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THE EFFECT OF REVERSIBLE COOLING OF CAT'S PRIMARY VISUAL CORTEX ON THE RESPONSES OF AREA 21a NEURONS

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SUMMARY

1. Responses of sixty-four neurons in cortical area 21a were studied with areas 17 and 18 reversibly deactivated by cooling. From anatomical studies, most of area 21a input in the cat originates from these primary areas with no input from the A laminae of the lateral geniculate nucleus.

2. Both responses and spontaneous activity of all sixty-four area 21a neurons were markedly reduced when primary areas were cooled. In sixteen cells the responses were totally blocked. Temperatures of primary cortex required to produce total blockade varied between 25 and 4·5 °C.

3. The effect of cooling the primary visual cortex on the shape of orientation tuning curves was analysed in thirteen neurons from area 17 and in fifty-eight neurons from area 21a. In both areas, the width of the curve, when measured at its half-height, was preserved even when spike activity was reduced to below 10% of the original level. All neurons also retained their original directional preferences during cooling of the primary visual cortex.

4. The responsiveness of forty-seven neurons from area 21a was tested after rewarming of primary cortex. All but one neuron recovered their initial responsiveness within half an hour of restoring physiological temperature of primary visual cortex.

5. The results of the present study give an indication of the extent to which area 21a is sequentially related to the primary visual cortex in the processing of information.

INTRODUCTION

The analysis of the neuronal responses in two interconnected cortical areas that represent subsequent levels of information processing can provide an insight into the organization of the cortical network simply by revealing what is added, subtracted or changed at the higher level. On the other hand a strictly hierarchical model for the processing of visual information has often been challenged and it is difficult to find an appropriate pair of sequential areas. This difficulty is exemplified in the cat where cortical areas 17, 18 and 19 all receive strong direct inputs from the dorsal lateral geniculate nucleus (dLGN) (Geisert, 1980). In any pairing of these three areas the sequential flow is modified by the individual inputs coming directly from the dLGN.

Recent studies suggest that cortical area 21a in the cat (as defined by Tusa, Palmer & Rosenquist, 1981) may represent a secondary area that receives signals from the primary visual cortex (areas 17 and 18) with very little direct input from subcortical structures. Area 21a receives less than 20% of its thalamic input from cells that relay information directly from the retina (Graybiel & Berson, 1981*a*, *b*; Berson & Graybiel, 1983; Dreher, 1986). Most of its thalamic input comes from the cortico-recipient zone which, as its name implies, receives projections from the visual cortex (especially area 17).

Although there was initially some debate over the strength of the direct input from area 17 to area 21a (Sherk, 1986) there are now a number of anatomical experiments to indicate that area 21a receives a strong input from both areas 17 and 18 (Graybiel & Berson, 1981*a*, *b*; Berson & Graybiel, 1983; Symonds & Rosenquist, 1984*a*, *b*; Dreher, 1986; Mulligan & Sherk, 1991; Sherk & Mulligan, 1991). There is, therefore, an anatomical base for the concept that the primary visual cortex and area 21a could act as a sequential pair in the processing of visual information.

Recently, in the search for evidence of sequential processing, we have attempted to draw comparisons between the response properties of cells in the primary visual cortex (principally area 17) and those of area 21a (Ho, Lee & Dreher, 1982; Dreher, 1986; Mizobe, Itoi, Kaihara & Toyama, 1988; Michalski, Dreher & Cleland, 1989; Wieniawa-Narkiewicz, Wimborne, Michalski & Henry, 1992; Wimborne & Henry, 1992; Dreher, Michalski, Ho, Lee & Burke, 1992). In brief, the properties that appear to characterize the cells of area 21a are that they have receptive fields within 15 deg of the visual axis and in many of their response features, with some notable exceptions, they resemble C or complex cells in area 17. Thus, in general, area 21a cells have binocular receptive fields of similar dimension to those of C cells and they resemble C cells in their composite on–off responses to flashing stimuli, in their responses to moving dots and gratings and in their preference for stimuli moving slower than 20 deg s^{-1}. They differ from C cells, however, in that fewer are direction selective and, in a significant quantitative distinction in orientation selectivity, the majority of area 21a cells are more sharply tuned than C cells (half-width at half-height; C cells: mean = 27·5 deg, range = 20·5–40 deg; 21a cells: mean = 17 deg, range 9–29 deg; Henry, Dreher & Bishop, 1974; Wimborne & Henry, 1992).

In the present study we have attempted to take the comparison with cells of the primary visual cortex a stage further by extracting the contribution made by the primary visual cortex to the firing of cells in area 21a. This was achieved by recording the response of an area 21a cell, before and after removing the primary cortical input or, in other words, before and after cooling retinotopically corresponding regions in areas 17 and 18. To assess the effectiveness of cooling in causing deactivation, the recording electrode was first inserted through the cooling device to follow the course of deactivation in area 17 itself. These response changes were then compared with those obtained from the cells of area 21a following similar cooling of the primary visual cortex. The results obtained by this reversible removal of the input from the primary visual cortex were then used to shed light on the concept that the principal input to area 21a comes directly from the primary visual cortex.

METHODS

Animal preparation

Experiments were performed on ten adult cats, weighing between 2·5 and 3 kg. Cats were anaesthetized for surgery with intramuscular injections of 20 mg kg^{-1} of ketamine hydrochloride (Ketalar; Parke Davis, Victoria, Australia) plus 2 mg kg^{-1} of xylazine (Rompun; Bayer Australia Ltd, NSW, Australia). The saphenous vein was cannulated and a tracheotomy was performed to allow for the insertion of a tracheal cannula. Bilateral cervical sympathectomy was used to reduce the residual eye movements. The animal was then placed in a stereotaxic instrument and a craniotomy was performed over areas 17 and 18 of both hemispheres (HC co-ordinates: +2·0 mm to −10·0 mm anterior–posterior; 6 mm laterally on both sides). The dura was bilaterally removed and the cortical surface covered with a thick layer of silicone grease. A second opening was made over area 21a of one hemisphere (HC co-ordinates: 0 mm to −5 mm anterior–posterior; 10 mm to 15 mm laterally). A circular well was cemented over this opening, the dura removed and the cortex protected with agar gel. EEG and ECG electrodes were attached, the pupils dilated with 1% atropine sulphate (Atropt; Sigma Co. Ltd, USA) and the nictitating membranes were retracted with 2·5% phenylephrine hydrochloride (Neosynephrine; Winthrop Laboratories, NSW, Australia). The animals' eyes were protected with contact lenses and refractive errors were corrected with spectacle lenses.

After completing all surgical procedures anaesthesia was maintained with 67% N_2O, 33% O_2 gaseous mixture and a continuous intravenous infusion of gallamine triethiodide (Flaxedil; May & Baker, Australia Pty Ltd, Victoria, Australia) at a rate of 5 mg kg^{-1} h^{-1} and sodium pentobarbitone (Nembutal; Boehringer Ingelheim Pty Ltd, NSW, Australia) at a rate of 1 mg kg^{-1} h^{-1} in compound sodium lactate (Hartmann's solution; Abbott Australasia Pty Ltd, NSW, Australia) containing 5% glucose. Heart rate and EEG activity were monitored throughout the experiment as a guide in maintaining an appropriate level of anaesthesia. The expired CO_2 level was monitored with a Datex Normocap Medical Gas Analyzer (Datex Instrumentarium OY, Finland) and maintained at between 3·5 and 4·0%. Normal body temperature of 38 °C was maintained with the aid of a heated blanket.

Cooling

Cooling of cortical areas 17 and 18 was achieved with a silver plate or foot attached to a laboratory-built device that cooled electrically through the application of the Peltier principle (28 W Peltier element, Cambion, USA). The cooling power of the device could be adjusted by changing the electric current and the same device was used for rewarming the cortex by reversing the current polarity. The silver contact foot, a square of dimension 12 mm × 12 mm, covered the entire craniotomy over areas 17 and 18. The surface of the silver was shaped to match the curvature of the cortical surface. The layer of silicone provided good thermal contact and reduced the pulsation of the tissue. The high electrical resistance of silicone made it possible to locate the cortical surface at the point where the electrode or themosensitive probe were pushed out of the silicone layer.

Temperatures were measured continuously in both areas 17 and 21a of the same hemisphere. One thermocouple, inserted into area 17, passed through a small, thermally insulated opening in the cooling foot; a second thermocouple was inserted into area 21a and both were positioned 1 mm below the cortical surface. To minimize heat loss within the probe, the thermocouples made of 25 μm thick constantan and copper wires (Omega, USA), were glued to the tips of glass-coated tungsten microelectrodes. A third thermocouple was mounted directly onto the silver cooling foot. The temperature was read from digital thermometers with the precision of 0·1 °C (HH 72T; Omega, USA).

Visual stimulation and recording

Extracellular single unit recordings were made with glass-coated tungsten microelectrodes with an impedance of 2–10 MΩ. The optic disc and area centralis of each eye were plotted on a tangent screen, located 1 m from the cat's eyes, using a back-projecting ophthalmoscope. After plotting the receptive field with hand-held stimuli the screen was replaced with a computer-controlled, oscilloscope display where visual stimuli were presented on a 26 cm square raster (Bullier, Mustari & Henry, 1982). Moving bars, used as visual stimuli, varied in width from 0·3 to 1·0 deg and usually

had a length of 14 deg. The luminance of light bars was 5 cd m^{-2} against a background of 1 cd m^{-2} and these values were reversed for dark bars. The velocity of the bar, which was chosen to be optimum for the particular cell, ranged in value from 1 to 5 deg s^{-1}.

Average response histograms were constructed to record a cell's response to stimuli set at different orientations and with different directions and velocities of movement. For all neurons, orientation tuning curves were prepared using random interleaving of orientation values for each presentation of the stimulus. The stimulus display frequency was 100 frames s^{-1} and this, with the comparatively small receptive fields, made it impractical to use stimulus velocities in excess of 20 deg s^{-1}. Nevertheless, velocity tuning curves were prepared for a small sample of cells with a lower cut-off velocity than 20 deg s^{-1}.

All tests were carried out under conditions in which the temperature of areas 17 and 18 was progressively lowered from its physiological level. Occasionally, to produce a complete effect, it was necessary to reduce the temperature in the primary visual cortex to around 4 °C. To avoid the possibility of permanent damage to areas 17 and 18 through excessive cooling, the reduction in temperature was frequently restricted to the level at which there was an obvious effect in area 21 a. After cooling, the temperature of areas 17 and 18 was then allowed to recover before further recordings in area 21 a were undertaken.

Termination of experiment

At the end of the experiment animals were injected intravenously with an overdose of sodium pentobarbitone (more than 60 mg kg^{-1}) and respired until the ECG and EEG became flat.

RESULTS

Results were obtained from the application of two experimental protocols, both of which employed cooling of the primary visual cortex (areas 17 and 18) but which differed in that cell responses were monitored in different locations, area 17 in the first experiment and area 21 a in the second. The assessment of the cell's responsiveness rested heavily on the preparation of orientation tuning curves at different levels of cooling. We concentrated upon orientation selectivity firstly because it was an outstanding response feature of the cells of both areas and secondly because the shape of the orientation tuning curve could reflect the influence that cooling has on both excitatory and inhibitory processes occurring in the primary visual cortex.

Temperature and temperature gradients in the cortex

The temperature of the cortex varied according to the size of the craniotomy and the seal used to close it off. The insertion of the thermocouple through small holes made at the beginning of the preparation of the craniotomy indicated that the temperature, at about 1 mm below the surface of area 17, was between 34 and 36 °C. At the time the cat's body temperature, measured deep under the scapula, was 37·5 °C. Later, when the craniotomy over the primary visual cortex was enlarged and the cooling probe inserted, the cortex temperature was maintained at 35·5 °C by using a small heating current to compensate for the effect of cold metal on the cortical surface that otherwise could produce a temperature gradient, with the lower temperature at the surface. The temperature of area 21 a, which was protected with a separate small well and a layer of agar gel, stabilized in individual animals at values between 31 and 35 °C.

The size and the position of the cooling foot was designed to fit maps of the cortex (Tusa, Palmer & Rosenquist, 1978; Tusa, Rosenquist & Palmer, 1979) in an attempt

to achieve direct cooling over the region representing the central part of the visual field (including the area centralis and out to 5 deg of eccentricity). At a given depth, the cortex directly beneath the cooling foot should be of uniform temperature and by adjusting the depth of the thermocouple it was possible to estimate the temperature

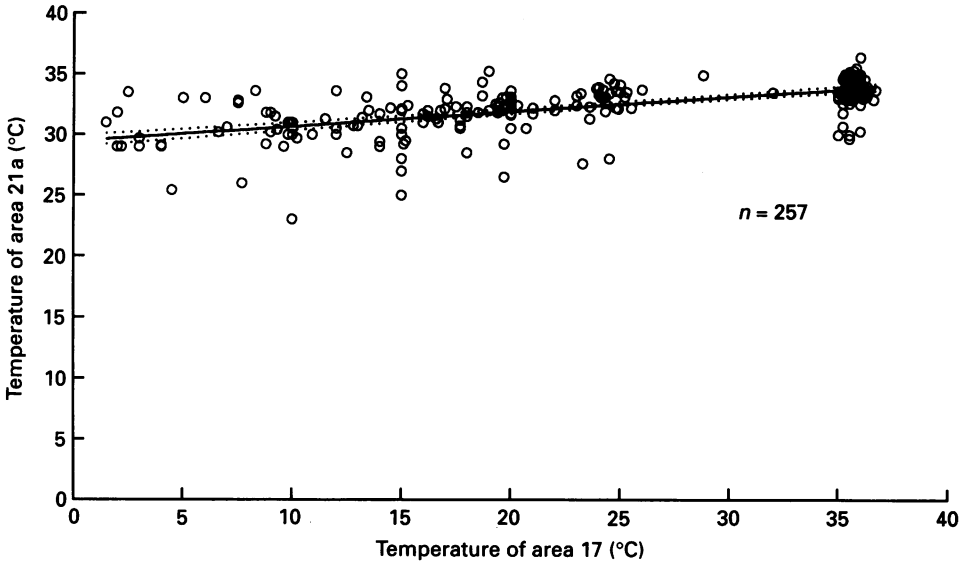

Fig. 1. The direct effect of cooling area 17 on the temperature measured simultaneously in area 21a. The near horizontal regression line shows a low level of temperature dependence (regression slope = 0·12; 257 temperature pairs were analysed). Dotted lines show 95% confidence limits. Typically, when area 17 was cooled to 2 °C the temperature in area 21a would fall only to around 30 °C but the starting temperature of the agar-protected cortex was between 35 and 31 °C. In 80% of area 21a neurons the largest temperature change with difference due to cooling was smaller than 3·5 °C.

gradient. These temperature gradients were measured in two cats and when the tissue at a depth of 1 mm was cooled to 10 °C the temperature gradients were 4–5 °C mm^{-1}.

In recording sessions the temperature of areas 17 and 18 was lowered gradually and, to avoid damage, cooling was usually terminated when the cell activity dropped below 20–30% of its original value. In fifteen cases, however, the temperature of areas 17 and 18 was lowered to 2–7 °C, a temperature where earlier findings suggested that all neuronal activity would be blocked.

To assess the spread of cooling into area 21a, its temperature was directly monitored throughout the course of cooling areas 17 and 18. Figure 1 shows the temperatures of area 21a as a function of the temperature of the primary cortex prepared from 257 concurrent measurements in the two areas. For the most extreme cooling of areas 17 and 18 (a reduction of around 30 °C to a level of 3 °C), the mean temperature drop in area 21a was 4 °C. The greatest temperature fall recorded in area 21a during cooling of the primary visual cortex was 7·3 °C but this applied only

for a single cell. In only thirteen neurons (20% of the sample) did the fall in area 21a exceed 3·5 °C and in eight of these the decline did not exceed 5 °C. At the other end of the scale, the temperature drop did not exceed 2 °C in eleven neurons (17%).

The ability to compensate for the effects of cooling of the primary cortex and to keep the temperature of area 21a constant differed slightly in different cats, probably due to variations in the efficiency of the circulatory system. Greater temperature drops were also usually encountered during the later stages of the experiment.

Cooling the primary visual cortex and its effect on the neurons of area 17

Responsiveness to visual stimulation

The aim of these recordings was to evaluate the changes that occur in visual responsiveness when cells in area 17 are cooled below physiological temperatures. Selectivity to stimulus orientation and direction of movement were also studied quantitatively at different times.

Orientation tuning curves were prepared for different levels of cooling from thirteen neurons in area 17 in three cats. All receptive fields were located within 5 deg of the area centralis and all neurons ceased to respond to visual stimuli when the temperature of area 17 was lowered sufficiently. For two neurons this critical temperature was close to 18 °C, although in both these cases spontaneous activity persisted at around 1 spike s^{-1}. In another two units, temperatures as low as 5 °C were necessary to block the responses. The remaining neurons ceased to respond at temperatures between 10 and 16 °C. Even at lowest temperatures, when neuronal activity was reduced to only 5% of its original value, the width of the orientation tuning curve, derived from the residual responses, was the same as the original one.

The reduction in neuronal responsiveness due to cooling is shown in Fig. 2. The graphs in Fig. 2 show the decline in responsiveness recorded in four neurons in area 17. The measure of responsiveness in this case came from the peak response recorded in the orientation tuning curve for each temperature of the primary visual cortex. Each tuning curve was derived from average response histograms prepared from five presentations of a bar stimulus set at ten different orientations each separated by 10 deg. In later experiments responsiveness was represented by measuring the integrated number of spikes under the entire tuning curve. In the curves of Fig. 2 the responses were plotted as a percentage of the value obtained at physiological temperatures. All neurons showed a reduction in responsiveness with cooling and the form of the reduction was remarkably similar for each neuron in the sample.

Responses of ten neurons were tested immediately after rewarming the tissue to 35·5 °C and marked recoveries were observed in all cases. In four cells the activity was higher than originally recorded (103–142%); in one it was similar to the original value (91%) and five neurons showed a partial recovery (50–83%).

Shape of the orientation tuning curve

An examination of the shape of the orientation tuning curve at different levels of cooling was undertaken for thirteen striate neurons. The tuning curves were all prepared using 10 deg steps in orientation and covered the full response range of each cell, usually of 80–100 deg. All these tuning curves were first constructed by joining the data points with straight lines and then later, by drawing the best-fit Gaussian

curves. For the first construction the sharpness of tuning curves (half-width at half-height), at physiological temperatures, ranged from 10 to 28 deg (mean = 17 deg) while with the Gaussian fit the range was 11 to 23 deg (mean = 16 deg). For tuning curves obtained by joining data points the widths were measured by hand while

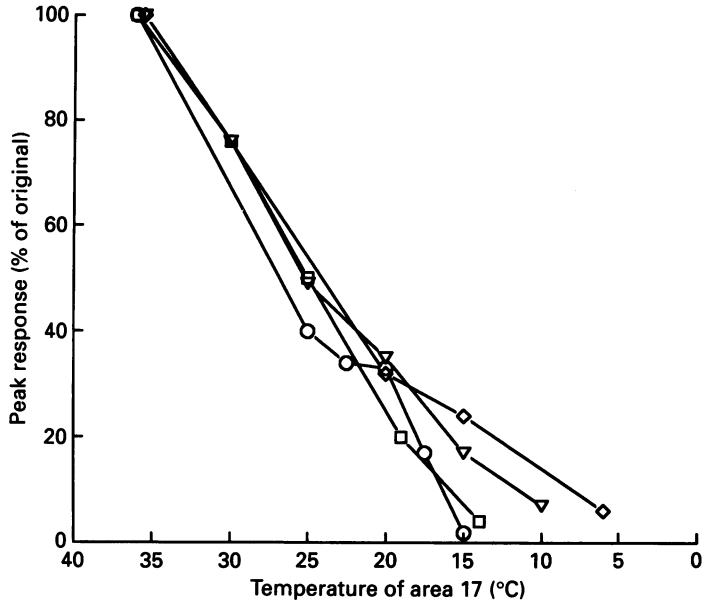

Fig. 2. The responsiveness (peak mean response in the orientation tuning curve) of four directly cooled neurons in area 17 as a function of temperature. The consistent nature of the decline in responsiveness in each of the four cells was a common feature of direct cooling in area 17.

those derived from Gaussian curves were calculated mathematically. Figure 3 shows sets of straight line tuning curves obtained for four representative neurons in area 17; the curves are presented in this form to emphasize the location of the experimental data points. Lowering the temperature reduced the response at each stimulus orientation but the curves retained their basic shape (same half-width at half-height) until the temperature was lowered to a level where both the responses and spontaneous activity were almost entirely extinguished.

Both methods of constructing the tuning curve indicated that the retention of the width of the orientation tuning curve during cooling was a common feature in striate neurons and it held even when the individual responses were reduced to as low as 5% of the initial value. The variation in tuning curve width with reduction in temperature for all area 17 cells is reproduced below in Fig. 8*A*. These values are calculated from the best-fit Gaussian curve and are expressed as a percentage of the width recorded at physiological temperatures. In this case the slope of the regression line was −0·03 while with the method of joining data points it was 0·25. In twelve neurons, the reduction in amplitude of the tuning curves during cooling followed a pattern where the responses appeared to be divided by a constant factor so that,

although the height of the curve was diminished, the half-width at half-height remained constant. In one exceptional example there was broadening of the orientation tuning curve so that, at the lower temperature, the half-width at half-height was 187% that of the original. In this neuron rewarming of the tissue restored the original sharpness of the tuning curve (to 119% of the original).

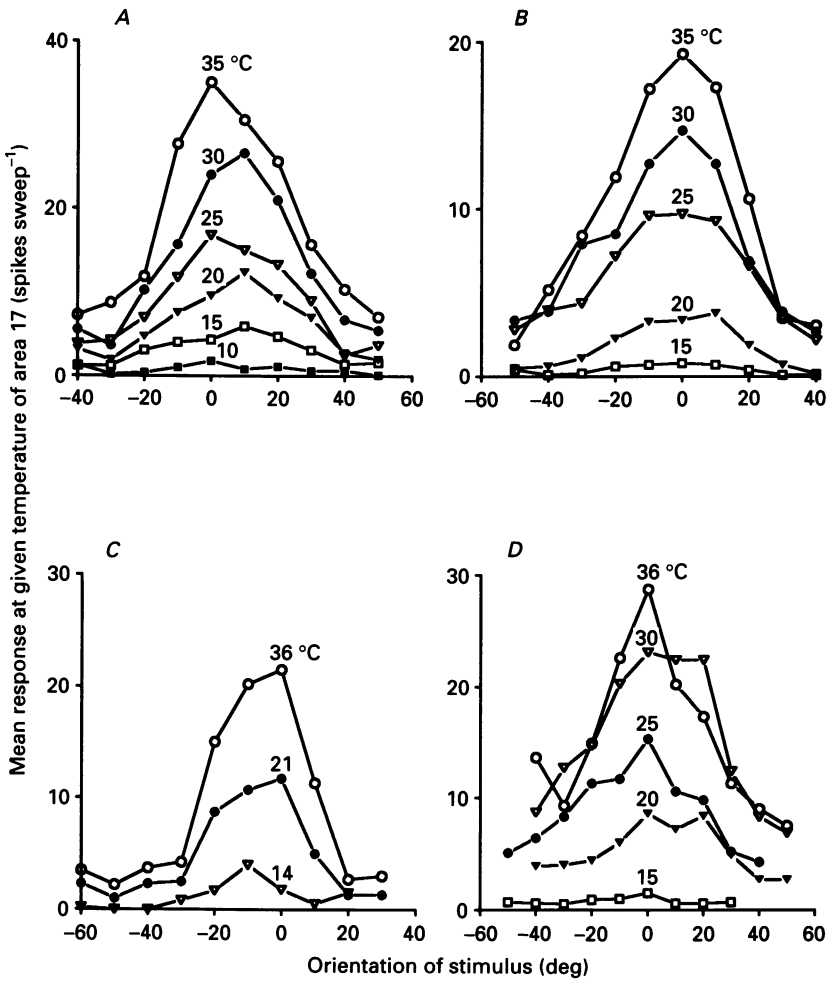

Fig. 3. Orientation tuning curves of four area 17 neurons plotted at different cortical temperatures. Note, at each cooling step, the divisive nature of the change that reduced the height of the curve without altering its width. Note also that orientation selectivity persisted at very low levels of responsiveness (i.e. at temperatures around 15 °C).

Direction selectivity

The orientation tuning curves were also analysed for direction selectivity in all striate neurons. The degree of direction selectivity was measured as the ratio of the area under the curve for each of the two directions (preferred and non-preferred) of stimulus movement. In this calculation there was an advantage in taking account of

the responses to ten stimulus orientations since it reduced the variability of the measurement. In all neurons, direction selectivity was preserved with cooling and there were no changes in the polarity of the preferred direction, even at the lowest temperatures. Although cooling produced variations in the degree of direction

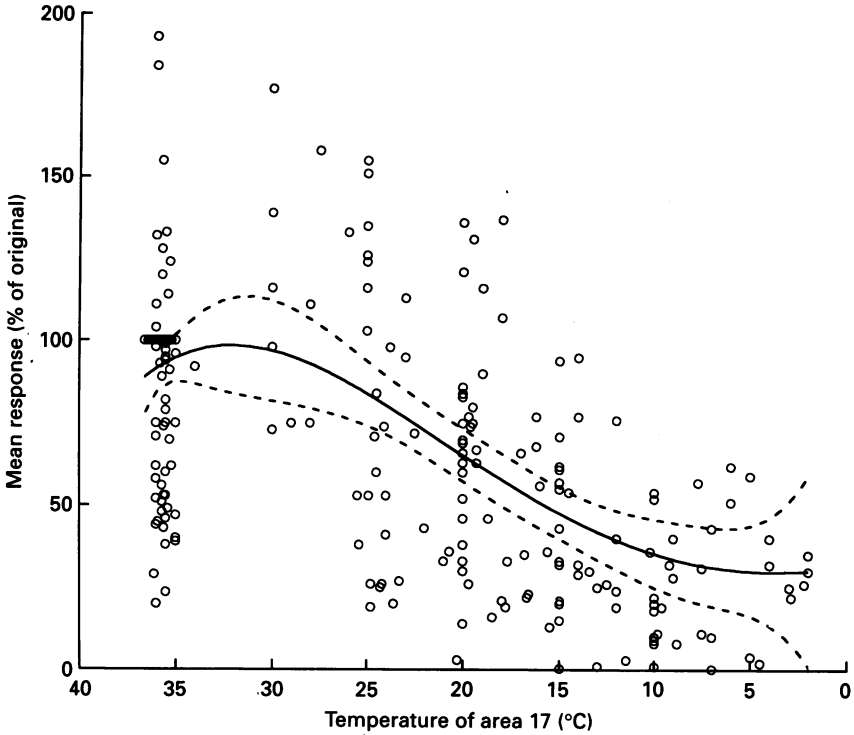

Fig. 4. The responsiveness (mean response; obtained by integrating the area under orientation tuning curve and expressed as a percentage of original), of sixty-four neurons in area 21a, plotted as a function of temperature of area 17. Points obtained from both cooling and rewarming experiments. The continuous line is derived from a fourth-order quadratic function, fitted by method of least squares; the dashed lines show the 95% confidence limits.

selectivity in individual neurons there was no tendency for the level of preference to either increase or decrease in a systematic fashion.

Cooling the primary visual cortex and its effect on the neurons of area 21a

Responsiveness to visual stimulation

Response properties were recorded for sixty-four neurons in area 21a while the temperature in the primary visual cortex was successively lowered to different levels. Neuronal receptive fields varied in size from 1 to 26 deg^2. The receptive field centres of fifty-two neurons were located within 5 deg of the area centralis. For the remaining twelve neurons the eccentricity of their receptive field centres varied from 5·9 to 7 deg. The receptive fields of thirty-four neurons were entirely within the central 5 deg of the visual field while those of twenty-four neurons were partially within the

5 deg limit but did not extend beyond the 8 deg circle. Finally, six other neurons had receptive fields located entirely outside the central 5 deg and extending up to 9·6 deg. The neurons with the most peripheral receptive fields were included in the analysis because they showed typical effects associated with cooling of the primary cortex.

In all of the sixty-four analysed cells in area 21 a the visual response was markedly reduced when the primary cortex was cooled. In fourteen cells, however, the initial step, which cooled the primary visual cortex to between 20 and 30 °C, resulted in an increase in responsiveness. The largest observed enhancement within this range of cooling was 209% although the mean for all sixty-four cells was only 13·8%. When subject to further cooling, however, these cells always showed reduction of responsiveness below the original level.

Figure 4 shows the levels of responsiveness attained by all the recorded neurons in area 21 a when the primary visual cortex was cooled to different temperatures. Here, the responsiveness was measured from the area under the orientation tuning curve and expressed as a percentage of the uncooled finding (see above). The curved line in Fig. 4 (a best-fit fourth-order quadratic) shows both the weak decline, or even increase, in responsiveness at temperatures around 30 °C and the strong reduction in responsiveness that occurred below 25 °C.

The plotted points in Fig. 4 were taken from all findings obtained during the course of both cooling and rewarming the primary visual cortex. The original data for all neurons were pooled together to show the general pattern of change in responsiveness in the entire population of cells. It should be stressed, however, that Fig. 4 cannot be used to trace the behaviour of individual neurons. To analyse individual changes the profiles of responsiveness as a function of primary cortex temperature were constructed for each of the recorded cells using linear interpolation between the data points. From these graphs the responsiveness of each cell was evaluated for six temperatures of the primary cortex. Figure 5 presents the distribution of area 21 a neurons with different degrees of response suppression corresponding to these temperature levels.

The data in Fig. 5, although derived from the same results as in Fig. 4, are not directly comparable for two reasons. The first reason is that Fig. 4 plots actual experimental measurements of responsiveness at individual temperatures while in Fig. 5 the temperature was selected for each histogram and the linear interpolation was used if there were no data points available at a particular temperature. The second distinction in the data used in Fig. 5 is that once cooling caused a reduction in responsiveness below 20% a cumulative count was added to the lowest bin in each histogram. In other words, at a given temperature, the lowest bin may duplicate the count of neurons that were already blocked (or had their responsiveness reduced to less than 20%) at higher temperatures.

The distribution histograms in Fig. 5 are included to bring out the finding that the lower the temperature of the primary visual cortex the greater the number of cells in area 21 a with a severely diminished responsiveness. Based on earlier results, a temperature of 5 °C, would be expected to block all activity in the primary visual cortex but, at this temperature, few area 21 a cells were totally unresponsive. The responses were all markedly diminished, however, and in 77% of cells (extreme left bar of the bottom histogram) were reduced to less than 20% of the original level.

In sixteen cells of area 21 a, the cooling of the primary visual cortex was effective in removing almost all the response to visual stimulation. These cells were interpreted as undergoing total blockade in that, in all cases, the remnant of the tuning curve lost its regular form and firing that did occur was intermittent and did

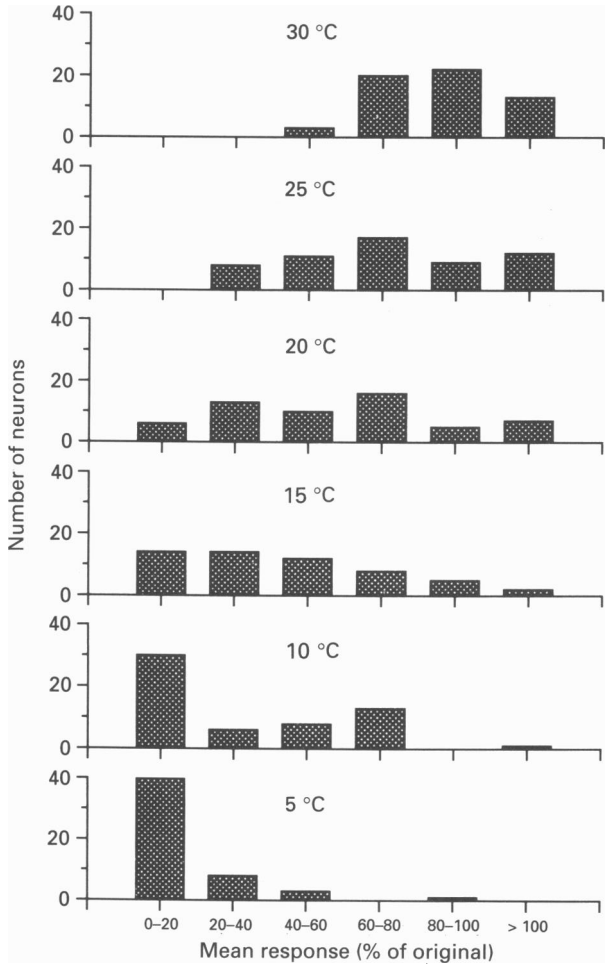

Fig. 5. Distribution histograms, derived from area 21 a neurons, showing how the level of responsiveness declines in the sample (the same sample and measure of responsiveness as Fig. 4) with the cooling of the primary visual cortex. Responsiveness of each neuron was separately plotted as a function of primary cortex temperature. Then the values needed for the histograms were read using linear interpolation.

not exceed more than 10% of the original. Other cells with less than 10% of the original responsiveness that retained the shape of their orientation tuning curve were not regarded as totally blocked. The level of cooling of the primary visual cortex required to produce total blockade ranged between 4·5 and 25 °C. In four cells the blocking temperature was greater than 20 °C, in seven cells it was between 10 and 15 °C, in four cells it was between 5 and 10 °C and in one it was less than 5 °C.

In the remaining forty-eight neurons, recorded in area 21 a, cooling applied to the primary visual cortex was insufficient to totally extinguish the visual response although, in thirty-four cases, responsiveness was reduced to below 30% of the original, in ten other cells it was below 50% and in four more, below 70%. Where

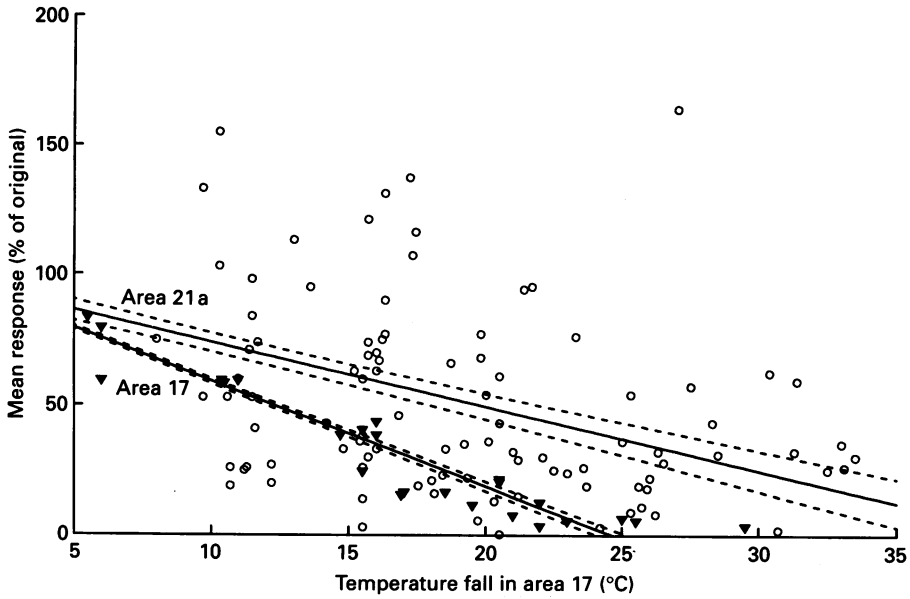

Fig. 6. Superimposed graphs showing the responsiveness of area 17 neurons (▼) and area 21 a neurons (○) as a function of the temperature of the primary visual cortex. Data points derived only from cooling experiments. First-order regression lines shown as continuous lines and 95% confidence intervals as dashed lines.

incomplete extinction occurred, we found little correlation between the degree of cooling of the primary areas and the extent to which the response was diminished. Some neurons in area 21 a showed a marked drop in responsiveness even to slight cooling of the primary visual cortex while others were much more resistant. Neurons with markedly different sensitivity to cooling were encountered next to each other in the same electrode track. It seemed possible that two groups of cells were present in area 21 a: one that could be blocked totally by cooling the primary visual cortex and the other where the blocking was only partial.

A comparison of responsiveness in areas 17 and 21 a with cooling of the primary visual cortex

Figure 6 shows the changes in responsiveness (area under orientation tuning curve as a percentage of the original) of neurons in area 17 (▼) and area 21 a (○) plotted as a function of temperature reduction of the primary visual cortex. The plotted points, taken only from cooling experiments to avoid the hysteresis that frequently accompanied rewarming, show the scatter of response values for different degrees of cooling. The regression lines (continuous lines) for the two groups of neurons, one from area 17 and the other from area 21 a, are of different slope and the 95%

confidence limits (dashed lines) do not overlap. The less marked decline in the regression line in area 21a appeared to be due to two factors: firstly, at moderate temperature drops, many neurons in area 21a showed an increase rather than a decrease in responsiveness; and secondly, there was a group of neurons in area 21a that retained some response even to temperature reductions as great as 30 or 35 °C. Despite the difference in the two regression lines, there were many points from neurons in area 21a that clustered around the regression line for area 17 neurons.

Statistical analysis performed on the original data using numbers of spikes rather than percentages produced inconclusive results. The difference between the slopes of regression lines in area 17 and 21a was just below the level of statistical significance. To obtain an idea of how close the difference was to being significant the data were further analysed. When a logarithmic scale was used to obtain a similar scatter of data points for different temperatures, the analysis of residual values indicated that the ten most 'aberrant' points (all belonging to area 21a neurones) might not have belonged to the main cluster. When these points were removed the difference between the slopes of the regression lines in area 17 and 21a was significant (Student's t test, $t = 2{\cdot}74$, $P < 0{\cdot}05$).

Shape of orientation tuning curve

The effect of cooling the primary visual cortex on the shape of orientation tuning curves was analysed in fifty-eight neurons in area 21a. All these neurons were strongly orientation selective. As in area 17, all the tuning curves were recorded for eight to ten orientations, each separated by 10 deg. Again, straight lines and best-fit Gaussian curves were fitted to the data points. At physiological temperatures the half-width at half-height in these curves ranged from 7 to 24 deg with a mean of 14 deg in the straight line fit; and from 10 to 25 deg with a mean of 16·7 deg in the Gaussian fit. For each neuron, irrespective of the type of curve fitting, the sharpness of the orientation tuning curve was preserved when the primary cortex was cooled, even though in some cells the responsiveness was reduced to 5% of its original level. Alterations in the preferred orientation, though sometimes observed, were restricted to the range of adjacent orientations (10 deg apart) and had the character, more of random fluctuations, than of systematic changes.

Figure 7 shows sets of tuning curves for four area 21a neurons obtained for different levels of cooling of the primary visual cortex. As for area 17, the curves in Fig. 7 take the form of straight lines joining individual data points. For the family of tuning curves shown in Fig. 7*A* cooling caused a regular decline in height with little change in width. The form of this decline closely followed that of the neurons in area 17 (cf. Fig. 3). In contrast, the examples in Fig. 7*B–D* showed a more irregular decline in the height of the tuning curve, a feature that was more common in the cells of area 21a than in those of area 17. Where the decline in the tuning curve was irregular we failed to detect any systematic pattern; in some instances the responsiveness remained unchanged with a step down in temperature (Fig. 7*B* and *C*) while in others there was an increase in responsiveness. Such irregularities were seldom observed in the responses of cells in area 17.

In most area 21a neurons, however, the amplitude of the tuning curves produced by cooling the primary visual cortex diminished by a fixed proportion with each

cooling step. To discover how frequently this process of 'diminishing through division' occurred in the sample of area 21a cells we prepared Fig. 8 to see if the relative width of the tuning curves remained unchanged at different temperatures of the primary visual cortex. The widths of the tuning curves were computed at the

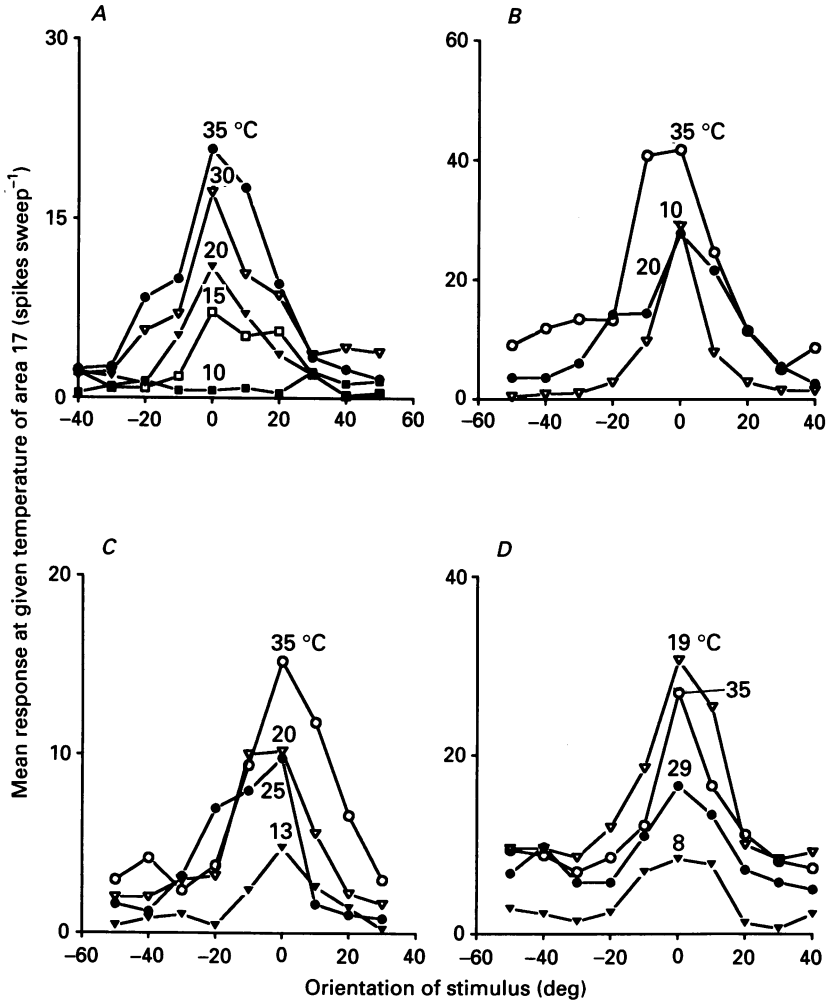

Fig. 7. Orientation tuning curves of four area 21a neurons plotted at different temperatures of the primary visual cortex. The orientation tuning curves of these, and all other neurons tested in area 21a, declined in the divisive manner reported earlier in Fig. 3 for directly cooled neurons in area 17.

half-height of fitted Gaussian curves and expressed as a percentage of the values obtained at physiological temperatures. In Fig. 8*A* these results are presented for the neurons of area 17 where the temperature changes were induced by direct cooling. The results in Fig. 8*B* came from cells in area 21a and the cooling was applied to the primary visual cortex. In both areas the near horizontal regression lines (slope of −0·03 in Fig. 8*A* and 0·04 in Fig. 8*B*) and the very narrow confidence limits indicate

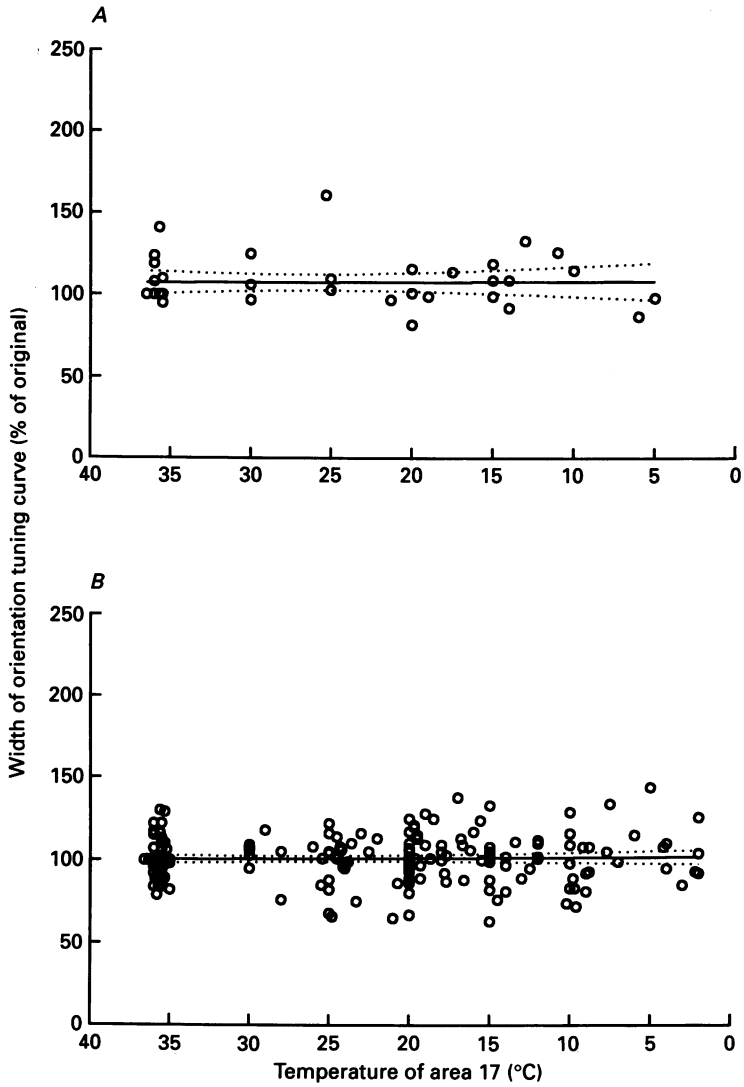

Fig. 8. The effect that cooling of primary visual cortex had on the sharpness of the orientation tuning curves (half-width at half-height). All widths were computed from Gaussian curves fitted to data points. *A*, the effect in directly cooled area 17. *B*, the effect in area 21a. In spite of considerable scatter the near horizontal regression lines (continuous) and 95% confidence intervals (dotted lines) reveal a tendency to preserve the original sharpness of tuning in both areas. Scattered points corresponding to a temperature of 35·5 °C were obtained after rewarming the primary visual cortex; the scatter of these points provides a control since it was comparable to that observed during the cooling experiments.

that there is little or no tendency for changes to occur in the width of the orientation tuning curve as the temperature was lowered in the primary cortex. The almost identical regression lines in Fig. 8*A* and *B* were obtained despite the marked difference in local temperature in the two regions; the temperature changes ranged

from 5 to 30 °C in area 17 and only from 2 to 3 °C in area 21a. The widths of the orientation tuning curves obtained with physiological temperature of the primary cortex were always defined as 100% so that the scattered points at 35·5 °C in Fig. 8*A* and *B*, include the values obtained after rewarming of the primary visual cortex.

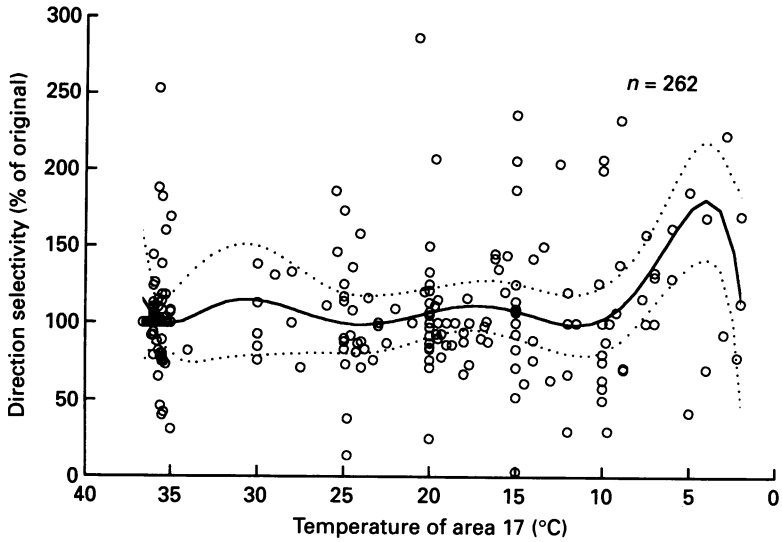

Fig. 9. Effect of area 17 temperature on the direction selectivity of fifty-eight area 21a neurons. The continuous line (seventh-order quadratic best-fit curve) and the dotted lines, the 95% confidence intervals, show the tendency for the original direction selectivity to be preserved at temperatures above 10 °C and to increase it at lower temperatures. Scattered points at the temperature of 35·5 °C, recorded after rewarming of the primary visual cortex, provide a control for the scatter during cooling.

These points show a scatter similar to that apparent at lower temperatures and this constancy suggests that the variations are random and are not temperature dependent. The uniformity of the interval of confidence (dotted lines in Fig. 8) also indicates that there was no tendency for the scatter of the data points to increase at the lower temperatures of the primary visual cortex.

Direction selectivity

The direction selectivity (see above) measured for fifty-eight neurons in area 21a varied between 1 and 7·14 under physiological conditions. The direction selectivity, however, only had a mean of 1·66 and, for thirty-seven neurons, it measured less than 1·5. If an arbitrary dividing line, set at a value of 3, is drawn between direction selectivity and a directional bias then only five out of fifty-eight neurons would be classed as direction selective.

When the temperature of the primary visual cortex was lowered all neurons retained directional preference even at the lowest temperatures. Figure 9 shows the direction selectivities of all neurons as a function of the primary cortex temperature. The line of best fit indicates that there was no systematic change in the degree of

direction selectivity when temperatures of the primary cortex were higher than 10 °C. Below this temperature there was a tendency to increase the degree of direction selectivity but, at the lowest temperature, the response to movement in either direction was often very weak.

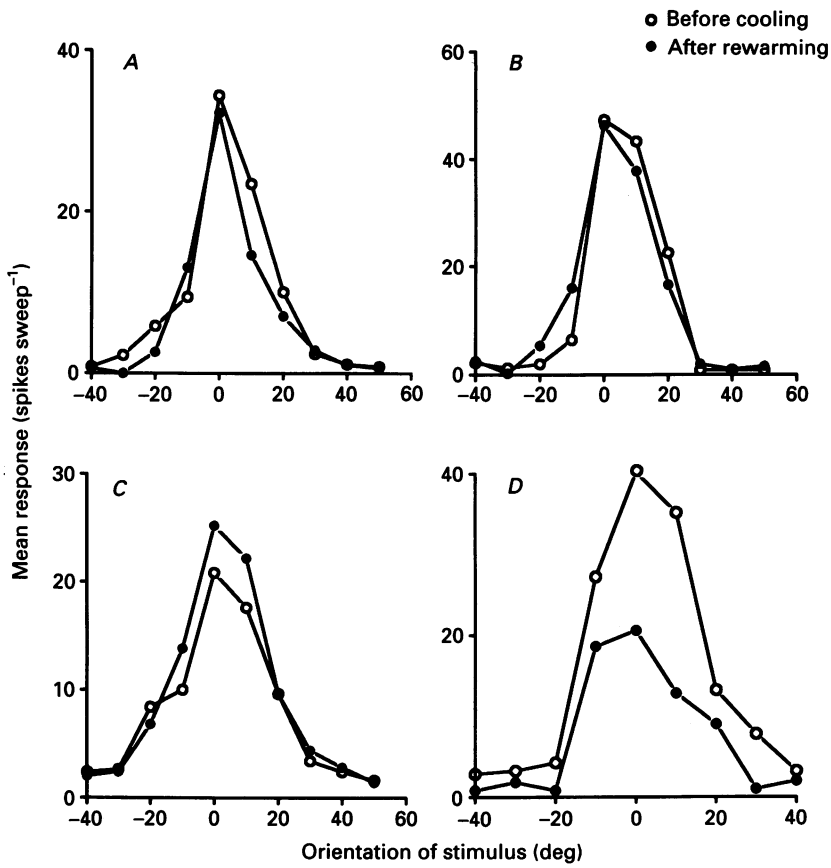

Fig. 10. Orientation tuning curves of four area 21a neurons recorded before cooling and after rewarming of the primary visual cortex to show the level of recovery from cooling. The activity of all these neurons was strongly reduced throughout the cooling phase of the experiment.

Velocity selectivity

The frequency of the visual display (100 Hz) used in this study (see above) was not high enough to justify its use in testing the response to stimulus velocities greater than 20 deg s^{-1}. Even though some of the cells ceased to respond before the velocity reached 20 deg s^{-1} the resulting tuning curve was not as regular as that obtained with changes in orientation. As a result velocity tuning curves were prepared for only eight neurons in area 21a; for two of these the temperature of the primary visual cortex was reduced below 5 °C, for five others it was between 10 and 15 °C and for one it reached 18 °C. In this relatively small sample, there was no systematic variation

in the shape of the tuning curve during the cooling of the primary cortex. In four neurons cooling reduced the response to stimuli moving slowly more than the responses to other velocities; in three others it reduced predominantly the responses to faster moving stimuli and in one, the responses were all uniformly diminished. It was concluded, for this small sample, that although cooling of the primary visual cortex frequently blocked all responses in the cells of area 21 a, the manner of the decline could not be correlated with any particular range of stimulus velocities.

Recovery

In forty-seven of the area 21 a neurons responsiveness was tested after rewarming the primary visual cortex to 35·5 °C. In forty cases some recovery was immediately apparent; in nineteen of these, the initial recovery was total (from 90 to 120 % of the original response level) and only in seven was it below 40 %. In the neurons where the initial recovery was poor or absent, all but one had recovered responsiveness within half an hour of restoring physiological temperature to the primary visual cortex.

The recovery of responsiveness is also demonstrated in Fig. 10 which shows four examples of tuning curves, again with the data points joined with straight lines, obtained before cooling and after rewarming of the primary cortex. The cooling regime called for the preparation of orientation tuning curves at a number of cooling stages (between 3 and 11) and the subsequent rewarming of the primary visual cortex. In the neurons in *A* and *B* the 'before' and 'after' tuning curves were of an identical height. For the neuron in *C*, the responses were higher after the test session whereas, in *D*, they were substantially lower. In each case, the preferred orientation and its width at half-height were unchanged and in most instances there was also little change in responsiveness.

DISCUSSION

The dual approach adopted in the present study has allowed us to look at the effects of cooling at two different stages in a neural pathway. At the first point, in area 17, the neuron was directly cooled and, at the second in area 21 a, we studied the effect of cooling a presumed parent neuron. Subsequently our findings supported the concept of parent cells in the primary visual cortex and in many instances these cells appeared to provide an input that was necessary to cause responses in the cells of area 21 a. Not all the cells recorded in area 21 a were totally silenced by cooling areas 17 and 18, however, and we were left with the possibility that some area 21 a neurons depended entirely on the input from the primary visual cortex while others derived a supplementary input from elsewhere. On the other hand no area 21 a cell was left unaffected by the cooling in the primary visual cortex and the evidence suggested that the supplementary input was comparatively weak.

The effectiveness of cooling the primary visual cortex

In evaluating the effects of direct cooling, it is possible to compare our results with those of others even though the cooling has been conducted in different locations. A point of divergence to emerge from these comparisons is that the critical temperature

required to extinguish a response in our experiments was frequently substantially lower than reported previously. It has been a common experience to find that cortical neurons, when cooled directly, cease to be active at around 20 °C (Moseley, Ojemann & Ward, 1972; Sherk, 1978) whereas in most of our recorded neurons the blocking temperature was between 10 and 20 °C and in a small proportion it was even less than 10 °C. A potential source for this discrepancy could be the use, in earlier experiments, of large thermistors encased in metal needles which, through their own conductance, could raise the temperature of the sensor. In the present experiment we used micro-thermocouples built with 25 μm thick wires. We are not alone with our findings, however, and other experimenters have also reported low blocking temperatures when small thermocouples were used (50 μm wires; Girard & Bullier, 1989) in the monkey cortex. The blocking temperatures in this study were as low as 4 °C and the most common blocking temperature was between 10 and 18 °C. Blocking temperatures as low as 5–10 °C have also been reported in an experiment on cultured neurons, where the size of the thermosensor should be less critical (Gahwiler, Mamoon, Schlapfer & Tobias, 1972).

Our lower blocking temperatures are also consistent with the finding that the EEG and evoked potentials were present at temperatures above 10 °C (Jasper, Shacter & Montplaisir, 1970; Kalil & Chase, 1970; Benita & Conde, 1972; Schiller, Stryker, Cynader & Berman, 1974; Schmielau & Singer, 1977). Since both EEG and evoked potentials are developed from sizeable populations of neurons it would seem that many cells would have blocking temperatures lower than 10 °C.

During an experiment it was difficult to estimate the exact spatial extent of deactivated cortex attributable to cooling but it was important to have some idea of the spread for two reasons. Firstly, the cooling should extend far enough to deactivate parent cells in area 17 but no so far that it directly diminished the responses of cells in area 21 a. From our data and that of others (Gahwiler *et al.* 1972; Moseley *et al.* 1972; Sherk, 1978; Girard & Bullier, 1989; Girard, Salin & Bullier, 1991 *a*, *b*) it is possible to infer that the majority of cortical neurons will have declined to about a third of their original responsiveness at a temperature of 20 °C and that the depth–temperature gradient, measured directly in our experiment, would be close to 5 °C mm^{-1} (see Girard & Bullier, 1989, for comparable findings). Based on these figures the cortex would reach a temperature of 20 °C at a depth of 4 mm when the full cooling power produced temperatures of 5 °C at a depth of 1 mm. When compared with the visual field maps (Tusa *et al.* 1978, 1979) the extent of cooled cortex (at less than 20 °C) corresponded to the area representing the central 5 deg of the visual field in both areas 17 and 18. In contrast, the central representation in area 19, at the same antero-posterior co-ordinates as the cooling probe, is located on the lateral wall of the lateral sulcus, where the temperature is likely to be above 20 °C.

The second requirement, that excessive cooling should not spread into the recording region in area 21 a, seemed to be met since our electrode tracks were located at a lateral distance of 7–8 mm from the edge of the cooling plate. In addition, the lateral sulcus separates the primary visual cortex from the suprasylvian gyrus, the location of area 21 a. In monkey cortex, where the temperature gradients are similar, it has been possible to record responses from cells 3 mm beyond the cooling plate (Schiller & Malpelli, 1977; Girard & Bullier, 1989).

Since the temperature drop was measured directly in both cortical areas in the present experiment, it is possible to assess the effect coming from the spread of cold into area 21 a. To complete the analysis, however, it was necessary to assume that the neurons in areas 17 and 21 a react in a similar manner at low temperatures. In

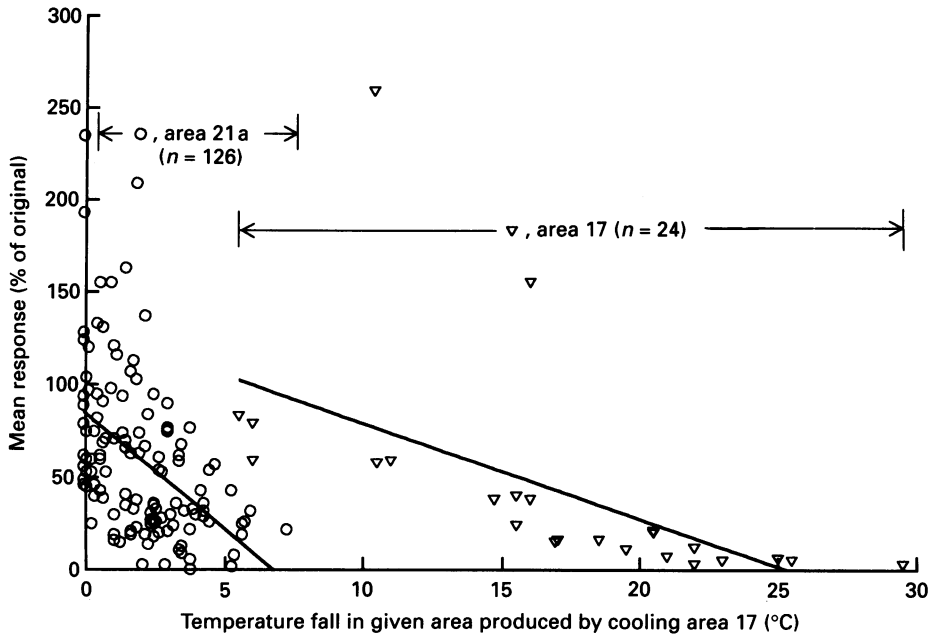

Fig. 11. Superimposed graphs showing the responsiveness of area 17 neurons as a function of the measured temperature fall in area 17 (▽) and the responsiveness of area 21 a neurons (○) as a function of the corresponding temperature fall in area 21 a. The separation of the two sets of data points and the variation in the slope of the two regression lines highlight the difference in the two populations and indicate that the spread of cold from the primary visual cortex could not account for the reduction in response in area 21 a.

applying this analogy, the decline in responsiveness for area 21 a cells was always more than 40 % greater than that anticipated from the effect of spreading cold. This distinction between the effects of direct and indirect cooling is further emphasized in Fig. 11, where the reductions of responsiveness in area 21 a and area 17 are related to changes in local temperature, resulting from direct cooling in area 17 and from its spread in area 21 a. The clustering of the two groups of points and their distinctive regression lines suggest that the changes in activity of area 21 a neurons cannot be attributed in full to the spread of cooling.

Changes in responsiveness in area 17 with cooling

When the temperature was lowered, all the neurons recorded in area 17 showed a decrease in their responsiveness to visual stimulation. It was striking, however, that the basic features of the responses remained virtually intact. There were no significant changes in the direction selectivity or in the width of the orientation

tuning curve despite reductions to as little as 5% of the original response. Assuming that the reduction of activity to 5% is derived from a comparable blockade of the synaptic inputs to the analysed neuron then it is remarkable that the neuronal network should preserve its basic response properties. The retention of these characteristics would allow them to be passed on to the next stage of processing where the full response could be restored simply through the amplification of spike numbers. Such compensatory amplification could be provided if the neurons at the next stage were supplied with a sufficient number of inputs.

The reduction in the amplitude of the tuning curves, caused by direct cooling in area 17, was such that the outcome could be obtained by dividing the values of the original function by some constant rather than by subtracting a fixed amount. It would be helpful in interpreting this result to know which functional input, whether it is excitation and/or inhibition, is responsible for bringing orientation specificity to the neurons of area 21a. At the moment there is no consensus on the mechanism underlying orientation specificity (Henry *et al.* 1974; Ferster, 1986; Vidyasagar, 1987; Douglas & Martin, 1991) but some inference concerning the behaviour of excitatory and inhibitory components during cooling can be drawn from simple graphical analysis. Thus the representation of excitatory and inhibitory components may take the form of a Gaussian function if orientation specific or a horizontal straight line if not orientation specific. Using such representations it was possible to plot orientation tuning curves by summing theoretical excitatory and inhibitory components in various, arbitrary combinations of amplitudes and widths. The components were then reduced, separately or together, in a divisive or subtractive manner and the effect on the resulting tuning curve was assessed. When all possible combinations of the reduction mechanisms were modelled it was found that irrespective of which component (excitation or inhibition or both) was orientation selective the cooling must have diminished it through division. Only then did the sharpness of the resulting tuning curve remain constant. A subtractive reduction of one of the components with cooling, irrespective of the behaviour of the other, resulted in an alteration in the width of the combined turning curve.

Responsiveness in area 21a following cooling of area 17

If the decline in responsiveness in area 21a is attributable, only in small degree, to the direct spread of cooling then the deactivation of the cells in the primary visual cortex can be held responsible. The finding that one-quarter or sixteen neurons recorded in area 21a had their responses extinguished by cooling the primary visual cortex indicates that a sizeable proportion of neurons in area 21a receive an essential part of their excitatory input from the primary cortex. Additional inputs from other areas, such as areas 19, 20 or the lateral suprasylvian cortex (Symonds & Rosenquist, 1984*a*,*b*; Sherk, 1986), are possible but acting alone these do not appear capable of producing an excitatory response.

In the remaining neurons, where the responses were not totally extinguished, they were still markedly diminished to be nearly always less than half that at the physiological temperature. The large reduction in responsiveness experienced by most neurons in area 21a following the cooling of primary visual cortex gives an indication of the extent to which area 21a is sequentially related to the primary

visual cortex. At one extreme, therefore, the direct pathway from the primary visual cortex could provide most of the afferent supply to the majority of neurons in area 21a. On the other hand, the input from primary visual cortex could take one of two indirect pathways either through other cortical areas associated with the primary visual cortex or via the cortico-recipient zone of the thalamus. Our results do not help to resolve this question of directness of the supplementary input, although its existence seems necessary to explain how some cells (8 or 13% in our sample) maintain some of their responses even during cooling below 5 °C. Axonal tracing experiments advance the path through area 19 as the more likely prospect for this input since it is the only connection, other than that coming from the primary visual cortex, to contribute more than 9% to the total input to area 21a (Sherk, 1986).

An interesting side issue to arise with the use of cooling to deactivate the primary visual cortex was that mild cooling caused an increase in responsiveness in 20% of neurons in area 21a. It was also noteworthy that we did not observe a similar increase in any of the neurons of area 17. There are a number of earlier reports that spinal and cerebral neurons become hyper-responsive when cooled only 1–2 °C below physiological temperature, presumably because of increased resistance of post-synaptic membrane (for review see Brooks, 1983). Such small temperature drops could spread into area 21a if the temperature of the primary visual cortex was reduced below 20 °C but the increased responsiveness in area 21a was invariably noticed at much higher temperatures. Another possible explanation for the increase in responsiveness could be the depolarization of presynaptic terminals as reported in spinal and cuneate neurons (Brooks, 1983). This depolarization occurs within the temperature range of 30–34 °C, which is generally below the level of spreading cold into area 21a, and is more common in the direct cooling of area 17 where there was no sign of an increased responsiveness.

Our failure to find an increased responsiveness in area 17 that corresponded to the response enhancement in area 21a set us on a search to explain its appearance in area 21a. Unfortunately, at this stage, most of the possibilities have unsatisfactory features that require further evaluation. For example, it is possible that the area 17 neurons sending axons to area 21a are uniquely affected by mild cooling but have gone unencountered in our study. Another possibility is that there is an inhibitory pathway, arising from the primary visual cortex, that is more susceptible to cooling than the excitatory one. Such a selective influence on inhibition is not reflected, however, in the orientation tuning curves, direction selectivity or spontaneous activity of area 21a neurons.

Despite the difficulties in explaining all the details of the changes in responsiveness with cooling there remain good reasons for believing that area 21a is principally dependent on the primary visual cortex for its input. For example, there is strong support in the finding that response properties of neurons in area 21a (such as cut-off velocity, orientation tuning and composite on–off responses to flashing stimuli; Wimborne & Henry, 1992; Dreher *et al.* 1992) can all be simply derived from C or complex cells of area 17. In these terms, if the cooling of area 17 blocked the input to area 21a it would remove the C cell drive. The neurons of area 21a that are only partially extinguished by cooling the primary visual cortex presumably receive input from neurons other than those of the primary visual cortex.

We conclude, therefore, that the majority of cells in area 21a are either totally or principally driven by inputs from the primary visual cortex. When taken in association with the results of tracer experiments (Symonds & Rosenquist, 1984*a*, *b*; Dreher, 1986; Sherk, 1986; Mulligan & Sherk, 1991; Sherk & Mulligan, 1991) there is growing support for the view that the primary cortex and area 21a represent adjacent levels of processing of the visual signals. On the other hand, even in the presence of a high proportion of sequential linking, we had expected to find more obvious differences in the receptive field characteristics in the two regions. That few distinctions were observed would seem to suggest that future studies will need to concentrate on the detection of subtle differences in visual response properties in areas 17 and 21a.

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