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Visual response properties of neurons in cortical areas MT and MST projecting to the dorsolateral pontine nucleus or the nucleus of the optic tract in macaque monkeys

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Abstract

Neurons in cortical medial temporal area (MT) and medial superior temporal area (MST) projecting to the dorsolateral pontine nucleus (DLPN) and/or to the nucleus of the optic tract and dorsal terminal nucleus (NOT-DTN) were identified by antidromic electrical stimulation in five macaque monkeys. Neurons projecting to either target were located in close proximity to each other, and in all subregions of MT and MST sampled. Only a small percentage of the antidromically identified projection neurons (4.4%) sent branches to both the NOT-DTN and the DLPN. Antidromic latencies of neurons projecting to the NOT-DTN (0.9–6 ms, median 2.1 ms) and to the DLPN (0.8–5 ms, median 2.0 ms) did not differ significantly. Visual response properties of the neurons antidromically activated from either site did not differ significantly from those of cells that were not so activated. On the population level only neurons activated from the NOT-DTN had a clear preference for ipsiversive stimulus movement, whereas the neurons activated from the DLPN and neurons not antidromically activated from either target had no common directional preference. These results are discussed in terms of specification of cortico-subcortical connections and with regard to pathways underlying slow eye movements in different visuomotor behaviours.

Introduction

One of the most interesting questions in systems neuroscience concerns the functional specificity and impact of information being exchanged between specific brain areas via their projection neurons. The literature contains a wealth of information about cortico-cortical and cortico-subcortical connectivity mainly based on extensive anatomical tracing studies. Even more decisive for the above question, for some areas the anatomical studies were supplemented by electrophysiological methods using orthodromic or antidromic electrical stimulation. In particular the analysis of response properties of antidromically identified neurons allows the assessment of the information being exchanged between areas (Finlay *et al.*, 1976; Segraves, 1992; Movshon & Newsome, 1996; Ferraina *et al.*, 2002; Churchland & Lisberger, 2005).

The neural substrate for the control of slow eye movements is well suited for this kind of investigation because, first, various visual and visuo-motor cortical and subcortical regions have been identified by functional criteria and, second, lesion studies link certain areas with specific deficits in oculomotor behaviour.

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Besides striate cortex, the motion-sensitive medial temporal area (MT) and medial superior temporal area (MST) in the superior temporal sulcus (STS) are thought to be specifically involved in the control of specific eye movements. This is because lesions of these areas cause deficits in smooth pursuit and optokinetic nystagmus as well as ocular following tracking eye movements with ultra-short latency (Newsome *et al.*, 1985; Segraves *et al.*, 1987; Duersteler & Wurtz, 1988; Komatsu & Wurtz, 1988; Takemura *et al.*, 2002, 2007).

At the subcortical level, direction-specific neuronal responses to large area as well as small visual stimuli and the fact that localized lesions cause specific oculomotor deficits have implicated the dorsolateral pontine nucleus (DLPN) as well as the pretectal nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN) in the subcortical control circuits for smooth pursuit, ocular following and the optokinetic reflex (OKR). Unresolved, however, is whether or not these nuclei are differentially involved in smooth pursuit, ocular following or OKR (Keller & Crandall, 1983; Suzuki & Keller, 1984; Kato *et al.*, 1986; Hoffmann *et al.*, 1988, 1995; May *et al.*, 1988; Mustari *et al.*, 1988; Simpson *et al.*, 1988; Thier *et al.*, 1988, 1991; Volchan *et al.*, 1989; Mustari & Fuchs, 1990; Schiff *et al.*, 1990; Suzuki *et al.*, 1990; Ilg & Hoffmann, 1993; Ilg *et al.*, 1993; Wallman, 1993; Inoue *et al.*, 2000; Yakushin *et al.*, 2000; Hoffmann & Fischer, 2001).

Anatomical studies have shown that both MT and MST project to the DLPN and to the NOT-DTN (e.g. Maunsell & Van Essen, 1983;

Ungerleider *et al.*, 1984; Boussaoud *et al.*, 1992). In recent anatomical experiments we quantitatively determined that the main cortical input to the NOT-DTN originates from area MT, whereas the main input to the DLPN comes from MST. Nevertheless, neurons projecting to the NOT-DTN and/or the DLPN overlapped extensively in the posterior STS, including areas MT and MST. However, only about 4% of the labelled neurons were double-labelled, suggesting that only a minority projects to both targets (Distler & Hoffmann, 2001; Distler *et al.*, 2002). This raises the question whether the two distinct cortical populations may transmit different information to their subcortical targets.

In order to find out in what respect the two corticofugal projections may differ or are alike, we antidromically identified neurons in areas MT and MST that project to the NOT-DTN and/or the DLPN, and compared their antidromic latencies as well as their response properties to a variety of visual stimuli.

Materials and methods

Subjects

All experiments were approved by the local ethics committee and carried out in accordance with the Deutsche Tierschutzgesetz of 12 April 2001, the European Communities Council Directive of 24 November 1986 (86 609 EEC), and NIH guidelines for care and use of animals for experimental procedures. Adult macaques (*Macaca mulatta*), one female and four males were used for the present investigation. All animals had also taken part in other projects (Paolini *et al.*, 2000; Hoffmann *et al.*, 2002).

Surgery

Animals were initially anaesthetized with ketamine hydrochloride (10 mg/kg i.m., Pharmanovo, Hannover, Germany), intubated through the mouth, and an intravenous catheter was introduced into the saphenous vein. Then the animals were placed into a stereotaxic apparatus and artificially ventilated throughout the experiment with nitrous oxide : oxygen as 3 : 1 containing 0.3–1% halothane as needed according to the heart rate during algetic stimuli (high concentrations during surgery, 0.3–0.5% during recording). After additional local anaesthesia with bupivacain hydrochloride 0.5% (Bupivacain®, DeltaSelect, Pfullingen, Germany) or prilocainhydrochloride 0.5% (Xylonest®, Astra Zeneca, Wedel, Germany), the skin overlying the skull was cut and craniotomies performed to allow access to the midbrain, the brainstem and the STS. Heart rate, SPO_2, blood pressure, body temperature and end-tidal CO_2 were monitored constantly and kept at physiological levels. The corneae were protected with contact lenses chosen with a refractrometer (Rodenstock®) to focus the animals' eyes on the projection screen.

The NOT-DTN was localized in vertical penetrations in the frontal plane based on its position relative to the foveal representation in the superior colliculus (SC) and on its characteristic preference for ipsiversive stimulus movement (Hoffmann *et al.*, 1988). The pons was approached from the contralateral side. The electrode was angled 20° relative to vertical in the frontal plane. The DLPN was identified based on: (i) stereotactic coordinates; and (ii) its direction-selective response properties (Mustari *et al.*, 1988). Motion-sensitive areas MT and MST in the STS were approached either orthogonally, 45° from lateral or 60° from posterior. In some of the animals anatomical NMR scans of the head were available to guide the electrode approach.

Electrical stimulation

After the NOT-DTN and the DLPN had been localized and the response properties documented, the tungsten in glass microelectrodes were left in place to be used as stimulating electrodes. Electrical stimulation consisted of 100 μs wide single pulses at stimulus strengths varying between 10 μA and 1 mA. Antidromic action potentials were identified based on their very constant latencies and shapes, and by collision tests where spontaneous spikes are used to trigger the electrical stimulation at various delays and progressively greater strengths (Fuller & Schlag, 1976). If the delay is equal to 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 spike travelling along the same axon in opposite directions.

Visual stimulation

First, receptive fields were plotted for both eyes separately. We did not align the eyes because in all cases the receptive field separation was smaller than 2°. When tested binocularly responses did not differ qualitatively from the monocular response through the dominant eye. Whole-field visual stimulation consisted of large area random dot patterns projected by a slide projector via mirrors mounted on an *X–Y* galvanometer system to move the pattern on a circular path over a tangent screen (60° wide), which could be adjusted to different azimuths along a semicircle (radius 135 cm) with the animal in the centre. The circular path of the pattern was optimized by adjusting the gain of the galvanometers separately. In addition, random dot patterns were generated by a Silicon Graphics Workstation (Indigo2 High Impact) in real time (temporal resolution: 72 Hz, spatial resolution: 1280 × 1024 pixel) using Performer 2.1 software and were back-projected onto a large tangent screen 48 cm in front of the monkey by a video projector (Elektrohome 4100). The size of the projection covered a visual field of 90 × 90°. These stimuli also moved on a circular path and/or expanded or contracted in the frontoparallel plane. In some experiments sinewave gratings moving in eight different directions were presented on a computer screen. One or more of these different stimuli were employed to determine the neurons' direction selectivity. Computer-generated stimuli simulating self-motion across a plane were also projected on the tangent screen in front of the animal. Finally, small moving spots or bars were presented.

The random dot patterns consisted of sequences with 500 white dots (1° diameter) on a black background. As described previously (e.g. Bremmer *et al.*, 1997), by adding a sinusoidal position change in the *X*- and a cosine in the *Y*-axis the trajectory of the movement consists of a continuously changing translation of the whole stimulus pattern forming a circular pathway in the frontoparallel plane. Adding a sinusoidal movement along the *Z*-axis (expansion and contraction) and a cosine movement along the *X*- or *Y*-axis generates a circular stimulus pathway in the horizontal or sagittal plane, respectively. In this way the observer viewed a virtual 3D cloud of random dots presented on a flat screen perpendicular to his visual axis while undergoing pure translation along circular paths whose axes could be either horizontal and parallel to the screen (random dots would move up and down in addition to expanding and contracting) or vertical and parallel to the screen (random dots would move to the left and right in addition to expanding and contracting). The foci of expansion/contraction traversed only the horizontal and vertical meridians passing through the screen centre. For further information see the videos in the supplementary material. For a human observer these stimuli viewed

bi- or monocularly created a vivid impression of 3D movements. From the responses to these stimuli each cell's direction preference in the frontoparallel plane and its sensitivity to expansion or contraction of the full-field stimulus was determined. By combining continuous movement in the fronto-parallel and sagittal plane in clockwise and counterclockwise directions, expansion or contraction each appeared in four conditions. This allowed us to determine whether a response to expansion or contraction was a side-effect due to local stimulus motion or whether this was a 'real' response feature. Six hundred milliseconds after trial onset the stationary random dot pattern appeared on the screen. After 250 ms it started to move for 2500 ms, i.e. 1.25 cycles with a tangential velocity of ∼40°/s. Then it stopped moving and vanished from the screen after an additional 250 ms.

In another set of experiments, we presented optic flow fields that simulated self-motion with respect to a flat horizontal plane. Stimuli simulated realistic, natural flow fields that could have been experienced by the animal during combined self-translation and eye rotation, or during self-translation alone, over a virtual horizontal plane 37 cm below eye level. Simulated forward speed was 1 m/s. The virtual ground plane was a large textured plane that used the texture-mapping hardware of the computer. Individual texture elements grew in size as they approached the observer.

Three different headings, straight ahead or 30° left or right, were tested in each of three eye movement conditions. In the first condition (no simulated eye movements), a pure radial flow pattern (with shifted singularity depending on the heading direction) was presented (for comparison, see Lappe *et al.*, 1998; their fig. 17a). In the other two conditions the same simulated self-motion was combined with simulated eye movements, thereby distorting the retinal flow pattern but keeping the simulated heading intact (for comparison, see Lappe *et al.*, 1998; their fig. 17B and C). Spontaneous eye movements elicited by radial optic flow in monkeys have a gain < 1, typically in the range of 0.5 (Lappe *et al.*, 1998). The gain of the tracking eye movement is defined as the eye speed in the direction of the stimulus motion on the fovea divided by the stimulus speed on the fovea. We therefore used two conditions of simulated eye movements, one which simulated perfect tracking with gain 1.0 and one which simulated the typical behaviour during spontaneous eye movements, i.e. a gain of 0.5. In all cases, the stimulus covered the lower half of the projection screen. The horizon (upper border of the stimulus) was positioned about 5° above eye level.

Data analysis

The neurons' preferred direction (PD) of stimulus movement within each movement plane (frontal, horizontal and sagittal) was determined using the weighted average method, i.e. each spike was weighted by the stimulus direction corrected for the neuron's latency (see below). All these directional values were averaged, resulting in the PD of the neuron. In order to determine the neuron's PD in full 3D movement space, we weighted each 2D PD vector with the neuron's discharge along this stimulus direction and then averaged these values for each movement axis (left–right, forward–backward, up–down) individually. In order to determine the tuning width, we considered the distribution of spikes around this PD. We first determined the total number of spikes elicited by a full stimulus cycle. The half tuning width was considered the stimulus direction interval for which 25% of the spikes were encountered. This estimate was obtained independently for stimuli shifted in clockwise (cw) and counterclockwise (ccw) directions with respect to the neuron's PD. The full tuning width was obtained as the sum of absolute values of the half tuning widths.

A stimulus moving on a circular path changed direction continuously, i.e. the neuronal response observed at time $t = x$ ms was related to the stimulus direction at time $t = (x$ – latency) ms. Thus, the computation of a cell's PD included latency correction. Average firing rates of the neuronal response during stimulation along a circular path were usually determined over two 400 ms periods centred in the temporal domain at a point corresponding to the cell's PD and non-preferred direction (NPD), respectively. Differences in activity between these PD and NPD responses were tested for statistical significance with a Mann–Whitney rank test. For a population analysis we averaged the responses of all neurons for the respective planes. For statistical analysis we used a Rayleigh test (Batschelet, 1981).

Histology

At the end of the experiments, the animals were killed with an overdose of pentobarbital. The histological procedures used for this and related studies were published recently (Distler & Hoffmann, 2001). For verification of the stimulation sites the midbrains were cut frontally at 50 μm, and Nissl and Klüver–Barrera stains were performed. The stimulation sites were reconstructed at a microscope (Zeiss Axioskop) with camera lucida (Fig. 1). For reconstruction of the cortical recording sites the cerebral hemispheres were cut in the frontal (four cases) or parasagittal plane (one case). Serial sections were cut in five alternate series, and stained for Nissl, Klüver–Barrera, neutral red, myeloarchitecture (Gallyas, 1979; as modified by Hess & Merker, 1983), SMI-32 (Hof & Morrison, 1995) and Wisteria floribunda agglutinin (WFA; Brückner *et al.*, 1994). Cortical penetration tracks were reconstructed from serial sections with the aid of the penetration scheme, and electrolytic microlesions placed at identified recording sites. Recording sites of NOT-DTN-projecting, DLPN-projecting and other neurons were marked on these tracks according to the location of the microlesions and the depth reading on the microdrive during the experiment.

Two-dimensional cortical reconstructions were made by bending wires along layer IV of enlarged drawings of Nissl-stained sections through the entire hemisphere spaced 2 mm apart. Landmarks as lip and fundus of sulcus were marked on the wires, which were then soldered together appropriately to form 3D models. These models were unfolded into 2D maps of the hemispheres (Van Essen & Maunsell, 1980).

Borders of cortical areas were determined based on myeloarchitecture and SMI-32 and WFA staining as described in the literature (summarized in Distler *et al.*, 1993; Cusick *et al.*, 1995; Hof & Morrison, 1995). These areal borders together with the identified recording sites were then transferred onto the 2D maps of the cortex (Fig. 2).

Results

The present investigation is based on five cases (Figs 1 and 2). Altogether, 1208 cortical neurons were tested with antidromic stimulation in the NOT-DTN and the DLPN. Of these neurons, 1010 were located in area MT and 198 in the dorsal part of MST (MSTd). Of 182 antidromically identified projection neurons, 72 neurons projected to the NOT-DTN (39.6% of our antidromic sample; 70 were located in MT, two in MSTd), 102 neurons projected to the DLPN (56% of our antidromic sample; 80 were located in MT, 22 in MSTd). Only eight neurons projected simultaneously to both the NOT-DTN and the DLPN (4.4% of our antidromic sample; seven were located in MT, one in MSTd; Table 1). A differential picture emerged if the success rate to record antidromic cells by stimulation in the

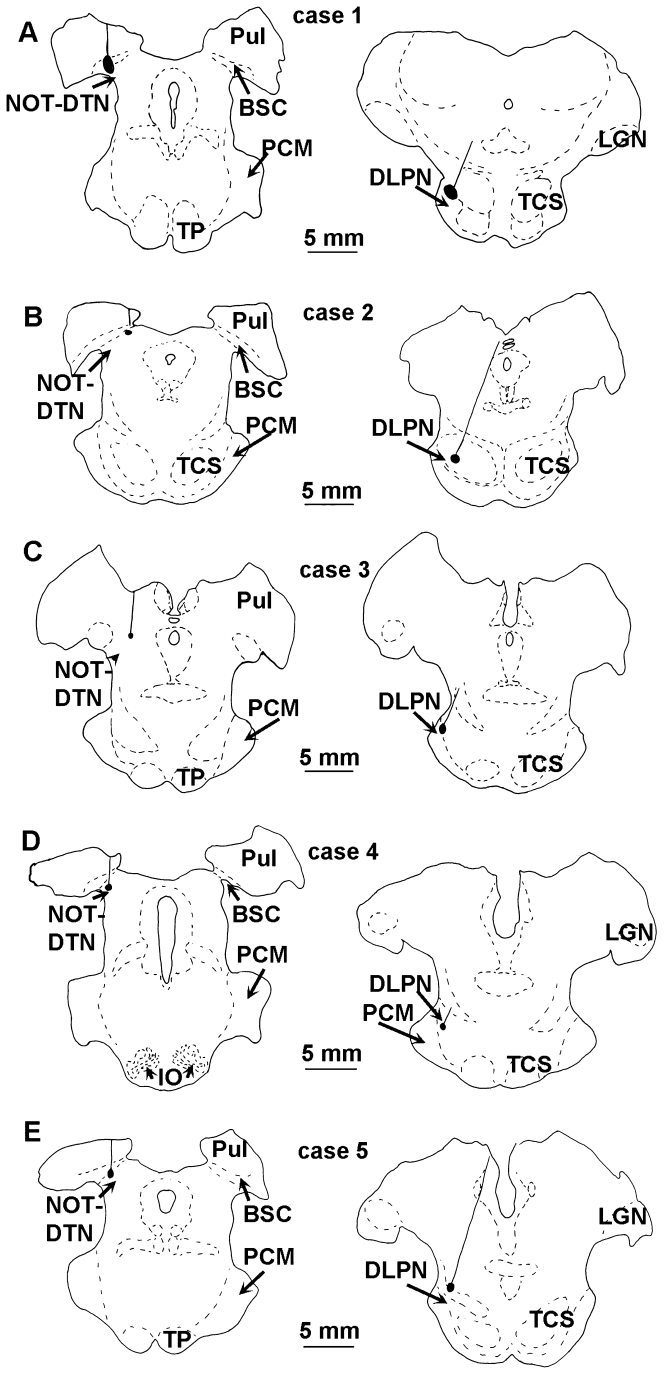

FIG. 1. Line drawings of frontal sections through the pretectum and brainstem showing the location of the stimulation sites in the NOT-DTN (left row) and the DLPN (right row) of the five cases (A–E). The stimulation sites are shown as black areas, at least part of the penetration track is shown as well. All experiments are presented as left hemispheres. BSC, brachium of the superior colliculus; DLPN, dorsolateral pontine nucleus; IO, inferior olive; LGN, lateral geniculate nucleus; NOT-DTN, nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system; PCM, pedunculus cerebellaris medialis; Pul, pulvinar; TCS, tractus corticospinalis; TP, tractus pyramidalis. Scale bars: 5 mm.

NOT-DTN vs. the DLPN was considered. Whereas the percentage of cells antidromically identified in MT from the NOT-DTN and from the DLPN was almost equal (7–8%), only 1% of the cells in MSTd could be antidromically identified from the NOT-DTN against 11% from the DLPN (χ^2-test, $P < 0.001$).

Stimulation and recording sites

Figure 1 summarizes the stimulation sites in the NOT-DTN (left row) and the DLPN (right row). Although the targets were always identified by their characteristic response properties as described in the literature (e.g. Hoffmann *et al.*, 1988; Mustari *et al.*, 1988), there was some variability in the placement of the electrodes. Comparison with Table 1 does not indicate any clear correlation of stimulation site and number of antidromically identified neurons. For example, the pontine stimulation site in case 1 (Fig. 1A) was rather more anterior than in the other cases, yet it yielded numbers of antidromically identified projection neurons comparable to those of cases 2 and 3. By contrast, the NOT-DTN stimulation site of case 3 (Fig. 1C) was far more anterior than in other cases and yielded only a few antidromically identified projection neurons.

Figure 2 documents the cortical recording sites on 2D maps of the posterior STS of the five cases. Recording sites of neurons projecting to the NOT-DTN are marked by red dots, those of neurons projecting to the DLPN by green dots, recording sites of neurons projecting simultaneously to the NOT-DTN and the DLPN are marked by yellow dots. Open circles represent recording sites of neurons that could not be antidromically driven from either target. Cortical neurons projecting either to the NOT-DTN or the DLPN could be found in all subregions of MT and MSTd sampled in the present investigation. There was no clustering of projection neurons in certain parts of MT or MSTd, for instance the foveal representation. Within single penetrations, neurons projecting to the DLPN could be recorded in direct proximity to NOT-DTN-projecting neurons or to non-antidromically activated neurons and vice versa. We did not attempt to relay our recording sites to specific cortical layers. Thus, neurons that could not be antidromically activated could have been located in cortical layers outside layer V. In our sample, neurons projecting both to the NOT-DTN and the DLPN were found in three out of five animals. In two of these three cases double-projecting cells were found in MT or in close neighbourhood to MT, in one case in MSTd (Fig. 2; Table 1). Neurons with axons branching to both targets were found primarily in the anteriomedial part of MT where the more peripheral part of the horizontal meridian is represented (e.g. Gattass & Gross, 1981).

Antidromic latencies

Antidromic latencies measured for MT and MSTd neurons after electrical stimulation in the NOT-DTN ranged from 0.9 to 6 ms with a median of 2.1 ms ($n = 72$), antidromic latencies after stimulation in the DLPN ranged from 0.8 ms to 5 ms with a median of 2.0 ms ($n = 110$). Figure 3 shows the frequency distributions of antidromic latencies after stimulation in the NOT-DTN (Fig. 3A) and the DLPN (Fig. 3B). There was no significant difference between NOT-DTN and DLPN latencies, or between MT and MSTd neurons (Mann–Whitney rank test).

Directional preference in the frontoparallel plane

The neurons' PD was determined for 616 cortical neurons either qualitatively or quantitatively. To test whether the population of DLPN-projecting neurons had a biased directional preference as shown for the NOT-DTN-projecting neurons (Hoffmann *et al.*, 2002), we sorted the PD of each neuron into eight 45° sectors: upward, downward, ipsiversive, contraversive and the oblique directions. The results of all neurons of the five monkeys whose directional preference was determined either quantitatively or qualitatively are shown in Fig. 4. The left row of plots shows the PD of neurons antidromically

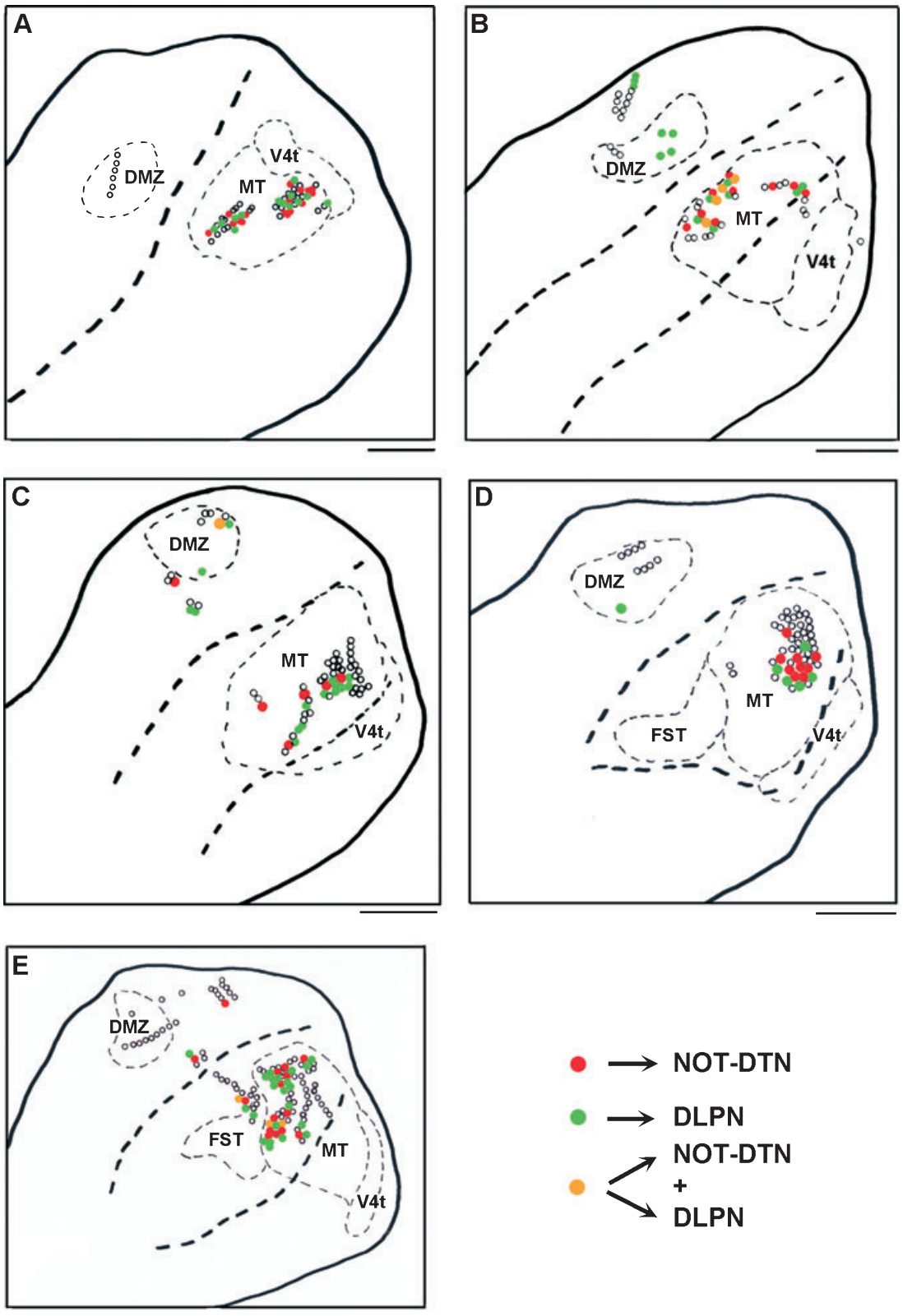

FIG. 2. Two-dimensional maps of the posterior part of the STS showing recording sites of neurons projecting to the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN; red), to the dorsolateral pontine nucleus (DLPN; green), to both targets (yellow), and of not antidromically driven neurons (open circles) of the five cases (A–E). Thick outlines represent the lip, thick broken lines the fundus of the STS. Thin broken lines indicate the areal borders of V4t, the middle temporal area (MT), the densely myelinated zone of MST (DMZ), and in cases 4 and 5 (D, E) also of visual area in the fundus of the STS (FST). To facilitate comparison all experiments are shown as left hemispheres. Scale bars: 5 mm.

TABLE 1. Summary of projections from MT and MST neurons to NOT-DTN and DLPN

	MT neurons (*n*) projecting to				MST neurons (*n*) projecting to			
Case	Neither	Only NOT	Only DLPN	NOT+ and DLPN	Neither	Only NOT	Only DLPN	NOT+ and DLPN
1	209	23	14	0	30	0	0	0
2	111	23	19	5	75	0	18	0
3	166	6	15	0	23	2	4	1
4	177	10	5	0	28	0	1	0
5	190	15	34	2	17	1	0	0
Total	853	77	87	7	173	3	23	1

DLPN, dorsolateral pontine nucleus; MST, medial superior temporal area; MT, medial temporal area; NOT+ (NOT-DTN), nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system.

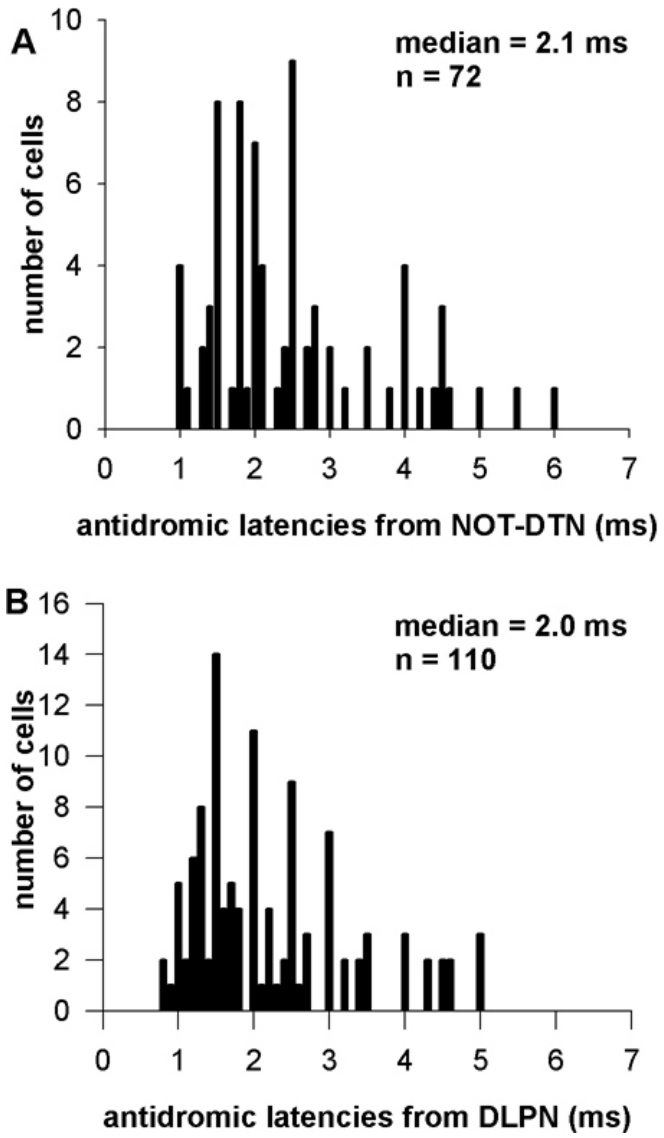

FIG. 3. Frequency distributions of antidromic latencies of STS neurons after electrical stimulation in the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN; A) and the dorsolateral pontine nucleus (DLPN; B). Abscissa: antidromic latencies (ms); ordinate: number of cells.

activated from the NOT-DTN, the middle row shows the plots of neurons activated from the DLPN, the right row presents the data of neurons not antidromically activated from either target. The length of the arrows indicates the number of cells normalized to the direction with the maximal count. The numbers next to each plot indicate the total number of cells included in this plot. The lowermost plots represent the summary of all five cases.

As shown earlier, the population of NOT-DTN-projecting neurons had a strong preference for ipsiversive stimulus movement (Hoffmann *et al.*, 2002). With the exception of case 3 where the PD was only determined for three NOT-DTN-projecting neurons, the ipsi : contra ratio varied between 7 : 1 (case 5) and 6 : 0 (case 1; total ipsi : contra ratio 36 : 1). A somewhat similar preference for ipsiversive movement was found for the DLPN-projecting population only in case 5 (Fig. 4; ipsi : contra ratio 3.25 : 1) and, less clearly, in case 2 (Fig. 4; ipsi : contra ratio 1.8 : 1), but not in any other case. Taking all cases together, DLPN-projecting neurons did not show a common directional preference (ipsi : contra ratio 1.13 : 1). Similarly, neurons projecting neither to the NOT-DTN nor to the DLPN did not have a common directional preference either (ipsi : contra ratio 1.04 : 1). With the exception of case 5, the directional preference of the neuronal populations projecting to the NOT-DTN or to the DLPN differed significantly from each other (χ^2-test, $P < 0.05$–$P < 0.001$). For vertical stimulus directions a weak bias for downward motion was found only in the DLPN-projecting population (up : down ratio 2.5 : 1, χ^2-test, $P < 0.05$). No common preference was detectable for the two other populations (up : down ratio NOT-DTN-projecting cells 1.8 : 1, not antidromically activated cells 0.9 : 1).

In a subpopulation of 262 cortical neurons the directional tuning in the frontoparallel plane was determined quantitatively using random dot patterns or sinusoidal gratings. Neuronal tuning to frontoparallel stimulus motion is a continuous periodic function and thus can be treated by means of Fourier theory. We hence computed the Fourier transforms of the normalized stimulus responses of individual neurons. The population response was then approximated by the Fourier retransform

$$R(t) = a_0 + \sum_{n=1}^{4} a_i \cos(t) + b_i \sin(t)$$

We considered only the first four Fourier components, which, effectively, resembles a low-pass filtering of the data. Figure 5 demonstrates the directional tuning of these cells with neurons projecting to the NOT-DTN shown by the continuous line (55

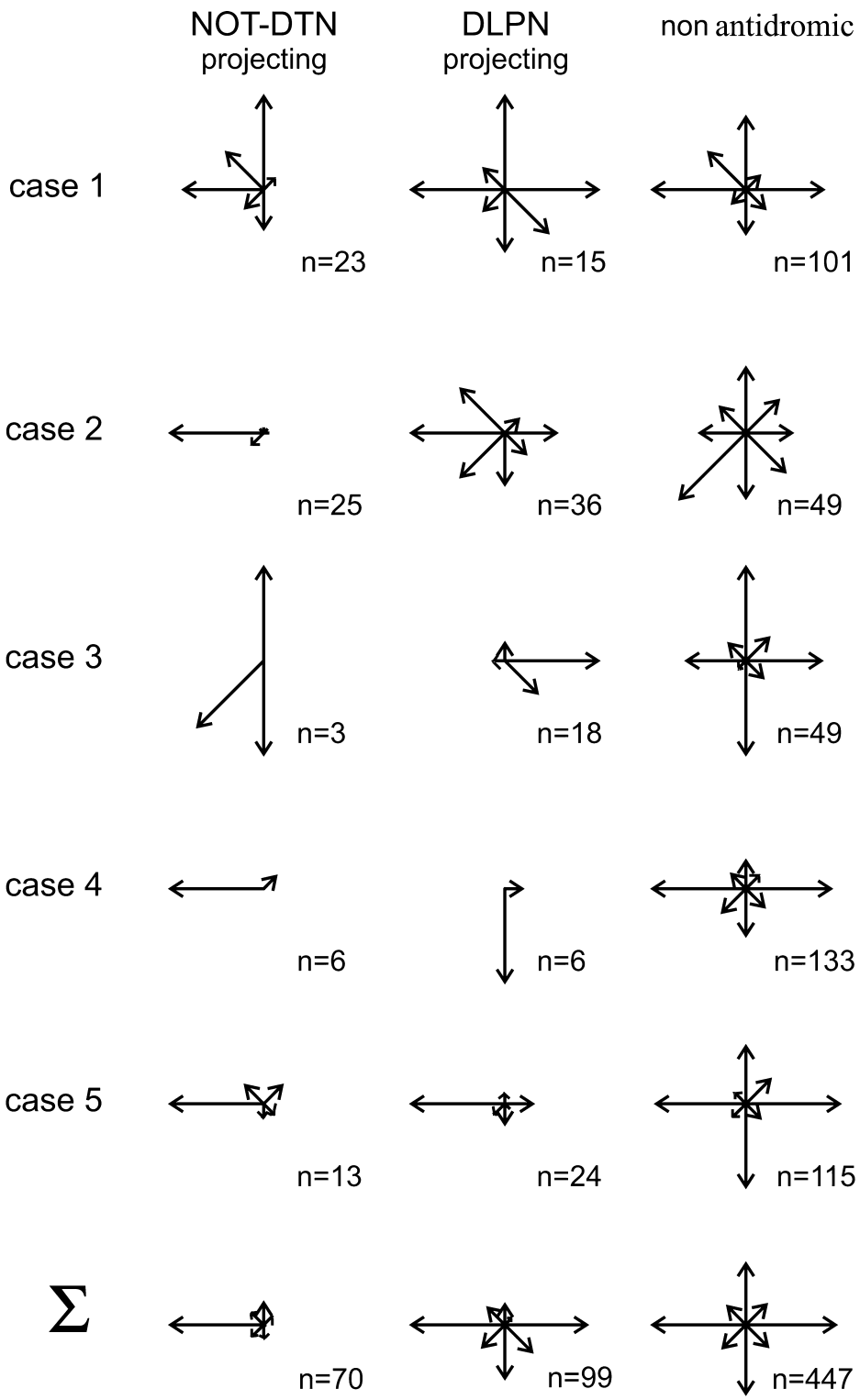

FIG. 4. PDs of cortical neurons projecting to the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN; left), to the dorsolateral pontine nucleus (DLPN; middle), and not antidromically activated from either target in the five individual cases (right; cases 1–5) and in all cases (last row). The length of the arrows gives the proportion of neurons preferring stimulus movement in the direction indicated by the arrow. The numbers next to the plots indicate the number of cells included in this analysis.

neurons), those projecting to the DLPN shown by the broken line (31 neurons), and those not projecting to either target shown by the dotted line (176 neurons). There was no significant difference in the individual tuning widths between the three neuronal subpopulations ($P > 0.05$, ANOVA on ranks). Both the NOT-DTN-projecting and the DLPN-projecting population showed a tendency for an over-representation of horizontal stimulus movement, but only the NOT-DTN-projecting population showed the known ipsiversive preference

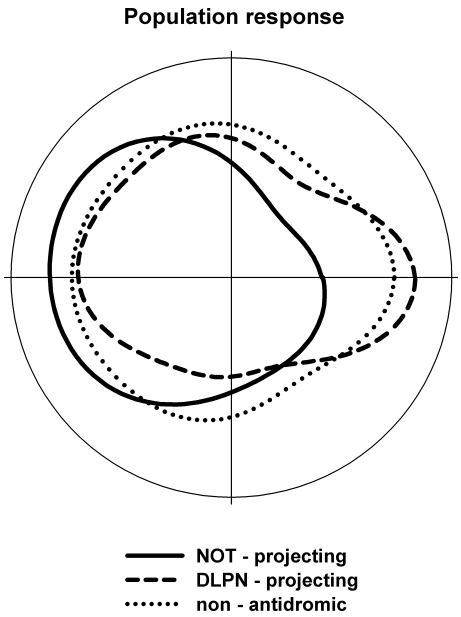

FIG. 5. Polar plots of the directional preference of the cortical neuronal populations projecting to the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN; continuous line), the dorsolateral pontine nucleus (DLPN; broken line), or not antidromically activated from either target (dotted line), respectively. The data are presented as if coming from the left hemisphere.

(χ^2 = 7.874 with 3 degrees of freedom, $P < 0.05$). The population not projecting to either target did not show any common preference, i.e. the PDs were equally distributed (χ^2 = 4.677 with 7 degrees of freedom, $P = 0.699$).

Directional preference for expansion or contraction

Information about the direction of global visual motion is not only important for gaze stabilization but also for counteracting body sway. We therefore tested the directional tuning with the superimposition of frontoparallel and expanding or contracting movement of random dots in 142 neurons of two animals (see Materials and methods). A significant tuning could be determined for 120 cortical neurons, 20 projecting to the NOT-DTN, 18 projecting to the DLPN and 82 neurons not projecting to either target. Figure 6 shows the response of an exemplary MT neuron projecting to the DLPN to random dot movement in the frontal plane (upper panel), in the sagittal plane (middle panel) and in the horizontal plane (lower panel). As can be clearly seen in the middle and lower panels, expansion of the stimulus yielded the strongest response irrespective of whether horizontal or vertical movement was added to the expansion–contraction movement. This was the case for clockwise (shown) as well as counterclockwise (not shown) circular paths. In order to determine the directional preference, we first determined the PD for visual stimuli moving in each of the above-mentioned planes (frontoparallel, horizontal plus expansion–contraction, vertical plus expansion–contraction). Neuronal discharges were weighted by the respective stimulus direction (corrected for the neuron's response latency). This computation resulted in three vectors whose directions gave the PD within the respective stimulus plane. For each individual neuron the vector average of these three preferred vectors determined its overall 3D PD. The projection of this 3D preferred vector onto the 2D planes

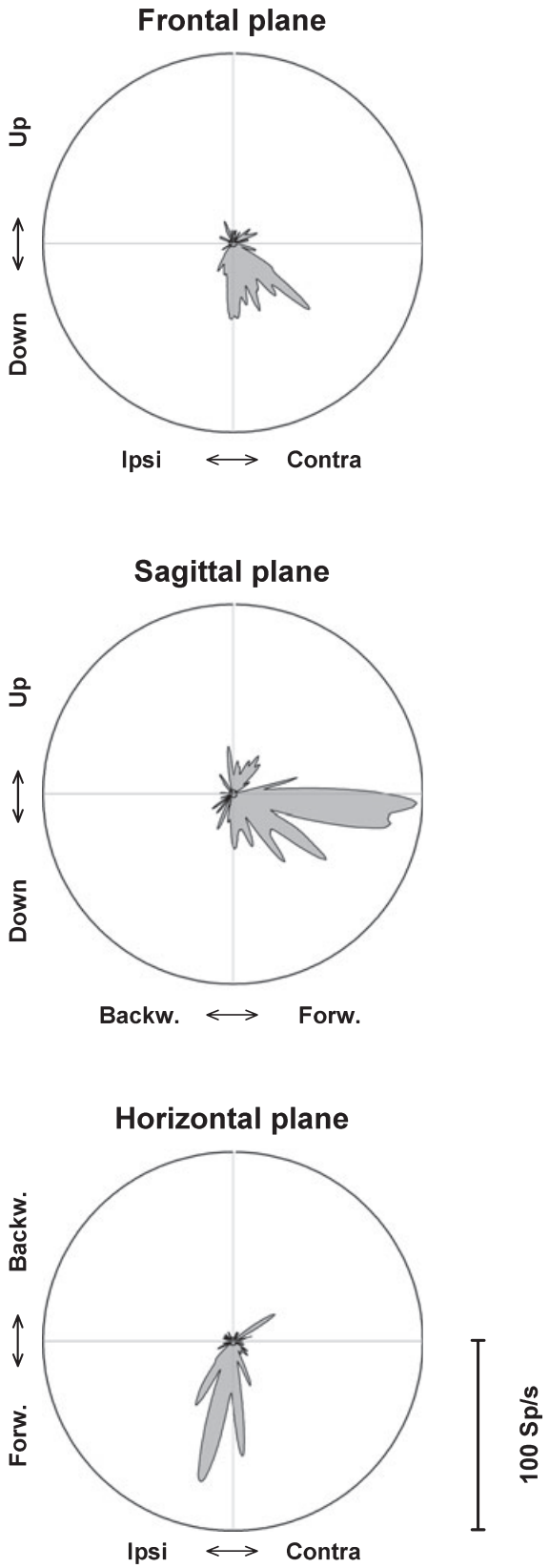

FIG. 6. Polar histograms for an example neuron from area MT with a preference for optic flow created by forward motion of the observer. The histograms were recorded during sequential continuously changing directions in the frontal (upper), sagittal (middle) and horizontal plane (lower panel). Axes are scaled in spikes/s.

is shown in Fig. 7. The resulting distributions of these preferred motion vectors for the population of NOT-DTN-projecting cells are shown in the left column of Fig. 7. It becomes very obvious that PDs were not uniformly distributed. Rather, the PDs were strongly biased towards ipsiversive motion (Rayleigh test, $P < 0.03$). It becomes also evident that preferred motion vectors were 'compressed' but unbiased along the expansion–contraction motion axis (horizontal and sagittal plane; Rayleigh test, $P > 0.1$). In other words, NOT-DTN-projecting

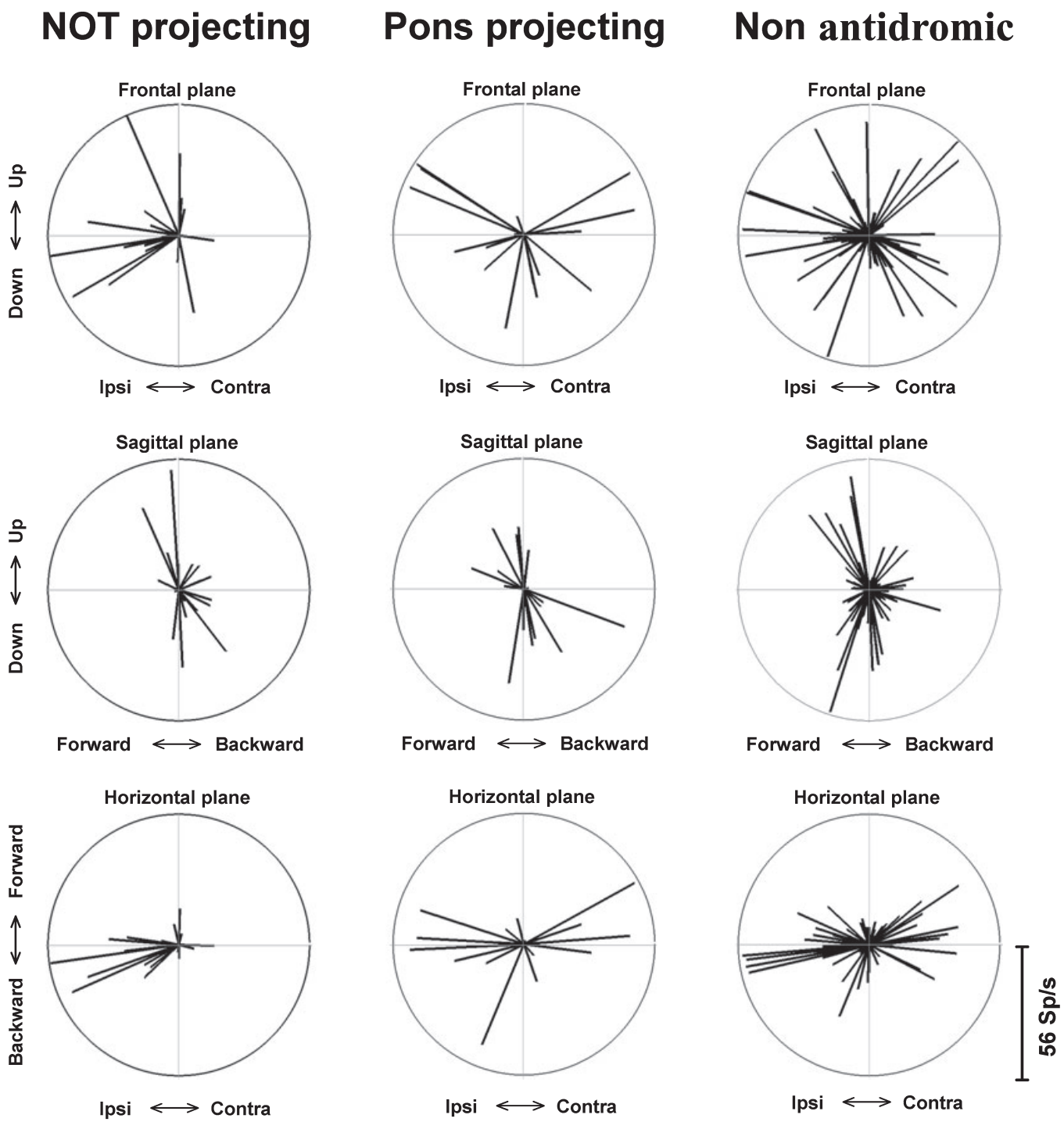

FIG. 7. Directional selectivity for frontoparallel translational and expanding–contracting motion in MT and MSTd. Neurons antidromically identified from nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN) are shown in the left column, from the dorsolateral pontine nucleus (DLPN) in the middle column and those not antidromically identified in the right column. Preferred motion directions within the frontal plane (up–down, contra–ipsiversive) are presented in the upper row, within the sagittal plane (forward–backward, up–down) in the middle row, and within the horizontal plane (forward–backward, left–right) in the lower row. For each individual neuron the vector average of the three preferred vectors determined its overall 3D PD. The projection of this 3D preferred vector onto the 2D planes is shown. Looking at the panels in the middle and lower row, it becomes evident that there is little preference for motion along the forward–backward axis.

neurons respond moderately to upward/downward motion and strongly to ipsiversive motion, but not to contraversive motion and movements along the expansion–contraction axis. The middle column in Fig. 7 summarizes the data for the subpopulation of neurons projecting to the DLPN, while the right column in Fig. 7 shows the data for neurons projecting to neither of the two target structures, NOT-DTN and DLPN, respectively. PDs of the DLPN-projecting neurons within the frontoparallel plane were uniformly distributed (Rayleigh test, $P > 0.1$). It would appear as if cells preferring the upward direction were missing. However, nine neurons had an upward component of their PD while eight had a downward component. The resulting vector length was rather small and hence not easy to identify. Again, only weak preferences for motion along the expansion–contraction axis were observed. The same was found for the not antidromically activated cells (Rayleigh test, $P > 0.1$).

This is further highlighted by the cartoons in Fig. 8. The six axes (best visible in Fig. 8C) represent the two opposite directions in each of the three movement planes. The numbers indicate the number of cells whose PD falls along the respective axis. These data indicate again that only a small fraction of cortical neurons in each of the three subpopulations preferred expanding or contracting stimuli, and that there is no bias for coding either expanding or contracting movements.

It is a generally accepted finding that visual motion in depth as tested with expanding–contracting random dot patterns or optic flow stimuli is predominantly activating STS neurons in MSTd (e.g. Lagae *et al.*, 1994). In contrast, Albright (1989) demonstrated that neurons in peripheral MT are sensitive to centrifugal motion that is also present in optic flow. Indeed, in our sample the 16 neurons (out of 142) that preferred either expanding or contracting visual stimuli to stimuli translating in the frontoparallel plane were all localized in area MT.

Responses to stimuli simulating self-motion across a ground plane

We determined the sensitivity of individual neurons to simulated self-motion (heading) across a ground plane at 1 m/s in one of three directions during one of three different simulated eye movement patterns, resulting in nine different stimuli. During a single trial one self-motion direction (30° to the left, straight-ahead or 30° to the right) was combined with one simulated eye movement (straight fixation, ideal tracking of a ground target or realistic tracking with a gain of 0.5). This 3×3 factorial design allows to test for the response preferences (heading vs. eye movement) of individual neurons. Altogether, 64 neurons were tested in two animals (seven neurons projecting to the NOT-DTN, eight neurons projecting to the DLPN, 49 neurons not projecting to either target). Only 52% of the neurons tested showed a significant response to this stimulus (three of the seven NOT-DTN projecting, four of the eight DLPN projecting, 26 of the 49 non-antidromically activated neurons). There was no obvious difference in the neuronal responses during this stimulation between the three subpopulations. We could not observe a significant dependence on heading direction or the addition of simulated eye movements on the responses of these neurons.

Discussion

In the present investigation we could show that cortical neurons with subcortical projections match the response properties of neurons in their target areas: that is, MT and MST neurons projecting to the NOT-DTN as a population prefer ipsiversive stimulus movement as is characteristic for NOT-DTN neurons (Hoffmann *et al.*, 2002), whereas

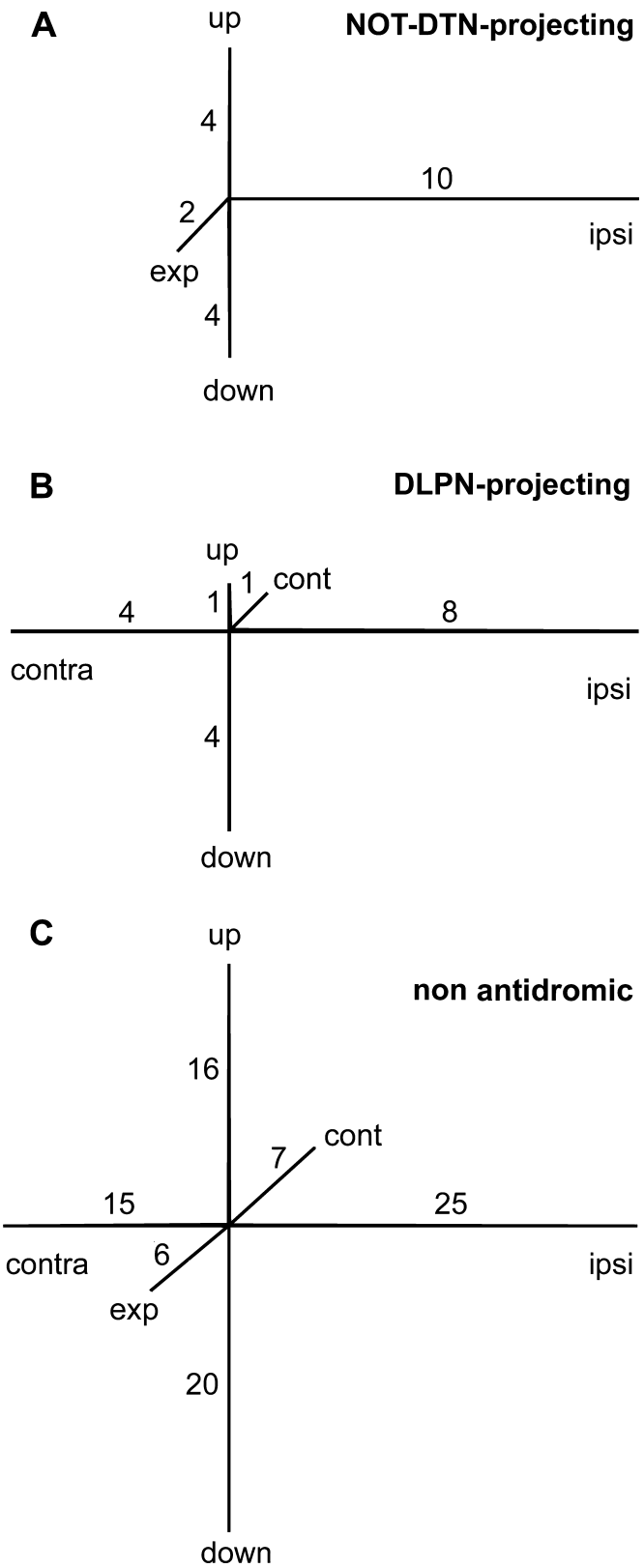

FIG. 8. Summary of the number of cells preferring one of the six axes in the up–down, ipsi–contraversive and expansion–contraction plane. Nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT-DTN)-projecting cells are presented in (A), dorsolateral pontine nucleus (DLPN)-projecting neurons in (B), and not antidromically activated cells in (C). Altogether, only 16 out of 142 neurons preferred a direction in the expansion or contraction axis.

cortical neurons projecting to the DLPN do not show a common directional preference, which in turn is also the case for neurons in the DLPN (Thier *et al.*, 1988; Suzuki *et al.*, 1990; Kawano *et al.*, 1992, 1994). Pure expanding or contracting visual movement on the retina as it occurs during forward and backward body sway is rarely encoded by NOT-DTN- or DLPN-projecting cells. Surprisingly, the neurons sensitive to expanding or contracting random dot fields were all recorded in area MT. It may well be that some MT neurons have receptive fields tuned to sense local fore-aft components of expanding–contracting random dot patterns (Albright, 1989) and that our limited repertoire of stimuli was not adequate to overcome the more stringent requirements of MST neurons to signal heading direction. Nevertheless, simple information about optic flow during simulated self-motion like expansion or contraction seems not to be conveyed from MT and MST to NOT-DTN or DLPN on a significant scale. Rather, this finding indicates that the information sent to the NOT-DTN and DLPN is mostly associated with motion of the observer causing retinal image slip in the frontal plane, which can be compensated by eye movements such as ocular following or the OKR.

Neurons projecting to the NOT-DTN and/or to the DLPN were found closely intermingled with neurons not projecting to either target in all subregions of MT and MST sampled in our experiments. Thus, there is no regional segregation of the cortical input structures for the NOT-DTN and the DLPN. The projection strength from MT to DLPN and NOT-DTN seems to be about equal (7–8% of the MT neurons tested were antidromically identified as projection neurons from either target). By contrast, the projection strength from MST to the DLPN seems to be almost 10 times stronger than that from MT to the DLPN, even though this result is based on a much smaller sample. Nevertheless, a similar trend was shown in our recent dual-tracer study: after NOT-DTN injection the ratio of labelled cells in MST compared with MT was 0.77 : 1, whereas after DLPN injection the ratio between labelled cells in MST and MT was 1.89 : 1 (Distler *et al.*, 2002). In addition, a stronger projection to the DLPN from MST than from MT can be recognized in the work of other groups (Ungerleider *et al.*, 1984; Glickstein *et al.*, 1985; Boussaoud *et al.*, 1992). Neurons projecting to both targets were found very rarely, i.e. only in three out of the five monkeys. Altogether, such neurons only present about 4% of our sample of antidromically identified projection neurons. Interestingly, this result is almost identical to our anatomical results reported recently (Distler *et al.*, 2002). After dual-tracer injections into the NOT-DTN and the DLPN neurons retrogradely labelled by these injections coincided only in the posterior STS, mainly in areas MT and MST. Thus, both the anatomical and physiological experiments clearly indicate that the NOT-DTN and the DLPN both receive strong cortical input from area MT, whereas MST more strongly projects to the DLPN. At the cellular level, however, the two projections are largely segregated. These results suggest that the neural circuitries underlying the optokinetic response, ocular following and smooth pursuit involve the same brain areas but different cortical cell populations.

The great majority of projection neurons to the NOT-DTN prefer ipsiversive stimulus movement, thus matching the direction preference of their target cells (Ilg & Hoffmann, 1993; Hoffmann *et al.*, 2002). These findings help to explain why lesions of an area that as an entity has an unbiased distribution of directional preference (e.g. area MT) lead to direction-selective deficits in oculomotor behaviour. The ipsiversive directional deficit after STS lesions is present in both OKR and pursuit. It has been argued that the DLPN is particularly involved in pursuit, whereas the NOT-DTN is clearly the visuo-motor link for OKR (Kato *et al.*, 1986; May *et al.*, 1988). Lesions of the NOT-DTN have a dramatic effect also on ipsiversive pursuit (Ilg *et al.*, 1993; Yakushin *et al.*, 2000). This is in line with the report by Mustari & Fuchs (1990) that half of the NOT-DTN neurons are sensitive to small pursuit stimuli, and with our finding that NOT-DTN-projecting cells in MT are also sensitive to pursuit stimuli.

Pursuit deficits after lesions of the DLPN are also directional in nature, with the largest effect for pursuit directed ipsiversive to the lesion (May *et al.*, 1988). However, as shown by our data the ipsiversive directional bias holds true only for the cortical projection to the NOT-DTN but not for the projection to DLPN. We have to assume that the selection of ipsiversively driving signals for smooth pursuit via the DLPN appears later in the pathway, e.g. in the cerebellum, or that the STS lesion effect on pursuit is due to the disruption of its output to the NOT-DTN.

Other studies indicate that individual MST and DLPN neurons are each encoding some selective aspects of the sensory stimulus (visual motion), whereas the Purkinje cells in ventral paraflocculus (VPFL) are encoding the complete dynamic command signals for the associated motor response (ocular following; Kawano *et al.*, 1996; Gomi *et al.*, 1998; Kobayashi *et al.*, 1998; Takemura *et al.*, 2001). Our data support their prediction that the sensory-to-motor transformation for the ocular following response occurs not before the Purkinje cells in VPFL. Our data further support the expectations of Kawano *et al.* (1992, 1994) who by comparing the neuronal responses of MST and DLPN neurons during ocular following hypothesized that MST may provide visual information to the DLPN relevant for ocular following. Lesions of MST lead to significant impairments of short-latency tracking eye movements (Takemura *et al.*, 2002, 2007). It has to be noted, however, that the lesion study by Inoue *et al.* (2000) links ocular following also to the NOT-DTN and thereby to the cortical projection to the NOT-DTN. The effects of lesions in DLPN on ocular following have yet to be studied.

Do cortical projection neurons match the properties of their targets?

The question whether functionally distinct classes of neurons from one cortical area project to different target areas has been asked several times. In the context of our findings we want to restrict the discussion on cortico-cortical and cortico-subcortical connections to the visuo-motor system of macaque monkeys. Finlay *et al.* (1976) reported that corticotectal cells in V1 form a relatively homogeneous population. Projecting cells were found primarily in layers 5 and 6, and could usually be classified as complex-type cells, but showed broader orientation tuning, larger receptive fields, higher spontaneous activity and greater binocular activation than V1 cells do in general. Only one-third of the corticotectal cells were direction selective. On the other hand, analysing cortico-cortical connections of V1, Movshon & Newsome (1996) showed that neurons in V1 projecting to area MT comprise a homogeneous and highly specialized subset of V1 neurons. They were all direction selective and responded only to the motion of components of complex patterns. Thus, in the case of V1 there seems to be a segregation of information sent to the SC and to MT. This is not surprising given the lack of direction selectivity in the superficial layers of SC in comparison to the overwhelming direction selectivity of MT cells.

For other areas the findings are more heterogeneous. Churchland & Lisberger (2005) found no statistically significant differences in the response properties of the antidromically activated MST neurons projecting to the pursuit area of the frontal eye field (FEF) and control samples. Analysing the response properties of neurons in the lateral intrapariatal sulcus (LIP) that could be antidromically

activated from the SC, Paré & Wurtz (1997) judged these neurons to be fairly homogeneous and distinct from collicular inputs from other cortical areas as the FEF. In a later report, Ferraina *et al.* (2002) identified three main differences in the discharge properties of neurons in LIP that project to the FEF or the SC concerning their activity during the delayed-saccade task, their saccadic activity or their lack thereof. However, the FEF- and SC-projecting neurons also had similarities: both had visual, delay and saccadic activity, both had stronger delay and saccadic activity with visually guided than with memory-guided saccades, and both had broadly tuned responses for disparity stimuli, suggesting that their visual receptive fields had a 3D configuration. Thus, despite extensive overlap in response properties between the two LIP subpopulations there was also clear evidence for functional segregation of the FEF- and SC-projecting neurons. Most FEF neurons antidromically identified from the pons were either movement neurons or foveal neurons (Segraves, 1992). Corticopontine movement neurons fired before, during and after saccades made within a restricted movement field. In this respect their activity was very similar to the activity of FEF neurons antidromically excited from the SC where a similar proportion of neurons had movement- or fixation-related activity. A third group of corticotectal neurons had heterogeneous response properties (Segraves & Goldberg, 1987). Segraves (1992) concluded that the FEF provides both the pons and the SC specifically with information about the 'when' and 'where' of impending saccades. The functional specificity of corticotectal connections was corroborated by the findings of Everling & Munoz (2000), who suggested that the similar responses of FEF and SC neurons in pro- and anti-saccade trials are mediated by the direct descending projections from FEF to SC. By contrast, Sommer & Wurtz (2000, 2001) found in their sample of FEF neurons projecting to the SC a substantial diversity, i.e. a population of signals rather than specific subsets of signals. In addition to the movement- and fovea-related neurons identified in earlier studies (Segraves & Goldberg, 1987; Segraves, 1992), they found delay responses and 'gap increase' responses reflecting more cognitive operations.

The few examples given above suggest that in many cases projections from a given cortical area to different cortical or subcortical areas are not identical. Interestingly, most studies showing evidence for functionally distinct projections concern brain regions that have been very well characterized, e.g. V1, MT, LIP, FEF. Thus, maybe for detecting functionally distinct subpopulations one has to fully understand the diversity of response properties in a given brain area and to test the response properties in awake behaving animals. Nevertheless, a common feature is that the response properties of the projection neurons and the target area are always very similar. This raises an important issue for developmental neurobiology. How are these distinct projections established during ontogeny? Obviously, in addition to molecular guidance cues activity-dependent matching mechanisms (Hebb, 1948) have to play an important role to set up these parallel and functionally distinct cortical and corticofugal processing streams.

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Abbreviations

DLPN, dorsolateral pontine nucleus; FEF, frontal eye field; LIP, lateral intraparietal sulcus; MST, medial superior temporal area; MSTd, dorsal part of MST; MT, medial temporal area; NOT-DTN, nucleus of the optic tract and dorsal terminal nucleus of the accessory optic tract; NPD, non-preferred direction; OKR, optokinetic reflex; PD, preferred direction; SC, superior colliculus; STS, superior temporal sulcus; VPFL, ventral paraflocculus; WFA, Wisteria floribunda agglutinin.

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