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Directional Asymmetry of Neurons in Cortical Areas MT and MST Projecting to the NOT-DTN in Macaques

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Hoffmann, K.-P., F. Bremmer, A. Thiele, and C. Distler. Directional asymmetry of neurons in cortical areas MT and MST projecting to the NOT-DTN in macaques. *J Neurophysiol* 87: 2113–2123, 2002; 10.1152/jn.00488.2001. The cortical projection to the subcortical pathway underlying the optokinetic reflex was studied using antidromic electrical stimulation in the midbrain structures nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN) while simultaneously recording from cortical neurons in the superior temporal sulcus (STS) of macaque monkeys. Projection neurons were found in all subregions of the middle temporal area (MT) as well as in the medial superior temporal area (MST). Antidromic latencies ranged from 0.9 to 6 ms with a median of 1.8 ms. There was a strong bias in the population of cortical neurons projecting to the NOT-DTN for ipsiversive stimulus movement (towards the recording side), whereas in the population of cortical neurons not projecting to the NOT-DTN a more or less equal distribution of stimulus directions was evident. Our data indicate that there is no special area in the posterior STS coding for ipsiversive horizontal stimulus movement. Instead, a specific selection of cortical neurons from areas MT and MST forms the projection to the NOT-DTN and as a subpopulation has the same directional bias as their subcortical target neurons. These findings are discussed in relation to the functional grouping of cortical output as an organizational principle for specific motor responses.

INTRODUCTION

The important role of midbrain nuclei and extrastriate visual areas of the monkey cortex for the control of slow eye movements is well established. A unique possibility to study how evolutionary newer areas of the neocortex are linked with the older structures in the midbrain and pretectum to control visuomotor behavior is provided by the optokinetic reflex and its underlying neuronal pathways. This basic behavior is present in all seeing animals, and its neuronal realization is remarkably constant across all vertebrates studied. In primates electrical stimulation as well as inactivation studies have shown unequivocally that the middle temporal area (MT) and the medial superior temporal area (MST) in the superior temporal sulcus (STS) of the cortex as well as the nucleus of the optic tract and the dorsal terminal nucleus of the accessory optic system (NOT-DTN) in the midbrain are involved in the generation of slow eye movements during optokinetic nystagmus (OKN) and smooth pursuit (Dürsteler and Wurtz 1988; Yakushin et al. 2000).

However, it has been a paradox so far why lesions of various cortical areas lead to severe direction selective deficits in slow eye movements, and the question about the neuronal basis of this so-called directional asymmetry of the smooth pursuit and optokinetic system has intrigued neuroscientists for some time (e.g., Barton et al. 1996; Braddick 1996; Dürsteler and Wurtz 1988; Heide et al. 1996; Lynch and McLaren 1983; Morrow and Sharpe 1993, 1995; Ter Braak and Van Vliet 1963; Thurston et al. 1988; Tusa et al. 1989; Wood et al. 1973; Zee et al. 1987). In normal cats, monkeys, and humans, monocularly as well as binocularly elicited slow eye movements are largely equivalent during clockwise and counterclockwise stimulation (symmetrical OKN). Unilateral cortical lesions lead to an impaired reaction during stimulation towards the lesioned side, whereas slow eye movements towards the intact side are normal. This finding is not readily explained by the loss of a certain visual cortical area coding for this direction of movement because there is no clear evidence that cortical areas like MT and MST (Albright 1989; Bremmer et al. 1997b; Erickson and Thier 1991; Komatsu and Wurtz 1988), LIP (Bremmer et al. 1997a), or the pursuit area in the frontal eye field (FEF) (Gottlieb et al. 1994) have a strong bias for a particular direction of stimulus or pursuit movement. Nevertheless, electrical stimulation of MT/MST during ongoing pursuit frequently increased eye velocity when the eye moved towards and decreased eye velocity when it moved away from the stimulated hemisphere (Komatsu and Wurtz 1989). These authors hypothesize that the directional bias for pursuit originates in the visual signal conveyed to the pursuit system.

Consequently, lesions of the midbrain NOT-DTN in monkeys receiving input from cortical areas MT and MST lead to deficits in the slow phase of OKN during visual stimulation towards the lesioned side (Cohen et al. 1990; Ilg et al. 1993; Kato et al. 1986; Yakushin et al. 2000). This result can easily be deduced from the loss of direction-selective neurons in the NOT-DTN strongly biased towards ipsiversive stimulus movement (Hoffmann et al. 1988; Mustari and Fuchs 1990). The NOT-DTN has been recognized as the key sensorimotor interface in the pathway underlying the optokinetic reflex not only in monkeys but in all mammals investigated so far (for review see Simpson et al. 1988; Wallman 1993; wallaby: Hoffmann et al. 1995; opossum: Volchan et al. 1989). Recently, the NOT has also been identified in the human brain by microstimulation

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(Taylor et al. 2000). It relays visual information from the retina and, at least in some species from cortical areas, to the inferior olive, the nucleus praepositus hypoglossi, the nucleus reticularis tegmenti pontis, and the dorsolateral pontine nucleus. Projections of these structures, directly and via the flocculus of the cerebellum to the vestibular nuclei, close the loop for eliciting slow eye movements (Buettner-Ennever et al. 1996; Mustari et al. 1994; Simpson et al. 1988). The key feature of retinal slip neurons in the NOT-DTN projecting to these structures is their direction-selective response to ipsiversive stimulus movement; i.e., neurons in the left NOT-DTN are activated during horizontal stimulus movement to the left, and neurons in the right NOT-DTN are activated during stimulus movement to the right. In addition, in the NOT-DTN of cats and monkeys, all neurons are activated binocularly, i.e., each eye activates neurons in the left as well as in the right NOT-DTN. This connectivity leads to the symmetrical optokinetic response also with monocular stimulation. Other mammals have less binocular neurons depending on the laterality of the position of their eyes in the head and lack of a fovea (Tauber and Atkin 1968). It is always the contralateral eye that has the stronger or sometimes even exclusive input to one NOT-DTN. With this connectivity, i.e., right eye only to left NOT-DTN, which codes leftward movement and vice versa, the monocular optokinetic response becomes asymmetric.

How can we relate the deficits observed after unilateral cortical lesions to this scheme? Using orthodromic electrical stimulation as well as neuroanatomical tracing techniques, we recently reported that the main cortical projection to the NOT-DTN originates from area MT and MST (Distler and Hoffmann 2001; Hoffmann et al. 1991). Preliminary data showed that cortical neurons projecting to the NOT-DTN as a population have a bias for ipsiversive stimulus direction and are binocularly activated (Hoffmann et al. 1992; Ilg and Hoffmann 1993). It has, however, been questioned whether the database was large enough to make such claim (Sommer and Wurtz 2000). By a case-by-case analysis we confirm that the great majority of cortical neurons projecting to the NOT-DTN prefer stimulus movements in the ipsiversive direction, thus matching the direction preference of their target neurons as well as the bias of the impairment after unilateral cortical lesions. Neither direct neighbors that do not project to the NOT-DTN nor the overall population of MT neurons show such a common direction preference. It will be argued that the directionally biased reduction in slow eye velocity after unilateral cortical lesions can be explained by the loss of a specific subpopulation of cortical neurons that relayed to the NOT-DTN strong direction selective activity when the eye lagged behind the stimulus velocity during movements towards the lesioned hemisphere. The remaining retinal input to the NOT-DTN is not sufficient to maintain high gain eye velocities towards the decorticated side.

METHODS

Subjects

All experiments had been approved by the local ethics committee and were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86 609 EEC) and National Institutes of Health guidelines for care and use of animals for experimental procedures. The data for the present investigation were accumulated over the last 10 yr in 12 hemispheres of adult macaque monkeys of both sexes, 6 *Macaca mulatta* and 4 *M. fascicularis*, some of which prior to this terminal experiment were involved in other studies. Brain tissue from these animals served for anatomical studies (Distler and Hoffmann 2001; Telkes et al. 2000).

Surgery and recordings

After initial anesthesia with ketamine hydrochloride (10 mg/kg im), an intravenous catheter was placed, and the animals were intubated through the mouth. Following additional local anesthesia with bupivacainhydrochloride 0.5% (Bupivacain) or prilocainhydrochloride 0.5% (Xylonest), the animals were placed into a stereotactic apparatus. During surgery they received additional doses of pentobarbital as needed. After completion of all surgical procedures, the animals were paralyzed with pancuronium chloride (Alloferin). During the whole session the animals were artificially ventilated with nitrous oxide: oxygen as 3:1 containing 0.3–1% halothane. Heart rate, SPO_2, blood pressure, body temperature, and endtidal CO_2 were monitored and kept at physiological levels. The skin overlying the skull was cut, and craniotomies were performed according to stereotaxic coordinates to allow access to the midbrain and pretectum (Snider and Lee 1961; Szabo and Cowan 1984) and according to nuclear magnetic resonance (NMR) scans of the animals' heads for access to the STS. Corneae were protected with contact lenses that were chosen with a refractrometer (Rodenstock) to focus the animals' eyes at the distance of the tangent screen used for visual stimulation.

Visual stimulation

Visual stimulation consisted of large area random dot patterns projected onto a tangent screen in front of the animal. These patterns could be moved on a linear or a circular path at variable stimulus velocities via a galvanometer-driven double-mirror system (Hoffmann and Distler 1989). In some of the experiments, random dot patterns or sinewave gratings were created on a computer and presented on a monitor in front of the animal. In addition, neurons' responses to small single dots were tested.

Electrical stimulation

The NOT-DTN was localized electrophysiologically according to its position just anterior and lateral to the foveal representation in the superior colliculus (SC) and by its characteristic preference for ipsiversive stimulus movement (Hoffmann et al. 1988). The microelectrode was then left in place to be used later as a stimulating electrode. In histological reconstructions all but one stimulation sites were verified in the NOT-DTN. Thus in these experiments terminals or fibers from cortical neurons were stimulated inside the NOT-DTN. One stimulation site was in the anterior pretectum. Data from this experiment are not included in this study. Single pulses 100 μs wide were applied through the NOT-DTN recording-stimulating electrode at stimulus strength settings varying from 10 μA to 1.0 mA. Actual measurements of the peak currents in 100-μs-wide pulses revealed only about one-half of the amplitudes compared with the settings on the WPI constant current isolation unit. These corrected values are given in the results of this paper. The antidromic nature of the elicited spikes was assessed, first, by the very constant latencies and shapes of the action potentials and, second, by a collision test where spontaneous spikes are used to trigger the electrical stimulation at various delays. If the delay is equal or shorter than the latency of the antidromically elicited spike, this spike will be abolished because of collision of the spontaneous and the electrically elicited action potential traveling along the same axon in opposite directions.

Data analysis

In all quantitatively tested cells the preferred direction was determined using the weighted average of individual bins of the response

histogram representing different stimulus directions. As tuning width (TW), we considered the interval comprising one-half of the response around the preferred direction. Because the response was not always symmetrical around the preferred direction, we determined independently the intervals comprising 25% of the overall response strength to the left and to the right of the preferred direction. A directional tuning index (TI) was calculated as TI = 1 − (TW/360 − TW). Sharp tuning is indicated by values close to 1.0, and broadly tuned cells are characterized by values close to 0.

Anatomical reconstructions

The histological procedures followed the protocol published previously (Distler and Hoffmann 2001). For verification of the stimulation sites 50-μm-thick frozen sections of the midbrains were cut either coronally (8 cases), parasagitally (1 case), or perpendicularly to the layers of the SC (1 case). At least two alternating series were cut: one for Klüver-Barrera and one for Nissl stain. The cortical hemispheres were cut at 50-μm thickness on a freezing microtome in the parasagittal (6 cases) or the frontal plane (6 cases). Five alternate series were cut and used for visualization of retrogradely labeled cells (1 case), Nissl stain, neutral red stain, Klüver-Barrera stain, for myeloarchitecture (Gallyas 1979; as modified by Hess and Merker 1983), and for SMI-32 immunohistochemistry (Hof and Morrison 1995) and Wisteria floribunda agglutinin histochemistry (Brückner et al. 1994). Cortical penetration tracks were reconstructed from serial sections with the aid of the penetration scheme and marking lesions made at certain recording sites. Along these penetration tracks the recording sites of NOT-DTN projecting neurons and of neurons not projecting to the NOT-DTN were marked according to microlesions and the depth reading of the microdrive during the experiment. Two-dimensional reconstructions of the cortex were made by bending wires along layer IV of enlarged drawings of Nissl-stained sections of the entire hemisphere spaced at 2-mm interval for each hemisphere. After indicating landmarks as lip and fundus of sulcus on these wires, they were soldered together appropriately to form three-dimensional models. These models were then unfolded to form two-dimensional maps of the cortical hemisphere (Van Essen and Maunsell 1980). The reconstructed recording sites and myeloarchitectonic borders were then transferred on these maps. The area-specific myeloarchitecture as described in the literature was used to distinguish extrastriate areas V2, V3, V4, V4t, MT, the densely myelinated zone of MST, FST, and LIPv (summarized in Distler et al. 1993). Myeloarchitectonic borders were verified with the material stained for SMI-32 and Wisteria floribunda agglutinin (Cusick et al. 1995; Hof and Morrison 1995).

RESULTS

For this study, a total of 2,139 cortical neurons was recorded from 12 cortical hemispheres of macaques and tested with electrical stimulation in the NOT-DTN ipsilateral to the recorded hemisphere. Of these, 1,957 cells were recorded in areas of the STS, and 182 cells were tested in other regions. Altogether 247 neurons could be antidromically activated from the NOT-DTN, thus comprising 11.5% of our tested sample of cortical neurons (Table 1).

Recording sites

All but 13 antidromic cells were found in the STS. The recording sites of these NOT-DTN projecting neurons as well as recording sites of neurons not projecting to the NOT-DTN are summarized in the two-dimensional maps of the STS of 11 of the 12 hemispheres in Fig. 1, *A–K*. In this figure, recording sites of NOT-DTN projecting cells are indicated by red dots; those of nonantidromically activated cells are shown by open symbols. The areal borders of V4t, MT, the densely myelinated zone of MST (DMZ), and in some cases of the visual area in the fundus of the STS (FST) are shown by broken lines. To facilitate comparison, all maps are shown as left hemispheres. It is clear from Fig. 1 that the bulk of our data comes from area MT (1,717 tested neurons, 221 of these, corresponding to 12.9%, could be driven by antidromic stimulation). Less data stem from area MST and the surrounding cortex [240 neurons tested, 14 antidromic neurons (6.2%)]. Even though we did not cover the whole extent of MT in single experiments, taking all experiments together neurons projecting to the NOT-DTN were found in all subregions of MT. This finding is further emphasized by the summary of recording sites of antidromically identified projection neurons shown in Fig. 1*L*. For this summary we superimposed the maps of all hemispheres and marked the recording sites of NOT-DTN projecting neurons. The dashed lines indicate the approximate common outlines of areas MT and MST in all these hemispheres. Even though some parts of MT may have been sampled more closely than others, the present data, together with recent anatomical results (Distler and Hoffmann 2001), suggest that the NOT-DTN is

TABLE 1. *Summary of the data base*

Case	Cells Tested STS (Other)	NOT Antidromic STS (Other)	NOT Orthodromic	PD Qualitative		PD Quantitative	
				Non	Anti	Non	Anti
Case 1	49 (67)	20 (6)	1	29	3	10	8
Case 2, left	101 (22)	19 (0)	5	40	4	8	4
Case 2, right	105 (17)	11 (1)	3	34	4	1	4
Case 3, right	67 (1)	17 (0)		18	9	11	2
Case 3, left	227 (0)	41 (0)	5	72	9	52	24
Case 4	236 (14)	29 (0)	9	119	19	8	8
Case 5	66 (0)	17 (0)	3	42	11	5	4
Case 6	262 (0)	23 (0)	5	55	8	45	15
Case 7	209 (32)	23 (2)	11	22	12	27	17
Case 8	197 (0)	8 (0)	2	23	2	25	1
Case 9	215 (0)	10 (0)	3	108	5	25	1
Case 10	223 (29)	16 (4)	10	92	9	23	4
Summary	1,957 (182)	234 (13)	57	654	95	240	92

Table 1 summarizes the number of cells tested with electrical stimulation, antidromically identified cells, cells orthodromically activated, and the number of cells in which the directional preference (PD) was determined qualitatively or quantitatively. Numbers in parentheses indicate the number of neurons tested and of antidromic neurons found outside the STS. STS, superior temporal sulcus; NOT, nucleus of the optic tract; anti, antidromically activated from the NOT–dorsal terminal nucleus; non, non-projecting cells.

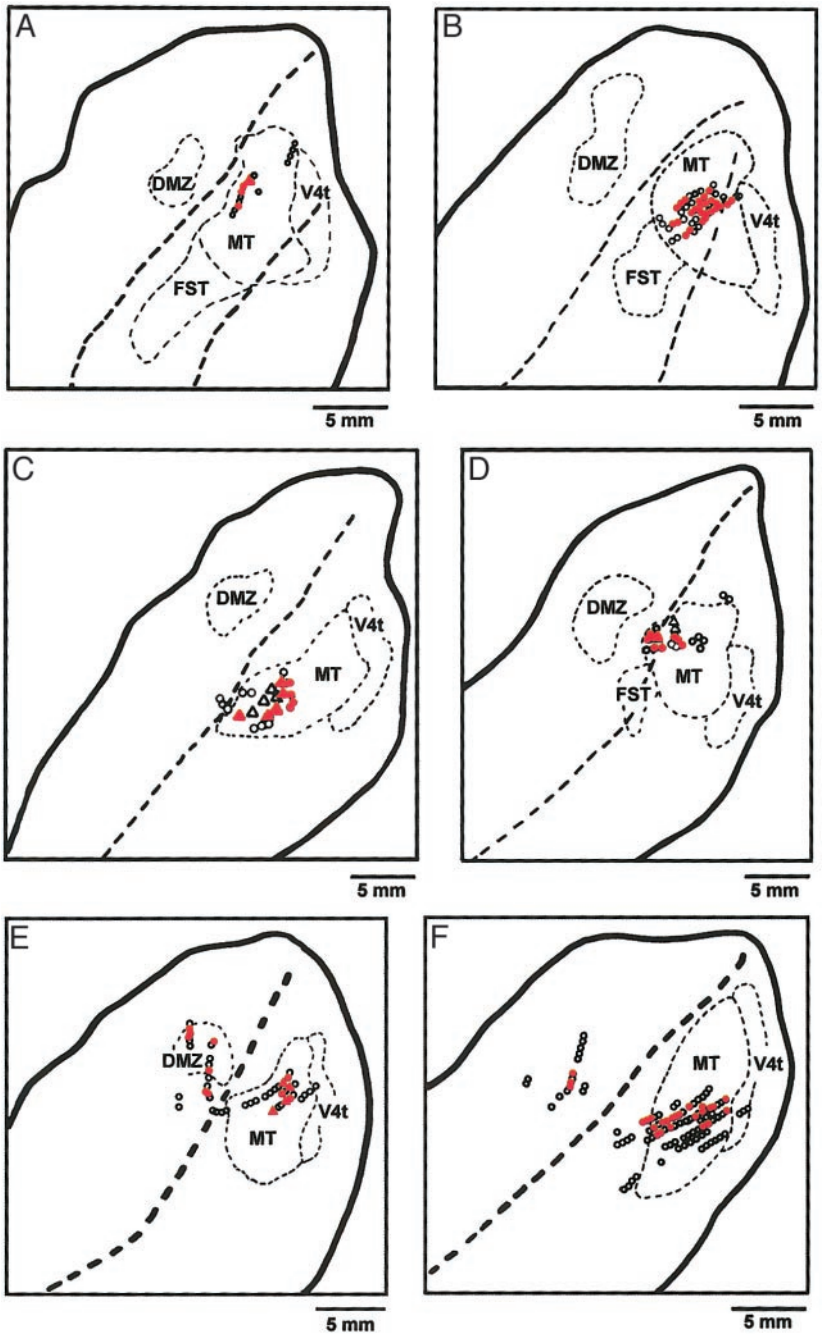

FIG. 1. Flat maps of the posterior part of the superior temporal sulcus (STS) of 11 of the 12 experimental hemispheres. All maps are shown as left hemispheres, i.e., anterior is to the left, posterior is to the right. The thick solid lines indicate the outline of the sulcus; the thick broken lines indicate the fundus of the sulcus. Thin broken lines outline the areal borders of area V4t, the middle temporal area (MT), the visual area in the fundus of the STS (FST), and the densely myelinated zone of the medial superior temporal area (MST) (DMZ) as determined on the basis of myeloarchitecture. Maps in *A, B, G, H, J,* and *K* are derived from frontal sections; maps in *C, D, E, F,* and *I* are derived from sagittal sections. Red symbols mark recording sites of antidromically identified projection neurons; open symbols indicate recording sites of neurons not projecting to the NOT-DTN. In some maps, marking lesions are indicated by triangles. *L* shows a superposition of all maps. Here only the recording sites of antidromically identified projection neurons are shown (red dots), the thin broken lines indicate the approximate average areal outlines of MT and MST. Scale bars indicate 5 mm.

evenly connected with all subregions of MT. Thus there is no subregion of MT (central or peripheral field; horizontal streak) specialized for transmitting information about horizontal stimulus movement to the subcortical optokinetic system.

Antidromic latencies

All stimulation sites were inside the NOT-DTN as ascertained by the characteristic direction specificity of neurons recorded with the same electrode before used for stimulation and verified by anatomical reconstructions. The latencies of antidromic action potentials were determined for 211 of the 234 STS cells. They ranged from 0.9 to 6 ms with most cells having latencies between 1 and 2.6 ms (MT: 2.12 ± 1.08 ms, mean ± SD, $n = 200$, MST: 2.24 ± 1.25 ms, $n = 11$). Because the latencies of MT and MST cells did not differ, data were pooled. The median of the latency distribution was 1.8 ms (Fig. 2*A*). Assuming a conduction distance D between MT and the NOT-DTN of 20–25 mm (see DISCUSSION), the conduction velocity $V = D/\text{Latency} - U$ (U is utilization time, 0.2 ms) (Lemon 1984) falls in a range of 4–30 m/s (median 16 m/s). For 102 neurons the threshold for antidromic activation was determined. Thresholds ranged from 18 μA up to 0.5 mA with 90% of the neurons having thresholds below 250 μA. The median of this distribution was 130 μA. There was a slight correlation between threshold and latency of antidromic action potentials ($r = 0.2368$, $P = 0.0145$) with some neurons with higher thresholds also having longer latencies (Fig. 2*B*). This

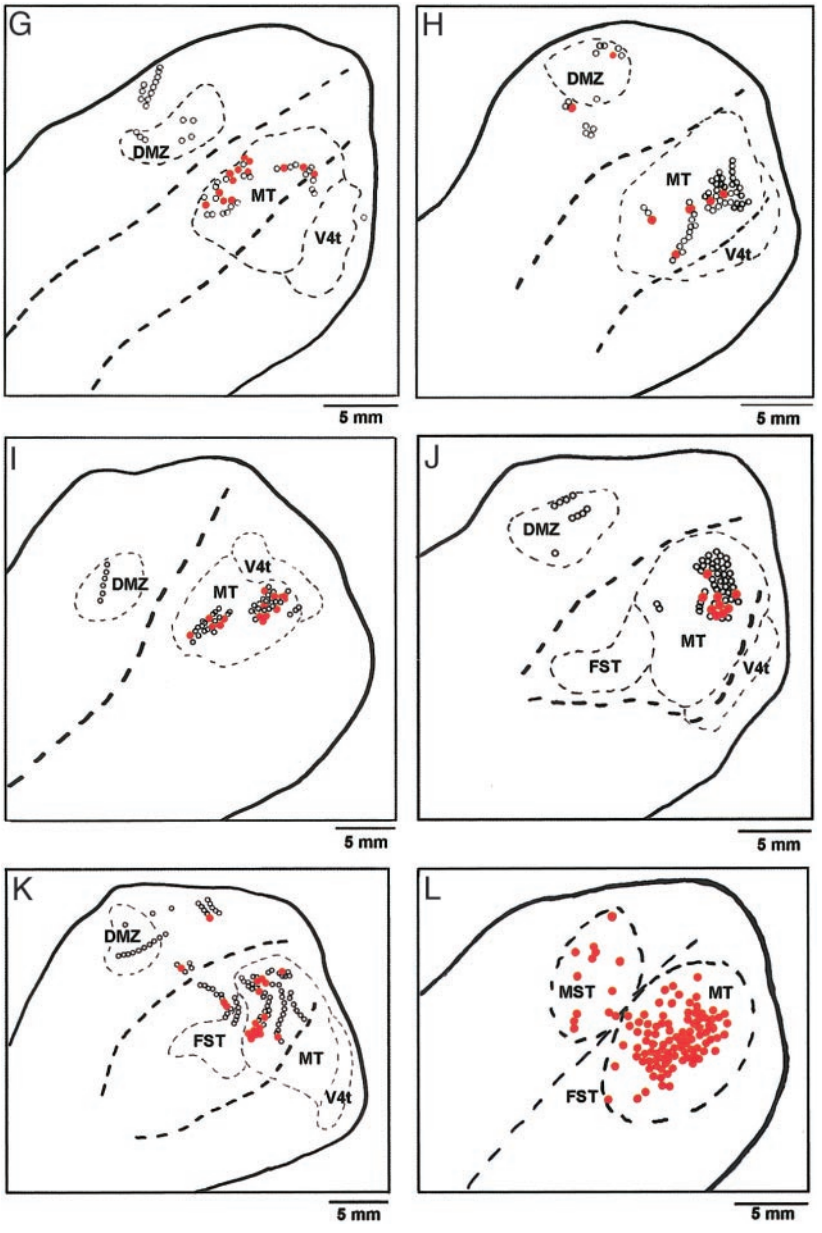

FIG. 1. (*continued*)

suggests that thin fibers with slower conduction velocity and therefore longer latencies can be electrically stimulated only at higher thresholds and that thicker fibers were not regularly stimulated by the spread of current from supramaximal stimulation strengths.

To determine to which degree the unavoidable spread of current during electrical stimulation to neighboring structures, i.e., the SC, the pulvinar, or other pretectal nuclei may have influenced our data, in Fig. 3 we analyzed the thresholds (Fig. 3*A*) and the antidromic latencies (Fig. 3*B*) with respect to the stimulation sites. The anterior-posterior position of the stimulation sites was determined by the distance between stimulation site and the posterior edge of the pretectal olivary nucleus, the position of which was set as anterior 1.0 (Snider and Lee 1961). The mediolateral position had very little variability. We did not find any influence of the position of the stimulation electrode in the NOT-DTN on the thresholds (correlation coefficient, $r = 0.03$) and resulting antidromic latencies (correlation coefficient $r = 0.03$) measured for corticofugal fibers, indicating that even if we involved neighboring structures by our current spread, it did not systematically influence our results.

Orthodromic latencies

In most experiments we also identified few neurons (2.91% of the STS neurons tested with electrical stimulation) that were orthodromically activated by stimulation of the NOT-DTN. Of these neurons 52 were located in area MT, and 5 were located in area MST. Most latencies ranged from 2 to 8 ms (MT: 3.5 ± 3.2 ms, $n = 43$, median $= 2.7$ ms; MST: 3.76 ± 1.67 ms, $n = 5$, median $= 3$ ms). The median of the overall distribution of orthodromic latencies shown in Fig. 4 is 2.75 ms. Again, the data were pooled in Fig. 4 because there was no significant difference between MT and MST cells (Mann-Whitney *U* test, $P > 0.1$). Furthermore, 4 cells were recorded with orthodromic latencies

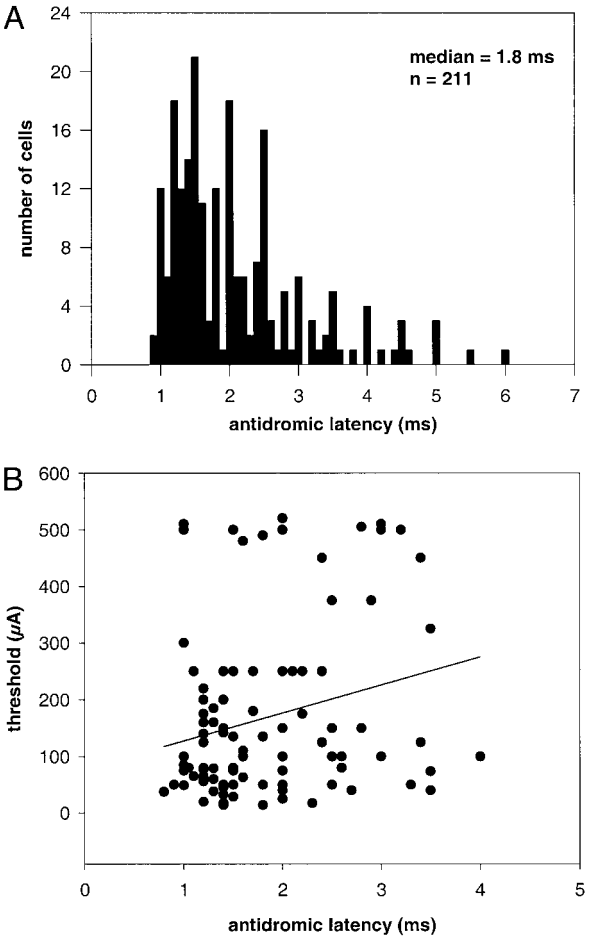

FIG. 2. *A*: frequency distribution of latencies of action potentials of STS neurons elicited by antidromic electrical stimulation in the ipsilateral nucleus of the optic tract and dorsal terminal nucleus (NOT-DTN). Most latencies lie between 1 and 2 ms, with a median of 1.8 ms. Ordinate: number of cells; abscissa: antidromic latencies in ms. *B*: relationship of antidromic latencies (abscissa, ms) and thresholds of excitability (ordinate, μA). There is slight correlation of the 2 parameters indicating that at least some of the fibers with longer latencies have higher thresholds.

ranging from 20 to 40 ms. The orthodromically activated neurons did not show a common direction preference; some of them were non–direction selective. Otherwise they seemed indistinguishable from the antidromic or not activated cells.

Directional preference

A preferred direction could be determined quantitatively for 332 and qualitatively for additional 749 cortical neurons. Most antidromically identified NOT-DTN projecting neurons preferred ipsiversive stimulus movements thus corresponding to the preferred direction of their target neurons in the NOT-DTN. Much less often did NOT-DTN projecting neurons prefer contraversive stimulus movement. By contrast, cortical neurons not projecting to the NOT-DTN did not have a bias for ipsiversive movement as a population. Figure 5 shows the quantitative and qualitative data of all cells separately for 9 of the 10 animals. The data from the 10th animal are omitted because the preferred direction could be tested only in 3 antidromic neurons (*case 8* in Table 1). Cells were grouped according to their preferred direction in upward (90 ± 22.5°), downward (270 ± 22.5°), ipsiversive (180 ± 67.5°), and contraversive (0 ± 67.5°) sectors. We chose this unequal width of the sectors (vertical 45°, horizontal 135°) because our main emphasis was on the ipsi-contra bias. Plus/minus 22.5° from vertical was considered to be within the error range of directional estimates, and neurons in this range were thus counted as either up or down preferring but were not included in the ipsi-contra count. All other neurons were classified as either ipsi- or contraversive preferring. The *left row* of data plots shows the preferred directions of antidromically driven cells; the *right row* shows the neurons not driven antidromically. The direction of the arrows indicates the preferred direction (ipsi, contra, up, down); the length of the arrows mirrors the number of cells preferring this direction. The preferred direction with the maximal cell count was set 100%, and the number of cells preferring other directions was normalized to the direction with the maximal count. The numbers indicate the total number of cells included in the individual plots. All data are shown as if derived from the left hemisphere to facilitate comparison.

The ratio between antidromic cells with ipsiversive preferred direction and contraversive preferred direction is >5:1. For nonantidromical cells it is 1:0.9. This difference between the preferred directions of antidromically identified projection neurons and not antidromically identified neurons is highly signif-

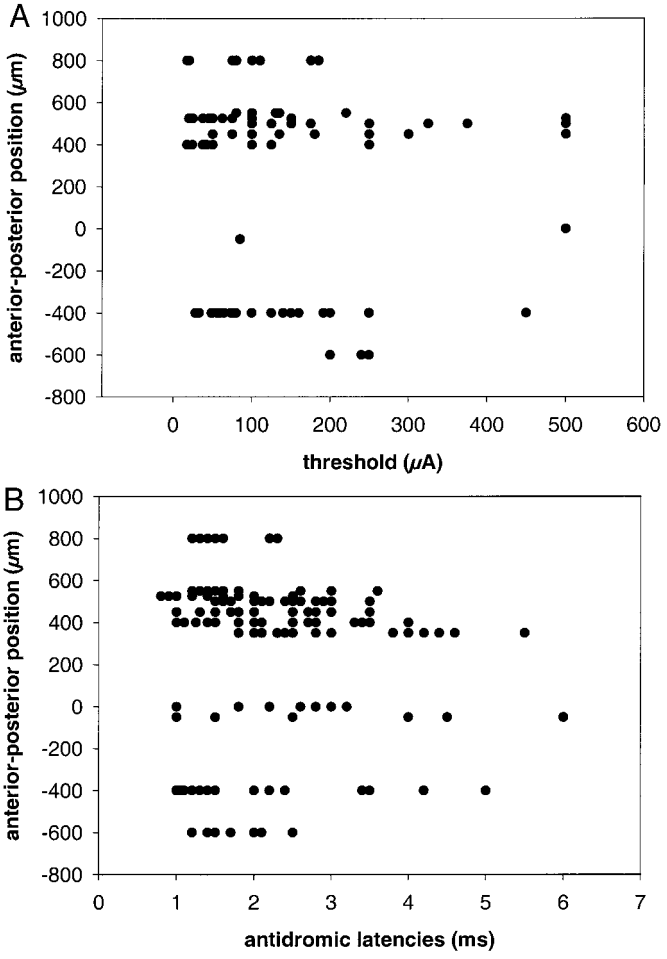

FIG. 3. Influence of the position of the stimulation site within the NOT-DTN given in anterior-posterior coordinates (ordinate; mm) on the thresholds of excitability (*A*) and the antidromic latencies (*B*). There is no significant correlation between these parameters.

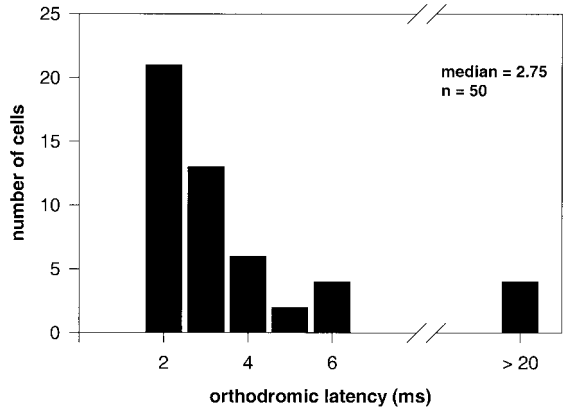

FIG. 4. Frequency distribution of the shortest orthodromic latencies measured at STS neurons after electrical stimulation in the NOT-DTN. The median of the distribution is 2.75 ms. Abscissa: orthodromic latency in ms; ordinate: number of cells.

icant (χ^2 test, $P < 0.0001$) not only on the population level but also in all but one individual cases [χ^2 test, $P < 0.05$ to $P < 0.0001$; in one case the difference was not significant (ipsi: contra = 13:9 neurons)].

There is a clear bias for horizontal stimulus movement also in the group of neurons not projecting to the NOT-DTN, however, not a bias for either ipsi- or contraversive preferring. In part this is due to the unequal sector size used for this analysis (see above). In addition, not antidromic neurons were often sampled near antidromic neurons to specifically compare the properties for pyramidal neurons from layer V. Neighboring neurons in MT often share a preference for the same or the opposite movement direction (Albright 1984; Lagae et al. 1993; Malonek et al. 1994). Further qualitative tests of the direction preference in some of the experiments revealed a similar bias.

When the preferred direction was not absolutely clear-cut along the horizontal axis with qualitative testing or in a quantitative test where only horizontal movement was presented, the preferred direction and tuning width was measured quantitatively using the circular stimulation or a bar grating moving in eight different directions (see METHODS). The polar plots in Fig. 6 show the preferred direction and tuning index of these difficult to judge qualitatively neurons projecting to the NOT-DTN ($n = 56$; *top plot*) and of neurons not projecting to the NOT-DTN ($n = 176$; *bottom plot*) from the same experiments. By this selection of neurons that are not unequivocally direction selective during horizontal stimulation for analysis, more neurons show upward or downward preferred directions than in the total population. The position of the dots within the sectors indicates the preferred direction of the cells; their distance from the origin of the circle indicates their tuning index. Sharply tuned cells are characterized by tuning indexes close to 1 (outer circle). Data from MT and MST were pooled because no difference was obvious. Also, there was no significant difference in the tuning index of NOT-DTN projecting and nonprojecting cortical neurons. The preferred directions of the two populations, however, were significantly different from each other (χ^2 test, $P < 0.01$). Whereas in these quantitatively analyzed populations the preferred directions of the nonprojecting population were not statistically different from a uniform distribution (χ^2 test, $P > 0.1$), the NOT-DTN projecting population again shows a clear bias for ipsiversive preferred directions and was significantly different from an equal distribution (χ^2 test, $P = 0.0023$). Note that the directional preference of most neurons included in this latter analysis was less clear-cut and could not unequivocally be determined by qualitative testing. This may explain the somewhat lower but still highly significant ipsi:contra bias in this subpopulation of cells (3:1 as compared with the >5:1 in the total population; see above). To unequivocally prove the ipsiversive bias in preferred directions also for this NOT-DTN population, we performed descriptive circular statistics (Rayleigh-test) (Batschelet 1981). The mean direction vector (normalized length 0.207) was significantly one-sided to 173° with 180° being horizontally ipsiversive ($P < 0.01$). In the non-projecting population the directions were random, and the mean direction vector length (0.075 at 154°) was not significantly skewed ($P > 0.1$). A quantitative comparison of the NOT-DTN pro-

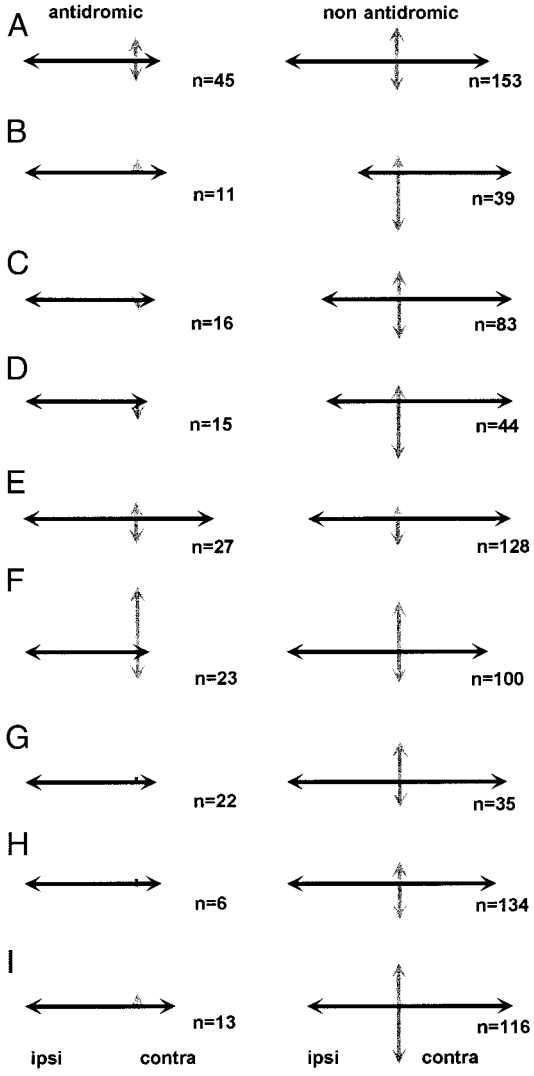

FIG. 5. Preferred directions of stimulus movement of antidromically identified projection neurons (*left row*) and of neurons not projecting to the NOT-DTN (*right row*) of 9 of the 10 animals used in this study. For this case-by-case analysis, both qualitative and quantitative data were included. Again, data were treated as if all were derived from the left hemisphere. Cells were grouped in ipsiversive (112.5–247.5°), i.e., to the left; contraversive (292.5–67.5°), i.e., to the right; and vertical (90 ± 22.5° and 270 ± 22.5°). The numbers next to each plot indicate the number of neurons included. For further explanations, see text.

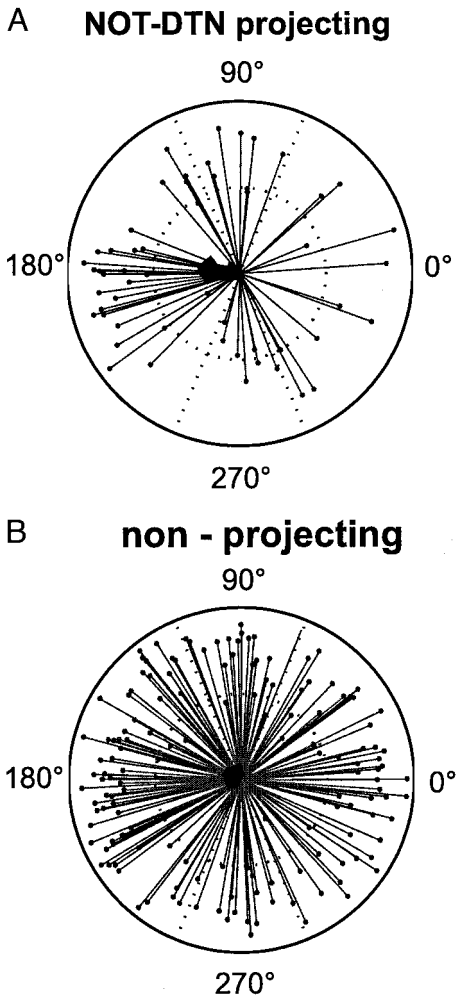

FIG. 6. Quantitative measure of preferred directions and tuning width of cortical neurons projecting to the NOT-DTN (*A*) and not projecting to the NOT-DTN (*B*). The polar diagrams indicate the preferred direction of a neuron (position in the various sectors) as well as the tuning width index: the greater the distance from the origin of the plot, the sharper is the tuning of the cell. Each dot represents one cell; the data are presented as if only recorded from the left hemisphere. Thin dotted lines indicate the sectors of analysis used in Fig. 5 to facilitate comparison.

jecting and nonprojecting populations taking into account both the tuning widths as lengths and the peak directions as angles by Moore's nonparametric modification of the Rayleigh test for directionality (Batschelet 1981) again showed a significant directionality toward 173° ($P < 0.01$), i.e., toward the recorded hemisphere only in the NOT-DTN projecting population but not in the non-projecting population ($P > 0.1$).

DISCUSSION

Location of cortical NOT-DTN projection neurons

In none of the 12 experimental hemispheres included in this study did we find any indication for a cortical area or a subregion of a cortical area specialized for the analysis of ipsiversive horizontal stimulus movement. Most of our data come from area MT, and within MT neurons projecting to the NOT-DTN could be identified both in central and peripheral field representations. This is not surprising because receptive fields in the NOT-DTN are large and include both foveal and peripheral parts of the visual field. Furthermore, there is no clear retinotopic organization in the NOT-DTN. In addition, there are no reports of subregions of MT dedicated to ipsiversive movement. Note, however, that we probably did not sample the exact part of area MT and its surrounding cortex that was damaged in earlier experiments by Dürsteler and Wurtz (1988) producing the direction-selective defects in optokinetic and pursuit eye movements. Electrophysiological recordings and 2-deoxy-glucose studies have revealed a columnar organization of direction selectivity and related response properties in area MT (Albright 1984; Geesaman et al. 1997; Lagae et al. 1993; Malonek et al. 1994). Since most of our penetrations were not perpendicular to the cortical layers, we did not see strong indications for a columnar organization. On the contrary, preferred directions could vary considerably between neurons recorded within 100 μm of each other or they could be quite similar. The fact that NOT-DTN projecting neurons were found in all subregions of MT sampled in this experimental series corresponds well with our anatomical findings. Retrograde tracer injections into the NOT-DTN led to retrogradely labeled neurons in all parts of MT as well as in the surrounding cortex (Distler and Hoffmann 2001).

Fewer antidromically identified cortical neurons were found in area MST. Our sample is clearly biased toward MT [MT: 1,717 tested, 221 (12.9%) antidromic; MST: 240 tested, 14 (6.2%) antidromic]. Nevertheless, our data indicate that a higher proportion of MT neurons than of MST neurons projects to the NOT-DTN. However, because MST was not sampled in all of the experiments, we cannot adequately compare the prevalence of NOT-DTN projecting neurons in the two areas.

Some NOT-DTN projecting neurons were identified in area V1 as well as in areas V2 and V3 in the depth of the lunate sulcus. Again, these physiological findings confirm earlier anatomical results from anterograde and retrograde tracing studies where a consistent albeit weaker projection to the NOT-DTN was found to arise from V1, V2, and V3 (Distler and Hoffmann 2001; Hoffmann et al. 1991).

Input to areas MT and MST from the NOT-DTN

Surprisingly almost 3% of the neurons recorded in MT/MST were orthodromically activated with short latency (<3 ms) by electrical stimuli applied to NOT-DTN. We have no evidence for a direct projection from the pretectum to the visual areas in the STS. We assume a disynaptic pathway via the pulvinar or other thalamic nuclei for the connection between the pretectum and the visual areas in the STS because the orthodromic latencies are about 1 ms longer than the antidromic ones. Similar differences between orthodromic and antidromic latencies were reported in a study of connectivity between frontal eye field and SC (Sommer and Wurtz 1998), and these authors have shown recently that this pathway from the colliculus to the frontal cortex is relayed via thalamic nuclei.

Other studies identifying corticofugal neurons by antidromic stimulation in the midbrain

There are only few studies investigating cortical projections to the midbrain using antidromic identification of projection neurons. Nevertheless, we can compare the thresholds and antidromic latencies found in our study with those reported for

cortical neurons in the FEF and the lateral intraparietal area (LIP) that project to the SC (Paré and Wurtz 1997; Sommer and Wurtz 2000). Due to the close neighborhood of LIP and MT and, therefore the similar cortex-midbrain conduction distances, the LIP data are directly comparable to our study: the latency range for LIP-SC neurons was 0.8–11 ms (Paré and Wurtz 1997), for our MT-NOT/DTN neurons it was 0.9–6 ms. Also the thresholds for eliciting antidromic action potentials were similar for both neuronal populations [LIP-SC: mean 196–304 μA (Paré and Wurtz 1997), MT-NOT-DTN: 228 μA, this study]. When comparing our MT-NOT/DTN latencies with the FEF-colliculus data from Sommer and Wurtz (1998), one has to take into account the greater distance between FEF and SC ($\sim$40 mm) (Segraves and Goldberg 1987) than between MT and NOT-DTN ($\sim$20–25 mm reconstructed from NMR images of the brains of our monkeys and from Fig. 6 of a study by Tusa and Ungerleider (1988). We therefore calculated the conduction velocity to be 4–30 m/s (median 16 m/s) from MT to NOT-DTN, which is slower than the conduction velocity from FEF to the colliculus with 7–34 m/s (Segraves and Goldberg 1987) or $<$10 to $>$80 m/s (Sommer and Wurtz 2000). These values confirm that the corticopretectal neurons in MT have thinner axons and probably smaller somata than the corticotectal neurons in FEF (Fries 1984) but are similar to the corticotectal neurons from LIP. This leads, however, to the astonishing fact that the latencies from cortex to the midbrain are rather similar irrespective of the output area and conduction distance.

So far no other study has investigated the projection from area MT and MST to other nuclei in the midbrain by antidromic stimulation. We are in the process of completing a similar study to the present one with antidromic stimulation in the dorsolateral pontine nucleus while recording in MT and MST. In this cortico-pontine population we did find a uniform distribution of the preferred directions contrasting our present result for the NOT-DTN projecting population (Hoffmann et al. 2000).

Segraves and Goldberg (1987) reported in their study of neurons in the FEF antidromically identified from the SC that purely saccade related signals are overrepresented and purely visual-related signals are underrepresented in this projection. Sommer and Wurtz (2000) also examined the composition and topographical organization of signals flowing from the FEF to the SC by recording a larger sample of FEF neurons that were antidromically activated from rostral or caudal SC. Their first and most general result was that, in a sample of 88 corticotectal neurons, the types of signals relayed from FEF to SC were highly diverse, reflecting the general population of signals within FEF rather than any specific subset of signals. They conclude that the FEF most likely influences the activity of SC neurons continuously from the start of fixation, through visual analysis and cognitive manipulations, until a saccade is generated and fixation begins anew. Furthermore, the projection from FEF to SC is highly topographically organized in terms of function at both its source and its termination.

Paré and Wurtz (1997) investigated the connection between the posterior parietal cortex (PPC) and the SC by antidromically activating neurons within the LIP area with single-pulse stimulation delivered to the intermediate layers of the SC and found that the neuronal signal sent by LIP to the SC carries both visual and saccade-related information. Antidromically identified neurons in LIP resemble SC buildup neurons in that they are also active during the delay period in a visual and a memory-guided saccade task. Taken together, the authors conclude that properties of these antidromically identified neurons in LIP are consistent with the characteristics of most neurons in LIP and therefore form no subpopulation.

Our present data indicate that the information transmitted from the motion-sensitive areas MT and MST to the NOT-DTN is highly nonuniform concerning the preferred direction of motion. A subpopulation mostly preferring ipsiversive movement projects to the NOT-DTN. This finding based on a large population of neurons (247 antidromically identified cells in 12 cases) is highly significant, and doubts on the validity of our previously published results (Ilg and Hoffmann 1993) by Sommer and Wurtz (2000) can definitely be rejected. Thus it seems that the various corticofugal systems differ not only in their overall quality of information but also in the selectivity of information from within an area they transmit to subcortical centers like the SC or the NOT-DTN.

What leads to the ipsiversive bias in the cortical projection to the NOT-DTN?

Is our result an artifact of selectively stimulating subpopulations of terminals or corticofugal fibers from MT and MST in the NOT-DTN? The assertion is made that stimulating at the physiologically identified site of the putative postsynaptic neurons of corticofugal fibers gives us the least possibility of artifacts from stimulating fibers of passage or nearby structures as well. The possibility always remains that many more cortical fibers project to the NOT-DTN that our stimulating electrodes did not reach, but we have no arguments against the assumption that they should have the same asymmetric direction selectivity distribution. In fact all actual stimulation sites distributed over the entire NOT-DTN gave rise to an asymmetric direction selectivity distribution (Fig. 5). In all but one case these asymmetries were statistically significant.

A more likely explanation is a selective selection of cortical input by the postsynaptic NOT-DTN neurons. If the Hebbian rule that only synapses between neuronal elements firing in a correlated manner are being consolidated during development applies also for the cortico-subcortical projection from area MT to the ipsilateral NOT-DTN, one can postulate that only neurons that share the same direction selectivity will be connected. The probability of occurrence of action potentials in close temporal correlation should be higher in groups of neurons coding for the same stimulus, i.e., the same direction of stimulus movement, than in neurons reacting to different stimuli, i.e., different directions of stimulus movement (Hoffmann 1987). Recent data from wallabys in which the anlage of the eye had been rotated at a very early stage in development unequivocally indicate that the direction selectivity in the NOT-DTN depends on direction-selective influences from the retina (Hoffmann et al. 1995). Under the presumption of the Hebbian rule, one can assume that, after the direction selectivity in the NOT-DTN has been predetermined by the retinal input early during development, the direction-selective NOT-DTN neurons will then consolidate only terminals from cortical axons that code for the same direction.

Functional considerations

In normal cats, monkeys, and humans, monocularly as well as binocularly elicited slow eye movements are largely equivalent during clockwise and counterclockwise stimulation (symmetrical OKN). Unilateral cortical lesions lead to an impaired reaction during stimulation toward the lesioned side, whereas slow eye movements toward the intact side are normal. This finding can now readily be explained by the loss of a specific population of neurons in the visual cortical areas MT and MST coding for this direction of movement and providing the input to the NOT-DTN. In line with this hypothesis are the results from electrical stimulation of MT/MST during ongoing pursuit. This manipulation increased eye velocity when the eye moved towards (ipsiversive) and decreased eye velocity when it moved away from the stimulated hemisphere (Komatsu and Wurtz 1989). These authors hypothesize that the directional bias for pursuit originates in the visual signal conveyed to the pursuit system. The present study shows that the NOT-DTN receives such a visual signal and, to our knowledge, is the only structure receiving such a biased visual signal from MT and MST.

In monkeys as well as in humans with early onset esotropia, pursuit with monocular viewing was much stronger for nasalward motion than for temporalward motion, especially for targets presented in the nasal visual field (Kiorpes et al. 1996). Single-unit recordings made from the same monkeys revealed that MT neurons were rarely driven binocularly, but otherwise had normal direction-selective response properties. Most importantly their direction preferences were uniformly distributed. These authors conclude that the pursuit defect in these monkeys is not due to altered cortical visual motion processing and suggest that the asymmetry in pursuit may be a consequence of imbalances in the two eyes' inputs to the "downstream" areas responsible for the initiation of pursuit. We suggest that one of these downstream areas is the NOT-DTN. Because, if in strabismic primates the cortical influence on the NOT-DTN preferring ipsiversive stimulus motion is much stronger from the contralateral eye than from the ipsilateral eye, the right eye then would automatically have a high gain through the left NOT-DTN during stimulus movement to the left (nasalward) but not in the opposite direction (temporalward). The opposite directions would hold true for the left eye.

In summary, the cortical projection to the NOT-DTN seems not only to be involved in optokinetic eye movements but also in pursuit and also may play a role in the initiation and support of the short-latency ocular following response. Consequently, lesions of one hemisphere or the ipsilateral NOT-DTN should lead to the same asymmetric deficits also in these oculomotor functions (Inoue et al. 2000; Yakushin et al. 2000).

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