OKAN were closely related to those that involved smooth pursuit, but pursuit recovered in all cases, whereas there were persistent severe deficits in OKN and OKAN for longer periods of observation (5 months). Lesions that affected aVOR gain adaptation tended to be located more caudal in NOT.

Discussion

The results of this study show that NOT plays an important role in maintenance of ipsilateral horizontal ocular pursuit. After unilateral lesions of NOT, ocular pursuit was defective to the ipsilateral side, and after bilateral lesions of NOT, the monkey completely lost pursuit for 5 days and, then, had a prolonged deficit in centrifugal pursuit. The electrolytic lesions that caused these changes were small (1–2 mm in diameter), suggesting considerable sensitivity of pursuit function to damage in NOT. In confirmation, simple passage of microelectrodes through NOT was sufficient to cause deficits in ocular pursuit for several days. Deficits in pursuit after NOT lesions were not permanent and recovered within the first week. This probably reflects the fact that NOT is not a unique pathway carrying information related to ocular pursuit from the retina and visual cortex to the brainstem. Pursuit was more severely affected by bilateral than unilateral NOT lesions, and a pursuit deficit persisted for more than 4 months after the bilateral lesions. The saccadic system was intact in all animals, and they were able to locate spatially fixed targets accurately. This demonstrates that they were able to see the target and had an accurate estimate of its position in space.

Deficits in pursuit found in this study are consistent with bilateral deficits in pursuit in a monkey following lesions that destroyed the pretectum and part of the pulvinar (Ilg et al. 1993). While the deficits were bilateral in the animal in that study, pursuit in the ipsilateral direction was affected to a greater degree. In another study (Kato et al. 1986), pursuit was normal in one animal on the 27th day after a complete unilateral NOT lesion that affected OKN. In light of our findings, pursuit may have been defective initially in the Kato et al. study, but normalized over the next month.

Unilateral NOT lesions had no discernible effect on contralateral pursuit. This was surprising, given that firing rates of cells in NOT are inhibited by contralateral retinal slip (Hoffmann and Schoppmann 1981; Hoffmann and Distler 1989; Mustari and Fuchs 1990; Ilg and Hoffmann 1991), and there are powerful connections between the NOT's on either side (Mustari et al. 1994; Buettner-Ennever et al. 1996a). It is consistent, however, with the findings that unilateral NOT lesions only affected the slow phase velocity of ipsilateral OKN and OKAN and had no effect on contralateral OKN and OKAN (Kato et al. 1986; Schiff et al. 1990). It is also consistent with the idea that it was the deficit in ipsilateral pursuit or OKN that was responsible for the inability of lesioned animals to adapt the gain of aVOR-induced contraversive-eye velocities (Yakushin et al. 2000).

Vertical pursuit was unaffected by bilateral NOT lesions, at a time when horizontal pursuit was defective. This agrees with earlier findings that vertical OKN and OKAN were normal

after NOT lesions (Kato et al. 1986; Schiff et al. 1990). The lack of effect on vertical pursuit after NOT lesions supports the conclusion that only horizontal retinal slip is processed in NOT, and that vertical retinal slip is processed elsewhere, possibly in the lateral terminal nucleus (LTN) (Mustari and Fuchs 1989).

Pursuit deficits were present during both sinusoidal pursuit and when tracking targets at a constant velocity. Tracking at a constant velocity revealed that pursuit was affected more when the eyes were moving away from rather than toward the midline. This could not be due to the presence of contralateral spontaneous nystagmus, which is often observed after unilateral NOT lesions (Kato et al. 1986, 1988; Schiff et al. 1990; Ilg et al. 1993), since it was not present after bilateral NOT lesions. This suggests that each NOT may exert its maximal effect as the eyes move farther into the ipsilateral movement field. Pursuit is comprised of both velocity and position controls (Robinson 1965; Young 1971; Pola and Wyatt 1980; Morris and Lisberger 1987; Segraves and Goldberg 1994). If the velocity-gain control dropped as the eyes followed across the midline and if this gain were not compensated by position control during pursuit, then tracking would become saccadic. Unit activity in NOT is predominantly related to retinal slip, however, and a gradation in frequency related to retinal-slip velocity as a function of eye position has never been noted (Hoffmann and Schoppmann 1981; Hoffmann and Distler 1989; Mustari and Fuchs 1990; Ilg and Hoffmann 1991; Fuchs et al. 1992). Therefore, while information provided by NOT may be important for pursuit in different portions of the movement field, such processing is likely to be done outside this nucleus. This could occur if NOT provided input to the neural integrator responsible for gaze fixation in the ipsilateral hemifield. The projection from NOT to the prepositus hypoglossi nucleus (PPH), including the projection through the lateral geniculate nucleus (LGN), could be utilized in this regard.

OKN in the monkey is comprised of two components, one causes rapid changes in slow-phase velocity (the rapid component); a second is responsible for slower changes in eye velocity and for OKAN, the “velocity storage” component (Cohen et al. 1977; Raphan et al. 1979; Waespe et al. 1983). While pursuit is not identical to the rapid component of OKN, it utilizes many of the same reflex pathways in tracking moving targets. Thus, the same neurons in DLPN (May et al. 1988), NRTP (Cazin et al. 1980a; Keller and Crandall 1983; Suzuki and Keller 1984; Mustari et al. 1988; Thier et al. 1988; Suzuki et al. 1990), the flocculus (Waespe et al. 1983, 1985; Büttner and Waespe 1984; Büttner 1989; Krauzlis and Lisberger 1996), and the vestibular nuclei (Cazin et al. 1980b; Waespe et al. 1992) are activated by pursuit as by the rapid eye-velocity component of OKN. Ilg and Hoffmann (1991) also showed that the same neurons in NOT were activated by retinal slip during both smooth pursuit and OKN (Ilg and Hoffmann 1991). Deficits in pursuit in these various structures have also frequently been accompanied by concurrent deficits in the rapid slow-phase eye-velocity component of OKN. Clinically, deficits in pursuit are almost invariably accompanied by deficits in OKN and by a failure of visual suppression of the aVOR.

To determine whether damage in the same regions of NOT produced concurrent deficits in pursuit and OKN and/or OKAN, we superimposed lesions from this and a previous study (Schiff et al. 1990; Yakushin et al. 2000). Lesions that caused deficits in pursuit and the rapid slow-phase eye-velocity component of OKN tended to cluster in rostral NOT, in the region of the pretectal olivary nucleus (Fig. 9B, C). From this, it is likely that information that is important for producing pursuit and the rapid component of OKN is processed in rostral portions of NOT, perhaps associated with involvement of the pretectal olivary nucleus in the “near response”. In support of this, the rostral medial region of NOT projects both to NRTP and DLPN (Torigoe et al. 1986; Korp et al. 1989; Büttner-Ennever et al. 1996a, 1996b), which are both important for production of pursuit and OKN. May et al. (1988) showed that ipsilateral pursuit was affected by ibotenic acid lesions of DLPN, but as with our NOT lesions, the accuracy of on-target saccades was unaffected. The visual hemifield was not important for demonstrating the deficit,

and the rapid component of OKN was similarly affected. After the DLPN lesion, there was only a very slow buildup in OKN slow-phase velocity, and steady-state velocity was reduced. There was prolonged OKAN just after the DLPN lesion. The difference between the DLPN and the NOT lesions is that both OKN and OKAN were affected by NOT lesions, whereas mainly the rapid component of OKN and pursuit were affected by the DLPN lesions. The explanation is probably that the rapid component of OKN and smooth pursuit are both generated by NOT and DLPN activity that reaches the flocculus, whereas OKAN is generated by NOT activity that projects to the vestibular nuclei, probably through the prepositus hypoglossi nucleus. Another difference is that both vertical and horizontal retinal slip were represented in DLPN, whereas only horizontal retinal slip is represented in NOT, a reflection of the fact that DLPN is closer to the motor mechanism for pursuit and OKN in the flocculus.

A possible explanation for at least some of the findings is that there might have been damage to input pathways from the cortex in NOT, which join the brachium of the superior colliculus as it passes through the pulvinar and enters the pretectum. These pathways carry retinal-slip-related activity from the cortex and/or retina that are important for both OKN and pursuit. The lesions in M9121 that caused changes in pursuit and OKN would not have caused substantial damage to input pathways, but there is no way to separate these two alternatives definitively. Simple penetration with microelectrodes through NOT that caused significant deficits in pursuit would also not be expected to substantially decrease the input to the nucleus, yet there were profound deficits in ipsilateral pursuit after such penetrations. We also questioned whether the regions that controlled pursuit and OKN were different from those that controlled aVOR-gain adaptation. The latter, plotted in Fig. 9D, appeared to lie more caudally than the lesions that produced changes in pursuit and OKN. In agreement with this, projections to the prepositus nucleus, where OKAN is produced, and to the inferior olive exit from caudal portions of NOT (Büttner-Ennever et al. 1996a). However, the number of animals in each series is relatively small, and the conclusions drawn from this are tentative. It should be noted that the deficits in pursuit and/or the rapid component of OKN were ipsilateral after NOT lesion, whereas the failure of visual suppression was contralateral (Yakushin et al. 2000). This is consistent with the postulate that pursuit and/or the rapid component of OKN are utilized to null eye velocities generated through the aVOR when viewing head-fixed targets.

In the preceding study, we have demonstrated the importance of NOT in maintenance of the gain of the VOR. The results of this study demonstrate the importance of NOT in tracking objects during pursuit and in maintaining gaze stability during head movement that produces full field movement of the visual surround. Taken together, we infer that NOT is a critical structure for maintaining stability of gaze during head movement in a lighted environment.

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Pursuit Before and After Left NOT Lesion (M9121)

Sinusoidal Pursuit

Triangular Pursuit

Fig 1.

Samples of sinusoidal (**A**, **C**) and constant-velocity (**B**, **D**) ocular pursuit obtained before (**A**, **B**) and after (**C**, **D**) unilateral lesion of the nucleus of the optic tract (*NOT*) in monkey M9121. Target and eye position are overlaid in the *top row* of each panel, and eye and target velocity are shown superimposed in the *third traces*. Retinal error (degrees, *2nd trace*), retinal-slip velocity (°/s, *3rd trace*), and instantaneous gain (*5th trace*) are also shown. Time (s) is on the *abscissa*. There was an increase in saccadic tracking when the eyes moved ipsilateral to the lesion (**C**, **D**). Note also that the drop in gain was maximal as the eye moved to the contralateral side for both sinusoidal (**C**) and smooth (**D**) pursuit

Fig 2A-L.

Gain of sinusoidal smooth pursuit in monkey M9121 before and after first and second lesions in the left nucleus of the optic tract (NOT). Unity gain is shown by the *dashed lines*. *Open circles* represent gains before lesion, while *filled symbols* represent gains at various times after lesions (see *inserts* in **D** and **G** for specific times). The ipsilateral gain was reduced in the first days after lesion and then recovered. There was no effect on the contralateral pursuit gain. Changes in pursuit after the second lesion were the same as after the first lesion. *Vmax* Maximum target velocity

Fig 3A-F.

Gain of ipsilateral smooth pursuit during constant velocity (triangular) tracking in monkey M9121 before and after first and second lesions in the left nucleus of the optic tract (NOT). Effects were similar to those observed during sinusoidal pursuit. V_{max} Maximum target velocity

Fig 4.

Gain of sinusoidal smooth pursuit in monkeys M9121 (A–F) and M8916 (G–L) before and after one nucleus of the optic tract (NOT) had been penetrated with a microelectrode. Deficits in pursuit were to the side ipsilateral to the penetrations. The effects observed in the first several days were compatible with the effects of unilateral NOT lesions. *Vmax* Maximum target velocity

Fig 5.

Samples of sinusoidal (**A**) and constant-velocity (**B**) ocular pursuit obtained after bilateral lesions of the nuclei of the optic tract in monkey M9314. The schema is similar to that shown in Fig. 1. Note that pursuit away from the midline (centrifugal pursuit) was saccadic after lesion, while pursuit toward the midline (centripetal pursuit) was intact

Fig 6.

Gain of centrifugal sinusoidal (A–F) and constant-velocity (G–L) smooth pursuit before and after bilateral lesions of the nuclei of the optic tract in monkey M9314. *Open circles* represent gains before lesions, while *filled symbols* represent gains at various times after lesions (see *insert* in C for specific times). Pursuit to the left was more affected and the deficit was still present 2 months after the lesions (*filled diamonds*). The deficits were more pronounced at higher velocities, and the animal was unable to follow targets moving at 40°/s constant velocity as long as 2 months after the lesions. *Vmax* Maximum target velocity

Fig 7. Vertical smooth pursuit before (**A**) and 6 days after (**B**) bilateral lesions of the nuclei of the optic tract (*NOT*) in monkey M9314. Target position and eye position are superimposed in the *top trace*. The *second trace* is superimposed eye and target velocity. On average, there was no effect of the *NOT* lesions on vertical pursuit in either direction (**C**)

Fig 8.

Effect of unilateral lesions of the nucleus of the optic tract (*NOT*) in monkey M9121 on optokinetic nystagmus (OKN) and optokinetic after-nystagmus (OKAN) before (**A**) and on different days after the first (**B, C**) and second (**D–F**) left NOT lesions. Only the envelopes of slow-phase velocity are shown. The remnants of the saccades that were removed are represented by *dotted lines*. Zero velocity is shown by the *horizontal dashed line*. The stimulus was full-field movement of the visual surround at 60°/s for the period shown by the *solid bars* under **F**. OKAN was recorded in darkness. OKN and OKAN to the right were not affected by either lesion (*left column*). OKN and OKAN to the left (*right column*) were reduced after the first lesion, but recovered by the 23rd day after lesion. The effects of the second lesion were more profound, and there was no recovery after 4.5 months. Spontaneous nystagmus to the right was present after both lesions in left NOT. *H_{eye} Vel* Horizontal eye velocity

Fig 9A–D.

Diagram of transverse sections through the pretectum. **A** Filled circles show the extent of the nucleus of the optic tract (NOT) from rostral (left) to caudal (right). **B–D** Location of lesions that caused changes in smooth pursuit (**B**), optokinetic nystagmus (OKN) and optokinetic after-nystagmus (OKAN) (**C**), and adaptive reduction in the gain of the angular vestibulo-ocular reflex (**D**). The first lesion in monkey *M9121* and both lesions in monkey *M9314* are shown in **B**. The second lesion in *M9121*, the left lesion in *M9314*, and the lesion in *M1169* and *M1176* are shown in **C**. Monkeys *M1169* and *M1176* are from an earlier study (Schiff et al. 1990) and were not tested for smooth pursuit. The second lesion in monkey *M9121*, the right lesion in *M9314*, and the kainic-acid lesion in *M9221* are shown in **D**. Scale in mm shown

below **D**. *BSC* Brachium of the superior colliculus, *DTN* dorsal terminal nucleus, *LI* nucleus limitans, *MGN* medial geniculate nucleus, *NIII* oculomotor nucleus, *OLN* pretectal olivary nucleus, *PUL* pulvinar, *SC* superior colliculus

Table 1

Frequency (Hz) determined from target amplitude and peak velocity

Amplitude	Peak Velocity						
	6°/s	9°/s	12°/s	10°/s	20°/s	40°/s	60°/s
5°	0.191	0.287	0.382	0.320	0.640	—	—
10°	0.096	0.143	0.191	0.160	0.320	0.640	—
15°	0.064	0.096	0.127	0.100	0.210	0.420	0.640
20°	0.048	0.072	0.096	0.080	0.160	0.320	0.480

Table 2
Parameters of saccades before and after bilateral lesions of the nucleus of the optic tract (*NOT*) in monkey M9314

	Horizontal				Vertical	
	Right		Left		Up	Down
	10°	20°	10°	20°	10°	10°
Amplitude						
Before	11±1	21±1	10±1	18±1	10±1	8±1
After	10±1	19±2	10±1	18±2	9±2	8±1
Duration						
Before	22±5	32±6	22±4	31±6	23±5	22±4
After	24±5	30±6	23±5	30±7	22±5	21±5
Maximal Velocity						
Before	433±88	731±204	436±87	768±129	421±91	312±62
After	430±93	858±211	425±102	823±185	380±127	293±88