Modulatory Influence of Feedback Projections from Area 21a on Neuronal Activities in Striate Cortex of the Cat

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We have examined the influence of 'feedback' projections from extrastriate visual cortical area 21a on the responses of neurons in area 17 of the cat, by cooling area 21a to 5–10°C while the temperature over the recording sites was kept at 36°C. Orientation, direction and length selectivities as well as contrast sensitivity were tested before and during cooling and after rewarming of area 21a. Overall, for the sample of cells recorded from the part of area 17 visuotopically corresponding to area 21a, the 'spontaneous' activity (at background illumination of 1 cd/m^2) and the responsiveness to visual stimuli of standard contrast (15) were significantly reduced by inactivation of area 21a. In about half of the cells inactivation of area 21a affected substantially the sharpness of orientation-tuning. However, only in a minority of the cells were the direction or length selectivities significantly affected by inactivation of area 21a. Thus (i) the feedback projections from area 21a appear to exert mainly an excitatory influence on the background activity and responsiveness of area 17 cells and (ii) only in subgroups of area 17 cells does the feedback activity originating from area 21a appear to modulate specifically certain receptive field properties.

Introduction

Starting with the early 'classical' work of Hubel and Wiesel (Hubel and Wiesel, 1959, 1962, 1965), a substantial amount of data about the functional organization of neurons in the mammalian visual cortices has been accumulated. The general consensus has emerged that the retino-geniculo-cortical pathway and the so-called 'feedforward' cortico-cortical association pathway provide the principal excitatory drive to cortical neurons in both the primary and the 'higher-order' mammalian visual cortices (Douglas and Martin, 1991; Domenici *et al.*, 1995; Shao and Burkhalter, 1996) [for reviews see (Stone *et al.*, 1979; Orban, 1984; Dreher, 1986; Maunsell and Newsome, 1987; Livingstone and Hubel, 1988; Felleman and Van Essen, 1991; Henry, 1991; Coogan and Burkhalter, 1993; Bullier *et al.*, 1994; Salin and Bullier, 1995; Burke *et al.*, 1998)].

On the other hand, much less is known about the functional role of the extensive cortico-cortical 'feedback' projections from the higher-order visual cortical areas to the lower-order cortical areas (Rockland and Pandya, 1979; Van Essen and Maunsell, 1983; Dreher, 1986; Zeki and Shipp, 1988; Shipp and Zeki, 1989a,b; Felleman and Van Essen, 1991; Van Essen *et al.*, 1992; Rockland, 1994; Salin and Bullier, 1995). Most of the experimental data so far available suggest that feedback projections from the higher-order cortical areas play only a modulatory role in processing of visual information in the lower-order cortical areas (including the primary visual cortices). Thus, inactivation of cytoarchitectonic area 18 in a New-World primate, the squirrel monkey, did not abolish the responses to visual stimuli of the great majority of neurons in the striate cortex, but did affect the magnitude of the responses of about one-third of area 17 cells and, in most cases, the magnitude of these responses was substantially reduced (Sandell and Schiller, 1982). Furthermore, Hupé and colleagues (Hupé *et al.*, 1998) have demonstrated that many neurons in area V1 as well as those in two other relatively lower-order areas (V2 and V3) of the macaque visual cortex exhibit reduced ability to differentiate low-salience figures from the background when one of the motion areas, the middle temporal area (MT, or area V5), is reversibly inactivated by cooling. Thus, it appears that the feedback connections could affect the 'functional performance' of neurons located at a lower level of visual information-processing hierarchies.

In the cat, cytoarchitectonic area 17 (which, together with area 18, constitutes the primary visual cortex since both areas receive their principal thalamic input from the dorsal lateral geniculate nucleus) projects directly to and receives direct feedback input from a number of visuotopically organized cortical areas [Fig. 1*A*,*B*; for reviews see (Rosenquist, 1985; Dreher, 1986; Burke *et al.*, 1998)]. We wished to examine a possible functional role of feedback projections to area 17 originating from area 21a, which is located at some distance from the primary visual cortices (Fig. 1*A*). Michalski and colleagues (Michalski *et al.*, 1993, 1994) have demonstrated by reversible inactivation (cooling) of area 17 that the well documented and numerically large inputs from area 17 (Symonds and Rosenquist, 1984a,b; Dreher, 1986; Mizobe and Toyama, 1989; Dreher *et al.*, 1996b; Morley *et al.*, 1997) provide a major excitatory drive to area 21a neurons. The studies in our laboratory (Dreher, 1986; Dreher *et al.*, 1993, 1996a; Wang and Dreher, 1996) as well as those in several other laboratories (Mizobe *et al.*, 1988; Wimborne and Henry, 1992; Toyama *et al.*, 1994; Tardiff *et al.*, 1996; Morley and Vickery, 1997; Vickery and Morley, 1997, 1999) have shown that, despite their relatively large receptive fields and relatively low spatial frequency tuning, the neurons in area 21a are characterized by low temporal resolution, preference for slowly moving stimuli and sharp orientation-tuning. Furthermore, almost all area 21a neurons are binocular and in most of them responses are strongly modulated by binocular retinal disparities of a stimulus (Wang and Dreher, 1996; Vickery and Morley, 1997, 1999). Overall, the receptive field properties of area 21a neurons tend to be quite similar to those of neurons in area 17 of the cat [cf. for reviews (Orban, 1984; Dreher, 1986; Burke *et al.*, 1992; Dreher *et al.*, 1992)]. It appears that areas 17 and 21a are involved in the same functional information-processing stream, that is, form rather than motion analysis, and area 21a represents a gateway area to a distinct form-processing stream in the temporal cortex (Dreher, 1986; Wimborne and Henry, 1992; Dreher *et al.*, 1993, 1996a,b; Morley and Vickery, 1997; Burke *et al.*, 1998).

Specifically, in the present study we have attempted to examine the influence of feedback projections from area 21a on 'spontaneous' (background) activity and responses of neurons in the part of area 17 visuotopically corresponding to the part of the visual field represented in area 21a. This was achieved by comparing the responses of area 17 neurons to visual stimuli presented before and during inactivation by cooling of area 21a

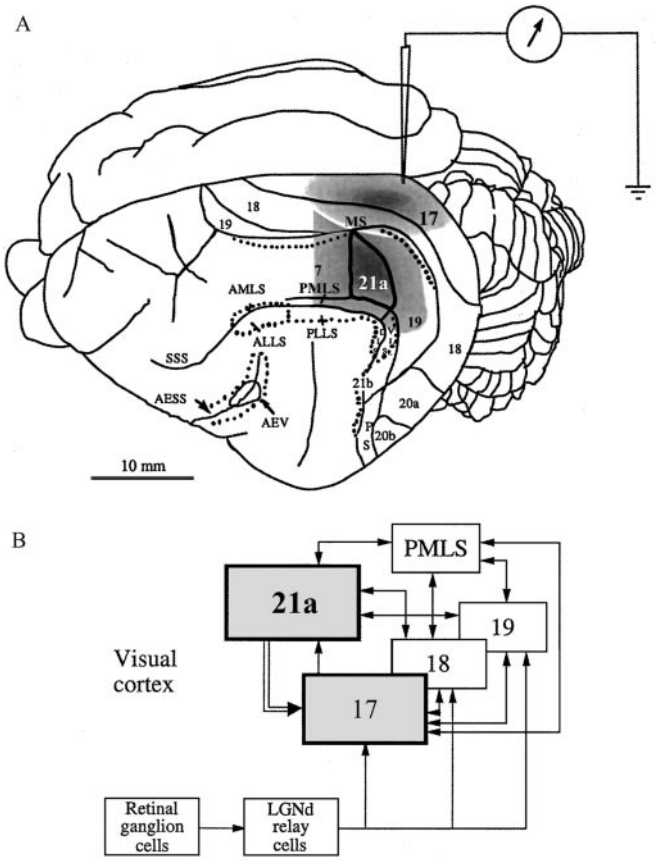

Figure 1. (*A*) Dorsolateral view of the left cerebral hemisphere of the cat with outlines of areas 17, 18, 19, 21a, 21b, 20a and 20b, as well as lateral suprasylvian areas (anteromedial, anterolateral, posteromedial and posterolateral, dorsal and ventral; AMLS, ALLS, PMLS, PLLS, DLS and VLS, respectively), area 7, posterior suprasylvian (PS) and anterior ectosylvian visual area (AEV). AESS, anterior ectosylvian sulcus; MS, marginal (lateral) sulcus; SSS, suprasylvian sulcus. The borders outlined by the interrupted lines are buried in sulci (Tusa *et al.*, 1981; Updyke, 1986). The diagrammatic electrode indicates the general location of most of our electrode penetrations through area 17. The dark gray regions within areas 17 and 21a indicate respectively the locations of warming (36°C) and cooling (5–10°C) plates. Paler gray regions indicate the regions over which, due to a temperature gradient, there was a substantial spread of heat from the warming plate positioned over area 17 or cold from the cooling plate positioned over area 21a. (*B*) Simplified neuronal circuitry of central visual pathways and several visuotopically organized cortical areas of the cat. The feedforward pathway includes the retinal ganglion cells, relay cells in the dorsal lateral geniculate nucleus (LGNd) and cells in the primary visual cortices (areas 17 and 18) projecting to areas 19, 21a or PMLS as well as cells in area 17 projecting to area 18 and cells in area 19 projecting to area 21a or PMLS. The feedback pathway involves cells in areas 21a and PMLS projecting to the primary visual cortices as well as those projecting to area 19, cells in area 19 projecting to the primary visual cortices and cells in area 18 projecting to area 17. The connections in the diagram are based on reviews (Stone *et al.*, 1979; Rosenquist, 1985; Dreher, 1986; Dreher *et al.*, 1996b). Following our recent publications (Dreher *et al.*, 1996a,b; Burke *et al.*, 1998), area PMLS is regarded here as the entrance area to a distinct motion-processing stream in the parietal region (lateral suprasylvian areas and AEV area) while area 21a represents a gateway area to a distinct form-processing stream in the temporal region (areas 20a, 20b and PS).

as well as after rewarming of area 21a. Preliminary results were reported previously (Wang *et al.*, 1999).

Materials and Methods

Animal Preparation

Experiments were carried out on eight adult cats of either gender weighing 2.5–4.0 kg. The animals were initially anaesthetized with 2.5–5.0% halothane in an N_2O/O_2 (67%/33%) gaseous mixture. A surgical level of anaesthesia was maintained with 1.5–2.5% halothane in the same gaseous mixture while the surgery, intravenous and tracheal cannulation and bilateral cervical sympathectomy were performed. The animals were then placed in a stereotaxic headholder and craniotomies were performed over area 21a (Horsley–Clarke or HC coordinates: lateral 8–16 mm; posterior 0–8 mm) and area 17 (HC coordinates: lateral 0–5 mm; posterior 0–8 mm). Area 21a was cooled by means of a specially shaped metal probe put over the surface of the area while a second probe was placed over area 17 to keep the local temperature constant at 36°C (Fig. 1*A*).

During the recording sessions, the animals were paralyzed by intravenous infusion of gallamine triethiodide at the rate of 7.5 mg/kg/h in a mixture of equal parts of 5% dextrose and sodium lactate (Hartmann's) solutions and artificially ventilated. Anaesthesia was maintained with gaseous mixture of halothane (0.5–0.7%) in N_2O/O_2 (67%/33%). Peak expired-CO_2 was continuously monitored and maintained at 3.7–4.0% by adjusting the stroke volume or rate of the pulmonary pump. Body temperature was automatically maintained at ~37.5°C by an electric heating blanket. Heart rate and electroencephalogram (EEG) were monitored continuously. With the above regimen the EEG maintained a slow-wave record while the heart rate was kept below 180 beats/min. Antibiotic (amoxycillin trihydrate, 75 mg), dexamethasone phosphate (4 mg) and atropine sulphate (0.3 mg) were given intramuscularly on a daily basis. Experimental procedures followed the guidelines of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and were approved by the Animal Care Ethics Committee of the University of Sydney.

The corneas were protected with zero-power, air-permeable plastic contact lenses. Pupils were dilated and accommodation paralysed with 1% atropine sulphate solution. The nictitating membranes were retracted with 0.128% phenylephrine hydrochloride. Artificial pupils (3 mm in diameter) were placed in front of the contact lenses. Correcting lenses were used, if required, to focus the eyes on a tangent screen located 57 cm in front of the eyes. The locations of the optic discs and the areae centrales were plotted twice daily using a fibre-optic projector (Pettigrew *et al.*, 1979).

Recording

A plastic cylinder was glued to the skull surrounding the opening over area 17 to form a well. A smaller opening in the dura was made above the recording site. A stainless steel microelectrode (11 MΩ; FHC, Brunswick, ME) was positioned medially to the warming probe and lowered until its tip was positioned at the cortical surface; the cylinder was then filled with 4% agar gel and sealed with warm wax to reduce brain pulsations. The microelectrode was advanced into the cortex by a step-motor-controlled hydraulic micromanipulator. The action potentials of single neurons were recorded extracellularly, amplified conventionally and monitored both visually and via the loudspeaker; triggered standard pulses (again monitored both visually and aurally) were then fed to a microcomputer.

Temperature Control

Temperature control of cortical areas, for example, cooling of cortical area 21a as well as the subsequent rewarming of the area, was achieved by using a gold-plated metal probe attached to a Peltier element (9 W; Marlow, Dallas, TX) which, in turn, was controlled by a laboratory-built device. The temperature on the cortex could be preset and automatically maintained by adjusting the polarity and the amount of current passing through the Peltier element. With our temperature control units the preset temperatures (in a range of 5–40°C) could be reached within 1 min and could be maintained constantly for as long as required. In the same regime, area 17 was kept warm at 36°C. The probe placed over area 21a was quadrant-shaped with a radius of 7 mm, while the probe for controlling temperature of area 17 was rectangular, 3 × 6 mm. The contact surfaces of the probes were shaped to match the curvatures of the cortical surfaces on which they were placed. Temperatures over areas 17 and 21a were continuously monitored by the thermocouples built into the foot of each probe. The warming probe for area 17 with temperature maintained at 36°C was placed lateral to the recording site, which, together with the recording electrode, was covered with 4% agar and wax in the well. When area 21a was not being cooled its temperature

was also kept at 36°C. The responses of single neurons recorded in area 17 were first tested when the temperature of area 21a was maintained at 36°C, i.e. our control condition, and then the same test was performed again when area 21a was cooled to 5–10°C. To avoid possible irreversible damage to the cortex, the cooling process was discontinued after 10–15 min and the cortex was slowly (over the period of 2–3 min) rewarmed back to 36°C. Data collections usually started 3 min after the preset temperature was reached. After rewarming of area 21a to 36°C several runs were made until either complete recovery or an incomplete but steady-state recovery had been achieved.

Visual Stimulation and Qualitative Data Analysis

The receptive fields of recorded cells were first explored and plotted with a hand-held light slit projector on a tangent screen. The general features of the receptive field, such as size of the discharge field, receptive field organization, ocular dominance, orientation, direction and velocity preferences, were first examined qualitatively. The excitatory receptive field (discharge field) was defined as the area of visual space within which visual stimuli elicited an increase in the cell's firing rate detectable by ear. Cells which exhibited spatially separate ON and OFF discharge regions to optimally oriented, stationary flashing slits and non-overlapping discharge regions to moving, optimally oriented elongated bars darker or brighter than the background were identified as S-type cells [see S-cells and A-cells (Henry, 1977); cf. simple cells (Hubel and Wiesel, 1962; Gilbert, 1977)]. Cells which gave transient responses at both onset and offset of stationary flashing slits of light positioned anywhere within their discharge fields (ON/OFF discharge fields), and/or their discharge fields plotted with moving stimuli darker than the background overlapped completely with those revealed with moving stimuli brighter than the background, were identified as C-type cells [see C-cells and B-cells (Henry, 1977); cf. complex cells (Hubel and Wiesel, 1962, 1965; Gilbert, 1977)]. End-zone inhibition or end-stopping was defined as the reduction of the response magnitude when the length of the optimally oriented bar exceeded the length of the discharge field (Hubel and Wiesel, 1962; Dreher, 1972; Gilbert, 1977). S-type cells with end-zone inhibition were identified as S_H cells (Henry, 1977) [cf. hypercomplex type I cells (Dreher, 1972; Gilbert, 1977; Kato *et al.*, 1978)] while the C-type cells with end-zone inhibition were identified as C_H cells (Henry, 1977) [cf. hypercomplex cells (Hubel and Wiesel, 1965; Gilbert, 1977) and hypercomplex type II cells (Dreher, 1972; Kato *et al.*, 1978)].

Quantitative Data Analysis

After qualitative analysis of the receptive field properties of a cell, the screen was then replaced with a computer-controlled CRT monitor (BARCO, Belgium) where the visual stimuli were presented at a distance of 57 cm from the cat's eyes. Light bars of different orientations, lengths and contrasts were employed to examine the possible contributions of feedback from area 21a on the receptive field properties of area 17 neurons. After determining the receptive field properties, such as velocity preferences, orientation selectivity and length selectivity, we examined the effect of cooling area 21a on a particular receptive field property. Finally, area 21a was rewarmed to 36°C and the receptive field properties of the neurons were re-examined.

The stimulus velocities used for examination of the effects of reversible inactivation of area 21a were usually optimal for the individual cell under test and ranged from 2 to 25°/s. When testing the orientation or length selectivity, a set of bars of different orientations or different lengths moving at optimal velocities were interleaved and presentations were repeated 5–10 times. Orientation selectivity was examined with light slits which were 5–10 times the length of the tested receptive field (along its optimal orientation axis) moving in the direction orthogonal to the axis of orientation. As a measure of the sharpness of orientation selectivity of an individual neuron we used the orientation-tuning width at half-height.

Since we used single bars on a constant background we used the following definition of contrast:

$$C = (L_o - L_B)/L_B$$

where L_o and L_B are respectively luminance of the object (in our case single bars) and luminance of the background. Thus defined, the contrast used by us for testing orientation, direction and length selectivity was 15 at the background luminance of 1 cd/m^2. In testing contrast sensitivity a set of optimally oriented moving light bars of varying contrast was interleaved pseudo-randomly and presentations were repeated 5–10 times. Two 'control runs' were usually done before cooling was applied.

The peristimulus time histograms were constructed by summing the responses collected during the stimulus period. The peak discharge rate was determined as the maximum discharge rate after applying a smoothing algorithm, the Gaussian weighted average over five neighbouring bins.

The mean direction selectivity index (MDI), defined as the geometric mean of the direction selectivity indices (DI) at different orientation, contrast or length (Orban *et al.*, 1981), was used to evaluate the direction selectivity of a given cell. The MDI was calculated using the following formula:

$$\mathrm{MDI} = \left| \frac{\sum_{i=1}^{n} R_i \mathrm{DI}_i}{\sum_{i=1}^{n} R_i} \right|$$

where n is the number of orientations, contrasts or lengths tested and R_i is the response in the preferred direction for each orientation, contrast or length. DI was calculated by the following formula:

$$\mathrm{DI} = (R_p - R_{np})/R_p$$

where R_p and R_{np} are the responses to the stimuli moving in the preferred and non-preferred direction respectively.

For determining the strength of response suppression in the end-stopped region of end-stopped cells we introduced an 'end-stopped suppression index' (ESI). It was calculated according to the following formula:

$$\mathrm{ESI} = 1 - R_{min}/R_{max}$$

where R_{max} is the response produced by a stimulus of an optimal length for a given cell and R_{min} is the minimum average response to a number of stimuli of greater than optimal length (where the slope of response declination was <10% of its maximum). Usually, the lengths used to calculate R_{min} were >5 times the optimal length.

Localization of Cooling and Recording Sites

Area 21a was localized on the basis of its relationship to the lateral suprasylvian and marginal (lateral) sulci (Fig. 1*A*). The reconstruction of electrode penetrations in area 17 was based on small electrolytic lesions (5–7 μA for 20 s) at the end of the first and last electrode penetrations. At the end of the recording session (lasting usually 3–5 days) the animal was deeply anaesthetized with an intravenous injection of 120 mg of sodium pentobarbitone and perfused transcardially with warm (37°C) Hartmann's solution followed by a 4% solution of paraformaldehyde in 0.2 M phosphate buffer (pH 7.4). Localization of the position of the cooling probe was aided by the post-mortem location of the imprint left by the probe on the brain. Finally, the brains were stereotactically blocked and sectioned coronally at 50 μm on a freezing microtome, mounted on slides and counterstained with cresyl violet.

Statistics

Three non-parametric statistical tests were used: the Wilcoxon matched-pairs signed-ranks test, the Mann–Whitney *U*-test and the χ^2 test (Siegel, 1956). The tests were applied to single neurons and to the populations of neurons. Statistical significance of the differences between the two sets of data was accepted if the probability (P) using the two-tailed criterion was <0.05. Correlations were examined with the Pearson statistic (r). The statistics are given as mean values ± SEM. For individual cells a difference between the state when areas 17 and 21a were at 36°C and the state when area 17 was at 36°C while area 21a was at 5–10°C was deemed significant only if : (i) a significant difference was found between the initial control state (areas 17 and 21a at 36°C) and the cooled state (area 21a at 5–10°C);

and (ii) a significant difference was found between the cooled state and the subsequent rewarmed state (areas 17 and 21a again at 36°C).

Results

Cooling of Area 21a vs neighbouring areas and area 17

Multiunit activities (both 'spontaneous' and visually evoked) in area 21a were effectively abolished when the temperature of the area dropped to ~10°C. Despite the fact that our cooling probe was restricted to area 21a, due to the temperature gradient, cooling of area 21a resulted also in lowering the temperature in the number of cortical areas in proximity to area 21a. Indeed, even in area 17, which is relatively remote from area 21a (Fig. 1*A*), when the temperature of area 21a was at ~10°C and the warming probe was not placed over area 17, the temperature measured at 1 mm below the surface of the cortex dropped to 30–33°C. The dual temperature control approach used in the present study allowed us to maintain the physiological temperature at the recording sites in area 17 irrespective of the temperature of area 21a. This was true not only when the recording sites were near the marginal (lateral) gyrus, that is, in close proximity of the warming probe, but also when the recording sites in area 17 were 3–4 mm below the cortical surface along the medial aspect of the hemisphere. Since in our experimental set-up the warming probe covered not only area 17 but also most, if not all, of the part of area 18 visuotopically corresponding to area 21a, this area also was probably well protected against the cold spreading across the marginal sulcus from area 21a. However, since our warming probe (i) did not cover the areas in the immediate proximity of area 21a, such as area 19, the postero-medial lateral suprasylvian area (PMLS) and area 7, and (ii) the temperature gradient measured by us was ~5°C/mm, the temperature in parts of those areas was almost certainly substantially reduced during cooling of area 21a (see Discussion).

Receptive Field Location of Tested Area 17 Cells

The effects of reversible inactivation (by cooling and rewarming) of area 21a on the responses to visual stimuli were tested in 62 single neurons recorded from area 17. Fifty-one of the cells had their receptive fields located within 12° from the area centralis in the part of area 17 visuotopically corresponding to the part of the visual field represented in area 21a (Tusa *et al.*, 1978, 1981; Tusa and Palmer, 1980; Dreher *et al.*, 1993). For brevity, this region of area 17 will henceforth be referred to as the VC21a region. The remaining 11 cells tested by us had receptive fields located in the lower visual field at eccentricities exceeding 10° (range 14–23°), that is, outside the VC21a region (Tusa and Palmer, 1980; Tusa *et al.*, 1981; Wimborne and Henry, 1992; Dreher *et al.*, 1993).

Typical Result

Figure 2*A* shows peristimulus time histograms of responses of an S-type cell recorded from the VC21a part of area 17 to elongated light bars of different orientations moving across the cell's discharge field. Fairly typically, with background luminance of 1 cd/m^2, this cell had relatively low 'spontaneous' activity and responded selectively to particular stimulus orientations. Cooling area 21a to 10°C resulted in a 36% decrease in the magnitude of responses to an optimally oriented (almost horizontal) bar moving across the cell's receptive field (second row from the top in Fig. 2*A*). A very similar relative decrease in magnitude of responses was apparent when non-optimally oriented stimuli moved across the cell's discharge field. However, the cell's response profile (Fig. 2*A*) and its orientation-tuning curve were largely unchanged by inactivation of area 21a (Fig. 2*B*). Seven minutes after area 21a was rewarmed to 36°C, the responsiveness of the cell to stimuli of any orientation returned almost completely to the control (precooling) levels (Fig. 2*A*,*B*). Overall, the decrease in the magnitude of the responses following inactivation of area 21a in relation to the precooling data and the data collected after rewarming of area 21a was statistically significant ($P = 0.018$ in both cases, Wilcoxon test).

Effects of Cooling of Area 21a on Background Activities of Area 17 Neurons

Figure 3*A* shows the overall relationship between the mean background ('spontanous') activity of area 17 cells when the temperature of both area 21a and area 17 was 36°C and that during the time when area 21a was inactivated by cooling. It is apparent from the figure that, although with few exceptions background activity of area 17 was lower when area 21a was inactivated, all but eight cells exhibited some background activity during the cooling of area 21a. Furthermore, three of these cells did not exhibit any spontaneous activity even when area 21a was not inactivated by cooling.

For the entire sample of area 17 cells recorded from the VC21a region (51 cells) cooling area 21a resulted in a significant decrease in background activity (from 1.3 ± 0.3 spikes/s to 0.7 ± 0.2 spikes/s, $P = 0.0003$, Wilcoxon test). By contrast, the spontaneous activity of cells with receptive fields located ouside the VC21a region (11 cells) was not significantly affected by inactivation of area 21a (prior to cooling: mean background activity 1.2 ± 0.45 spikes/s; during cooling: mean background activity 1.5 ± 0.55 spikes/s, $P > 0.20$, Wilcoxon test).

When the data were examined for effects on single neurons it was found that cooling of area 21a resulted in significant changes in background activity ($P < 0.05$, Wilcoxon test) in a substantial proportion of cells recorded from the VC21a region (21/51; 41.2% of the sample). Of these, the great majority (17 cells) showed significant decreases in background activity, with only four cells showing significant increases. For cells recorded from the ouside of the VC21a region (11 cells) one cell showed a significant decrease in the spontaneous activity while three cells showed significant increases in background activity.

Effects of Cooling of Area 21a on Responsiveness of Area 17 Neurons to Visual Stimuli

Peak discharge rates were determined by measuring the response to an approximately optimal stimulus, i.e. at optimal orientation, length and velocity. The peak discharge rates of the cells recorded from the VC21a region of area 17, like their background activities (see above), were also significantly affected by inactivating area 21a (Fig. 3*B*). When area 21a was cooled, the mean peak discharge rate of cells with receptive fields located within the VC21a region at 45.3 ± 4.55 spikes/s was substantially lower than that (58.0 ± 4.7 spikes/s) when area 21a was at control (36°C) temperature. The difference between the two sets of data was highly significant ($P = 0.003$, Wilcoxon test). Furthermore, the changes in the peak discharge rates were significantly correlated with changes in background activity ($r = 0.30$, $n = 51$, $P < 0.05$).

However, for the whole sample of cells with receptive fields located outside the VC21a region the peak discharge rates prior to cooling of area 21a (like their background activity, see above) were not significantly different from those during cooling of area 21a (mean peak discharge rate prior to cooling: 73.9 ±

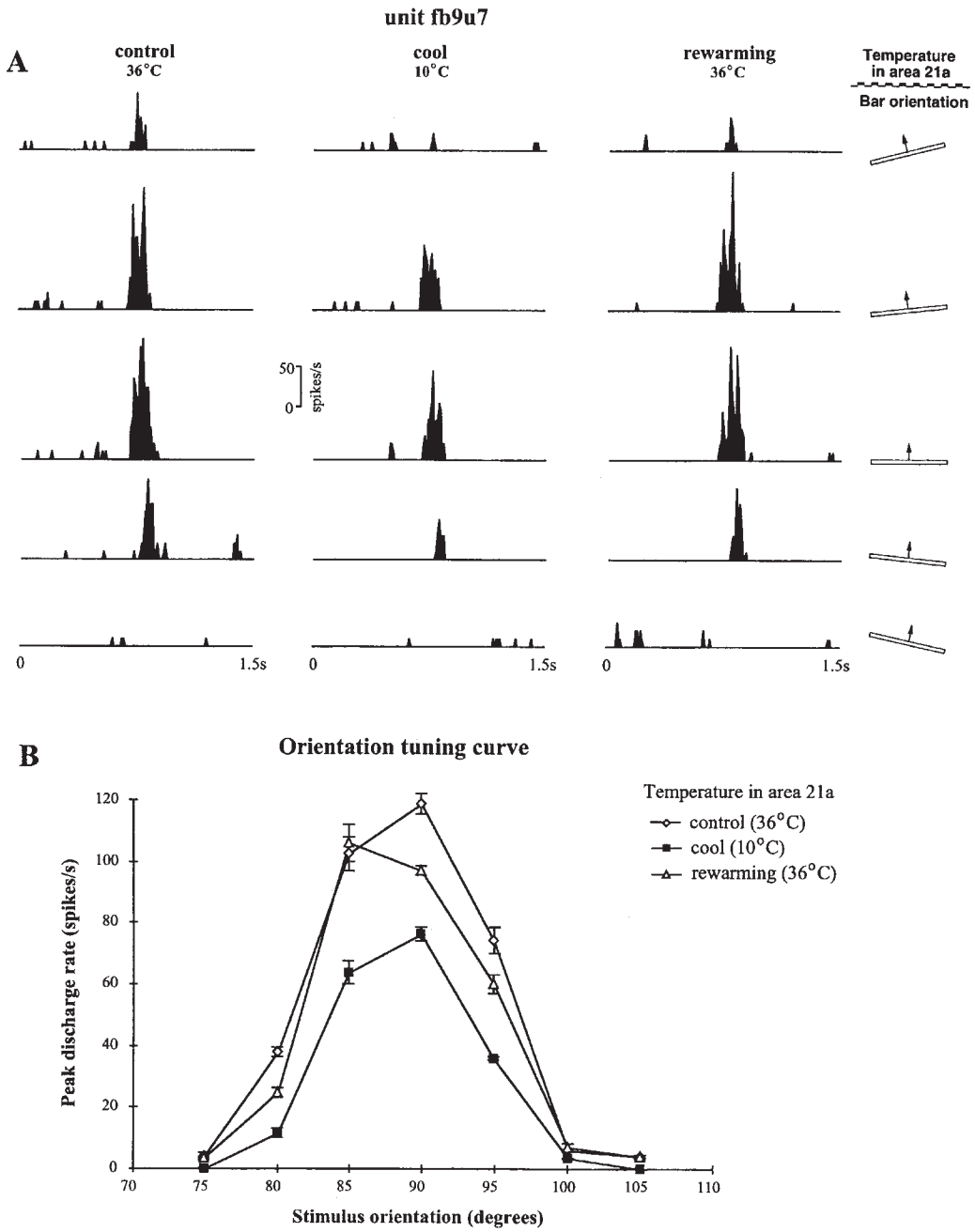

Figure 2. Responses of an S-type area 17 neuron to elongated bars of different orientation but of the same contrast (15) before and during the cooling and after rewarming of area 21a. (*A*) Peristimulus time histograms constructed for light bar (15° × 0.4°) of various orientations (indicated on the right) moving at 6.6°/s across the cell's receptive field and at two different temperatures (36 and 10°C) in area 21a. The temperature of area 17 remained constant throughout (36°C). Since this cell was not direction-selective, for reasons of clarity we show the responses in one direction only. The period of time necessary to complete a single sweep in one direction is indicated beneath the histograms. Each peristimulus time histogram was compiled from responses to 10 successive stimulus sweeps. Note that this cell had little background activity and was quite sharply selective to stimulus orientation. Note also that, although the magnitude of responses was substantially reduced during cooling of area 21a, the response profile of the cell was unaffected. (*B*) The orientation-tuning curves of the same cell at different temperatures in area 21a. Vertical bars on the individual data points in this figure and in Figures 4–7 indicate the standard errors of the mean. Note that after rewarming of area 21a to 36°C the orientation-tuning curve of the cell was very similar to that preceding cooling of area 21a.

13.9 spikes/s; during cooling: 70.6 ± 13.25 spikes/s, P = 0.42, Wilcoxon test).

When individual neurons were examined, in almost one-third of cells located within the VC21a region of area 17 (15/51; 29.5% of the sample) the magnitude of responses to visual stimuli was significantly affected ($P < 0.05$, Wilcoxon test) by inactivation of area 21a. In the great majority of these cells (14/15; seven S-type or S_H-type cells, five C-type cells and two unclassified cells) the magnitude of responses to visual stimuli was significantly reduced (the decreases ranged from 8 to 86%, with the median and mean decreases being 39 and 42% respectively) while in one cell (an S-type cell) there was a substantial (78%) and significant increase ($P < 0.05$, Wilcoxon test) in the magnitude of responses.

Of the 11 cells outside the VC21a region only one cell (an

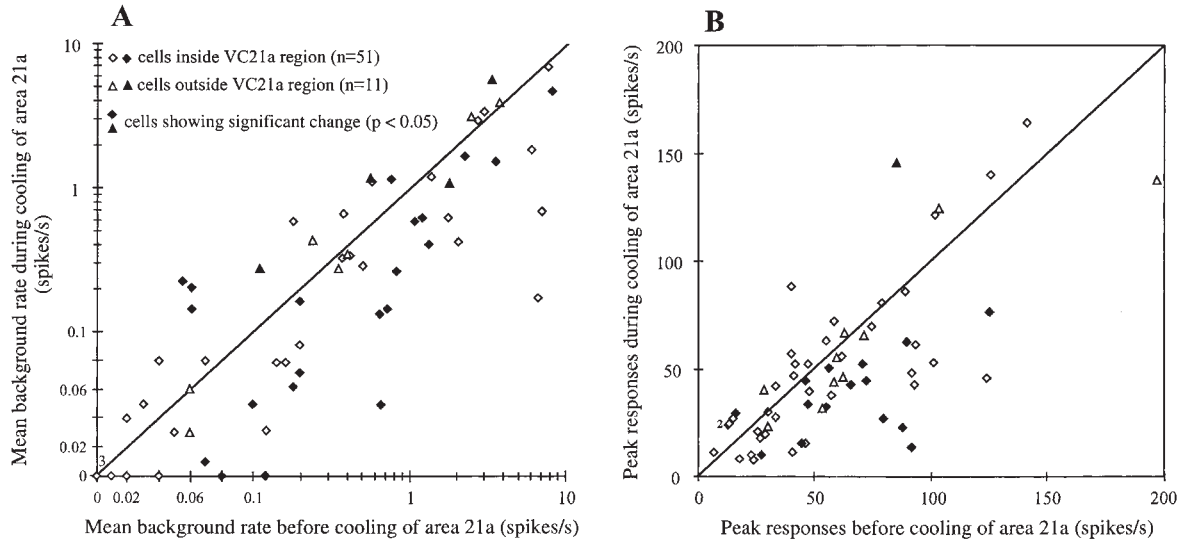

Figure 3. The relationships of mean background ('spontaneous') rates (*A*) and peak discharge rates (*B*) of area 17 neurons before and during cooling of area 21a. The 'spontaneous' rates were measured at the background illumination of 1 cd/m^2 while the peak discharge rates represent the responses to optimally oriented bars of optimal length (of standard contrast 15) moving at optimal velocity across the cells' receptive fields. Note that graph *A* is a combination of linear (<0.1 spikes/s) and logarithmic (>0.1 spikes/s) scales while graph *B* is in linear scale. The solid lines (main diagonals) in both graphs indicate equal values. In both graphs most data points are below these lines. Note also in *A* that eight neurons did not exhibit any background activity when area 21a was inactivated by cooling. Furthermore, three of these cells (3 in the lower left corner of graph *A*) had no background activity either before or during the cooling of area 21a.

S-type cell) showed a significant change in the magnitude of responses (an increase).

Eye Dominance

Unlike in areas 17 and 18, which provide the principal cortical inputs to area 21a (Dreher, 1986; Dreher *et al.*, 1996b; Morley *et al.*, 1997), the majority of cells in area 21a are either binocular cells dominated by the ipsilateral eye (class 4 cells) or monocular (class 5) cells activated exclusively via the ipsilateral eye (Dreher *et al.*, 1993; Wang and Dreher, 1996). One might have expected on this basis that inactivation of area 21a could have had a greater effect on responsiveness of class 4 and class 5 cells than on the responsiveness of class 1 and class 2 cells. However, the overall reduction in the magnitude of responses of class 4 and class 5 cells (mean peak discharge prior to cooling: 63.7 ± 8.6 spikes/s; during cooling: 50.55 ± 9.9 spikes/s) resulting from inactivation of area 21a was not significantly different (P = 0.84, Mann–Whitney U-test) from the reduction in the magnitude of responses of class 1 and class 2 cells (mean peak discharge prior to cooling: 56.55 ± 7.4 spikes/s; during cooling: 42.35 ± 5.2 spikes/s). Similarly, the proportion of class 4 and class 5 cells showing significant decrease in the magnitude of response was not significantly different from the proportion of such cells in classes 1 and 2 (35 versus 29%; $P > 0.9$, χ^2 test).

Recovery of Responsiveness of Area 17 Cells following Rewarming of Area 21a

For most area 17 cells (53/62; 85.5% of the sample) in which we examined the effect of cooling of area 21a we were also able to study the extent and time course of the recovery of their responsiveness following rewarming of area 21a to 36°C.

In the substantial majority of cells (39/53; 73.6% of the sample) the magnitude of the response recovered gradually to at least 80% of the precooling value. In a few cases the magnitude of responses following rewarming of area 21a was 10–20% greater than the magnitude of the control precooling responses. The mean level of recovery for the entire sample was 85 ± 21% of the precooling values. While the changes in background activity and responsiveness of area 17 neurons followed almost immediately on cooling of area 21a to 10°C, recovery of responsiveness of area 17 cells after rewarming of area 21a to 36°C was much more gradual. The time for the complete or an incomplete but steady state recovery varied from 5 to 50 min and the mean recovery time for the entire sample was 14.7 ± 10.9 min. We note that the recovery of responsiveness of area 21a after rewarming area 17 to physiological temperature had a very similar time-course (Michalski *et al.*, 1993).

Effects of Cooling of Area 21a on Orientation Selectivity

The effect of cooling area 21a on orientation selectivity was examined in forty- two area 17 cells recorded from the VC21a region and in nine cells recorded from outside the VC21a region. Most of them (38/51; 74.5% of the sample) were considered to be orientation-selective since their orientation-tuning width at half-height of response ranged from 14.5 to 81.3°. In the remaining cells orientation-tuning widths at half-height were either within the range 90–150° (8/51 'orientation-biased' cells; 15.5% of the sample) or exceeded 150° (5/51 non-orientation selective cells; 10% of the sample).

Figure 4*A–D* shows examples of orientation-tuning curves before and during cooling of area 21a and (with exception of Fig. 4*C*) after its rewarming. For the cell whose orientation-tuning is illustrated in Figure 4*A* inactivation of area 21a resulted in substantial reversible increases in the magnitude of responses to stimuli of most of the orientations presented and overall broadening of the orientation-tuning curve (measured at half-height). By contrast, for the cell whose orientation-tuning curves are illustrated in Figure 4*B*, cooling of area 21a resulted in substantial reversible reductions in the magnitude of responses to stimuli of most of the orientations presented and some narrowing of the orientation-tuning curve. For the cell whose orientation-tuning curves are illustrated in Figure 4*C* inactivation of area 21a also resulted in substantial reductions of the magnitude of responses to stimuli of different orientations.

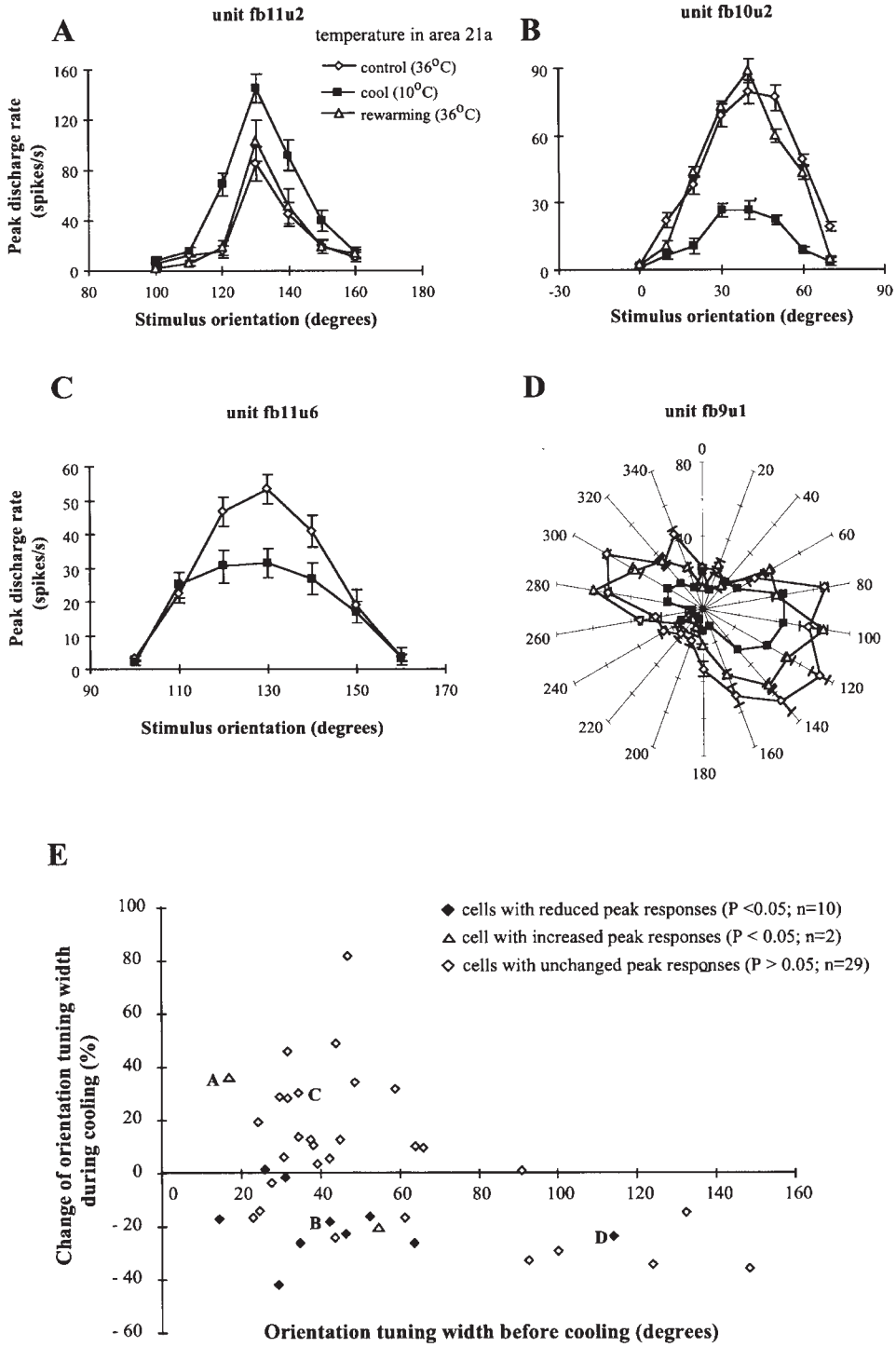

Figure 4. Effects of inactivation of area 21a on the orientation-tuning curves of cells recorded from the VC21a region of area 17. (*A*,*B*) Examples of orientation-tuning properties of two S-type area 17 cells before and during cooling and after rewarming of area 21a. Note in *A* that cooling of area 21a resulted in an increase in the magnitude of responses to stimuli in the 120–150° orientation range and substantial broadening (almost 40% since width at half-height increased from ~17 to ~23.5°) of the orientation-tuning curve. Note in *B* that cooling of area 21a resulted in reversible reduction in the magnitude of responses to stimuli in the 10–60° orientation range and narrowing (from ~42.5 to ~35°, a decrease of <20% in width at half-height) of the orientation-tuning curve. (*C*) Although cooling of area 21a resulted in a reduction in the magnitude of responses to stimuli in the range of 110–150°, the width (at half-height) of orientation-tuning of this cell was substantially increased (>30%, from ~35 to ~46°). (*D*) The magnitude of responses was reduced and there was reduction in the width (at half-height) of the orientation-tuning curve of this orientation-biased C-type cell during the cooling of area 21a. Note for *A–D* that irrespective of the direction of changes in the magnitude of responses (increase or decrease) and irrespective of the direction of changes in the orientation-tuning widths (broadening or narrowing) there were hardly any changes in preferred orientations of the cells. (*E*) The relationship between orientation-tuning widths of 41 orientation-selective or orientation-biased area 17 cells before cooling and the percentage changes during cooling of area 21a. Cells whose orientation-tuning curves are illustrated in *A–D* are marked by the appropriate letters. In a substantial proportion of cells, cooling of area 21a resulted in clear (>20%) changes in the width of orientation-tuning. The decrease in the tuning widths of cells with broad tuning (widths >90°) is significant ($P < 0.03$; Mann–Whitney *U*-test). Note that in a number of cells the substantial narrowing or broadening (20% or more) of the orientation-tuning curves was not associated with significant changes in the peak discharge rates.

However, at the same time there was a broadening, rather than a narrowing, of the orientation-tuning curve. Finally, in the case of the broadly tuned cell whose orientation-tuning curves are illustrated in Figure 4*D* cooling of area 21a resulted in substantial reductions in the magnitude of responses and a clear reduction in orientation-tuning width. This reduction in the width of the orientation-tuning curve was accompanied by some increase in direction selectivity. Irrespective of the direction of changes in the orientation-tuning width (broadening or narrowing), the preferred orientations of the cells were unaffected by inactivation of area 21a (Figs 2*A*,*B* and 4*A–D*).

Figure 4*E* graphs the relative changes (%) in the orientation-tuning widths of 41 area 17 cells during inactivation of area 21a against the orientation-tuning widths before cooling. Of the remaining 10 cells (not included in Fig. 4*E*) in which the orientation selectivity was tested quantitatively, five were non-orientation selective and inactivation of area 21a did not have any effect on their orientation-tuning. Furthermore, inactivation of area 21a resulted in complete loss of orientation selectivity in two orientation-tuned cells while in the other three orientation-tuned cells, inactivation of area 21a resulted in double-peak orientation-tuning curves.

It is apparent from Figure 4*E* that: (i) in a substantial proportion of cells (20/41; 48.5% of the sample) inactivation of area 21a resulted in clear changes (over 20%) in orientation-tuning width; (ii) all but one cell (eight cells) which, following inactivation of area 21a, exhibited a substantial (>20%) broadening of their orientation-tuning curves did not exhibit significant changes in the magnitude of their responses; and (iii) orientation-tuning of cells which showed significant decreases in the magnitude of responses to visual stimuli when area 21a was inactivated tended to become narrower. Indeed, as a group these cells (n = 10) exhibited greater changes (mean narrowing 19 ± 5%) of their orientation-tuning curves than the group of cells (n = 29) which did not show significant changes in the magnitude of their responses (mean broadening 7 ± 4%). The difference between the two groups was highly significant (P = 0.004, Mann–Whitney U-test). Finally, in a subpopulation of area 17 cells (seven cells) which were characterized by broad orientation-tuning (width > 90°) cooling of area 21a resulted in significant narrowing of orientation-tuning curves (P < 0.03, Mann–Whitney U-test).

However, the mean orientation-tuning width for the entire sample of cells tested for orientation when area 21a was at 36°C (52.4 ± 5.05°) was very similar to the mean orientation-tuning width when area 21a was inactivated (49.3 ± 3.75°) and the difference between the two sets of data was not significant (P = 0.44, Wilcoxon test). Furthermore, (i) the preferred orientations of the cells were unaffected by inactivation of area 21a (Figs 2*A*,*B* and 4*A–D*) and (ii) cooling of area 21a in most cases did not change the general shape of individual orientation-tuning curves.

Effects of Cooling of Area 21a on Contrast Sensitivity

Contrast sensitivity functions were examined before and during cooling of area 21a in 25 area 17 cells (21 cells located inside and four cells located outside the VC21a region). For about half of the cells (13/25; 52% of the sample) neither the magnitudes of responses at different contrasts nor contrast sensitivity functions were affected by reversible inactivation of area 21a (P = 0.60, Wilcoxon test, Fig. 5*A*).

However, in almost half of the cells (12/25; 48% of the sample) inactivation of area 21a resulted in significant changes (P < 0.05, Wilcoxon test) in magnitude of responses to visual stimuli of different contrasts. In nine of these cells (including two cells

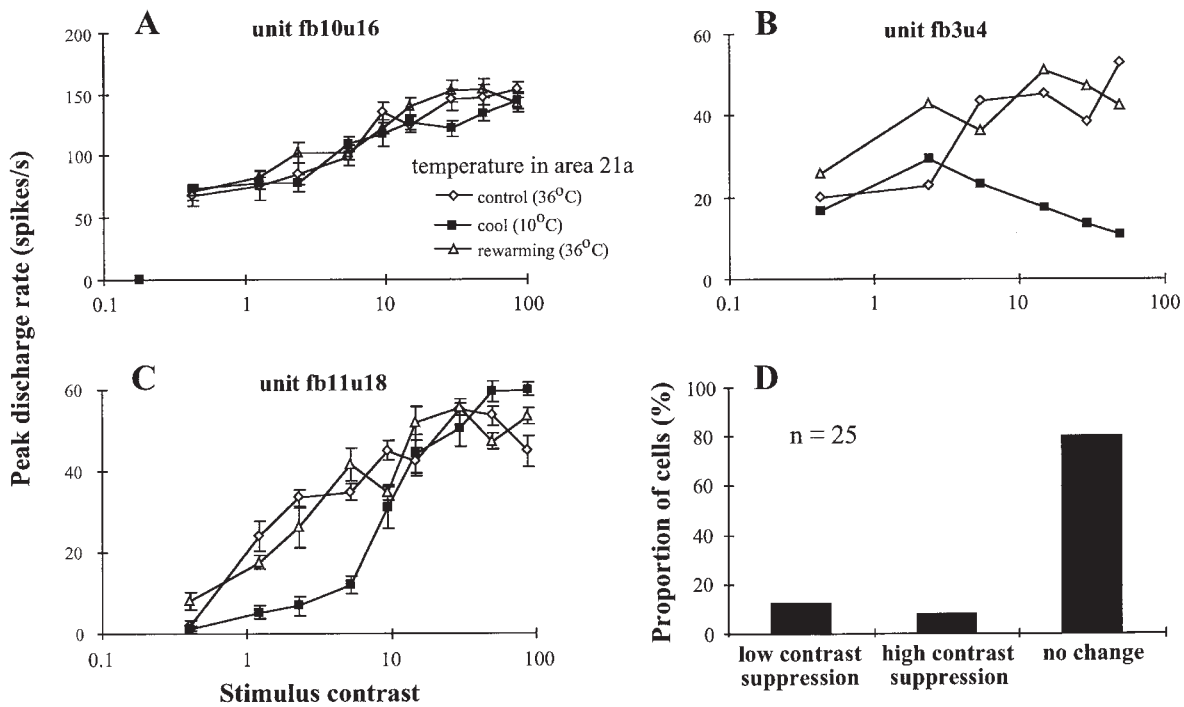

Figure 5. Effects of inactivation of area 21a on the magnitude of responses of area 17 neurons to visual stimuli of different stimulus contrasts. (*A*) Contrast sensitivity curve of fairly typical S-type cell. There was no change in contrast sensitivity during cooling of area 21a. (*B*) C-type cell in which inactivation of area 21a resulted in strong reduction of contrast sensitivity at high contrasts but virtually no effect at low contrasts. (*C*) S-type cell in which inactivation of area 21a resulted in strong reductions in contrast sensitivity at low contrasts but virtually no effect at high contrasts. In all cases the plots are based on the responses to optimally oriented elongated bars moving at optimal velocity across the cells' receptive fields. (*D*) Histogram summarizing the effect of cooling area 21a on contrast sensitivity of area 17 cells.

located outside the VC21a region) inactivation of area 21a resulted in a substantial reduction (range 21–63%) in response magnitude at different contrasts, and in three cells (all three located in the VC21a region) there were substantial increases (ranging from 27 to 135%) in response magnitude to different contrasts.

In a few cells the contrast sensitivity was selectively altered during cooling of area 21a. Thus, the magnitude of responses could be fairly selectively reduced at high contrasts (Fig. 5*B*) or at low contrasts (Fig. 5*C*). In three cells the reduction in the responsiveness at low contrasts was significantly greater ($P < 0.05$, Mann–Whitney *U*-test) than that at high contrasts while in two cells reduction in the magnitude of responses was significantly greater at high contrasts than that at low contrasts ($P < 0.05$, Mann–Whitney *U*-test).

Effects of Cooling of Area 21a on Direction Selectivity

The direction selectivities of area 17 cells ($n = 62$) were evaluated by calculating the geometric mean of the direction selectivity indices (MDI; see Materials and Methods) at different stimulus orientations ($n = 51$) and in some cells ($n = 11$) at different stimulus lengths or different contrasts.

In a substantial minority of cells recorded from the VC21a region of area 17 (11/51; 21.5% of the sample) inactivation of area 21a resulted in clear reductions in the magnitude of responses to stimuli moving in the preferred direction while a reduction in the magnitude of the responses to stimuli moving in the opposite direction was not as pronounced (Fig. 6*A*,*C*). However, although reductions in MDIs ranged from 0.21 to 0.59, in only one of those cells (the graph in Fig. 6*A* and the peristimulus time histograms in Fig. 6*E*) was the reduction in MDI

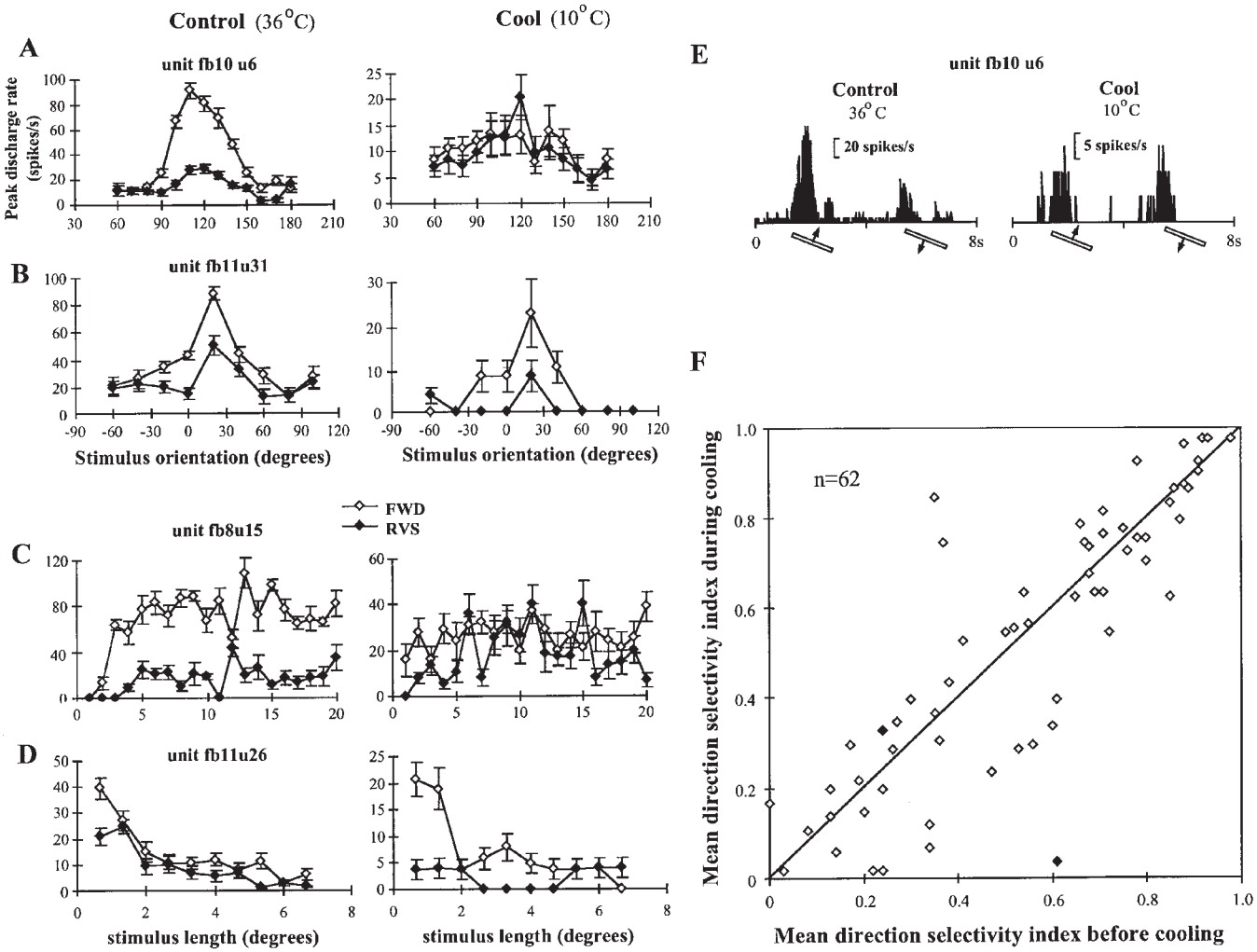

Figure 6. Effects of inactivation of area 21a on direction selectivity of area 17 neurons. It is apparent from *A–E* that the magnitude of responses to visual stimuli tends to be substantially reduced during cooling of area 21a. However, the inactivation of area 21a can have different effects on the direction selectivity of different cells. Thus, while the two S-type cells whose responses are illustrated in *A* and *C* became non-direction-selective during cooling of area 21a, the two cells whose responses are illustrated in *B* (S-type cell) and *D* (C-type cell) became more direction-selective. Note in *C* and *D* that during cooling of area 21a direction selectivity indices might vary with the length of the bar. FWD: forward direction; RVS: reverse direction. The ordinate label in *A* refers also to *B*, *C* and *D*. Note the different scales. (*E*) Peristimulus time histograms for the S-type unit whose responses to elongated light bar (10 × 0.4°) moving at 3.3°/s across the cell's receptive field are illustrated in graph *A*. The angle of the bar and the direction of movement are indicated beneath each histogram. The period of time necessary to complete a single sweep in both directions is indicated beneath each histogram. Each peristimulus time histogram was compiled from responses to five successive stimulus sweeps. Note that cooling of area 21a to 10°C resulted in reduction of both spontaneous activity and the magnitude of responses to movement in both directions. At the same time the reduction in the magnitude of response in the preferred direction was greater than that in the magnitude of response in non-preferred direction. In graph *F* the mean direction selectivity indices (MDIs) of 62 neurons recorded from area 17 during cooling of area 21a are plotted against the MDIs before cooling. Most data points are in the vicinity of the equal-value line (main diagonal). Only two cells (indicated by filled symbols) showed a significant change in direction selectivity.

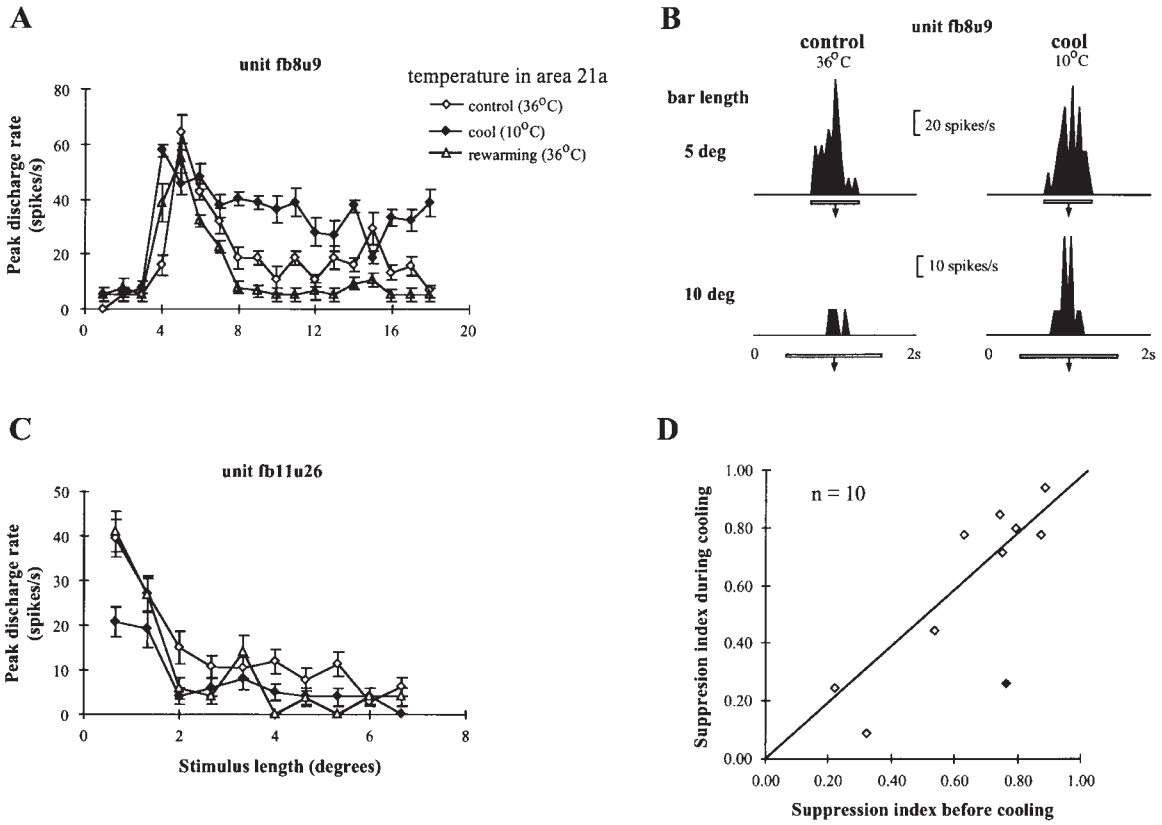

Figure 7. Effects of inactivation of area 21a on the length-tuning curves of end-stopped cells in area 17. Note that the suppression in the end-stopped region for the S_H cell whose responses to elongated light bars of different length (0.4° width) moving at 6.6°/s across the cell's receptive field are illustrated in graph *A* and in peristimulus time histograms in *B* was reduced significantly during cooling of area 21a. The angle of the bar and the direction of movement are indicated beneath each histogram. The period of time necessary to complete a single sweep in each direction is indicated beneath the histograms. Each peristimulus time histogram was compiled from responses to five successive stimulus sweeps. Note that when area 21a was at 36°C the response to a long (10°) bar was much weaker than that to a 5° bar. When area 21a was cooled to 10°C the magnitude of response to a 5° bar was very similar to that when the temperature of area 21a was 36°C. On the other hand, the magnitude of response to a 10° bar increased severalfold. However, for the C_H cell whose responses are illustrated in *C* the cooling of area 21a had no significant effect on the strength of suppression in the end-stopped region. Graph *D* compares the suppression indices in the end-stopped region (ESI, see Materials and Methods) before and during cooling of area 21a for all end-stopped cells examined in the present study. A cell showing significant change in ESI is indicated by the filled symbol.

significant ($P < 0.05$, Wilcoxon test). In a small proportion of cells (3/51 cells; 6% of the sample; Fig. 6*B*,*D*) inactivation of area 21a resulted not only in reductions in the magnitude of responses to stimuli moving in either direction but also in increases in their MDI (range 0.37–0.49). Only in one of those cells was the increase significant ($P < 0.05$, Wilcoxon test).

Overall, inactivation of area 21a did not result in a statistically significant change ($P = 0.38$, Wilcoxon test) in the mean MDI of the entire sample of area 17 cells recorded from the VC21a region (0.51 ± 0.04 versus 0.54 ± 0.04 when area 21a was kept at the control temperature).

Inactivation of area 21a resulted in a substantial change in direction selectivity (decrease of MDI from 0.60 to 0.27) in only one of the 11 area 17 cells with receptive fields located outside the VC21a region; this change, however, was not statistically significant.

Effects of Cooling of Area 21a on Length Selectivity

A small number of cells (10/51 cells; 19.6% of the sample) recorded in the VC21a part of area 17 were classified as end-stopped cells [hypercomplex cells (Hubel and Wiesel, 1965)] (Dreher, 1972; Gilbert, 1977) since they exhibited a reduction in the magnitude of their responses to optimally oriented moving bars when the bars extended outside the discharge fields. To assess quantitatively the strength of such a reduction for each cell we calculated the ESI, defined as the percentage reduction of responses to bars of optimal length, produced by long bars extending outside the cell's discharge field (see Materials and Methods). In eight of the end-stopped cells inactivation of area 21a resulted in reduction in their responsiveness to optimally oriented bars of any length.

Figure 7 shows the effects of cooling area 21a on the length selectivity of the end-stopped cells recorded from the VC21a part of area 17. Before cooling area 21a and after rewarming of area 21a to 36°C, the cell whose responses are illustrated in Figure 7*A*,*B* responded maximally to a 5° long bar and exhibited strong end-zone suppression (ESI = 0.75). Cooling area 21a resulted in some change of the optimal length: the cell gave the strongest response when a shorter bar of 4° was moved across its receptive field. Furthermore, the maximal response was ~90% of the maximal response before cooling of area 21a. On the other hand, inactivation of area 21a resulted in a much smaller reduction in the magnitude of the responses when the bar extended into the suppressive, end-stopped region (ESI = 0.26). The end-stopped suppression recovered gradually after the temperature in area 21a was restored to 36°C. Changes in length selectivity resulting from inactivation of area 21a were significant ($P < 0.05$, Wilcoxon test). A similar effect was observed in another end-stopped cell.

A more typical effect of inactivation of area 21a on the length selectivity index of end-stopped cells is illustrated in Figure 7*C*. Although inactivation of area 21a resulted in a substantial reduction in the magnitude of the responses to bars of any length, there was hardly any change in the length selectivity index (ESI = 0.79 versus 0.78 before cooling area 21a).

Overall, for the whole sample of end-stopped cells the characteristics of length tuning were largely unaffected by inactivation of area 21a (Fig. 7*D*). Indeed, the mean ESI for the whole sample of end-stopped cells before cooling of area 21a (0.64 ± 0.07) was not significantly different ($P = 0.51$, Wilcoxon test) from that (0.58 ± 0.10) when area 21a had been reversibly inactivated.

Discussion

The Effectiveness and Selectivity of Inactivation of Area 21a

We cooled area 21a to 5–10°C since multiunit activities in area 21a were only completely abolished when the temperature of the area dropped to ~10°C. Similarly, Michalski and colleagues (Michalski *et al.*, 1993), who monitored the temperature of the cortex using microthermocouples very similar to those used in the present study (25 μm thick wires), observed that virtually all cells in area 17 of the cat ceased both spontaneous and visually evoked activity when the local temperature was in the 10–20°C range. Despite the fact that our cooling probe was restricted to area 21a, due to the temperature gradient of ~5°C/mm, cooling of area 21a resulted in lowering the temperature also in a number of visual or polysensory cortical areas in close proximity to area 21a (see Fig. 1). Even in area 17, which is relatively remote from area 21a (see Fig. 1), when the temperature of area 21a was at ~10°C and the warming probe was not placed over area 17, the temperature measured at 1 mm below the surface of cortex dropped to 30–33°C. Indeed, a very similar temperature drop was observed in area 21a when area 17 was cooled to 10°C (Michalski *et al.*, 1993, 1994). Even such a small temperature drop appears to have some direct effects on the responsiveness of cells in the cooled area. Thus, on the one hand, when the temperature of area 17 was directly (without cooling of area 21a) reduced to 30–33°C, the magnitude of responses of area 17 neurons was usually moderately (10–20%) reduced (Michalski *et al.*, 1993).

On the other hand, it has been reported that some neurons in the mammalian central nervous system at temperatures slightly below physiological temperature could become hyper-responsive (Klee *et al.*, 1974) [for review see (Brooks, 1983)]. Similarly, Michalski and colleagues (Michalski *et al.*, 1993) have reported that some neurons in area 21a (but not those in area 17) of the cat increase their responsiveness when the temperature of the area drops to 30–33°C. Furthermore, most recently it has been reported that cooling slices of rat visual cortex to room temperature results in hyperexcitability of cortical neurons (Volgushev *et al.*, 2000). These documented direct effects of a small temperature drop on the responsiveness of cells in area 17 prompted us to use in the present study the dual temperature control approach which allowed us to maintain the physiological temperature at the recording sites in area 17 irrespective of the temperature of area 21a [cf. Sherk for a similar approach to testing effects of selective reversible inactivation of area 17 on area 18 neurons (Sherk, 1978)].

It should be mentioned that although area 21a sends a direct projection to area 17 it can also influence area 17 indirectly via projections to areas 18, 19, PMLS, 20a and 21b, via several thalamic nuclei (including several components of the LGNd complex, the lateral posterior-pulvinar complex and rostral intralaminar nuclei) and via the dorsolateral (visual) claustrum [for reviews see (Symonds and Rosenquist, 1984a,b; Rosenquist, 1985; Bullier, 1986; Dreher, 1986; Dreher *et al.*, 1996b)]. In the experiments described here we cannot distinguish between the effects exerted via direct and indirect pathways, although it is probable that the direct pathway is the more important if only because it involves fewer synapses.

While the dual temperature control approach allowed us to maintain the physiological temperature at the recording site in area 17 and the VC21a part of area 18 covered by our warming probe, our warming probe did not cover the areas in the immediate proximity of area 21a. Thus, lowering the temperature of area 21a would also result in lowering the temperature of, but not silencing, area 7, the PMLS area and area 19 (Fig. 1). Polysensory area 7 can influence area 17 only indirectly (Symonds and Rosenquist, 1984a). Part of the PMLS area corresponding visuotopically to area 21a is located in the deep part of the posterior suprasylvian sulcus, at least 3 mm from our cooling probe (Turlejski and Michalski, 1975; Palmer *et al.*, 1978; Tusa *et al.*, 1981; Djavadian and Harutiunian-Kozak, 1983; Grant and Shipp, 1991; Sherk and Mulligan, 1993). Since the temperature depth gradient measured along the centre of the cooling probe was 5–6°C/mm (Girard and Bullier, 1989; Michalski *et al.*, 1993; Zhang *et al.*, 1996) one can assume that, when area 21a was cooled to 10°C, the PMLS neurons located in the visuotopically corresponding part, although exposed to a temperature lower than physiological (perhaps as low as 30°C), will not be silenced. Visuotopically organized area 19 (Hubel and Wiesel, 1965; Tusa *et al.*, 1979, 1981; Mulligan and Sherk, 1993) is the area most likely to be affected by the cooling probe placed on area 21a. This area is strongly connected both directly and indirectly to area 17 (see Fig. 1), and an appreciable influence of altered activity of area 19 neurons on the area 17 neurons cannot be ruled out.

Overall, although cooling of area 21a might result also in a lowering of temperature, and therefore altered neuronal activity, of several surrounding areas, the effects we observe must be mainly due to silencing area 21a. Thus, (i) only area 21a was cooled to temperatures as low as 5–10°C, that is, to the temperature at which neuronal activity ceases; and (ii) neither the 'spontaneous' nor the evoked activity of cells recorded from the part of area 17 outside VC21a (but not outside the parts receiving direct inputs from areas 19 or PMLS) were significantly affected by cooling.

Changes in Background Activity and Peak Firing Rate of Area 17 Neurons following Inactivation of Area 21a

For the entire sample of cells located in the VC21a part of area 17, inactivation of area 21a resulted in: (i) a significant reduction in the 'spontaneous' (background) activity at the standard background illumination of 1cd/m^2; and (ii) a significant reduction in the magnitude of responses to visual stimuli of standard contrast 15. These population effects are supported by significant decreases in peak discharge rates in a substantial number of cells.

Consistent with the present findings, substantial morphological and functional evidence indicates that at least in primates, carnivores and rodents both intrinsic and extrinsic long-range associational cortico-cortical connections (including the feedback projections to the primary visual cortices) tend to be excitatory [for review see (Salin and Bullier, 1995); see also (Johnson and Burkhalter, 1996, 1997)]. The evidence for

excitatory function of long-range associational connections includes: (i) orthodromic, monosynaptic activation or monosynaptic depolarization of area 17 neurons in cats and rats by electrical stimulation of higher-order visual areas (Bullier *et al.*, 1988; Shao and Burkhalter, 1996); (ii) reduction of the magnitude of responses to visual stimuli of substantial proportions of cells in area 17 of squirrel monkeys, cats and macaque monkeys following reversible inactivation of area 18 or area MT (Sandell and Schiller, 1982; Bullier *et al.*, 1996; Hupé *et al.*, 1998; Martinez-Conde *et al.*, 1999); and (iii) substantial reduction in excitatory coupling between cells in the area 17/18 border regions of the two hemispheres following extensive bihemispheric lesions of the extrastriate cortices of the cat (Munk *et al.*, 1995).

It must be noted, however, that cooling of area 21a resulted in a significant increase in spontaneous activity or visually evoked responses of a small number of area 17 cells. In cats and in two species of simian primates similar effects on area 17 neurons were observed following reversible inactivations of area V2 [squirrel monkey (Sandell and Schiller, 1982); cat (Alonso *et al.*, 1993b; Martinez-Conde *et al.*, 1999); cynamolgus monkey (Bullier *et al.*, 1996)]. Furthermore, in 40% of layer 5 neurons in area 17 of the cat reversible inactivation of layer 5 in the visuotopically corresponding part of area 18 (area V2) revealed good responses to high-velocity stimuli to which they responded only very poorly or not at all when area 18 was not inactivated (Alonso *et al.*, 1993a). Despite the fact that the great majority (84%) of synapses in the cat's area 17 are round-asymmetrical, therefore presumably excitatory (Beaulieu and Colonnier, 1985), almost every neuron in area 17 appears to receive some input from local inhibitory interneurons (Eysel *et al.*, 1998). In view of the fact that long-range associational cortico-cortical connections tend to be excitatory (see above), it is likely that some projections from area 21a to area 17 exert an inhibitory effect via inhibitory interneurons in area 17.

The lack of effect of inactivation of area 21a on the responses of some area 17 neurons in the VC21a region might be related to the patchy distribution of feedback terminals. Generally, both intrinsic and extrinsic (feedforward and feedback) projections in mammalian visual cortices are patchy [for reviews see (LeVay, 1988; Salin and Bullier, 1995)] and, in particular, both the feedforward projections from areas 17 and 18 to area 21a (Symonds and Rosenquist, 1984a; Mizobe and Toyama, 1989; Dreher *et al.*, 1996b; Morley *et al.*, 1997) and the feedback projections from area 21a to areas 17 and 18 (Morley *et al.*, 1997) show patchy distribution.

Our finding that the significant changes in background activity and responsiveness of area 17 cells during cooling of area 21a were mainly confined to those cells which had their receptive fields located within the VC21a region is consistent with earlier hodological findings that the feedback projections from area 21a to area 17, like the forward projections from area 17 to area 21a, are restricted to visuotopically corresponding parts of the two areas (Symonds and Rosenquist, 1984a; Rosenquist, 1985; Dreher, 1986; Mizobe and Toyama, 1989; Dreher *et al.*, 1996b; Morley *et al.*, 1997).

Influence of Area 21a on Orientation Selectivity of Area 17 Neurons

There is substantial evidence indicating that orientation selectivity in area 17 of the cat is determined by a network of excitatory and largely intrinsic inhibitory connections [for reviews see (Sillito, 1984, 1992; Martin, 1988; Eysel, 1992; Henry *et al.*, 1994; Vidyasagar *et al.*, 1996); see also (Nelson *et al.*, 1994; Hammond and Kim, 1996; Eysel *et al.*, 1998; Shevelev *et al.*, 1998)]. There is also some evidence indicating that long-range associational projections from other visual cortical areas might contribute to the orientation selectivity of area 17 neurons. Thus, Alonso and colleagues (Alonso *et al.*, 1993b) concluded that layer 5 of area 18 of the cat makes specific excitatory or inhibitory contributions to the orientation selectivity of layer 5 cells in the visuotopically corresponding parts of area 17.

It has been postulated that the feedback projections from the higher-order cortical areas might constitute an important part of neurophysiological circuits underlying visual attention and perceptual grouping in the lower-order visual cortices including the primary visual cortices [for some recent expositions of this concept see (Grossberg *et al.*, 1997; Grossberg and Raizada, 2000)]. It is therefore interesting to note in this context that in behaving macaque monkeys attention enhances the responses of neurons in both area V4 [a presumed homologue of the cat's area 21a (Payne, 1993)] and, albeit to a lesser extent, in the primary visual cortex (McAdams and Maunsell, 1999). Furthermore, in both areas the attention-induced enhancement in the magnitude of responses is not accompanied by systematic changes in the width of the cells' orientation-tuning curves [multiplicative scaling (McAdams and Maunsell, 1999)].

In the present study inactivation of area 21a caused no changes in the preferred orientations of area 17 cells and, although following inactivation of area 21a we observed reversible changes in orientation-tuning width of up to 45% (or ocasionally even more), we are unable to say if those changes are significant. In the majority of cells (including five non-orientation-selective cells) in which the effect of inactivation of area 21a on orientation-tuning was tested quantitatively (26/51cells; 51% of the sample), the changes in orientation-tuning width, if present, were minor (<20%). Thus, in the majority of area 17 cells as far as orientation selectivity is concerned there is a multiplicative scaling of neuronal responses by feedback projections from area 21a.

On the other hand, in about a quarter (13/51) of area 17 cells in our sample inactivation of area 21a resulted in substantial (>20%) narrowing or broadening of the orientation-tuning curves without significant reductions or increases in the magnitude of responses. Furthermore, in a proportion of orientation-selective cells (7/51 cells; 13.5% of the sample) substantial changes (>20%) in the width of the orientation-tuning curves were associated with significant changes in the magnitude of responses. In particular, in these cells substantial narrowing of the orientation-tuning curve, following inactivation of area 21a, was associated with significant reductions in the magnitude of responses while substantial broadening of the orientation-tuning curve was associated with significant increases in the magnitude of responses. Finally, in ~10% of cells in our sample (5/51) inactivation of area 21a resulted in a complete loss of orientation selectivity or change of one-peak orientation-tuning curves into double-peak orientation-tuning curves.

Thus, it appears that in about a half (25/51) of area 17 cells in our sample area 21a interacted nonlinearly with local circuits responsible for the orientation selectivity.We believe that further analysis by modelling of orientation profiles may throw some light on the underlying mechanisms for the modulation of orientation selectivity in the primary cortex by feedback projections from higher-order visual areas such as area 21a.

Influence of Area 21a on Contrast Sensitivity of Area 17 Neurons

For the majority of area 17 cells inactivation of area 21a did not affect the contrast sensitivity functions. In a few cells, however, cooling of area 21a resulted in selective contrast-dependent changes in contrast sensitivity. Only in a very small proportion of cells was the reduction in the magnitude of responses restricted to stimuli of low contrast. Thus, the excitatory role of feedback projections from form-processing area 21a to area 17 of the cat, unlike the feedback projections from motion area V5 to areas V1, V2 and V3 of the macaque monkey (Hupé *et al.*, 1998), does not appear to be largely limited to the enhancement of visibility of stimuli of low salience.

There is substantial evidence indicating that virtually all neurons in the striate cortex of the cat have a 'contrast gain control' system which allows them to adjust their contrast gain dynamically and to keep the magnitude of their responses at a usable level over a wide range of ambient contrasts (Ohzawa *et al.*, 1982, 1985; Albrecht *et al.*, 1984; Bonds, 1989, 1991). The contrast gain control of cortical neurons appears to be largely determined by the intracortical network (Ohzawa *et al.*, 1985; Bonds, 1989, 1991) and adaptation in area 17 is a cooperative phenomenon (Vidyasagar, 1990). Our data suggest that in some area 17 cells feedback input from area 21a contributes to the intracortical contrast gain control network.

Influence of Area 21a on Direction Selectivity of Area 17 Neurons

The bulk of the data collected over the last several decades implicates a network of intrinsic inhibitory connections in the mechanisms underlying the direction selectivity of neurons in area 17 of the cat [for reviews see (Orban, 1984; Eysel, 1992); see also (Hammond and Kim, 1996)]. On the other hand, a number of recent reports indicate that the excitatory feedforward geniculocortical projections, cortico-cortical projections from area 18 and feedback projections from area 21a make some contribution to the direction selectivities of neurons in area 17 of the cat (Alonso *et al.*, 1993b; Thompson *et al.*, 1994; Michalski *et al.*, 1993). Although, for our entire sample of area 17 neurons, cooling area 21a produced no significant changes in direction selectivity (Fig. 6*F*), in a small number (three cells) of area 17 cells studied by us, inactivation of area 21a resulted in a significant decrease in the MDI. It appears therefore that area 21a makes a modulatory contribution to direction selectivity of some area 17 cells. The relative paucity of area 17 cells whose direction selectivity was significantly affected by inactivation of area 21a might be related to the paucity of strongly direction-selective cells in area 21a (Mizobe *et al.*, 1988; Wimborne and Henry, 1992; Dreher *et al.*, 1993, 1996a; Toyama *et al.*, 1994).

Influence of Area 21a on Length Selectivity of Area 17 Neurons

The main influence of area 21a on end-stopped cells in area 17 is excitatory. Only in two out of 10 end-stopped cells did inactivation of area 21a result in a significant change in the length suppression index, in each case reducing the magnitude of suppression. Such changes could be due to a reduction in the strength of inhibition in the end-stopped region or a reduction in the response at optimal length without an accompanying change in the strength of inhibition in the end-stopped region. It has been reported that reversible inactivation of layer 6 abolishes end-inhibition in cells in layers 2/3 and 4 of the cat's striate cortex without affecting their orientation and direction selectivities (Bolz and Gilbert, 1986) [see, however (Grieve and Sillito 1991)]. Furthermore, it has been shown by Sillito and colleagues (Murphy and Sillito, 1987; Sillito *et al.*, 1993) that the length tuning of the neurons in the cat's LGNd (Dreher and Sanderson, 1973: Cleland *et al.*, 1983) is substantially enhanced by cortico-fugal feedback from layer 6. The dorsocaudal (visual) claustrum also appears to contribute to the length selectivity (but not to other receptive field properties) of cells in layers 4 and 2/3 of area 17 (Sherk and LeVay, 1983). Since area 21a projects to infragranular layers 5 and 6 of area 17 (Morley *et al.*, 1997) as well as to the dorsocaudal claustrum (LeVay and Sherk, 1981) it can exert its selective contribution to the length selectivity mechanism of cells in granular and supragranular layers of area 17 through both of those relays. It is also worth pointing out that recently Rao and Ballard developed a computational model in which the removal of feedback from high level to lower level processing strata resulted in a change of the length selectivity properties of the end-stopped model neurons (Rao and Ballard, 1999).

Conclusions

We conclude that feedback projections from area 21a exert a predominantly excitatory influence on both 'spontaneous' and visually evoked neuronal activities in visuotopically corresponding parts of area 17 (the VC21a region). Furthermore, the feedback projections from area 21a appear to be involved in determining some specific receptive field properties of neurons in the striate cortex. For example, in a minority of area 17 cells recorded from the VC21a region area 21a appears to exert a specific modulatory influence on the mechanism(s) underlying contrast sensitivity, direction selectivity and length selectivity. Of course, feedback from area 21a might exert a specific modulatory influence on the mechanism(s) underlying receptive field properties of area 17 neurons which were not tested in the present study [e.g. modulation of responses by binocular retinal disparities (Wang and Dreher, 1996; Vickery and Morley, 1997, 1999)]. Furthermore, other 'higher-order' visual cortical areas such as area 19 or the PMLS area also send strong feedback projections to the striate cortex [for reviews see (Rosenquist, 1985; Bullier, 1986; Shipp and Grant, 1991)]. Since these areas appear to be strongly involved in processing respectively the length and direction selectivities [for reviews see (Dreher, 1986; Spear, 1991; Dreher *et al.*, 1996a)] it is likely that they make greater specific contributions to the mechanisms underlying the length and direction selectivities in the striate cortex. It is also likely that some important aspects of modulatory influence of the higher-order visual areas on the primary visual cortices could be revealed only in conscious, behaving animals (Vidyasagar, 1998). It has been postulated that the processing of information in the mammalian visual cortex is not based exclusively on a feedforward, hierarchical mode of operations but rather on interactions (feedforward and intrinsic horizontal as well as feedback) within a multilevel cooperative neuronal network involving the primary as well as the higher-order cortical areas (Zeki and Shipp, 1988; Shipp and Zeki, 1989a,b; Damasio, 1990; Tononi *et al.*, 1992; Van Essen *et al.*, 1992; DeYoe *et al.*, 1994; Douglas *et al.*, 1995; Grossberg *et al.*, 1997; Budd, 1998; Pollen, 1999; Sastry *et al.*, 1999; Grossberg and Raizada, 2000). The present data provide further functional support for this idea.

Notes

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