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A Motion-sensitive Area in Ferret Extrastriate Visual Cortex: an Analysis in Pigmented and Albino Animals

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In search of the neuronal substrate for motion analysis in the ferret (*Mustela putorius furo*), we extracellularly recorded from extrastriate visual cortex in five pigmented and two albino ferrets under general anaesthesia and paralysis. Visual stimulation consisted of large area random dot patterns moving either on a circular path in the frontoparallel plane or expanding and contracting radially. Strongly direction-selective neurons were recorded in a circumscribed area in and just posterior to the suprasylvian sulcus, thus named by us the posterior suprasylvian area (area PSS). Altogether, we recorded 210 (90%) and 95 (72%) PSS neurons in pigmented and albino ferrets, respectively, that were direction selective. In these neurons responses during random dot pattern stimulation in the preferred direction were at least twice as strong than stimulation in the non-preferred direction. Response strength in preferred direction and tuning sharpness of PSS neurons in albinos were significantly reduced when compared to pigmented animals (median values: 34.1 versus 14.8 spikes/s and 142 versus 165° for pigmented and albino ferrets, respectively). Inter-spike-intervals during visual stimulation were significantly shorter in pigmented (median 9ms) than in albino PSS neurons (median 14ms). Our data indicate that area PSS may play a crucial role in motion perception in the ferret.

Keywords: albinism, direction selectivity, extrastriate visual cortex, ferret, radial motion sensitivity

Introduction

Perception of moving objects in the external world is crucial for normal orienting in everyday life. If motion perception is reduced due to pathological processes patients are severely impaired (e.g. Zeki, 1991). Also in other higher mammals such as cats and primates cortical areas have been identified that are highly sensitive to moving stimuli, and lesions of these areas lead to distinct deficits in perception and oculomotor behaviour. In the cat, the posteromedial lateral suprasylvian area (PMLS) is characterized by a high proportion of direction-selective neurons, two-thirds of which also respond to optical flow patterns (e.g. Spear and Baumann, 1975; Strong *et al.*, 1984; Rauschecker *et al.*, 1987; Tusa *et al.*, 1989; Toyama *et al.*, 1994; Li *et al.*, 2000; Brosseau-Lachaine *et al.*, 2001). In monkeys, superior temporal areas MT and MST have been directly linked to motion perception and oculomotor behaviour (e.g. Maunsell and Van Essen, 1983; Newsome *et al.*, 1985; Mikami *et al.*, 1986; Duersteler and Wurtz, 1988; Komatsu and Wurtz, 1988; Albright 1989; Lagae *et al.*, 1993, 1994), and human correlates to these areas have been identified in functional magnetic resonance imaging (fMRI) studies (e.g. Zeki *et al.*, 1991; Nakamura *et al.*, 2003; Orban *et al.*, 2003). Due to these common properties areas PMLS and the middle temporal area (MT) and the middle superior temporal area (MST) have been proposed to represent at least analogous if not homologous areas (Payne, 1993; Dreher *et al.*, 1996).

In a series of experiments, Innocenti and colleagues recently described the location and the retinotopy of various visual cortical areas in the occipital, parietal and temporal lobe of the ferret (*Mustela putorius furo*) (Innocenti *et al.*, 2002; Manger *et al.*, 2002a,b, 2004). A motion-sensitive area comparable to PMLS and MT/MST, however, initially mentioned by Sherk (1988) has yet to be analysed in detail in the ferret's visual cortex.

Why study ferret visual cortex? Beside the suitability of the ferret for developmental studies due to its birth at a comparably early gestational age the ferret has the advantage that its visual system closely resembles the cat and that albinotic strains are easy to come by. Oculocutaneous albinism leads to various severe abnormalities in the visual system. Recently, we found that the optokinetic reaction is severely impaired in albino ferrets due to a loss of direction selectivity in the key visuomotor structure for this reflex, the nucleus of the optic tract and dorsal terminal nucleus of the accessory optic system (NOT–DTN) (Hoffmann *et al.*, 2004). In addition, behavioural investigations indicate that motion perception is reduced in albino ferrets (Hupfeld and Hoffmann, 2005).

In the present study we localized a motion-sensitive area in the ferret visual cortex. By comparing the response properties of cortical motion-sensitive neurons in pigmented and albino ferrets we tried to judge to which extent cortical physiology may contribute to the loss of direction selectivity in the NOT–DTN and to the behavioural deficits observed in albino ferrets. The data are discussed in relation to the evolution of neocortical function and organization in mammals.

Materials and Methods

Animals

All experiments were approved by the local authorities (Regierungspräsidium Arnsberg) and were carried out in accordance with the Deutsche Tierschutzgesetz of 12 April 2001, the European Communities Council Directive of 24 November 1986 (S6 609 EEC) and NIH guidelines for care and use of animals for experimental procedures. The electrophysiological experiments were performed on five pigmented and two albino ferrets of both sexes, 1–2 years old. All animals were bred and raised in the animal facility of the Department of General Zoology and Neurobiology, Ruhr-University Bochum and were group-housed in an enriched environment with access to an outdoor enclosure.

Surgery

Animals were initially treated with 0.05 mg atropine sulphate (Braun) and anaesthetized with 20 mg/kg ketamine and 2 mg/kg xylazine (Rompun®) i.m. Then they were intubated through the mouth, and an i.v. catheter was introduced into the forearm vein. After additional local

anaesthesia with bupivacain hydrochloride the animals were placed in a stereotaxic frame and artificially ventilated with air and 0.2–0.6% halothane as needed throughout the entire experiment. Pupils were dilated with atropine sulfate and corneae were protected with contact lenses. The skin overlying the skull was cut, the temporalis muscle deflected and a craniotomy was performed allowing access to the extrastriate visual cortex. In addition, a head post was implanted. During the experiment, the animal was held with this head post. During the entire procedure heart rate, endtidal CO_2 and body temperature were monitored and maintained at physiological levels. During the recordings, animals were paralysed with alcuronium chloride (Alloferin ®). The depth of anaesthesia was controlled based on the ongoing heart rate and cardiac reaction to tactile or acoustic stimuli. After completion of the recording session, the wound was closed in appropriate layers and covered with antibiotic ointment (Nebacetin®). After full recovery the animals were returned to their home enclosure and treated with analgetics (Carprofen, 2.5 mg/kg, Rimadyl ®) for 2 days and broadband antibiotics (enrofloxacin, Baytril®) for one week after surgery. Electrophysiological recordings were repeated 3–5 times with 2–3 weeks recovery in between. We chose this procedure because the quality of recordings during longterm acute experiments declined with time. With repeated shorter recordings (12–13 h duration during the chronic experiments and up to 48 h during terminal experiments), the quality and the amount of data recorded from individual animals dramatically increased. This procedure was well tolerated by the ferrets as shown by their normal feeding and play behaviour.

Electrophysiology

Electrophysiological recordings in extrastriate visual cortex were performed with tungsten in glass microelectrodes using standard procedures. The electrode was angled ~40° from medial to lateral in the coronal plane to achieve penetrations parallel to the cortical layers. Histological reconstruction of the recording sites implies that data were collected from all cortical layers. Neuronal activity was conventionally amplified, passed through a window discriminator and stored for offline analysis.

Visual Stimulation

The two visual stimuli used consisted of large area random dot patterns (43° horizontal, 39° vertical extent; dot size was 1° at a mean interdot distance of 4.5°; contrast was 0.975; dots: 65 cd/m^2; background: 0.8 cd/m^2) for appropriate 'full field' stimulation. These two patterns moved either on a circular path (6234 ms per cycle) in the frontoparallel plane or were expanding/contracting radially (7333 ms per cycle with the stimulus moving for 1634 ms in each direction; stimulus presentation was interrupted by two phases where dots first appeared on a black screen and paused for several milliseconds before they started to expand or contract). In addition, the neuronal activity was measured during a 5000 ms presentation of the stationary stimulus. To exclude transient activity after appearance of the pattern dots were visible for several seconds before starting the recording.

In order to determine a neuron's preferred direction for movement in the frontoparallel plane, the center of the random dot pattern followed a circular path 24.5° in radius (continuous mapping of directional selectivity; see also e.g. Schoppmann and Hoffmann, 1976). Thus, all random dots have the same direction and speed (tangential speed was typically 21.5°/s) at a given moment. In this paradigm the speed of the stimulus is constant throughout a stimulus trial (cycle), but stimulus direction changes continuously (0–360°) within a complete stimulus cycle. This stimulus is not sensitive to receptive field size. On the other hand, depending on the receptive field size and the radius of the circular pathway a given dot was visible only during a given period of its own pathway. This kind of stimulation is different from traditional mapping procedures to determine a neuron's preferred direction (PD), where responses to several (typically four or eight) unidirectional pattern movements are compared. Experiments in a number of species and areas, i.e. rat and cat pretectum, cat visual cortex, monkey pretectal nuclei (NOT/DTN) and monkey visual cortical areas MT, MST and VIP have shown that directional tunings obtained using the continuous mapping procedure are equivalent to the tunings obtained by unidirectional pattern movements (Schoppmann and Hoffmann, 1976; Hoffmann and Schoppmann, 1981; Bauer *et al.*, 1989; Hoffmann and Distler, 1989; Schmidt *et al.*, 1998, Bremmer *et al.*, 1997, 2002).

For each data point (obtained during circular path and expansion/contraction stimulation), the neuronal activity was sampled over 10 trials which were looped continuously. All data were collected at a stimulus velocity of 21.5°/s after qualitative tests had ensured that this velocity lies well in the range of stimulus speeds effective to drive the neurons under investigation. The visual stimuli were projected onto a semicircular screen (angular extent was ±90°) 143cm in front of the animal via a beamer (ProScan 4750, Philips).

We did not measure the receptive field location and extent of all neurons recorded quantitatively. Instead we determined the receptive field's position and boundaries by screening the visual field with a small (∅: ~0.5–8°) light spot using a handheld lamp. This ensured that we adjusted our stimuli to be centered on the receptive field and that the complete receptive field was covered by the large area random dot patterns.

The visual stimuli were viewed binocularly with unaligned eyes. Furthermore, because of technical problems, we could not determine where the center of gaze was for each eye.

Quantitative Analysis

Preferred directions of visual stimulus motion were determined utilizing the weighted average method. Each spike time was assigned a vector corresponding to the stimulus direction at this time corrected by the neuron's response latency. In other words: a response at time $t = x$ ms was related to a stimulus direction at t = (x – latency) ms. Unless otherwise determined, this latency was set to a fixed value of t = 100 ms, i.e. the assumed average response latency for a sample of 305 neurons (210 and 95 direction-selective neurons for pigmented and albino ferrets, respectively). Even if this value of t = 100 ms was not the neuron's 'correct' latency, this estimate of preferred direction is comparable to other measurements (e.g. testing four or eight different directions). This is for the following reason: assume that the response latency of a neuron was 150 ms rather than 100 ms. In such case, the estimate of this neuron's PD would have to be corrected for the directional difference corresponding to this latency difference, i.e. (150 – 100) ms = 50 ms. Given that the whole stimulus trial lasted T = 6200 ms, the resulting error in determining the PD would have been (50/6200) × 360° = 2.9°. This error in estimating the PD (Δ_{angle} < 3.0°) is an order of magnitude smaller than the error in determining a neuron's PD when testing with patterns moving linearly in typically four or eight different directions.

We wanted to determine whether or not the responses for PD stimulation were significantly different from responses for a stimulus moving into the non-preferred direction (NPD). Given the nature of the stimulus (direction changes continuously throughout a trial) we had to find a reasonable trade-off between the width of the response window being small enough to represent the response for PD (NPD) stimulation and being large enough to allow for a reliable statistical testing. We therefore decided for test windows being t = 620 ms wide, corresponding to a directional window of A = (620/6200) × 360° = 36°. This analysis window was centered in the temporal domain on two points corresponding to the cell's PD and NPD. In other words, we determined in a trial by trial analysis responses for stimulus directions [(PD – 18°) – (PD + 18°)] and [(NPD – 18°) – (NPD + 18°)], respectively. These data sets then were tested for significant differences with a distribution free Mann–Whitney rank test.

A direction selectivity index (DS) was calculated to quantify the neuronal responses as follows: DS = PD – NPD/PD + NPD, with PD being the neuronal activity during stimulation in the preferred direction, and NPD the activity during stimulus movement in the non-preferred direction. In case of expansion/contraction stimuli, PD was taken as activity during expansion, NPD as activity during contraction of stimulus movement. Neurons were defined as direction selective if DS ⩾ 0.33 for random dot patterns moving on a circular path or expanding radially, and DS ⩽ –0.33 (PD 100% larger than NPD) for contracting dot patterns. Wilcoxon signed rank and Mann–Whitney rank sum tests were used for statistical analysis.

Histology

After completion of the electrophysiological experiments the animals were sacrificed with an overdose of pentobarbital and perfused transcardially with 0.9% saline and 4% paraformaldehyde. Frontal sections were cut at 50 μm on a cryostat and stained for Nissl, myeloarchitecture (Gallyas, 1979, as modified by Hess and Merker, 1983) and cytochrome C histochemistry (Wong-Riley, 1979). Extrastriate recording sites were reconstructed based on microlesions, the penetration scheme and the depth reading of the electrode microdrive.

Results

Recording Sites

In search of direction-selective areas in ferret visual cortex we first mapped visual areas 17, 18, 19 and 21 according to the retinotopic organization of these areas described in the literature (Innocenti *et al.*, 2002; Manger *et al.*, 2002a). By the same procedure we found an area which in contrast to the more posterior visual areas responded very well to moving random dot patterns mostly in a direction-selective way. As such response properties were not prominent in more posterior recording sites, i.e. in area 18, 19 or 21 we were able to distinguish this area by the high incidence of motion and direction-selective neurons. Moving the recording electrode another 1–2 mm further anterior we would regularly record acoustic responses. Therefore, in later experiments acoustic responses served as vantage point to quickly localize the direction-selective area. The data presented in this study were collected in a region in and up to ~1 mm posterior to the suprasylvian sulcus (SS) and 5.5–7 mm lateral to the midline. Thus, the newly described area is positioned between the posterior parietal cortex PPc (Manger *et al.*, 2002b) and the recently described areas 20b and PS (Manger *et al.*, 2004) in the mediolateral axis, and between the auditory cortex and area 21 in the anterior–posterior axis (Wallace *et al.*, 1997; Innocenti *et al.*, 2002). Figure 1*B* summarizes the position of recording sites marked by microlesions of all animals used in the present study in a reconstruction of the lateral view of the left cortical hemisphere. Approximate areal borders of areas 17, 18, 19 and 21 averaged from all animals are indicated by dashed lines, and the location of areas PPc, 20b and PS are taken from the literature (Manger *et al.*, 2002b, 2004). Note that recording sites of direction-selective neurons in the depth of the posterior bank of the sulcus are projected on the surface of the brain and thus can come to lie anterior to the suprasylvian sulcus in the reconstruction.

Lesions marking recording sites of direction-selective neurons were always located in a densely myelinated region

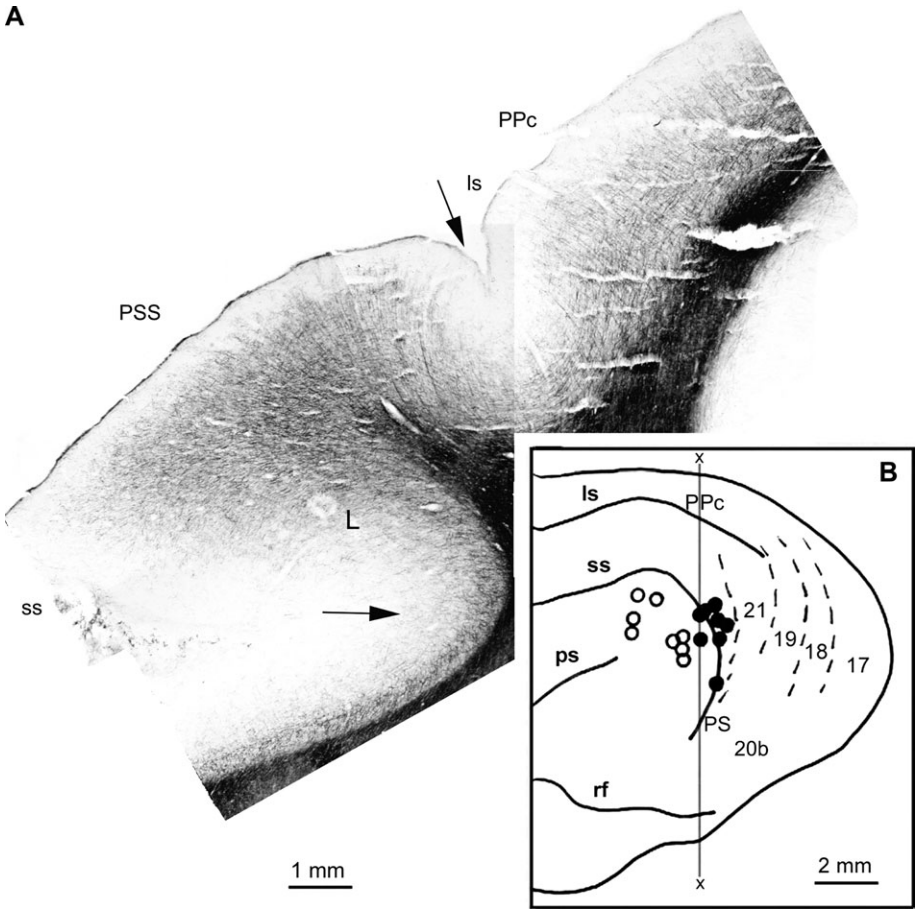

Figure 1. (*A*) Digital photomontage of a frontal section through ferret area PSS, parietal cortex PPc and temporal cortex stained for myeloarchitecture. Arrows point to the myeloarchitectonic borders of area PSS. Area PSS is characterized by dense myelination in all cortical layers. By contrast, in area PPc supragranular layers are less myelinated, deep layers are rich in horizontal fibres. Temporal cortex is readily distinguished from PSS by its weak myelination especially in supragranular layers. L, microlesion at the recording site of direction-selective neurons. (*B*) Composite reconstruction of the ferret left cortical hemisphere showing the area studied in the present investigation in six animals (four pigmented and two albino). Filled dots mark the projection of recording sites of direction-selective neurons onto the cortical surface, open circles mark recording sites of auditory responses. The vertical line indicates the anterior-posterior level of the frontal section shown in (*A*). ls, lateral sulcus; ps, pseudosylvian sulcus; rf, rhinal fissure; ss, suprasylvian sulcus. Scale bars represent 1 mm for (*A*), 2 mm for (*B*).

(Fig. 1*A*). Even though the lateral part of the posterior parietal cortex (PPc) (Fig. 1*A*) appears densely myelinated as well it could be readily distinguished from area PSS by the following criteria: first, in area PSS the dense myelination also includes the uppermost layers which are somewhat paler in PPc; secondly, PPc displays more horizontal fibres in deep cortical layers than area PSS (Fig. 1*A*). The lateral sulcus is always less myelinated than PP or area PSS. As this could be a consequence of the compression of cortical layers in the depth of the sulcus, we do not assume that there may be an additional area located between PSS and PPc. The distinction of area PSS from more lateral cortical areas was even easier because this region is unequivocally characterized by a very weak myelination especially in the upper cortical layers. Four of the brains were also stained for cytochrome C histochemistry. In three of the four cases area PSS was distinguishable from more medial and more lateral areas by the darker staining of the supragranular layers and the especially weak staining of the infragranular layers. These criteria were used to delineate area PSS from the surrounding cortex in the frontal sections shown in Figure 2. Myeloarchitectural borders are marked by arrows in Figures 1*A* and 2. All lesions marking recording sites of direction-selective neurons were located in the densely myelinated area just described and were thus used as the main criterion for characterizing area PSS. The myeloarchitecture around the lesion sites was extrapolated to indicate the borders of the whole area. At this time we do not have enough anatomical tract tracing data to verify the exact borders of area PSS and to exclude possible influences of cortical gross anatomy as curvature of the gyri and sulci on our myelin borders.

All neurons considered in our further quantitative analysis were recorded from this area PSS. The transition from medial areas to area PSS was marked by the sudden appearance of neurons with clearly direction-selective responses to moving random dot stimuli. In most cases, direction-selective cells were clustered (filled dots in Fig. 2). Non-selective visual (open triangles) neurons that did not respond to our random dot stimulus or a Julesz pattern and motion selective cells that reacted to moving dots in a non-direction-selective manner (open circles) were encountered less frequently in this region. Altogether, 217 direction-selective, 36 motion-sensitive and 16 non-selective visual cells were recorded in PSS of the pigmented ferrets and 95 direction-selective, 45 motion-sensitive and 5 non-selective visual cells were recorded in the albinos. Thus, 81 and 65.5% of the PSS neurons were direction selective in the pigmented and albino ferrets, respectively. The following results of our study are related only to cells which showed any modulation in their activity to our random dot stimulus and could thus be analysed quantitatively.

Preferred Directions in PSS Neurons during Frontoparallel Stimulus Movement

Of 235 neurons in the pigmented and 132 neurons in the albino ferrets for which we succeeded to compile average response time histograms with a random dot pattern moving along

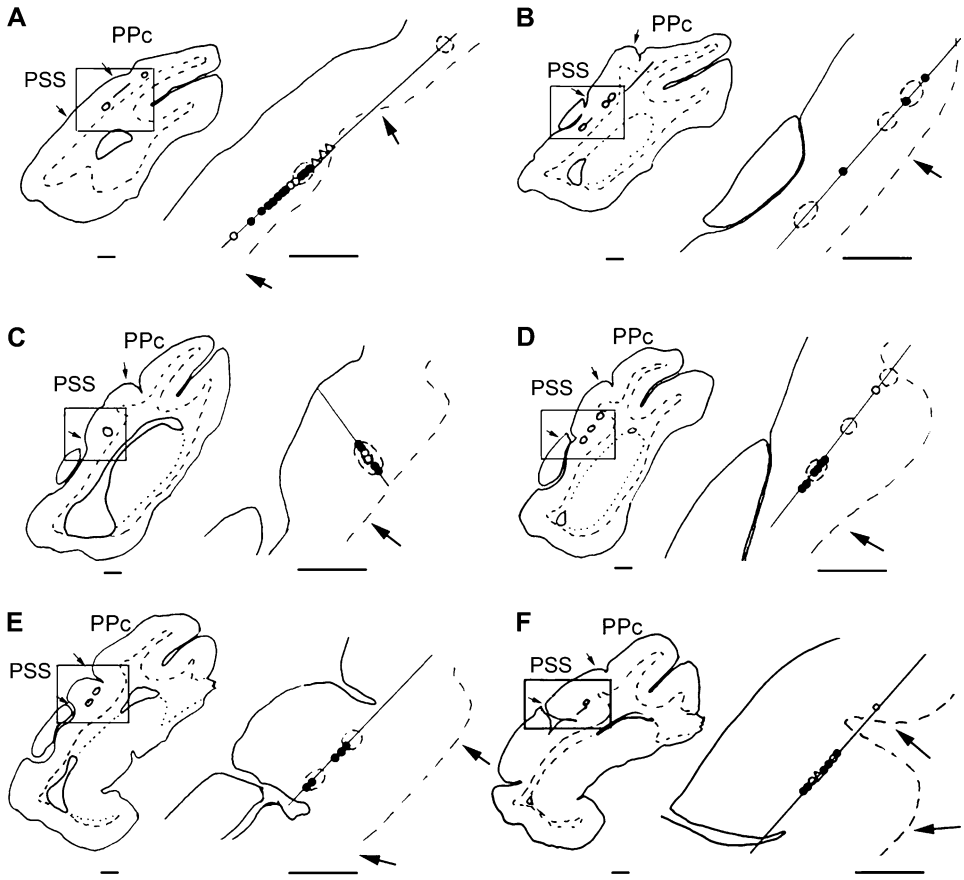

Figure 2. Drawings of frontal sections with microlesions marking recording sites of direction-selective neurons are shown on the left of each panel, the inset is enlarged on the right side of each panel. The enlargements show reconstructions of penetration tracks with filled dots marking recording sites of direction-selective neurons, open circles marking motion-sensitive neurons, and open triangles marking unspecific visual neurons. Microlesions are indicated by dashed areas. Arrows point to myeloarchitectonic borders. (*A–D*) Pigmented animals; (*E*, *F*) albinos. Scale bars represent 1 mm.

a circular path, 210 (90%) and 95 neurons (72%), respectively, showed significant direction selectivity (DS-index $\geqslant$ 0.33; Mann–Whitney rank sum test, $P < 0.05$; Fig. 3*A*,*B*). The remaining neurons were classified as motion-sensitive because their response properties showed no significant dependence on stimulus direction. Two-thirds of the PSS neurons in pigmented ferrets were highly direction selective with DS-indices $\geqslant$ 0.67, i.e. responses were five times stronger in preferred than in non-preferred directions (Fig. 3*A*; DS median: 0.79, Table 1).

By contrast, neurons in albino ferrets were significantly less direction selective. Less than one third of their PSS neurons reached the criterion of DS-indices $\geqslant$ 0.67 (Fig. 3*B*; DS median: 0.56; Mann–Whitney rank sum test, $P < 0.001$).

Because of the varying angle between electrode and cortical layers due to gyrification of the cortex it is difficult to decide if direction selectivity in area PSS is organized in columns as has been described for area MT of the macaque and suggested for the Clare-Bishop area of the ferret and the cat (Hubel and Wiesel, 1969; Albright *et al.*, 1984; Sherk, 1988). Within single penetrations preferred directions of neighbouring neurons could vary considerably. Because there was no obvious regularity in the change of preferred directions along individual penetrations, we employed the Pearson product moment correlation. We found that the variation of preferred directions did not follow a regular pattern corresponding to a continuous shift in preferred directions. Although presently claimed for

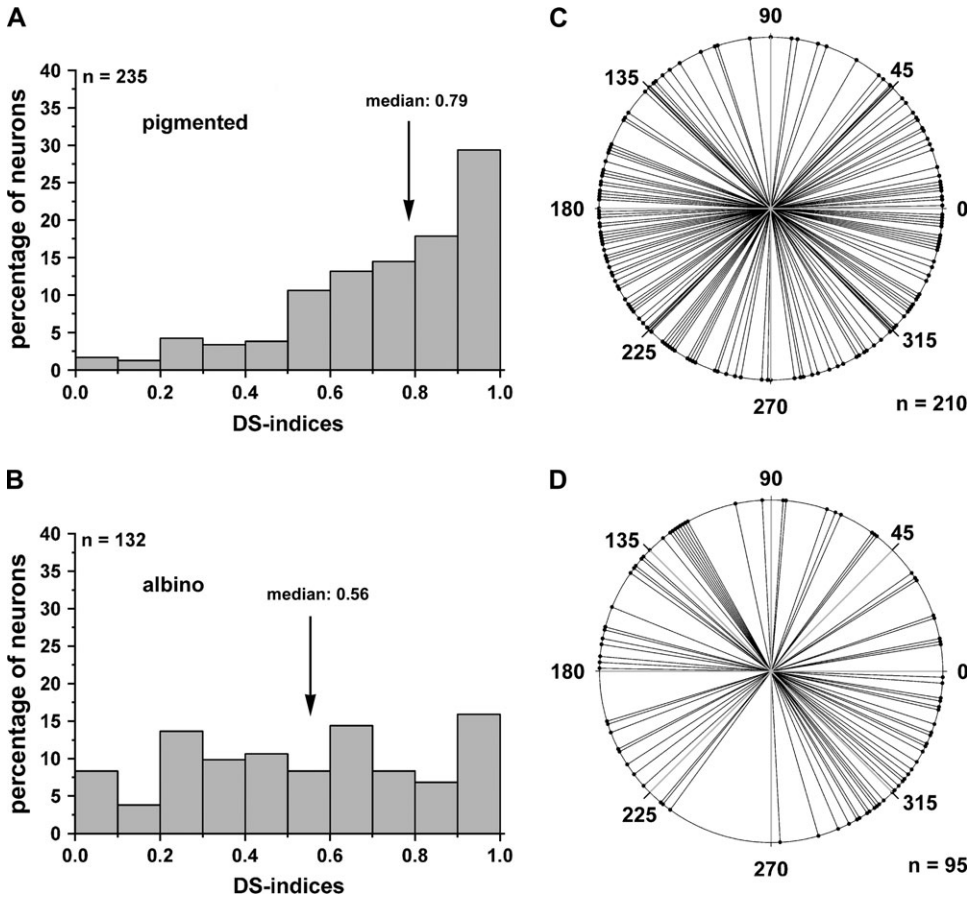

Figure 3. (*A*, *B*) Frequency distribution of DS indices for PSS neurons responding to circular movement of a random dot pattern in the frontoparallel plane (abscissa) in pigmented (*A*, 235 neurons) and albino ferrets (*B*, 132 neurons). Ordinate: percentage of cells; abscissa: DS indices. Arrows indicate median DS-indices. (*C*, *D*) Vectors of preferred directions of significantly direction-selective neurons in area PSS recorded in the left hemisphere in pigmented (*A*) and albino (*B*) ferrets, respectively. The vectors are shown equal in length, irrespective of differences in firing rates and tuning widths between examined neurons. Statistical analysis shows that significantly more neurons preferred horizontal than vertical movements in pigmented but not in albino ferrets. Note that the vectors of preferred directions are not corrected for the cells' response latencies.

Table 1
Medians and quartiles of DS-indices and tuning widths of PSS neurons in pigmented and albino ferrets

	Frontoparallel motion						Radial motion (expansion/contraction)					
	DS-indices			Tuning width			DS-indices			Tuning width		
	Median	Q_{25}	Q_{75}	Median	Q_{25}	Q_{75}	Median contraction	Q_{25}	Q_{75}	Median expansion	Q_{25}	Q_{75}
Pigmented	0.79	0.60	0.92	142°	123°	162°	−0.29	−0.49	−0.15	0.35	0.16	0.59
Albino	0.56	0.28	0.78	165°	139°	175°	−0.17	−0.34	−0.11	0.26	0.13	0.48

the ferret (Sherk, 1988) and documented for cat and monkey movement-sensitive areas, our data do not support the notion of a systematically mapped columnar organization of direction selectivity in ferret PSS. They do not exclude, however, individual directional columns perpendicular to the layers in PSS.

There was no obvious difference in the demarkation of receptive fields between pigmented and albino animals. Our sample of cortical neurons includes central as well as peripheral receptive field locations in the entire contralateral visual hemifield. In a qualitative analysis we were unable to detect any correlation between receptive field location and medio-lateral location of neurons in the brain. Likewise, we did not find any correlation between receptive field eccentricity and direction selectivity or preferred direction.

Figure 3*C,D* demonstrates the vectors of preferred directions of all neurons whose response to stimulus movement in the preferred direction differed significantly from the response to movement in the non-preferred direction (Mann–Whitney rank sum test, $P < 0.05$). To investigate if certain directions were more strongly represented than others we divided the polar plots in four 90° sectors (contraversive: 315° to 45°; up: 45° to 135°; ipsiversive: 135° to 225°; down: 225° to 315°). A statistical analysis showed a tendency that the preferred directions of neurons in area PSS were not equally distributed (Kolmogorov–Smirnov, $P = 0.001$). In pigmented ferrets, more neurons coded for horizontal than for vertical stimulus movement (χ^2-test, $P < 0.0001$). A preference for ipsiversive or contraversive stimulus movement did not exist (χ^2-test, $P > 0.05$). In albino ferrets, a preference for horizontal stimulus movement or an ipsiversive–contraversive asymmetry was not evident (χ^2-test, $P > 0.05$).

Directional Tuning of Neurons in Area PSS

We determined the tuning width of direction-selective neurons as the range of directions that elicited a more than half maximal response (Fig. 4*A,B*). The tuning width was significantly narrower in pigmented than in albino PSS neurons (pigmented: median bandwidth: 142°, $n = 206$; albino: median bandwidth: 165°, $n = 95$; Table1). This difference was statistically significant (Mann–Whitney rank sum test, $P < 0.001$). Thus, individual albino PSS neurons respond to a broader range of directions than cells in pigmented ferret. This, together with the lower direction selectivity index found in PSS neurons, documents the degradation of direction selectivity in albino ferrets.

Quantitative Analysis of Visual Responsiveness to Stimuli Moving on a Circular Path

To investigate the cause for the lower direction selectivity in albino ferrets we plotted response strength to PD stimulation versus response to NPD stimulation on log scales (Fig. 5*A*). Activity during PD stimulation was significantly higher in pigmented (filled circles) than in albino ferrets (open circles) (pigmented: median 34.1 spikes/s, albino: median 14.8 spikes/s; Mann–Whitney rank sum test, $P < 0.001$). Furthermore, the range of response strength to PD stimulation was wider in pigmented than in albino ferrets where data points cluster below 30 spikes/s. Figure 5*A* again illustrates the weaker direction selectivity in albino ferrets indicated by the clustering of albino data points close to the unity slope.

The ongoing activity was measured in 203 neurons of pigmented and in 120 neurons of albino ferrets while the animals watched a stationary random dot pattern (Fig. 5*B,C*).

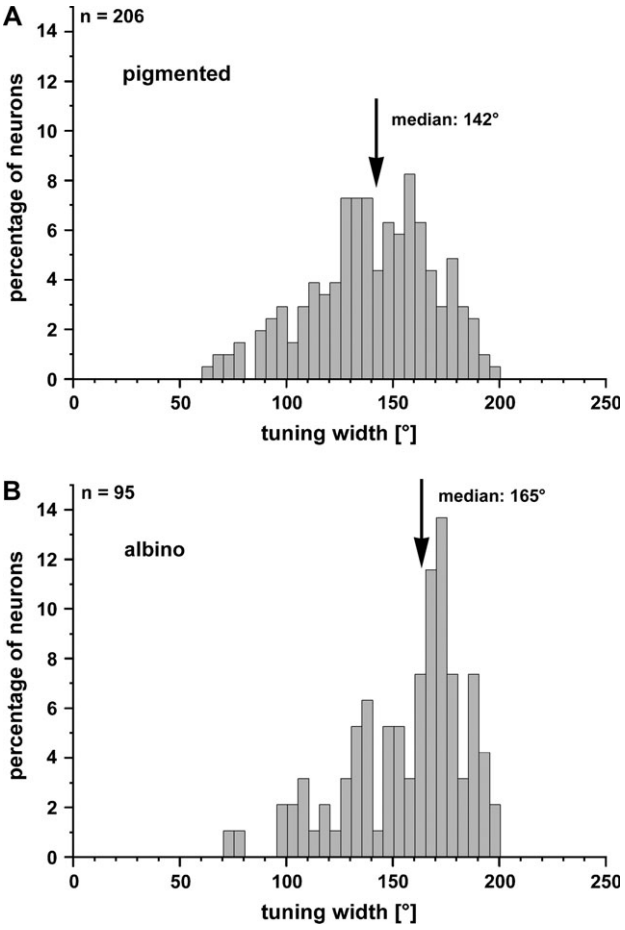

Figure 4. Frequency distribution of directional tuning widths of PSS neurons in pigmented (*A*) and albino ferrets (*B*). Ordinate: percentage of cells; abscissa: tuning width (°).

Cell activity was sampled after onset of stimulus presentation (see methods). The median of this activity was not significantly different between the two groups of animals (5.0 and 3.9 spikes/s, respectively; Mann–Whitney rank sum test, $P = 0.073$). In Figure 5 we plot the response to PD stimulation (filled circles in Fig. 5*B,C*) and to NPD stimulation (open circles in Fig. 5*B,C*) versus ongoing activity on log scales. In a high proportion of neurons in pigmented ferrets (71 cells out of 203 cells in our population) the activity during NPD was suppressed to 50% of the ongoing activity (Fig. 5*B*). This suppression was not as marked in albinos (27 cells out of 120 cells; Fig. 5*C*). This difference in the proportion of suppressed cells between albino and pigmented animals was significant ($P < 0.02$, χ^2-test). The above analysis indicates that the reduction in direction selectivity in albino compared to pigmented ferrets results at least from two factors, a lower response to stimulation in the preferred direction and a less frequent suppression of activity during stimulation in the non-preferred direction.

Responses to Radially Expanding or Contracting Stimuli

The location and extent of the receptive fields was mapped qualitatively using a handheld lamp before centering the focus of expansion and contraction of our stimulus in the center of the receptive field to ensure balanced whole field stimulation. Altogether, 186 neurons in pigmented and 114 neurons in albino ferrets were tested with the radially expanding or

contracting stimulus. Of those, 91 neurons (49%) in pigmented and 74 neurons (65%) in albino ferrets had DS-indices ranging from –0.33 to +0.33, and therefore were not considered selective to either expansion or contraction (Fig. 6). In pigmented ferrets (Fig. 6*A*), 68 neurons (36.5%) had DS-indices ⩾ 0.33, 27 neurons (14.5%) had DS-indices ⩽ –0.33. Thus, in our sample cells responding to expansion twice as strongly as to contraction were significantly more frequent (χ^2-test, $P < 0.0001$) than cells with the contrary firing pattern. By contrast, in albino ferrets only 19.3% of the neurons showed a twice as strong modulation during expansion than contraction and 15.8% of cells showed the opposite pattern (Fig. 6*B*; χ^2-test, $P > 0.1$).

By means of the paired *t*-test, we found that DS-indices of both pigmented and albino ferrets (178 and 113 cells tested with both stimuli, respectively) were significantly lower for radial than for frontoparallel motion (paired *t*-test, $P < 0.001$).

Despite their high DS-indices (⩾+0.33 or ⩽–0.33) a considerable number of neurons showed a significant increase in activity during both expansion and contraction phase compared to the stationary pattern. Therefore, ongoing activity was measured in 178 neurons in pigmented and in 113 neurons in albino ferrets while the animals watched the stationary pattern. We compared the activity of each cell during expansion or contraction with the stationary phase and formed three classes. The first class (38 cells, 20.5%) consisted of neurons with significantly higher

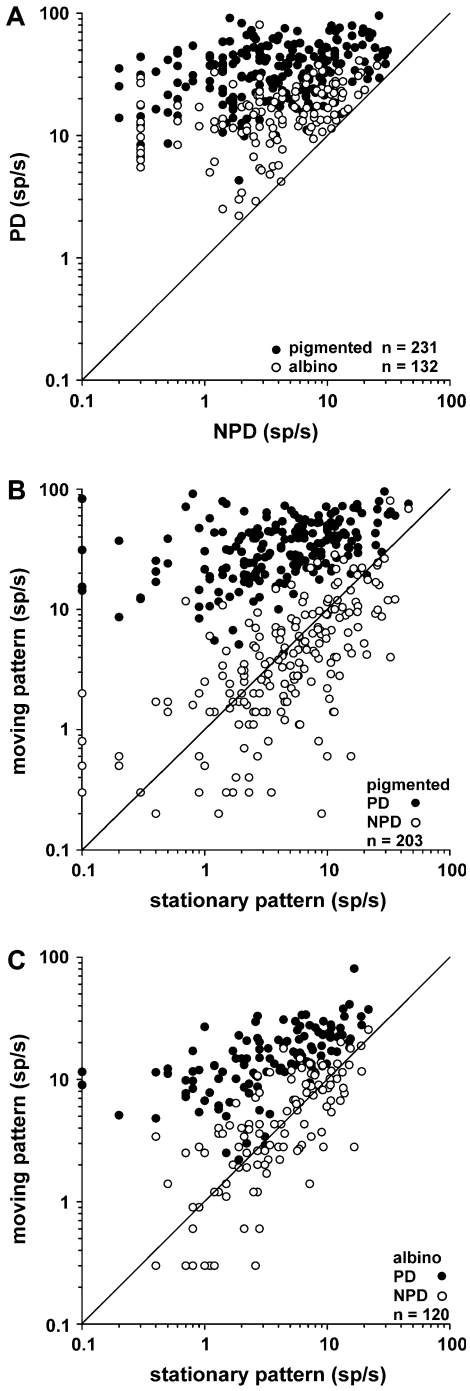

Figure 5. Scatterplots of responsiveness of PSS neurons to circular movements of a random dot pattern in the frontoparallel plane in pigmented and albino ferrets. (*A*) Discharge rate in spikes per second during stimulation in preferred direction (ordinate) is plotted against discharge rate during stimulation in non-preferred direction (abscissa) on log scales for pigmented (filled circles) and albino ferrets (open circles). (*B*) Discharge rate during stimulation in preferred (closed circles) and non-preferred stimulus direction (open circles) is plotted on the ordinate against ongoing activity during stationary pattern (abscissa) on log scales in pigmented ferrets. (*C*) Same analysis as in (*B*), for albino ferrets. Solid lines indicate unity slope.

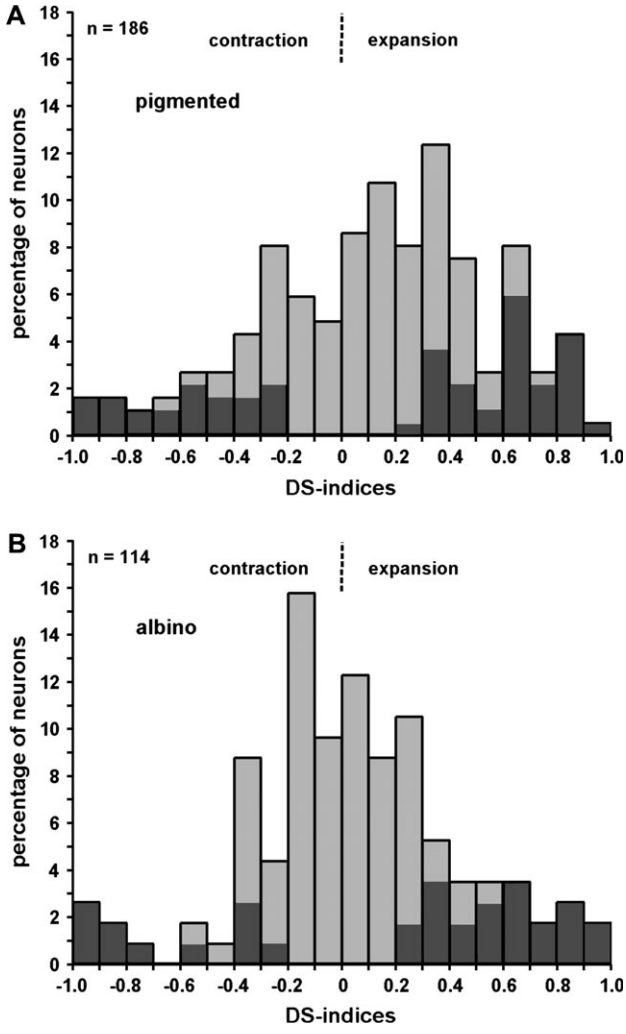

Figure 6. Frequency distribution of DS-indices of PSS neurons for random dot patterns expanding or contracting radially (abscissa) in pigmented (*A*) and albino ferrets (*B*). 0 indicates no response difference between expansion and contraction; −1 indicates responsiveness only to contraction; +1 indicates responsiveness only to expansion. Ordinate: percentage of cells. Dark grey area: expansion and contraction cells (for more details see text).

activity during expansion than contraction (t-test, $P < 0.01$). In addition the expansion activity was significantly higher than the activity during stationary pattern presentation (t-test, $P < 0.01$). The second class (24 cells, 12.9%) showed higher activity during contraction in the same way. In the following and to simplify the matter, we refer to these neurons as expansion and contraction cells, respectively (marked in dark grey in Fig. 6). All other neurons were described as not significantly modulated because their responses did not differ significantly from ongoing activity (based on t-test, third class). In albino ferrets 22 (19.5%) and 11 (9.7%) neurons were classified as expansion and contraction cells, respectively. There was no statistically significant difference between the proportion of expansion and contraction cells in pigmented or in albino ferrets (χ^2-test, $P > 0.05$).

In order to compare the response strengths of the entire populations in pigmented and albino ferrets also the cells with no significant difference between expansion and contraction activity were included in the analysis presented in Figure 7. Altogether 186 neurons in pigmented and 114 neurons in albino ferrets were analysed.

Neuronal activity during expansion is plotted versus activity during contraction on log scales for pigmented (Fig. 7*A*) and albino (Fig. 7*B*) ferrets. Filled circles indicate expansion neurons (activity during expansion was significantly higher than during contraction and stationary phase; t-test, $P < 0.01$) and open circles indicate contraction neurons (activity during contraction was significantly higher than during expansion and stationary phase; t-test, $P < 0.01$). All other neurons were classified as not significantly modulated (open triangles). Comparing response strength between pigmented and albino ferrets we found that stimulus driven activity in both expansion and contraction cells was significantly higher in pigmented than in albino ferrets (Mann–Whitney rank sum test, $P < 0.001$). Within each animal group, expansion cells did not differ from contraction cells (Mann–Whitney rank sum test, $P > 0.05$).

Temporal Structure of Neuronal Responses

In addition to the response strength measured as mean rate, we analysed the temporal structure of the neuronal responses. Because there was no difference between the response characteristics to frontoparallel and radial motion data were pooled. Assuming a gaussian distribution of inter-spike intervals, values of 200 ms for ongoing activity and 30–60 ms for stimulus-driven activity should be expected for pigmented and albino animals according to the discharge rates presented above. Figure 8 demonstrates the inter-spike interval histograms during moving (Fig. 8*A,C*) and stationary pattern presentation (Fig. 8*B,D*) in pigmented (Fig. 8*A,B*) and albino (Fig. 8*C,D*) PSS neurons. In pigmented ferrets, responses to moving stimuli were characterized by significantly shorter inter-spike intervals than responses to stationary patterns (moving: median 9 ms; stationary: median 13 ms; Mann–Whitney rank sum test, $P < 0.001$). This difference in the albino PSS neurons did not reach significance (moving: median 14 ms; stationary: median 19 ms; Mann–Whitney rank sum test, $P = 0.107$). Altogether, inter-spike intervals were significantly shorter in pigmented than in albino PSS neurons corresponding to the mean rate measurements above (Mann–Whitney rank sum test, $P < 0.001$ for motion responses, $P = 0.005$ for stationary pattern responses). Nevertheless, the inter-spike intervals indicate for pigmented as well as albino animals that most of the action potentials are fired in groups or bursts and no qualitative difference exists in this respect between the discharge patterns of pigmented and albino ferrets.

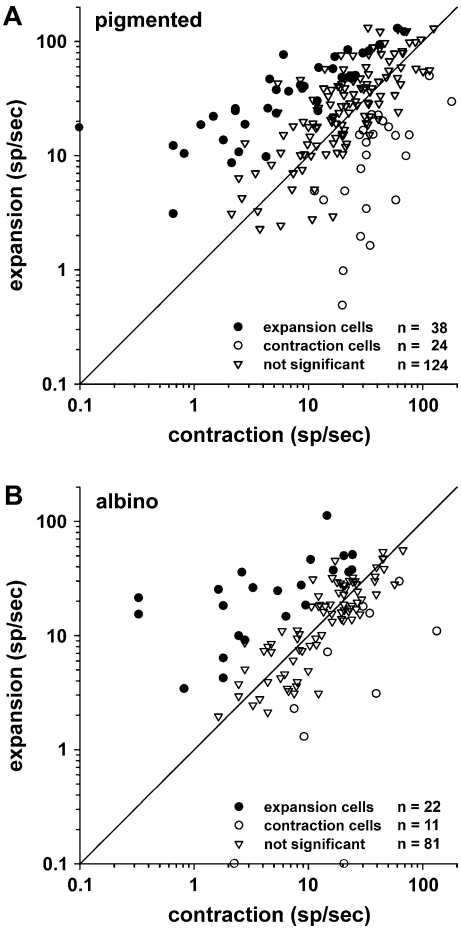

Figure 7. Scatterplots of responsiveness of PSS neurons to a random dot pattern expanding or contracting radially in pigmented and albino ferrets. (*A*) Discharge rate (in spikes per second, ordinate) during expansion is plotted against discharge rate during contraction of the dot pattern (abscissa) on log scales for pigmented ferrets. Filled circles indicate expansion neurons and open circles indicate contraction neurons (see text for more details). All other neurons were classified as not significantly modulated (open triangles). (*B*) Same analysis (with the same conventions) as in (*A*), for albino ferrets. Solid lines indicate unity slope.

Discussion

Characterization of Area PSS

In this study we identify a hitherto not clearly described area in the ferret extrastriate cortex that is characterized by large receptive fields, clear responses to random dot patterns, and a high incidence of direction-selective neurons. Area PSS is located in the posterior part of the suprasylvian sulcus and on its posterior bank bordering the parietal cortex medially, areas 20b and PS laterally, auditory cortex anteriorly and area 21 posteriorly. Area PSS is characterized by dense myelination and can thus be distinguished from the parietal cortex medially and the temporal cortex laterally. Unfortunately, based on this criterion alone, the anatomical distinction of area PSS from auditory area ME (Wallace *et al.*, 1997) and area 21 (Innocenti *et al.*, 2002) is far less clear than, for example, the distinction of macaque area MT from the surrounding cortex. As pointed out before, we cannot wholly exclude the possibility that our myelin borders

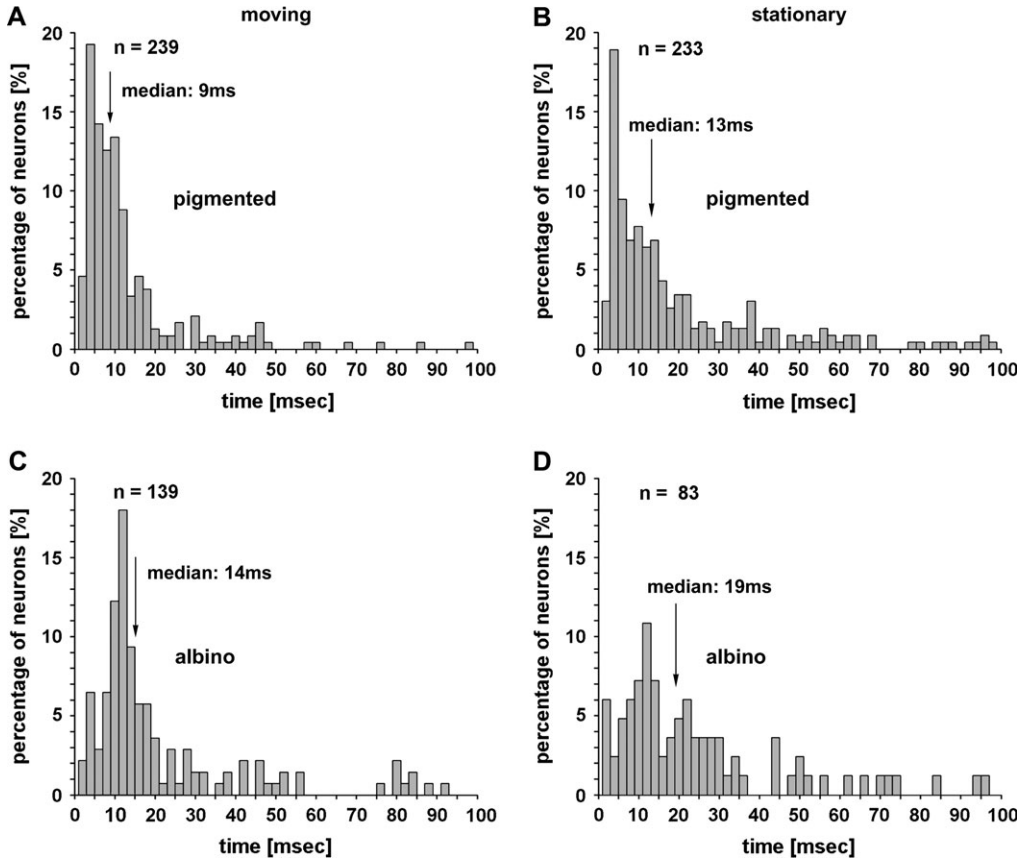

Figure 8. Frequency distribution of inter-spike intervals (ISI) (abscissa, in ms) of PSS neurons during moving (*A*, *C*) and stationary (*B*, *D*) patterns in pigmented (*A*, *B*) and albino (*C*, *D*) ferrets. Because there was no difference between the ISIs during frontoparallel and radial motion, data were pooled. Ordinate shows the relative number of cells in percent. For pigmented ferrets we found significantly shorter ISIs during moving stimuli than during the stationary pattern (moving: median 9 ms; stationary: median 13 ms, $P < 0.001$). This was not the case in the albino PSS neurons (moving: median 14 ms; stationary: median 19 ms, $P = 0.107$).

may have been confounded by gross cortical anatomy. However, by extrapolating the myeloarchitecture around lesions at recording sites of direction-selective cells we have a good estimate of the extent of this area. In our opinion, the combination of physiological characterization of response properties with anatomical criteria is much more valid than anatomical criteria by themselves.

The most characteristic response property of PSS neurons is their direction-selective response to moving dot patterns. In addition to motion sensitivity in the frontal plane, PSS neurons are sensitive to radial stimulus movements (expansion/contraction). We found significantly higher DS-indices for stimulation in the frontal plane than for radial stimulus movements. It could not be excluded that this difference was due to the neuron's reduced response strength to the preferred direction caused by the remaining dots moving in non-preferred directions. Further investigations will show whether this sensitivity to expanding/contracting stimuli is a prerequisite for a optic flow analysis in the visual system of the ferret. Data from the literature (Gibber *et al.*, 2001; Usrey *et al.*, 2003) and preliminary data from our laboratory indicate a significantly higher incidence of direction-selective neurons in area PSS as a distinguishing feature when compared with areas 17, 18, 19 and 21.

Direction Anisotropy

Our data reveal that in PSS of pigmented ferrets horizontal directions are more strongly represented and that upward directions are underrepresented. Directional anisotropies have also been described in other mammals and visual areas (Bauer *et al.*, 1989; Paolini and Sereno, 1998). In cat area PMLS a large proportion of neurons prefers centrifugal stimulus directions (Rauschecker *et al.*, 1987; Weyand and Gafka, 2001; but see also Sherk *et al.*, 1995). A similar finding was described for the peripheral field representation of macaque area MT (Albright, 1989) but not for MT in general.

Due to the varying angle between electrode track and cortical layers, it is difficult to decide if direction preference is indeed organized in cortical columns in ferret PSS as has been described for ferret Clare-Bishop area (Sherk, 1988), ferret area 17 (Gibber *et al.*, 2001) and macaque area MT (Albright *et al.*, 1984; Liu and Newsome, 2003), and indicated for cat area PMLS (Rauschecker *et al.*, 1987; Sherk, 1988). Optical recordings from ferret area 17 indicate a systematic representation of direction preferences consisting of a mosaic-like map (Weliky *et al.*, 1996). Unfortunately, this method has not been applied to area PSS so far to clarify the discrepancy between our data showing no systematic topographic arrangement of preferred directions and the claim by Sherk (1988) of such an arrangement in this area.

Comparison with other Species

There is ample evidence that area PMLS of the cat is involved in 3D motion analysis (Toyama and Kozasa, 1982; Toyama *et al.*, 1985, 1986a,b; Akase *et al.*, 1998). This area is characterized

by a high proportion of direction-selective neurons many of which prefer high stimulus velocities. PMLS neurons are only moderately orientation selective and most respond to random dot patterns (Rauschecker *et al.*, 1987; Toyama *et al.*, 1994; Dreher *et al.*, 1996; Li *et al.*, 2000; Brosseau-Lachaine *et al.*, 2001). Two-thirds of the PMLS neurons are sensitive for contraction or expansion, and about half of this population reacts direction selectively (Kim *et al.*, 1997; Mulligan *et al.*, 1997; Li *et al.*, 2000; Brosseau-Lachaine *et al.*, 2001). Evidence that PMLS is involved in motion analysis comes also from behavioural studies (Pasternak *et al.*, 1989; Krueger *et al.*, 1993; Lomber *et al.*, 1994, 1996; Rudolph and Pasternak, 1996; Sherk and Fowler, 2002).

Area MT of the macaque monkey is thought to be homologous to area PMLS of cat (Payne, 1993). It is characterized by a large population of direction-selective neurons (76–88%) (e.g. Maunsell and Van Essen, 1983; Albright *et al.*, 1984; Mikami *et al.*, 1986; Tanaka *et al.*, 1986). Neighbouring area MST also contains many direction-selective neurons that have larger receptive fields and also respond well to large area random dot patterns (e.g. Desimone and Ungerleider, 1986; Saito *et al.*, 1986; Tanaka *et al.*, 1986; Komatsu and Wurtz, 1988). Both areas also respond to optic flow patterns (Saito *et al.*, 1986; Lagae *et al.*, 1994) and specificity for various flow patterns is more pronounced in MST that in MT (Lagae *et al.*, 1994).

Comparing our results on area PSS in the ferret with data for area PMLS of the cat or area MT/MST of macaque monkey, it is clear that area PSS with its high amount of direction-selective cells and its responsiveness to expanding and contracting stimuli, with its mostly large receptive fields and a preference for higher stimulus velocities qualifies for an area specialized in the analysis of visual motion. Thus, we propose that area PSS is at least analogous if not homologous to area PMLS of the cat or area MT/MST of the macaque.

Deficits in Neurons of Albino Area PSS

Why study visual cortical neurons in albinos? The albino mutation leads, probably via a lack of dihydroxyphenylalanine in the retina, to a cascade of spatiotemporal perturbations of retinal maturation and by that to the well known misprojections to retinorecipient visual centers (Jeffery, 1997). These misprojections, i.e. the abnormal amount of crossing retinofugal fibres, in turn lead to alterations in the cortical representation of the visual field. as has been demonstrated in albino ferrets (Akerman *et al.*, 2003) and Siamese cats (Shatz, 1977; Chino *et al.*, 1984). It is only logical to assume that beside the retinotopical organization also physiological properties may be influenced by the albino mutation.

Indeed, we found fewer direction-selective neurons in albino ferret PSS which, in addition, were significantly less direction selective than neurons in pigmented ferrets. In pigmented ferrets, significantly more neurons coded for horizontal than for vertical stimulus movements. This was not the case in albinos. Also the tuning width was significantly wider in albino than in pigmented PSS neurons. An additional effect in pigmented ferrets was the prevalence of suppression of neuronal activity below the activity during stationary stimuli if PSS neurons were stimulated in non-preferred directions. A similar suppression of activity during stimulation in non-preferred directions has also been described for retinal slip cells in the NOT–DTN of pigmented ferrets and other mammals (Hoffmann *et al.*, 2004). In albino ferrets this suppression was not as evident. All these facts — response to a broader range of directions, lower response strength to stimulation in the preferred direction and a missing suppression of activity during stimulation in the non-preferred direction in albino PSS neurons — point to less effective inhibitory mechanisms which could contribute to the lower direction selectivity in albino ferrets. The moderate though significant degradation of direction selectivity in cortical area PSS as a probable source of input to the NOT–DTN certainly cannot explain the total loss of direction selectivity in this subcortical relay of visual information to the optokinetic system in albino ferrets (Hoffmann *et al.*, 2004). Altered inhibitory mechanisms as the cause for degradation or even loss of direction selectivity are currently investigated in our laboratory. So far we found a significant decrease in the amplitude of IPSCs in pyramidal cells in slices of visual cortex in albino rats in comparison to pigmented rats (Barmashenko *et al.*, 2005). This clearly shows that the albino central visual system is not only altered anatomically but also at the cellular and molecular level with severe influences on physiology and behaviour.

Position of Area PSS in the Cortical Hierarchy

In a series of experiments, Manger and colleagues recently undertook the identification of visual cortical areas in the ferret based on the retinotopic visual field representation and on callosal connections (Innocenti *et al.*, 2002; Manger *et al.*, 2002a,b, 2004). They conclude that the classical parcellation of primate visual cortex in a dorsal ('Where') and a ventral ('What') stream (Ungerleider and Mishkin, 1982) is not a *de novo* development in primates but can also be found in such carnivores as the cat (Lomber *et al.*, 1996) and the ferret. They argue that ferret area 21 may correspond to macaque area V4, that ferret posterior parietal areas PPc and PPr correspond to primate parietal cortex. Furthermore, area 20a of cat and ferret supposedly corresponds to macaque area TF, area 20b corresponds to TH and area PS corresponds to TG (Payne, 1993; Manger *et al.*, 2004). A further, not yet clearly identified, visual area, SSY, medial to PS and anterior to area 21, is thought to correspond to areas DLS and VLS of the cat and areas TEO and TE of the macaque, thus also belonging to the ventral processing stream.

The area indicated by Manger and colleagues seems to at least partly overlap with our area PSS. In our study, we did not put particular emphasis on the retinotopic order in area PSS. Rather, we concentrated on the neuronal responses to specific visual stimuli and found that in contrast to the posterior visual areas 17, 18, 19 and 21 area PSS is characterized by a high proportion of neurons with large receptive fields strongly responding to moving random dot stimuli. Based on our physiological data, area PSS in this respect clearly resembles area PMLS of the cat and areas MT/MST of the macaque and thus should be considered part of the dorsal processing stream.

Notes

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