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Comparison of receptive field properties of neurons in area 17 of normal and bilaterally amblyopic cats

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Abstract Receptive field properties of extracellularly recorded units in the visual cortex (area 17) of cats made bilaterally amblyopic by a variety of rearing conditions were measured and compared with the properties of units in normal cats. Properties studied included sensitivity to vernier offset, response facilitation to increasing bar length, receptive field size, responsiveness to moving and flashed stimuli, orientation tuning, the relation between mean firing rate and its variance, the amount of overlap of regions of on and off responsiveness in simple and complex cells, and, for flashed stimuli, latency to response onset, time to peak response, and response decay time constant. Behavioural testing of the amblyopic animals showed that spatial resolution was 2–4 times lower and vernier acuity thresholds 10–20 times greater than normal. Despite this, several neuronal response properties did not differ significantly from those in normal animals. These included peak responsiveness to moving stimuli, widths of orientation tuning curves, response variability, and latency to initial response for flashed stimuli. Other properties showed small but significant changes. Sensitivity to vernier offset (impulses per degree of offset) was reduced to nearly half its normal level; receptive field sizes increased by about 24% and an incomplete segregation of regions of on and off responsiveness was found in some cells, which made them hard to classify as simple or complex. Responses to flashed stimuli were smaller and more persistent. Their statistical significance notwithstanding, it seems unlikely that these relatively small response abnormalities in area 17 can fully account for the observed behavioural deficits.

Key words Amblyopia · Visual cortex · Monocular deprivation · Reverse suturing · Area 17 · Cat

Introduction

Amblyopia is a condition originating in childhood in which vision in one eye is poor even though any refractive error is corrected and there is no other obvious damage to the eye. It is generally caused by conditions such as strabismus, unilateral cataract, or anisometropia, which result in a reduction in the normal degree of similarity between the two retinal images. Behavioural testing has shown two distinct visual defects in amblyopic eyes: (a) a loss of spatial resolution and contrast sensitivity (Gstalder and Green 1971; Mitchell and Wilkinson 1974; Freeman and Thibos 1975; Hess and Howell 1977; Hess et al. 1981) and (b) a loss in positional acuity, as manifested by spatial distortions in perception (Pugh 1958; Hess et al. 1978; Bedell and Flom 1981) and a marked increase in the threshold for detecting vernier offset (Levi and Klein 1982). The loss of positional acuity is greater than can be explained by the loss of contrast sensitivity and resolution and probably interferes more with useful visual function (Howell et al. 1983; Levi and Klein 1985; Watt and Hess 1987).

Cats and monkeys made artificially strabismic or anisometropic have often been used as models of human amblyopia. Behavioural studies of such animals have shown defects similar to those found in human amblyopes (see Mitchell and Timney 1984; Mitchell 1988, for reviews), which suggests that they are good models of the condition. Physiological studies of the visual pathways in such animals have generally agreed in showing that the retina and lateral geniculate nuclei are physiologically normal and that the visual dysfunction is therefore likely to be cortical in origin. Although losses in positional acuity in amblyopia may be larger and more damaging than losses in spatial resolution and contrast sensitivity, most studies of visual cortical physiology in animal models have examined the neural cor-

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relates of spatial resolution and contrast sensitivity rather than of positional acuity. For example, in cats made artificially anisometropic, Eggers and Blakemore (1978) found a reduction in cut-off spatial frequency for cells driven by the anisometropic eye. In monkey Movshon et al. (1987) similarly documented a lower spatial resolution and contrast sensitivity of visual cortical neurons driven by an eye made myopic by topical atropine application early in life. Studies of the visual cortex in strabismic animals show a loss of binocular neurons (Hubel and Wiesel 1965; Blakemore and Eggers 1978; Freeman and Tsumoto 1983; Baker et al. 1974; Crawford and Von Noorden 1979) but have often not revealed other substantial abnormalities. For example, Blakemore and Eggers (1978), Freeman and Tsumoto (1983) and Freeman et al. (1983) reported normal orientation tuning and spatial frequency selectivity in cells driven by the strabismic eye in cats. Other workers, however, have reported changes, including increases in the receptive field sizes of complex cells (Berman and Murphy 1982), a loss of orientation and direction selectivity in remaining binocular cells (Mower et al. 1982) and losses in spatial frequency tuning, broader orientation tuning and increases in receptive field sizes of cells driven by both the deviating and non-deviating eye (Chino et al. 1983).

In this paper we report the results of a study of neuronal response properties in area 17 of cats made bilaterally amblyopic by periods of reverse occlusion following an initial period of monocular deprivation. Such procedures can lead to the development of severe bilateral amblyopia, in which spatial resolution may be decreased to half or less of normal levels and positional acuity thresholds increased tenfold or more (Mitchell et al. 1984; Mitchell et al. 1986; Murphy and Mitchell 1986, 1987; Mitchell 1991). In this respect the cats are similar to human (Levi and Klein 1982, 1985) and monkey (Kiorpes and Movshon 1989) strabismic amblyopes. We concentrated our attention on neuronal response properties which seem most likely to impact on positional acuity, including sensitivity to vernier offset (Swindale and Cynader 1986, 1989), receptive field size, the degree of segregation of regions of on and off responsiveness, and orientation tuning. We also measured the temporal dynamics of flash responses and responsiveness to moving and flashed stimuli and examined the relationship between response variance and firing rate. A preliminary account of some of these results has been published (Swindale and Mitchell 1992).

Materials and methods

Rearing and behavioural testing procedures

Table 1 gives details of the rearing histories of the eight bilaterally amblyopic cats used in this study, together with (when measured) the final spatial resolution and vernier offset acuity for each animal. In summary, each animal was first monocularly deprived by eyelid suture performed at about the time of eye opening and lasting from 3–12 weeks. The sutured eyelid was then reopened, and a second period of monocular vision began. In three animals this was done by reverse suturing for 9 days and in a fourth by reverse suturing for 12 weeks. Another two kittens underwent patching of the initially open eye for a period of 5 or 6 h each day, the remaining time being spent in the dark. The remaining two animals received alternating occlusion for two periods of 3.5 h in each eye each day, with the remaining time spent in the dark. When the entire reversal or patching procedure was over the animal was returned to the colony and allowed binocular visual input. These rearing procedures and their behavioural consequences are described in greater detail in an earlier paper (Mitchell 1991).

During the rearing periods for some of these kittens, longitudinal measurements of the visual acuity of one or both eyes were made with a jumping stand and behavioural testing protocols described earlier (Murphy and Mitchell 1987; Mitchell 1988, 1991). Once visual acuity had stabilized, measurements were made of the vernier acuity of the two eyes of three animals (C328, C447 and C479) by use of the procedure described in detail earlier (Murphy and Mitchell 1991). In cases where these measurements were not made it is possible to predict the probable outcome of the rearing procedure, since similar treatments have been carried out on other animals (see Mitchell 1991), with reproducible behavioural consequences in different animals.

Control physiological data were obtained from a total of 17 adult cats of unknown age and rearing history and no indication of any visual defect.

Table 1 Summary of the rearing conditions and behavioural acuities of the eight bilaterally amblyopic cats used in this study. The initial period of monocular deprivation (*MD*) was always of the left eye (*LE*). Animals C419 and C420 were both monocularly deprived in the left eye for 6 weeks, and then received periods of alternating monocular deprivation (3.5 h in one eye followed by 3.5 in the other) each day for a further 6 weeks, with the remaining time spent in the dark. The two animals were then allowed binocular vision (recovery) for periods of 20 weeks and 36 weeks, respectively. (*AMD* alternating monocular deprivation, *RE* right eye, *y* years, *w* weeks, *d* days)

Name	Initial MD	Reversal	Recovery	Resolution (cycles/deg)		Vernier acuity (min)	
				LE	*RE*	*LE*	*RE*
C303	7 w 5 d	6 h/d 6 w	2 y 6 w	1.75	1.65	–	–
C328	12 w	5 h/d 6 w 2 d	1 y 4 w	4.6	4.0	24.0	28.0
C417	5 w 1 d	12 w RE	17 w	3.0	2.3	–	–
C419	6 w	6 w AMD 3.5/3.5 h	20 w	2.5	3.1	–	–
C420	6 w	6 w AMD 3.5/3.5 h	36 w	2.6	3.1	–	
C423	4 w	9 d RE	49 w	–	–	–	–
C447	4 w 2 d	9 d RE	1 y 13 w	3.7	3.3	18.1	23.2
C479	4 w	9 d RE	37 w	4.2	3.3	15.0	15.0

Physiological recording

Animals were prepared for single-unit extracellular recording following guidelines laid down by the Canadian Council for Animal Care. Anaesthesia was introduced with intravenous thiopental sodium and a tracheotomy performed. The animal was then placed in a stereotaxic apparatus and connected to electrocardiogram (ECG), electroencephalogram (EEG) and temperature monitors. A craniotomy about 1–2 mm in diameter was made, generally on the right-hand side, 1–2 mm lateral to the midline and 1–3 mm posterior to ear-bar zero. The dura was left intact. At this location receptive field positions typically lay 2–10° below the area centralis and 0–5° lateral to the visual midline. During this period of surgery, withdrawal reflexes were monitored and anaesthesia maintained by further small injections of thiopental sodium. A local anaesthetic, bupivacaine hydrochloride (Marcaine) was injected subcutaneously around the ears and wound margins as a further precaution. Paralysis was induced by intravenous injection of Flaxedil, and anaesthesia was maintained by artificial respiration with 70% N_2O and 30% O_2. Respiration rate and volume were adjusted to produce end-tidal CO_2 levels in the range of 3.5–4.0%. Paralysis was maintained throughout the experiment by continuous infusion of gallamine triethiodide (Flaxedil, approx. 10 mg/kg per hour) together with pentobarbitone sodium (1 mg/kg per hour) dissolved in lactated Ringer's solution and 5% dextrose at an overall rate of about 10–15 ml/h. Body temperature was maintained at around 38° C by means of a heating blanket. The pupils were dilated with topical atropine (5%) and the nictitating membranes retracted with phenylephrine hydrochloride (10%). Protective contact lenses were placed on the eyes, and an hour or so after the pupils were fully dilated the refractive state of the eyes was assessed by retinoscopy. New contact lenses with 3-mm artificial pupils were then fitted, with a base curvature chosen so that the eyes would focus on the display used for visual stimulation. The positions of the optic discs and the *areae centrales* were plotted with a reversing ophthalmoscope. During the experiment the state of the eyes was assessed periodically by ophthalmoscopy to ensure that optical quality remained good.

Visual stimulation

In the majority of experiments a computer-controlled optic bench was used to project and move the images of one or two bars of adjustable size and orientation on a tangent screen 137 cm in front of the animal. Stimulus luminance was approximately 120 cd/m^2 and background luminance approximately 35 cd/m^2. Most recently we used a Picasso image synthesizer (Innisfree) controlled via a computer and digital interface boards, connected to a Tektronix 608 display oscilloscope placed 57 cm in front of the animal. Stimuli on this had a brightness of 22 cd/m^2 or 44 cd/m^2 against a background brightness of around 4 cd/m^2. Although low, these brightnesses are well above the scotopic/photopic boundary, which is at about 0.1 cd/m^2. This apparatus was used for experiments done on two normal and two amblyopic animals.

Single-unit responses were recorded with glass-coated, platinum-iridium electrodes with an impedance of around 1–3 MΩ at 1 kHz. The electrode was angled so as to pass down the medial bank of the lateral gyrus, and this was confirmed for all animals by subsequent histological reconstruction of the electrode track. Responsive units were typically encountered every 100–500 µm. Isolation was generally extremely good and could be improved when required by use of a window discriminator (Bak Electronics). A computer program controlled the visual display and at the same time stored the intervals between spikes with an accuracy of 1 ms, together with information about the stimulus parameters used for each trial.

A manually controlled bar stimulus was used to detect the presence of a visually responsive unit, and then to determine approximately its preferred orientation, velocity, receptive field location, bar length, width and ocular dominance. In many cases receptive field type (simple/complex) was also determined. Quantitative measurements (described in more detail below) were then made under computer control of: (a) orientation tuning for a moving bar; (b) a line-weighting function for a stationary bar with the same length and width, flashed in different positions within the receptive field; and (c) a vernier tuning curve for a vernier stimulus with the same overall length and bar width used for the orientation and line-weighting functions. Adjustments were made to ensure that the orientation and direction of motion used for the vernier tuning and line-weighting functions were close to the optimum shown by a quantitative measurement, and that each component bar of the vernier stimulus produced nearly equal responses when moved on its own through the receptive field. Stimulus conditions were always presented in pseudo-random order, and responses averaged over 8–32 presentations of each condition. Stimuli were always shown monocularly to the dominant eye.

Stability of eye position was assessed during experiments which used moving stimuli, by monitoring a dot raster display of impulses on a display screen in which the horizontal position of each dot (corresponding to one impulse) indicated the position of the stimulus along its trajectory over the receptive field. The position of the receptive field along this axis was clearly indicated by the region of highest dot density along each rasterline. Small variations over time (5–20 min) in the position of the field were rarely observed, but, when they were, measurements of receptive field size and of complex cell/simple cell (C/S) values (see below) were rejected from subsequent analysis. The raster display was also useful in making sure that the stimulus was correctly placed within, and moved across the entire extent of, the unit's receptive field. If this was not the case, the experiment was interrupted, and the stimulus repositioned before beginning again.

When an experiment on a unit was completed, the electrode was moved forward until the unit was lost and was then advanced in 10 µm steps until another visually responsive unit was encountered. Experiments were then done on this unit, and the process repeated. After about 24–36 h of recording the animal was given a lethal dose of anaesthetic (Euthanyl) and was perfused with saline and 4% formalin. The brain was then removed and later sectioned histologically to determine the location of the recording site.

Data analyses

Data from some of the normal animals used here have been reported in previous publications (Swindale and Cynader 1986, 1989). For the purposes of comparison with the amblyopic animals, however, the raw data files were re-analysed using exactly the same methods for both experimental and control animals. As far as possible the analytic procedures were automated. Receptive field properties were quantified as follows:

1. *Sensitivity to vernier offset.* Vernier tuning curves were obtained as described previously (Swindale and Cynader 1986, 1989): the stimulus consisted of two bars of the same length, width and orientation, placed end to end and moved through the receptive field at a constant velocity, which was typically 1°/s or 2°/s. On individual presentations the bars were offset by a fixed amount. Typically, 11 different offsets were used, equally spaced between -0.5 and $+0.5°$, thus including one in which the bars were aligned. In a further two conditions each bar moved on its own through the receptive field, following the same trajectory as in the other conditions. To analyse the resulting tuning curves a measure of spontaneous activity was first subtracted from a graph of response (the mean number of spikes per presentation) versus vernier offset. Next, an inverted V-shaped function (see Fig. 1) was fitted to the graph, using a least-squares, simplex curve-fitting algorithm (Nelder and Mead 1965). The mean of the absolute values of the slopes of the two arms of the function was then calculated, weighting each slope by the length of its horizontal projection onto the x-axis (although the lengths were typically similar). This value, expressed in impulses per degree of vernier offset, is referred to as the "raw slope" of the tuning curve. The

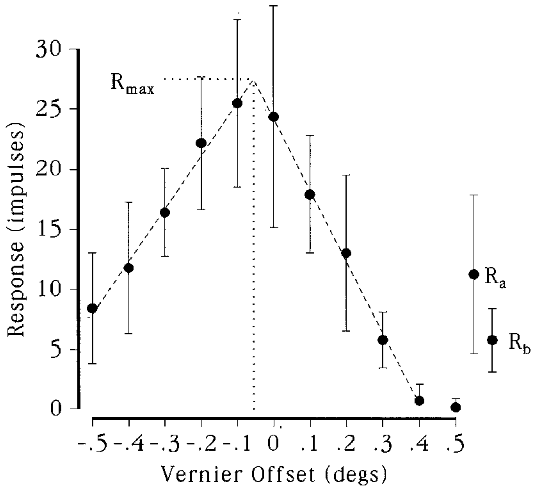

Fig. 1 The method of calculating vernier tuning ($V_{0.5}$) from a graph of responses elicited at different vernier offsets. *Filled circles* show the response (impulses per presentation) minus spontaneous activity, averaged over 16 presentations of each stimulus condition; *error bars* show the standard deviation of the responses; R_a and R_b are the responses to each bar presented in isolation; the *dashed line* is a triangle function fit to the data by a least-squares fit procedure (the response at 0.5° was omitted for this purpose). A weighted mean of the absolute values of the slopes of the two arms of the triangle was calculated, the weights being proportional to the horizontal length of each arm. This slope value, in impulses per degree, was then used for calculation of $V_{0.5}$ (Eq.1), with R_{max} given by the height of the triangle at its apex. H (Eq. 2) was calculated from the values of R_{max}, R_a and R_b

percentage reduction in response caused by an offset of 0.5° is then given by the expression

$$V_{0.5} = 50 \cdot (\text{raw slope})/R_{max} \tag{1}$$

where R_{max} is the maximum response as estimated by the curve-fitting procedure, i.e. the value of the inverted V function at the point where the two arms meet. This maximum generally occurred at offsets within $\pm 0.1°$ of alignment. As reported previously, the position of the maximum is a sensitive function of the overall orientation of the stimulus (Swindale and Cynader 1986).

2. A measure of *length summation*, H, was defined as

$$H = 1-(R_a+R_b)/R_{max} \tag{2}$$

where R_a and R_b are the responses to each bar presented individually (moving along its normal trajectory) and R_{max} is the maximum response elicited by the two bars moving at, or close to, alignment. H has a value of zero when the response is linearly related to bar length, i.e. $R_{max} = R_a+R_b$; its maximum value is 1, in which case R_a and R_b are both zero and the cell behaves like an "and" gate; and a value of -1 means the cell behaves like an "or" gate, since the response to both bars is the same as to either bar alone. H and $V_{0.5}$ are positively correlated in normal animals (Swindale and Cynader 1989).

3. *Orientation tuning* was measured by fitting a Gaussian function to a graph of response (less any spontaneous activity) versus stimulus orientation; tuning width was then defined as twice the standard deviation (2σ) of the Gaussian function.

4. *Receptive field size* was measured as twice the standard deviation of the best-fitting Gaussian to the response profile. The units along the x-axis, which are in time, were first converted to spatial coordinates by multiplying them by the velocity of the stimulus. The profiles used included both the responses to moving vernier stimuli in the aligned condition and the responses (i.e. the sum of both on and off responses) obtained to stationary flashed stimuli. This procedure was only attempted if the response profile was unimodal.

5. *Receptive field type.* During the initial experiments on bilaterally amblyopic cats it was noted that many units were hard to classify as simple or complex. In order to quantify this, a measure that would correspond to the simple/complex classification was devised. This classification normally depends on the degree of spatial overlap between regions of on and off responsiveness (if the regions overlap significantly the cell is complex and if they do not, the cell is simple). The amount of overlap (C/S) was calculated from a stationary line-weighting function, using the following normalised correlation measure:

$$\mathrm{C/S} = \Sigma(R^+_{x_i} \cdot R^-_{x_i})/\{\Sigma(R^{+2}_{x_i}) \cdot \Sigma(R^{-2}_{x_i})\}^{1/2} \tag{3}$$

where $R^+_{x_i}$ is the on response at position x_i in the receptive field, $R^-_{x_i}$ is the off response, and the summation is taken over the set ($i = 1, n$) of receptive field positions from which $R^+_{x_i}$ and $R^-_{x_i}$ are obtained. If there is no overlap between $R^+_{x_i}$ and $R^-_{x_i}$ (i.e. $R^+_{x_i}=0$ wherever $R^-_{x_i}>0$, and vice versa) then $\mathrm{C/S}=0$, whereas if $R^+_{x_i}$ and $R^-_{x_i}$ are perfectly correlated (i.e. if $R^+_{x_i} = kR^-_{x_i}$ for all i, where k is a constant) then $\mathrm{C/S} = 1$. (Note that C/S cannot be greater than 1, although negative values are possible if inhibitory responses occur, i.e. if $R_{x_i}<0$ for some values of x_i). One would therefore expect complex cells to have C/S values close to 1, and simple cells to have values close to zero. If the simple/complex classification is a real dichotomy then a histogram of C/S values should be bimodal.

6. The relative strength of on and off *flash responses* was calculated from the Michælson contrast formula:

$$(\Sigma R^+_{x_i} - \Sigma R^-_{x_i})/(\Sigma R^+_{x_i} + \Sigma R^-_{x_i}) \tag{4}$$

where, as above, the summation is over the set of receptive field positions, x_i, from which flash responses were obtained.

7. A number of *temporal properties* of the responses to flashed stimuli were measured. These included (a) latency between the onset or offset of a flash stimulus, and the beginning of a response; (b) the interval between the beginning of a response and the peak (time to peak); and (c) the time constant of the decay following the peak. Flash response histograms were compiled using narrow bin widths (3–8 ms) and judgements of the positions of the initial and peak responses were made by eye. Decay time constants were measured by fitting an exponential function to a 500-ms portion of the response histogram, beginning at the peak of the on or the off response. Spontaneous activity was subtracted from the mean response before doing this. The exponential function gave a good fit in the majority of cases, but when the fit seemed inadequate the data were rejected.

A number of the measurement values (e.g. receptive field size) yielded distributions that were skewed towards larger values on a linear axis, but had an approximately normal distribution after log transformation. In such cases (indicated by asterisks in Table 2) statistical tests were done using the means and standard deviations derived from the logarithm of each data value. The mean derived in this way is, after transformation back into the original measurement unit, the geometric mean of the sample, i.e. the nth root of the product of n data values, identical to $\exp[(1/n)\, \Sigma \log_e(x_i)]$. The limits of the distribution expressed by the standard deviation σ are found by dividing (lower limit) and multiplying (upper limit) the mean by σ.

The statistical significance levels of the differences between the data from normal and amblyopic animals were derived from a variant of Student's t-test which corrects for the effects of unequal population variances (Fisher-Behrens).

Results

Sensitivity to vernier offset

Vernier sensitivity, expressed as the percentage reduction in response caused by an offset of 0.5°, was lower in the amblyopic animals (Fig. 2a, c), and, although the difference in means was not large (31% in the amblyopes compared with 46% in the normals) it is statistically significant ($P < 1\%$). When tuning was expressed in impulses per degree of vernier (i/deg; offset Fig. 2d), the difference was somewhat larger (a mean of 13.1 i/deg for the amblyopes compared with 24.5 i/deg for the normals), and the difference was also significant ($P < 1\%$). It may be significant that no cell recorded from an amblyopic cat had a tuning slope greater than 65 i/deg, whereas eight cells from normal animals (11% of the total) had slopes greater than this. Table 2 summarizes the differences between the normal and experimental groups of animals obtained from analyses of vernier tuning data. The comparison of response properties in the two groups is unlikely to be confounded by the choices of stimulus length and width, as the values used in the two groups were similar (Table 2). Nor, within each sample, was any correlation between bar width, or length, and vernier tuning evident.

Length summation

Length summation H (Eq. 2), which is a measure of the net facilitation in response caused by presenting two aligned bars rather than one, is correlated with vernier tuning slope in normal animals (Swindale and Cynader 1989) and a similar correlation was also present in the data from the amblyopes (Fig. 2a). Values of H were lower overall in the amblyopes (Fig. 2b), but this difference was not statistically significant (Table 2).

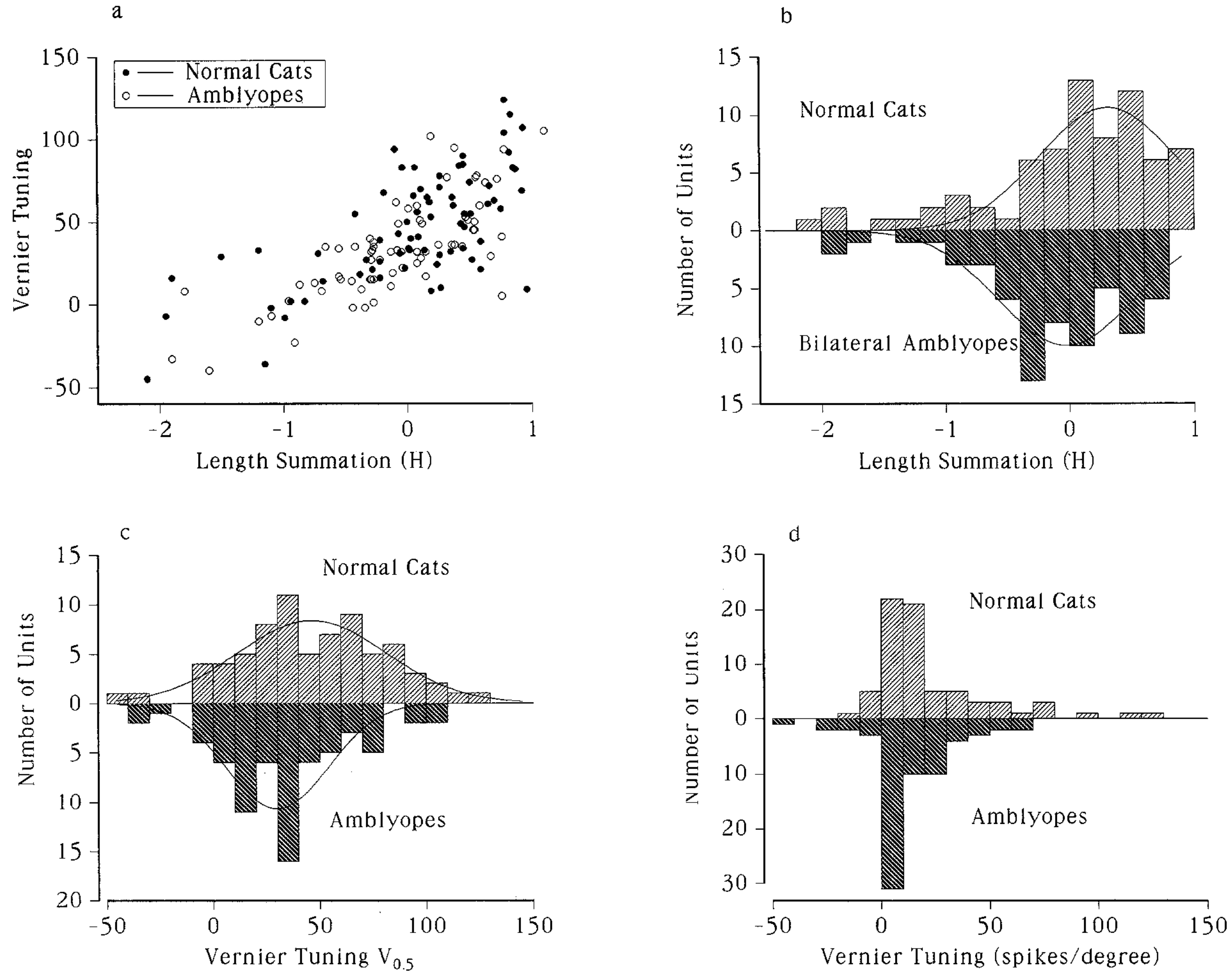

Fig. 2a–d Summary of vernier tuning and length summation data for 73 units from normal cats and 70 units from bilaterally amblyopic cats. See Table 2 for further quantification of the differences between the two groups. **a** A graph of vernier tuning ($V_{0.5}$) against length summation (H) for units from normal cats (*filled circles*) and units recorded from bilaterally amblyopic cats (*open circles*); each point is the value for one unit. **b** Histograms showing the distributions of the length summation (H) values measured in normal (*upper bars*) and amblyopic cats (*lower bars*); the *continuous lines* are Gaussian functions fitted to the histogram values. **c** Histograms showing the distributions of the vernier tuning values ($V_{0.5}$) measured in normal (*upper bars*) and amblyopic cats (*lower bars*); the *continuous lines* are Gaussian functions fit to the histogram values. **d** Histograms of the raw vernier slope values (impulses per degree of vernier offset) measured in normal and amblyopic cats

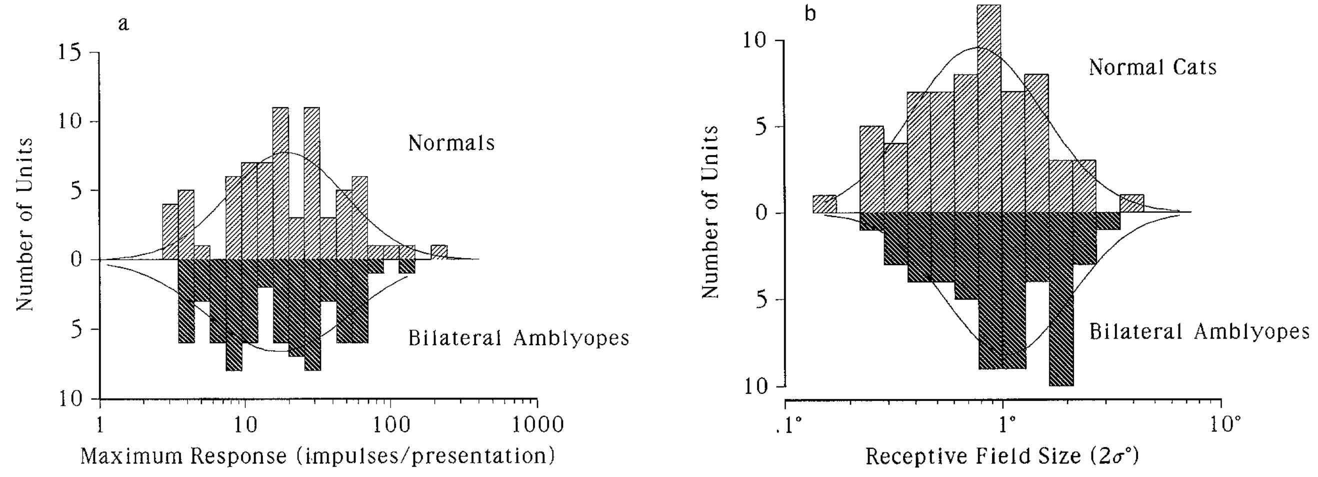

Fig. 3a The distribution of responsiveness (R_{max}) in the samples of units recorded from normal (*upper bars*) and bilaterally amblyopic (*lower bars*) cats. The method of determining R_{max} values is described in Fig. 1. The distributions are approximated by Gaussian functions (*continuous lines*) when graphed on a logarithmic scale as done here. **b** The distributions of receptive field sizes in the two groups of animals. Field size was measured as twice the standard deviation (2σ °) of a Gaussian function fit to a graph of the response to a moving bar stimulus, expressed as a function of position in space. As with responsiveness, the distributions were better approximated by Gaussian functions when a logarithmic transform of field sizes was done before binning the values

Responsiveness and receptive field size

Receptive field sizes, measured from the response profiles to moving stimuli, were larger in the amblyopes (Fig. 3b), by about 24%, and this difference was significant ($P < 5\%$). Field sizes were unlikely to have been affected by a difference in the overall responsiveness of cells in the two groups (a decrease in responsiveness might mask the fringes of a field) since, overall, response magnitudes were similar in both groups of animals (Fig. 3a). Receptive field sizes measured from the responses to flashed stimuli correlated well with the size measured from the response to a moving stimulus, although sizes for flashed stimuli tended to be larger than those for moving stimuli. Field sizes measured in this way were also significantly larger, by about 30%, in the amblyopes (Table 2). This was despite an overall decrease in the size of the on and off responses to flashed stimuli (Table 2), which might otherwise have been expected to reduce field sizes.

Receptive field organization

The measure of receptive field "complexity", C/S (Eq. 3), showed, as expected, a bimodal distribution in normal animals (Fig. 4a). The data suggested that C/S values are an objective means of classifying cells as simple (if $C/S < 0.5$) or complex (if $C/S > 0.5$). Using this criterion in normal animals, the C/S value always agreed with the classification made on other grounds. The bimodal distribution of C/S values, however, was less apparent, if at all, in the amblyopic animals (Fig. 4a). Correspondingly, many cells could not be classified as simple or complex on the basis of qualitative testing. The relatively weaker flash responses (see below) in the amblyopes also probably contributed to this difficulty. Two examples of cells with intermediate segregation of regions of on or off responsiveness are shown in Fig. 4c, d (their C/S values were 0.76 and 0.65, respectively).

Flash responses

Table 2 and Fig. 4b show that the balance between the magnitudes of on and off responses (on/off) did not differ significantly between the normal and amblyopic animals, although in both groups on responses tended to be slightly larger than off responses. The absolute values of on and off responses to flashed stimuli, measured in the most sensitive receptive field location for each, were lower in the amblyopes (9.6 spikes) than in the controls (15.6 spikes), and these differences were statistically significant (Table 2).

Temporal responses

Response latencies to visual stimulation did not differ in the two groups (Table 2). Time to peak on response was the same, but time to peak off response was significantly greater in the amblyopes. Both on and off responses of cells in the amblyopes were significantly more sustained than in normals. The decay time constant of the on response to flashed stimuli averaged 153 ms in normal animals and was 344 ms in the amblyopes. For off responses the values were 80 and 138 ms respectively. These differences were statistically significant ($P \ll 1\%$) and were the largest found in the study.

Response variance

A possible reason for degraded visual performance in the amblyopic cats might be a decreased signal-to-noise

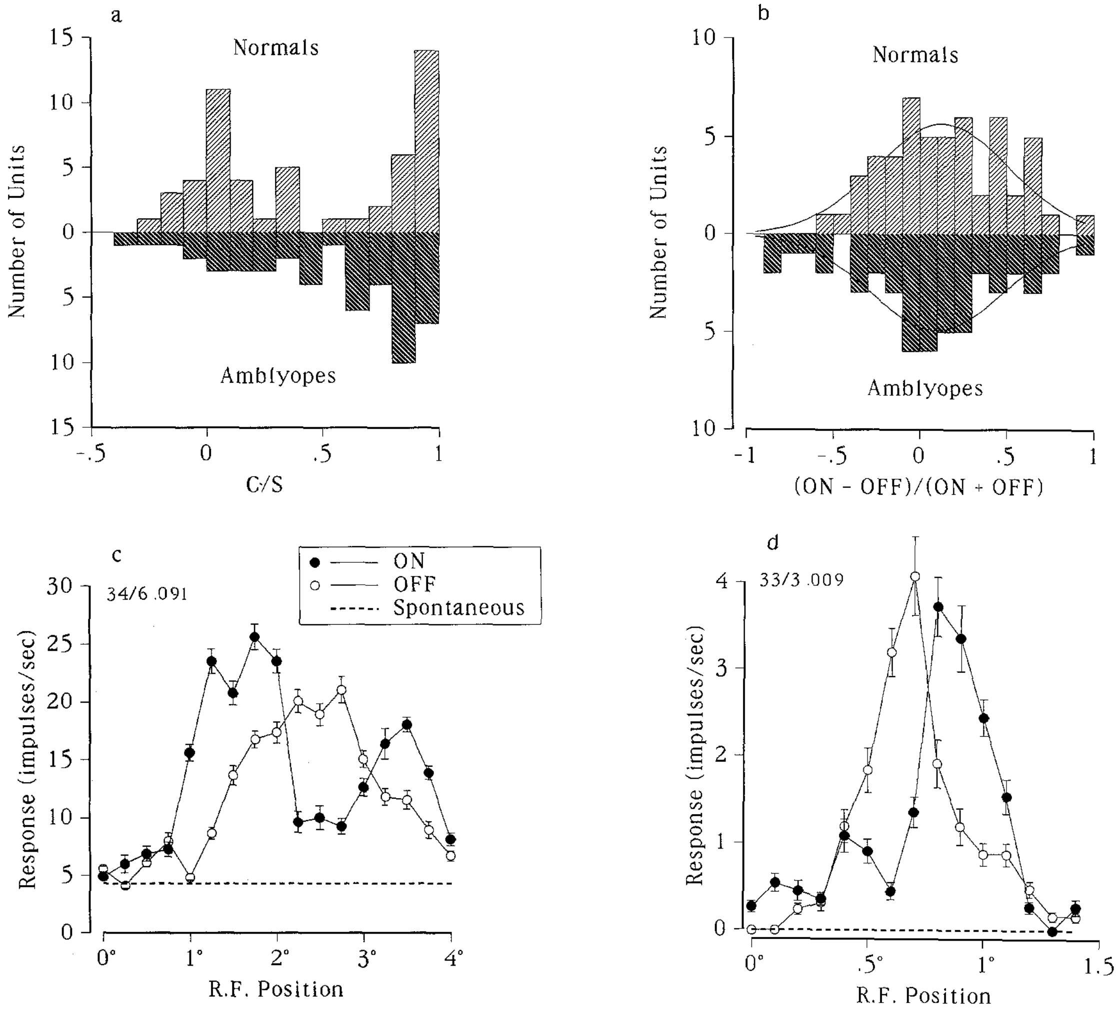

Fig. 4a–d Comparison of line-weighting data obtained from the on and off responses to stationary flashed bright bars in normal and amblyopic cats. **a** The distribution of overlap (*C/S*) values (Eq. 3) in normal cats (*upper bars*) and amblyopic cats (*lower bars*); cells with C/S values greater than 0.5 are complex, and cells with values less than 0.5 are simple. The distribution of values is bimodal in normal cats, and less so in the amblyopes. **b** The relative amplitudes of on and off responses in the two groups of animals (Eq. 4). The value graphed on the *x*-axis, (on − off)/(on + off), is zero if on and off responses are equally strong, is 1 if there was no off response, and equals −1 if there was no on response. The distributions were similar in normal and amblyopic cats. **c–d** Graphs of the distributions of on (*filled circles*) and off responsiveness (*open circles*) as a function of position in the receptive field (*R.F.*) measured in two units recorded from bilaterally amblyopic cats. *Error bars* show the standard error in the mean of each response. The cells show overlap between regions of on and off responsiveness that is intermediate between that found in simple and complex cells. The C/S value for the cell in **c** was 0.76 and in **d** it was 0.65

ratio in the responses of their cortical neurons. We therefore analysed response variance in the two groups of animals. Response variance is known to increase as firing rate increases (Tolhurst et al. 1981, 1983) and so we compared the dependence between the two properties in the two groups of animals (Fig. 5). Estimates of means and the corresponding variances were obtained from the responses (i.e. the total spike count on a single presentation) to 16 or more presentations of an identical stimulus (e.g. a given vernier offset). This was done for a total of 572 different stimulus conditions in four normal cats, and 961 conditions in six amblyopic cats. As in previous studies, the relation between mean firing rate and variance was well described by a power-law function:

$$v = \alpha r^{\beta} \qquad (5)$$

where v is the variance, r is the mean response and α and β are constants. Linear regression on log-log plots (Fig. 5a, b) of all the responses yielded values for $\alpha = 1.91$ and 2.3, and values of $\beta = 1.3$ and 1.09 for normals and amblyopes, respectively. These values are similar to those obtained by Tolhurst et al. (1983), who found values of α between 1.76 and 2.80, and $\beta = 1.09$ for 22 cells in normal cats and monkeys. Visual inspection of the graphs suggests that the differences between the two groups are not significant.

Other properties

A number of other properties did not appear to differ between the two groups: maximum responsiveness

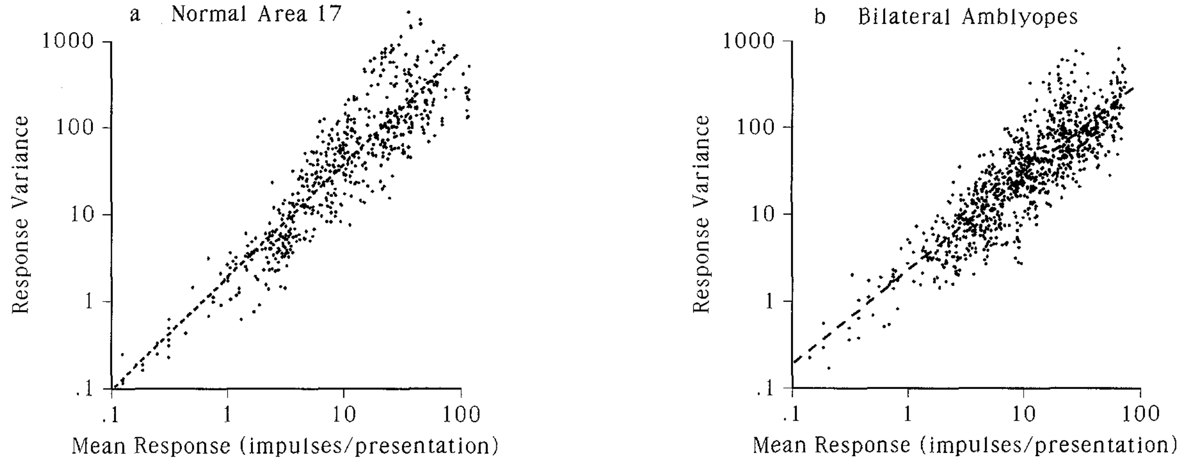

Fig. 5a, b The relation between mean response, measured for 16 or more presentations of the same stimulus to a cell over a period of up to 30 min, and the variance in the response. The response is the total number of impulses recorded during the interval in which the stimulus was presented (typically 1–4 s). The data are all from vernier tuning experiments. Each experiment (e.g. as illustrated in Fig. 1) contributed 13 points to the graph, since 13 different stimuli were used in the experiment. The data are graphed on log-log plots and the *dashed lines* are obtained by linear regression to the data values (Eq. 5). The regression yields the equation $y = 1.91x^{1.3}$ for normal animals (**a**) and $y = 2.3x^{1.1}$ for the amblyopes (**b**)

($R_{\max}$; Fig. 3a) and spontaneous activity (Table 2) were similar, and, surprisingly, orientation tuning (Table 2) was no broader in the amblyopes, despite the fact that there is a strong correlation between the sharpness of orientation tuning, and vernier sensitivity (Swindale and Cynader 1989, and unpublished observations). This may be because the sample of orientation tuning curves from normal animals was too small ($n = 31$) to reveal a difference, or because there is enough independent variation of the two properties for one to differ and not the other.

Discussion

This study has identified a number of possible abnormalities in the receptive field properties of neurons in area 17 of bilaterally amblyopic cats. These include:(a) a reduction in sensitivity to vernier offset; (b) an increase in receptive field size; (c) changes in the amount of over-

Table 2 Comparison of receptive field properties in normal and bilaterally amblyopic cats. (*i* impulses, R_{max} maximum response estimated by curve-fitting, *RFS* receptive field size)

Response property[a]	Units in normals			Units in amblyopes			
	Mean	±SD	N	Mean	±SD	N	Significance (%)[b]
Vernier tuning ($V_{0.5}$)	45.6	33.9	73	31.1	33.1	70	<1
Vernier slope (i/deg)	24.5	31.1	73	13.1	19.3	70	<1
Length summation (*H*)	−0.014	0.8	73	−0.18	0.92	70	n.s.
$R_{\max}$ (i/presentation)	18.5	2.6	73	17.5	2.6	70	n.s.
RFS (moving)	0.76°*	1.9°	66	0.97°*	1.9°	53	<5
Spontaneous	1.96	4.46	72	1.7	2.8	70	n.s.
Stimulus width	0.22°	0.08°	68	0.24°	0.06°	67	n.s.
Stimulus length	1.6°	0.6°	68	1.7°	0.6°	67	n.s.
Orientation bandwidth (2σ °)	57°	33°	31	53°	35°	61	n.s.
(on − off)/(on + off)	0.15	0.34	53	0.07	0.42	49	n.s.
$\text{on}_{\max}$ (impulses)	19.1*	2.6	54	10.6*	3.2	51	<1
$\text{off}_{\max}$ (impulses)	12.8*	3.2	54	8.8*	2.5	51	n.s.
RFS (stationary)	1.1°*	1.6°	47	1.4°*	1.7°	44	<5
on latency (ms)	54*	1.2	57	55*	1.3	44	n.s.
off latency (ms)	66*	1.3	47	70*	1.5	37	n.s.
Time to peak on (ms)	28*	2.7*	57	29*	2.6	44	n.s.
Time to peak off (ms)	23*	2.5	47	49*	3.3	37	<1
on decay (ms)	153*	2.7	59	344*	2.7	40	<1
off decay (ms)	80*	2.2	51	138*	2.1	35	<1

[a] In cases where distributions seemed more closely normal following logarithmic transformation of the data values, tests were done using means and SDs derived from the logarithm of the data values. Where indicated by the asterisks, these means and SDs have been transformed back again (by taking the antilogs) into the normal measurement units. SDs have to be interpreted as ratios, i.e. limits are to be estimated by multiplying or dividing the means by the SDs (see Materials and methods)

[b] Significance levels are derived from *t*-tests (Fisher-Behrens, assuming unequal population variances)

lap between on and off areas in simple and complex cells, and (d) smaller but more sustained responses to flashed stimuli. Other properties seemed normal in the amblyopes, including: (a) responsiveness to moving stimuli; (b) response variance for a given mean firing rate; (c) spontaneous activity; (d) sharpness of orientation tuning; and (e) response latency to flashed stimuli.

Sampling strategy

Possible artefactual explanations for the differences would include a biased sampling strategy, e.g. a tendency to select or reject units for further quantitative study on the basis of poor responsiveness, poor orientation tuning, a preliminary assessment of vernier sensitivity or some other property which might correlate with it. It is hard to prove that sampling strategies in single-unit studies are not biased in some way or other, but a number of points can be made against this explanation of our results. One is that the overall responsiveness of the units recorded from in the amblyopes did not differ from that of the normals. This suggests either that the sampling was not biased towards inclusion of poorly responsive units in the amblyopes or that units in the amblyopes were, on average, more responsive than in normals, which seems unlikely. Another point is that the primary objective of the experimenter during the recording sessions was to gain data from as many units a possible. In almost every case, once a cell showing some form of responsiveness to a visual stimulus was encountered, a vernier tuning experiment was done on it. Other aspects of the experimental procedures, such as the position and angle of the cortical penetration, the way in which the electrodes were made and their recording characteristics did not obviously differ between the two groups. Although a different visual stimulation system was used for two of the amblyopic animals, with a lower mean luminance (though similar contrast levels) than the optic bench system used in the earlier experiments, two of the normal animals were also experimented on with the same display. There was no indication that the difference in brightness levels had any effect on the results. Other stimulus parameters chosen by the experimenter, bar length, width and velocity, did not differ significantly between the two groups (Table 2).

A sampling bias towards units with larger receptive field eccentricities in the amblyopes might account for some of the differences observed between the two groups of animals. However there are no a priori reasons for supposing that the mean eccentricities would have differed significantly in the two groups, since craniotomies were made in similar locations in all animals. Measurements of eccentricity (total distance from the area centralis) in normal animals had a mean value of 5.6 ±2.6° ($n = 87$). Similar measurements were made for a small number of units in the amblyopic animals, and these values fell into the same range. We are confident that, at the very least, there must have been a substantial overlap in the distributions of eccentricities in the two samples of cells and that the majority, if not all, of the units in our sample had fields within 10° of the area centralis. In addition, the correlations between receptive field size and $V_{0.5}$ with eccentricity in area 17 in normal cats were small over the range of eccentricities encountered. Linear regression on plots of $V_{0.5}$ against eccentricity showed a correlation of -0.09 and a slope of $-0.6/°$ in normal cats. A difference in mean eccentricities of 5° in the two samples would account for a difference of 3.0 in the values of $V_{0.5}$ between the two samples, which is less than the difference that was observed (14.5). Linear regression on plots of receptive field size against eccentricity in normal animals showed a slope of 0.048% visual eccentricity. A difference in mean eccentricities of 5° would account for a difference in field sizes of 0.24°, which is similar to the difference observed. The differences between the two groups cannot all be explained in this way: although a sampling bias towards units with more eccentric receptive fields in the amblyopic cats might account for the larger receptive field sizes and some of the decrease in $V_{0.5}$ it would not explain the more sluggish temporal properties of the cells, since units tend to become more, rather than less, transient in their responses to flashed stimuli with increasing distance from the area centralis. Conversely, a bias towards smaller eccentricities in the amblyopic animals might account for the difference in temporal properties, but would imply the existence of larger changes in vernier tuning and field sizes than the ones measured.

A possible sampling bias exists in the case of units from which line-weighting responses were obtained, since these experiments were not done on every cell encountered in some animals, particularly those on the earlier normal animals in the series. As the reasons for deciding to obtain a line-weighting response on any particular cell were quite varied it is hard to say what systematic bias might have been introduced. An obvious possibility is that there would have been a tendency to do such an experiment on cells which proved hard to classify as simple or complex on the basis of manual testing, i.e. cells with poor flash responses or with a less distinct segregation of on and off areas of responsiveness. This bias, however, would tend to reduce rather than accentuate the differences between the two groups.

Positional acuity defects

Our results suggest a possible physiological correlate of the reduced sensitivity to vernier offset shown in behavioural tests of bilaterally amblyopic cats. Neuronal vernier acuity, expressed as the percentage reduction in firing rate caused by the presence of a 0.5° offset in a bar stimulus, was reduced from a mean of 46% in normal cats to 31% in the amblyopes. Though this reduction is not large in absolute terms it is statistically very significant. When vernier tuning is expressed as a raw slope, i.e. in impulses per degree of offset (which thus does not take overall firing rate into account), the reduction in acuities in the amblyopic cats is also significant, mean slope values being about half their value in the normal cats. Whether these differences are large enough to explain the behavioural deficits is another matter. A straightforward interpretation of our physiological results suggests that the behavioural vernier thresholds in the amblyopes might be roughly doubled. However the impairment in vernier acuity measured behaviourally is much greater than this and thresholds may increase by a factor of 10 or more (Table 1; Murphy and Mitchell 1991). This point can be further illustrated by considering the vernier tuning curve from the cell shown in Fig. 1, which is from an animal (C479) whose vernier acuity was estimated by behavioural testing to be no better than 15 min (0.25°) of arc. Figure 1 suggests that this cell could discriminate (by a statistically reliable change in its firing rate) an offset of this magnitude or less. In comparison, no cell has ever been found in a normal animal with an acuity level equal to (much less better than) the normal behavioural vernier threshold of 1–2 min of arc (Murphy and Mitchell 1991). The presence of cells in area 17 of amblyopic cats with acuities *better* than can be measured behaviourally suggests that higher levels of the visual pathways are unable to make use of the information relayed by lower cortical levels and that the amblyopia may reside within these centers, as well as within area 17.

In addition to a loss of neuronal vernier sensitivity, our results suggest some other sources of reduced positional acuity in amblyopia. An incomplete degree of segregation of on and off areas in simple cells, as found here (Fig. 4) might lead to a loss of ability to localise edges accurately. Receptive field widths also increased on average by about 28% and this might contribute to a loss of acuity, though arguably not enough to explain the behavioural data. Other workers have made similar findings in area 17 of strabismic cats: for example Berman and Murphy (1982) reported an increase in the field sizes of complex cells driven by the strabismic eye and Chino et al. (1983) reported a near doubling of field sizes in both eyes in kittens reared with convergent strabismus. This latter finding raises the possibility that there may be defects in the normal eyes of strabismic subjects. Such abnormalities have in fact been reported (Kandell et al. 1977; Kelly et al. 1984; Levi and Klein 1985).

Temporal properties

Although response latencies were normal in the visual cortex of the amblyopic animals, responses to flashed stimuli were more sluggish overall, with smaller peak responses to flashes, longer times between the onset and the peak of the off response, and much longer decay time constants following the onset or offset of a stimulus. Although responses to sinusoidal temporal modulations were not studied, these findings suggest that temporal frequency tuning functions would have shown a loss of sensitivity at high frequencies and a corresponding reduction in temporal resolution. In this respect our results agree with those of Chino et al. (1983), who found a loss of temporal resolution in area 17 neurons in strabismic cats. There have been no behavioural studies of temporal resolution in any animal model of amblyopia, possibly because of the lack of evidence that human amblyopes show consistent deficits in temporal contrast sensitivity (see Bradley and Freeman 1985). However, our results, and those of Chino et al. (1983), suggest that a reexamination of this issue might be worthwhile.

Correlations with rearing condition and severity of behavioural amblyopia

The various rearing conditions (Table 1) used to produce the amblyopia differed in detail, although they were broadly similar in that each animal was initially monocularly deprived, and this was followed by forced use of the deprived eye. The effects of these procedures, judged behaviourally, were similar: all the animals showed a moderate reduction in spatial resolution, from about 8 cycles/degree in normal animals to around 2–4 cycles/degree, and a much larger (ten-fold or more) increase in the threshold for detecting vernier offset. All of the animals can be considered to have been severely visually impaired, although the severity varied somewhat; e.g. C303 and C328 were probably the most severely amblyopic, and C479 the least. While the number of units recorded in individual animals was small, our data give an indication of a correlation between behavioural and physiological measures, since mean values of $V_{0.5}$ were smallest ($V_{0.5} = 16.3$, $n = 16$) in the two animals which were the most severely amblyopic (C303 and C328) and were largest ($V_{0.5} = 52$, $n = 9$) in the least severely affected animal (C479).

Nature of the defects

Many of our findings are consistent with the "scrambling" hypothesis of amblyopia and suggest that order in the retinal topography *within* individual receptive fields is disrupted. Local disorder in the mapping of geniculate inputs to the cortex would explain the less distinct segregation of on and off areas within simple cell receptive fields, as well as the increases in receptive field size and loss of sensitivity to vernier offset. This loss of accurate topography might come about as geniculate afferents alternately retract from, and expand into, regions of layer IV during the periods of initial monocular deprivation and subsequent reversal. As yet, there is no evidence that retino-cortical topography is disrupted on a larger scale, since the topography of the retinal projection within area 18 of bilaterally amblyopic cats (reared under conditions similar to those used in the present study) seems to be as accurate as in normal animals (Cynader et al. 1988).

The loss of temporal responsiveness in cortical neurons is consistent with results showing that the Y-cell pathway from retina to cortex, which has a higher temporal sensitivity than the X-cell pathway, is more severely affected by visual deprivation (see review by Sherman and Spear 1982). Other studies have shown, however (Blakemore and Vital-Durand 1979; Shapley and So 1980; Derrington and Hawken 1981), that the spatial and temporal properties of lateral geniculate nucleus (LGN) neurons are unaffected by quite severe forms of visual deprivation in young animals. These imply that both the retina and the LGN function normally in amblyopia (changes in LGN cell size notwithstanding) and that the defects must therefore be cortical in origin. Perhaps the most unambiguous evidence for an effect of visual deprivation in the LGN comes from studies showing that Cat-301 antigen, which is present only on Y-cells, has a reduced expression in monocularly deprived geniculate laminae (Sur et al. 1988). This expression remains reduced in the initially deprived LGN laminae after reverse suturing (Kind et al. 1991). It is quite likely that Cat-301 expression was also reduced in the animals studied here and, by implication, Y-cell function may have been compromised in some way. Overall, however, the abnormalities found in the present study, including an increase in receptive field size, loss of vernier sensitivity and losses of temporal responsiveness seem much more likely to be a consequence of changes in the visual cortex than in lower levels of the visual pathways. However, given the small size of most of these changes and the apparently normal properties of cortical surface topography in area 18 in other bilaterally amblyopic animals (Cynader et al. 1988), it is possible that the major defect is in some other cortical area, or is a consequence of distributed small changes at many levels. If this is true, then a simple physiological explanation of amblyopia may be hard to come by. The present study needs to be extended to include examination of physiological properties such as direction selectivity, spatial and temporal frequency selectivity, contrast sensitivity and binocular interactions. It remains to be proven, nevertheless, that the major neural deficit in amblyopia resides in primary visual cortex.

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