

Laminar differences in plasticity in area 17 following retinal lesions in kittens or adult cats

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Abstract

Circumscribed retinal lesions in adult cats result in a reorganization of circuitry in area 17 such that neurons in the lesion projection zone (LPZ) can now be activated, not from their original receptive fields (RFs) but from regions of normal retina adjacent to the lesion ('ectopic' RFs). We have studied this phenomenon further by making circumscribed monocular retinal lesions in 8-week-old kittens and recording responses to visual stimuli of neurons in the LPZ of area 17 when these cats reached adulthood. These responses have been compared with those in adult-lesioned cats either of relatively short postlesion survival (2–24 weeks) or long postlesion survival (3.5–4.5 years). In both kitten-lesioned and adult-lesioned animals most LPZ neurons recorded from the supragranular layers (II and III) not only exhibited new ectopic RFs when stimuli were presented via the lesioned eye but the RF properties (e.g. the sizes of excitatory RFs, orientation and direction selectivities, velocity preferences and upper cut-off velocities) were often indistinguishable from those seen when stimuli were presented via the nonlesioned eye. Similarly, in both kitten-lesioned and adult-lesioned animals, most LPZ neurons recorded from the granular and infragranular layers (IV, V, VI), like those recorded from the supragranular layers, were binocular. However, in adult-lesioned but not in kitten-lesioned animals, the responses and the upper cut-off velocities of LPZ cells recorded from the granular and infragranular layers to stimuli presented via ectopic RFs tended to be, respectively, substantially weaker and lower than those for stimuli presented via the nonlesioned eye. The age-related laminar differences in reorganizational plasticity of cat striate cortex correlate with the lamino-temporal pattern of distribution of *N*-methyl-D-aspartate glutamate receptors in striate cortex.

Introduction

It has been shown (for reviews see Chino, 1995, 1997; Dreher *et al.*, 2001) that damage to a circumscribed part of the retina of adult cats or macaque monkeys results in reorganization of the visuotopic (retinotopic) map in the primary visual cortex (area 17, striate cortex, area V1). Thus, neurons in the part of area 17 which normally contains the representation of the lesioned part of the retina, the lesion projection zone (LPZ), gain new receptive fields (RFs), which are topographically displaced ('ectopic') to the normal retina in the vicinity of the lesion. However, although in normal cats most area 17 neurons are binocular it has been reported that in adult-lesioned cats the ectopic RFs of LPZ neurons became apparent only when the other (nonlesioned) eye was enucleated (Kaas *et al.*, 1990; Chino *et al.*, 1992).

On the other hand, consistent with earlier studies from our laboratories (see for review Dreher *et al.*, 2001), we have recently shown that: (i) most neurons recorded in the LPZ of area 17 of cats in which monocular retinal lesions were made in adulthood were binocular and that their RFs revealed by stimuli presented via the lesioned eye were displaced to the vicinity of the lesion; and (ii) the RF properties of binocular cells recorded from the LPZ when the cells were stimulated via the lesioned eye were largely indistinguishable from those when the cells were stimulated via the normal nonlesioned eye (Calford

et al., 2000). However, based on direct within-cell comparison, the responses of binocular LPZ cells to stimuli presented via the lesioned eye tended to be substantially weaker and their upper cut-off velocities lower (Calford *et al.*, 2000).

In all mammals studied so far, manipulation of the visual environment of the animal in the early postnatal 'critical' period results in clear functional and morphological changes in the visual cortices (see for reviews Movshon & Van Sluyters, 1981; Sherman & Spear, 1982; Wiesel, 1982; Gordon, 1997). In the present experiments we attempted to determine whether making a monocular retinal lesion in kittens had different effects on the RF properties of cells in the LPZ of area 17 from those obtained when lesions were made in adults. The lesions were made in 8-week-old kittens, that is, in the middle of the critical period when the visual system is extremely sensitive to the environmental manipulation: see Hubel & Wiesel (1970); Olson & Freeman (1980). The RF properties of LPZ neurons in area 17 were tested when the animals reached adulthood. Indeed, our preliminary data (Burke *et al.*, 2000; Dreher *et al.*, 2000, 2001) indicated greater reorganizational plasticity in kittens. Consistent with this, Chino and colleagues reported recently (Chino *et al.*, 2001; Matsuura *et al.*, 2002) that neurons in the LPZ in area 17 of kitten-lesioned adult cats are binocular. In the present study, in order to control for the possible effect of the length of postlesion recovery period *per se* we also examined RF properties of LPZ neurons in area 17 of adult-lesioned cats which were allowed 3.5–4.5 years postlesion recovery period.

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Recording from the LPZ of kitten-lesioned animals, we have noticed significant laminar differences (supragranular vs. granular–infragranular layers) in relative strengths of the responses to stimuli presented via the lesioned and those presented via the nonlesioned eyes. When we re-analysed our data concerning LPZ cells recorded from area 17 of adult-lesioned cats (Calford *et al.*, 2000), similar laminar differences also became apparent (see Burke *et al.*, 2002).

Materials and methods

Retinal lesions and animal preparation

Experimental procedures and husbandry followed the guidelines of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and were approved by the Animal Care Ethics Committees at the University of Sydney and the Australian National University.

Discrete retinal lesions of ≈ 6 – 12° diameter were placed in the left eye of 8-week-old kittens or adult (11–14 months old) cats anaesthetized with ketamine (40 mg/kg, i.m.; Ketalar) and xylazine (4 mg/kg, i.m.; Rompun). Lesions of all neural layers in the near-upper nasal region of the retina were produced with an argon-green laser focused to $\approx 300 \mu\text{m}$, at an intensity of 450–650 mW (for details of delivery system see Schmid *et al.*, 1996). Lesions were produced by continuous sweeping of the spot of laser light across the chosen region, each traverse lasting ≈ 3 min. A few minutes after this procedure the lesioned part of the retina appeared uniformly white. No damage to retinal blood vessels within the lesioned part of the retina was apparent. After the lesioning procedure the kittens were returned to their mothers while adult cats recovered in a warm (27 °C) recovery box. No abnormal visual or behavioural traits were subsequently observed in any of the animals.

There were three groups of cats with monocular retinal lesions. One group consisted of five cats whose left retinas were lesioned when they were 8-week-old kittens and recording from area 17 then took place 28–68 weeks later. We call this group ‘kittens with long postlesion visual experience’ or the KL group. The second group consisted of three cats whose left retinas were lesioned in adulthood with cortical recording taking place 3.5–4.5 years later. We call this group ‘cats lesioned in adulthood with long postlesion visual experience’ or the AL group. The third group (a second control group described in one of our previous papers: Calford *et al.*, 2000) consisted of eight adult cats studied 2–24 weeks after a monocular retinal lesion was made. This group was designated ‘cats lesioned in adulthood with relatively short postlesion visual experience’ or the AS group. Finally, as an additional control we determined RF disparities (see below) of binocular area 17 neurons recorded in normal cats in one of our previous studies (Wang *et al.*, 2000).

In all three groups of cats with monocular retinal lesions, extracellular single-neuron recordings were made from the parts of area 17 corresponding to and surrounding the projection zone of the lesion. To reduce the possibility of brain oedema on the day preceding the experiment the animals were given dexamethasone phosphate (0.3 mg/kg, i.m.; Dexapent). During the experiment they were initially anaesthetized with ketamine (20 mg/kg, i.m) and injected i.m. with atropine sulphate (0.1 mg/kg, to reduce mucous secretion) and dexamethasone phosphate (0.3 mg/kg). Tracheal and cephalic vein cannulations were performed to allow artificial ventilation and infusion of paralyzing drugs. Eye movements were additionally minimized by bilateral sympathectomy.

During the recording session anaesthesia was maintained with a gaseous mixture of $\text{N}_2\text{O}:\text{O}_2$ (67:33%) and halothane (0.4–0.7%). Antibiotic (amoxicillin trihydrate, 75 mg), dexamethasone phosphate

(3 mg) and atropine sulphate (0.3 mg) were injected i.m. daily. Immobility was induced with i.v. injection of 40 mg of gallamine triethiodide in 1 mL of sodium lactate (Hartmann’s) solution and maintained with continuous injection of gallamine triethiodide (7.5 mg/kg/h i.v.) in a mixture of equal parts of 5% dextrose solution and Hartmann’s solution. Animals were artificially ventilated and body temperature was automatically maintained at $\approx 37.5^\circ\text{C}$ with an electric heating blanket. Expired CO_2 was continuously monitored and maintained at 3.7–4.0% by adjusting the rate and/or stroke volume of the pulmonary pump. The electroencephalogram and the heart rate were also monitored continuously: slow-wave synchronized activity and heart rate < 180 beats/minute were maintained by adjusting the halothane level in the gaseous mixture. Atropine sulphate (1–2 drops, 1%) to dilate the pupils and to block accommodation and phenylephrine hydrochloride (1–2 drops, 0.128%) to retract the nictitating membranes were also applied daily. Air-permeable zero-power contact lenses were used to protect the cornea, and artificial pupils (3 mm in diameter) were placed in front of each eye to reduce the amount of spherical aberration. If required (as assessed by streak retinoscopy) corrective lenses were used to focus the eyes on a tangent screen 57 cm away.

A fibre optic light source was used to monitor rarely occurring small eye movements by projecting the optic discs onto a tangent screen every few hours (Pettigrew *et al.*, 1979). The positions of the *areae centrales* were plotted by reference to the optic discs (Bishop *et al.*, 1962). Because all lesions were made in the upper retina, which contains the highly reflective *tapetum lucidum*, and destruction of the outer retinal layers (in addition to the inner layers) at the lesion site results in an absence of tapetal reflection from this region, the lesion boundaries were also easily plotted onto the tangent screen using this method.

Recording from area 17 and visual stimulation

For recordings from area 17 a plastic cylinder was mounted and glued around the craniotomy (Horsley–Clarke co-ordinates P3 to A5, and left 3 to right 5 from the midline) above the right visual cortex contralateral to the lesioned retina. A smaller dural opening was made and a stainless-steel microelectrode (9–11 M Ω ; FHC, Brunswick, ME, USA) was positioned just above the cortical surface, medially in the marginal gyrus ≈ 1 mm lateral to the sagittal sinus. The cylinder was filled with 4% agar gel and sealed with warm wax (melting point 40 °C). The microelectrode was advanced further along the medial aspect of the marginal gyrus with a hydraulic micromanipulator. Action potentials of single neurons were recorded extracellularly, conventionally amplified and then used to trigger standard pulses which were fed to a microcomputer for on-line analysis and data storage. The excitatory receptive fields, which from now on will be called RFs (minimum discharge fields; cf. Barlow *et al.*, 1967; Dreher *et al.*, 1980), were plotted with light slits from a hand-held projector and remapped with hand-held black bars. Cells were identified as simple (S-cells) or complex (C-cells) with optimally orientated stationary flashing light bars and/or with moving light and black bars. The cells were identified as simple if they had spatially separate ON and/or OFF discharge regions and/or their RFs revealed by moving stimuli brighter than the background did not overlap with those revealed by stimuli darker than the background (simple cells of Hubel & Wiesel, 1962, 1965 and Gilbert, 1977; cf. S cells and A cells of Henry, 1977). The cells were identified as complex if they had overlapping ON and OFF discharge regions in their RFs and/or their RFs as revealed by moving stimuli brighter than the background spatially overlapped with those revealed by stimuli darker than the background (complex cells of Hubel & Wiesel, 1962, 1965 and Gilbert, 1977; cf. C and B cells of

Henry, 1977). For the quantitative study of RFs, light slits with a luminance of 15 cd/m² against a background luminance of 0.9 cd/m², were projected from a slide projector onto the tangent screen via computer-controlled galvanic motors operating a dual mirror arrangement (cf. Dreher *et al.*, 1992; Calford *et al.*, 2000). Disparity of RFs was defined as the distance between the centers of the RFs of a binocular neuron when the *areae centrales* of left (lesioned) and right (nonlesioned) retinas were superimposed. Peristimulus time histograms (PSTHs) were constructed by summing the responses to 10–100 successive stimulus sweeps (number of sweeps related positively but not linearly to stimulus velocity) at each test condition. The responses were then smoothed using a Gaussian weighted average over five neighbouring bins.

Using elongated ($\geq 10^\circ$) light slits we determined optimal orientations and optimal velocities. The direction selectivity indices (DIs; %) for optimally orientated stimuli were calculated using the following formula:

$$DI = 100 \times (R_p - R_{np})/R_p$$

where R_p and R_{np} are, respectively, the peak discharge rates at the preferred and the nonpreferred directions along the axis perpendicular to the optimal orientation (cf. Burke *et al.*, 1992; Dreher *et al.*, 1992).

Localization of recording sites

Small electrolytic lesions (10 μ A for 20 s) were made at the end of each electrode track. At the end of the recording session the animal was deeply anaesthetized (120–200 mg of sodium pentobarbitone, i.v.) and perfused transcardially (with descending aorta clamped) with 700 mL of warm (37 °C) Hartmann's solution followed by 1200 mL of 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The electrode tracks were reconstructed from 50- μ m coronal sections stained for Nissl substance with Cresyl Violet. Depth readings on a hydraulic micromanipulator when the individual cells were recorded and location of electrolytic microlesions were used as guides.

Lesion projection zone and data analysis

The location and extent of each LPZ within area 17 was determined on the basis of the dimensions of each retinal lesion revealed by retinal back-projection and post-mortem verification of the extent of the lesion in retinal wholemounts (Calford *et al.*, 2000). Albus (1975) defined a cortical point-spread function which describes the extent of RF scatter for strictly radial electrode penetrations as a function of eccentricity. Schmid *et al.* (1996) then used the radial value of the point-spread function to define a region 1.4 mm, in cortical projection terms, inside the perimeter of the area 17 LPZ in which cells may still receive direct input from the dorsal lateral geniculate nucleus (LGNd). This region was referred to as the fringe projection zone.

Three nonparametric tests were used to assess statistical differences in the sampled data: the χ^2 test, the Wilcoxon matched-pairs signed-ranks test (it will be referred to as Wilcoxon test) and the Mann–Whitney *U*-test (Siegel, 1956). Statistical significance of the differences between the two sets of data was accepted when $P < 0.05$ at the two-tailed criterion.

Results

Retinal lesions

In all cases argon lesions were centred in the upper nasal retina of the left eye where the left lower visual field is represented (Fig. 1A–C).

Examination of retinal whole-mounts confirmed destruction of all neuronal layers (including the ganglion cell layer) within the circumscribed laser-lesioned area (Fig. 1D). The loss of retinal ganglion cells was also assessed by plotting the distribution of large ganglion cells, the so-called α -ganglion cells, in the whole-mounts (Figs 1C and 4A). In two retinas of cats in KL group (as in three retinas in the AS animals of Calford *et al.*, 2000; cf. their figs 1 and 2), there was an additional paucity of retinal ganglion cells over a region which spread well outside the lesioned area. This deficit was presumably a result of destruction of axons in the innermost nerve layer crossing the region of the lesion on their way to the optic disc with consequent retrograde degeneration of their parent retinal ganglion cells.

Reorganization of visuotopic (retinotopic) map in area 17

Plotting RFs of single cells recorded from area 17 of kitten-lesioned or adult-lesioned cats with subsequent long postlesion visual experience (KL and AL groups, respectively) revealed extensive topographic reorganization within the LPZ.

Thus, as in AS cats (cf. Schmid *et al.*, 1996; Calford *et al.*, 2000), binocular neurons recorded from the LPZ of KL 8-week-old (Fig. 2) or AL (Fig. 3) cats, when stimulated via the lesioned eye, had RFs which were displaced to normal retina in the vicinity of the lesion although not always to the nearest normal retina (Fig. 4A and B). Cells with ectopic RFs were recorded in supragranular layers II and III as well as in granular layer IV and infragranular layers V and VI (see insets in Figs 2A and B, and 3A and B, as well as subsection on ocular dominance vs. laminar location).

Figure 4C shows the distribution of binocular RF disparities in a sample of cells recorded recently in our laboratory from the visuotopically corresponding region of area 17 of normal cats (Wang *et al.*, 2000). The distribution of RF disparities of binocular neurons recorded from the lesion projection zone (LPZ) of KL, AL and AS cats are shown, respectively, in Fig. 4D–F. Note that in normal cats only a very small proportion of cells (3/54; 5.5%) exhibited RF disparities $>4^\circ$, and disparities $>6^\circ$ were not observed (cf. also Pettigrew & Dreher, 1987). By contrast, in about two-thirds (37/56; 66.1%) of binocular cells recorded in the LPZ of KL cats the RF disparities were $>4^\circ$ and in over a third (20/56; 35.7%) they were $>6^\circ$ (Fig. 4D). Similarly, as indicated in Fig. 4E and F in adult-lesioned cats, high proportions of binocular LPZ cells exhibited RF disparities $>4^\circ$ (9/13; 69.2% in AL cats and 21/47; 44.6% in AS cats).

The RF disparities of LPZ cells recorded from cats lesioned in adulthood (AL group vs. AS group) were not significantly different from each other ($P = 0.13$, Mann–Whitney *U*-test, one-tailed criterion). However, the RF disparities of such cells in KL cats were significantly greater ($P = 0.0046$; Mann–Whitney *U*-test, two-tailed criterion) than those in AS cats.

The comparison of the maximal RF disparities observed in all three groups of cats suggests that the spatial extent of topographic reorganization of area 17 does not change dramatically as a function of postlesion experience time. Thus, for KL cats the maximal RF disparity was 9.2° , for AS cats it was 8.6° while for AL cats it was 6.6° . Given that in all three groups the cells with maximal RF disparities were recorded at the border of monocular regions from which only responses from the nonlesioned eye could be obtained these values might represent the spatial limits of topographic reorganization in area 17. Taking into account the cortical magnification factor of the region of the retina in which virtually all lesions were made (Tusa *et al.*, 1978) and the fact that in all three groups the sizes of the lesions were very similar (6–12° in diameter), these displacements of RFs correspond in cortical terms to a distance of ≈ 5 –6 mm.

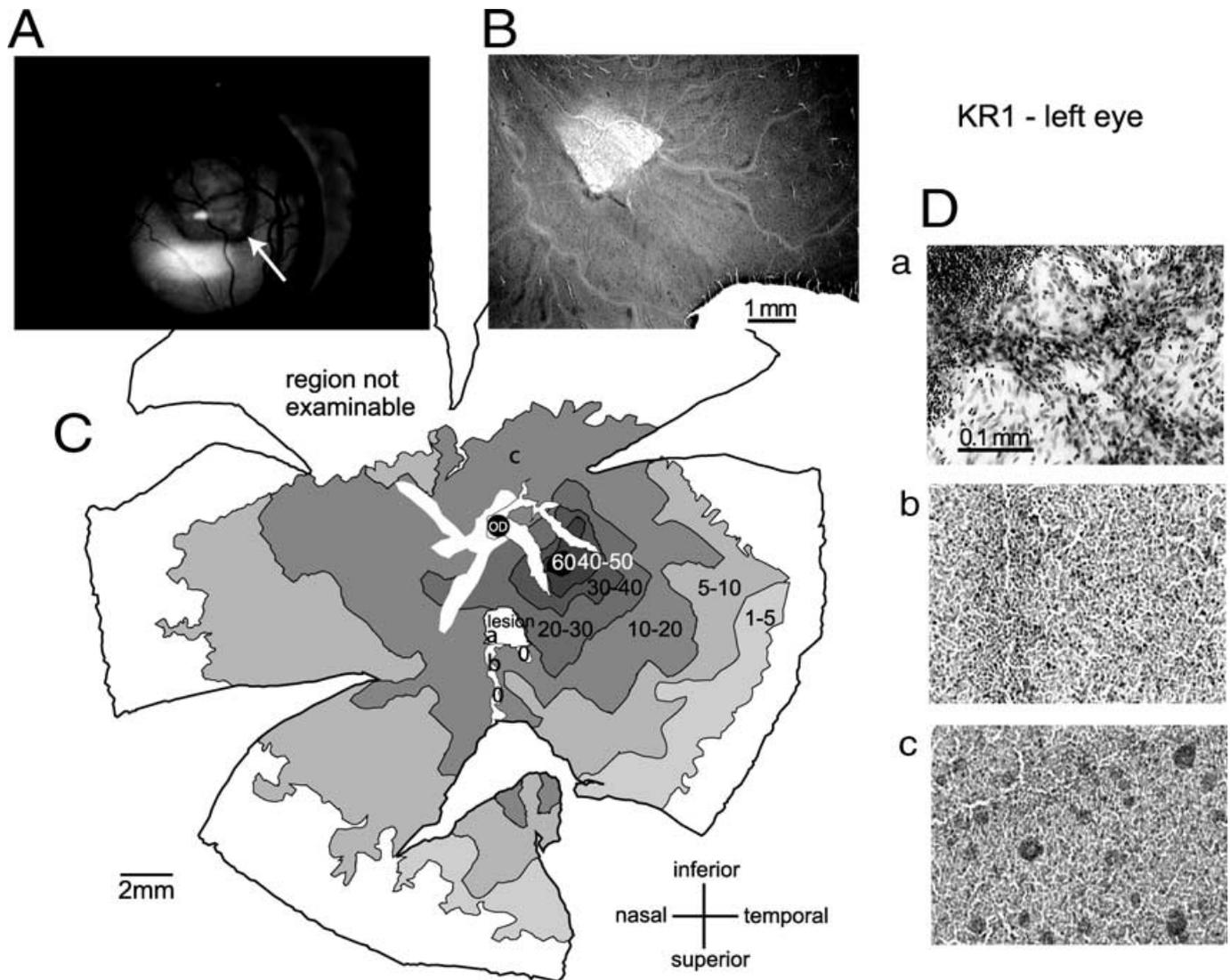


FIG. 1. Photographs of lesioned retina and reconstruction of the lesion in the retinal wholemount. (A) Photograph of the left eye of an 8-week-old kitten (KR1) taken immediately after completion of the retinal lesion. White arrow indicates the black outline of the lesion. (B) Photograph of part of the retinal wholemount from the same eye. The retina was removed at the end of the recording session, 28 weeks later. The lesion is the pale region. (C) Density contours of α -ganglion cells (per mm^2) in this retina. The contours were derived by extrapolation from the density of α -ganglion cells at each of 0.25-mm^2 sampled sites. Note that as a result of partial damage of fibre layer at the lesion site, the retinal lesion produced some loss of ganglion cells in the region extending radially from the lesion. OD, optic disc. Positions marked a, b and c indicate centres of the micrographs shown at the right in D. Micrograph (a) was taken from the edge of the lesion and shows the paucity of surviving neurons in the lesioned area. Micrographs (b) and (c) were taken from the regions that would normally have similar density of ganglion cells. However, due to presumed radial degeneration there is a complete lack of α -ganglion cells in micrograph (b). Note microglial activation in both the lesioned area (a) and in the area of radial degeneration (b).

Cells in the fringe projection zone vs. cells in the lesion projection zone

In both the kitten-lesioned animals (KL cats) and in the adult-lesioned cats (AL and AS cats) cells recorded in the fringe projection zone (see Materials and methods) and those in the lesion projection zone (LPZ; see Materials and methods) had almost identical RF properties. Indeed, for a given group of cats there were no significant differences in the quantitatively tested parameters (such as ocular dominance distribution, peak discharge rates, RF size, direction selectivity indices, the width of orientation selectivity curve or the upper-cut-off velocity) between the cells recorded from the LPZ and those recorded from the fringe projection zones. Therefore, throughout the rest of the paper we will not differentiate between the cells recorded from the fringe

projection zone and those recorded from the lesion projection zone but simply refer to them as the LPZ cells.

Ocular dominance of neurons recorded from the LPZ

Cats lesioned as kittens vs. normal cats

The clear majority (56/80, 70%) of neurons recorded in the LPZ of KL cats were binocular and, with the exception of one cell, their RFs could be plotted reliably irrespective of which eye (lesioned or nonlesioned) the stimuli were presented through. While half of the binocular cells (28/56) gave stronger responses when optimally orientated stimuli were presented via the normal eye (class 4 cells, Fig. 5), over a third of them (20/56) gave stronger responses when stimuli were presented via the lesioned eye (class 2 cells, Fig. 6) and almost 15% (8/56) responded equally well to stimuli presented via either eye (class 3 cells).

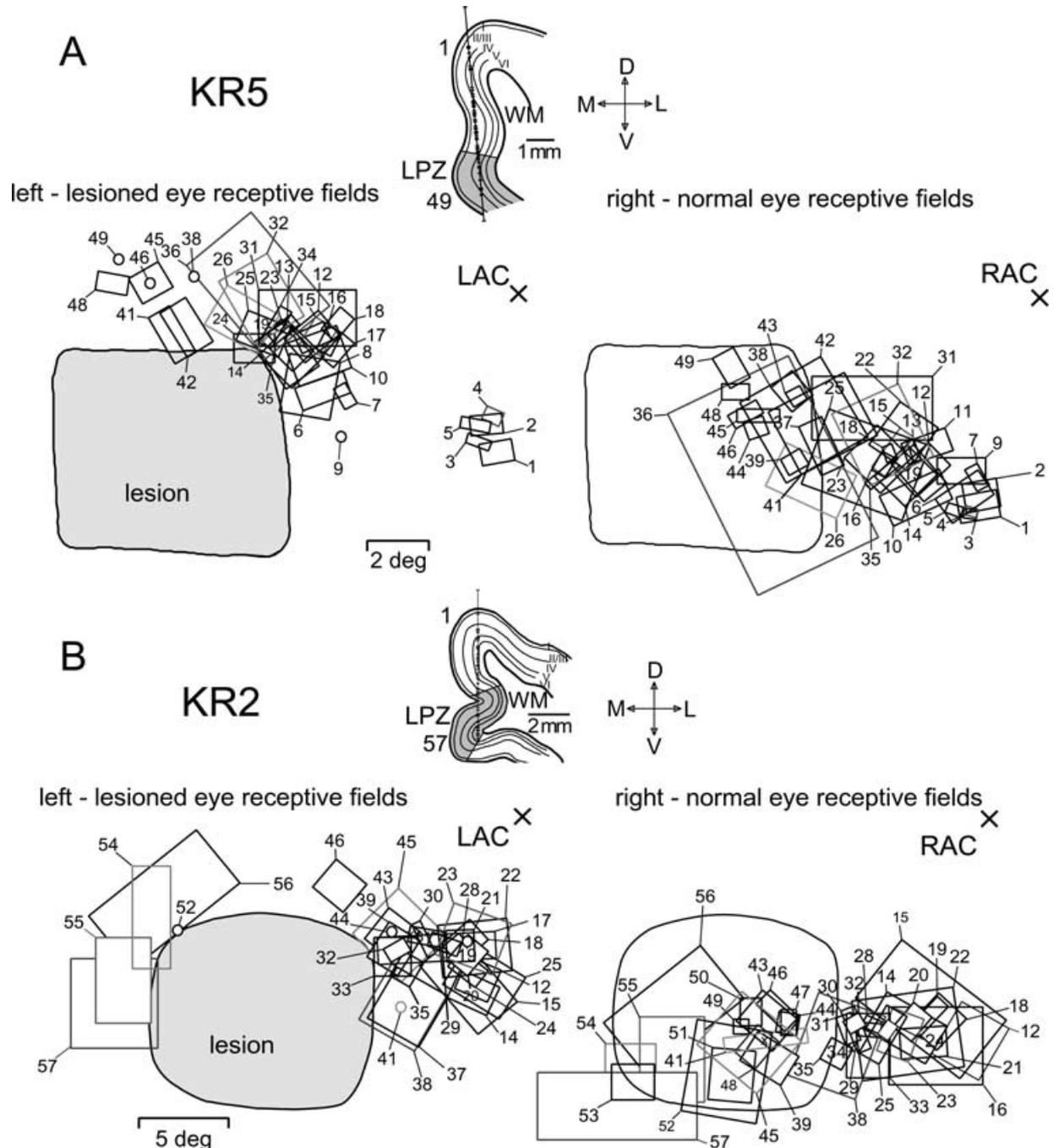


FIG. 2. Examples of normal and ectopic receptive fields (RFs) in kitten-lesioned animals. Outlines of RFs of single neurons recorded in area 17 of two cats lesioned at 8 weeks, (A) KR5 and (B) KR2. Recording took place 43 and 29 weeks, respectively, after making the retinal lesion. For reasons of clarity RFs of neurons recorded in only one track are shown. The outline of the lesion, the positions of RFs revealed by stimulation of the lesioned left eye and position of the left *area centralis* (LAC) are shown in the left panel. The right panel illustrates the 'reference position of the lesion' in the right eye, the positions of RFs revealed by stimulation of the normal right eye and the position of the right *area centralis* (RAC). In the case of RFs which were not plotted in their entirety, the centre of the RF is indicated (○). Insets in A and B show an outline drawing of a frontal section through occipital cortex and the reconstructed positions at which recordings were made. The grey shaded portions of the cortices are the lesion projection zones (LPZ). 'X' marks the left and right *area centralis* (LAC and RAC).

Overall, the ocular dominance distribution of cells recorded from the LPZ of kitten-lesioned cats (KL group) was not significantly different ($0.2 < P < 0.3$, $\chi^2 = 5.127$, d.f. = 4; one-tailed criterion) from that of neurons recorded from the visuotopically corresponding part of area 17 of normal cats (Fig. 7A). Despite the fact that in a substantial proportion of quantitatively tested LPZ cells the responses to stimuli presented via the normal eye tended to be stronger (Fig. 7B), the

median value for peak discharge rate of responses to stimuli presented via the lesioned eye was almost identical to that to stimuli presented via the nonlesioned eye (19.2 vs. 19.6 spikes/s, respectively). Furthermore, although the mean peak discharge rate of responses to stimuli presented via the lesioned eye (24.7 ± 3.3 spikes/s) was substantially lower than that for stimuli presented via the normal eye (38.1 ± 6.7 spikes/s) the difference was not significant ($P = 0.144$,

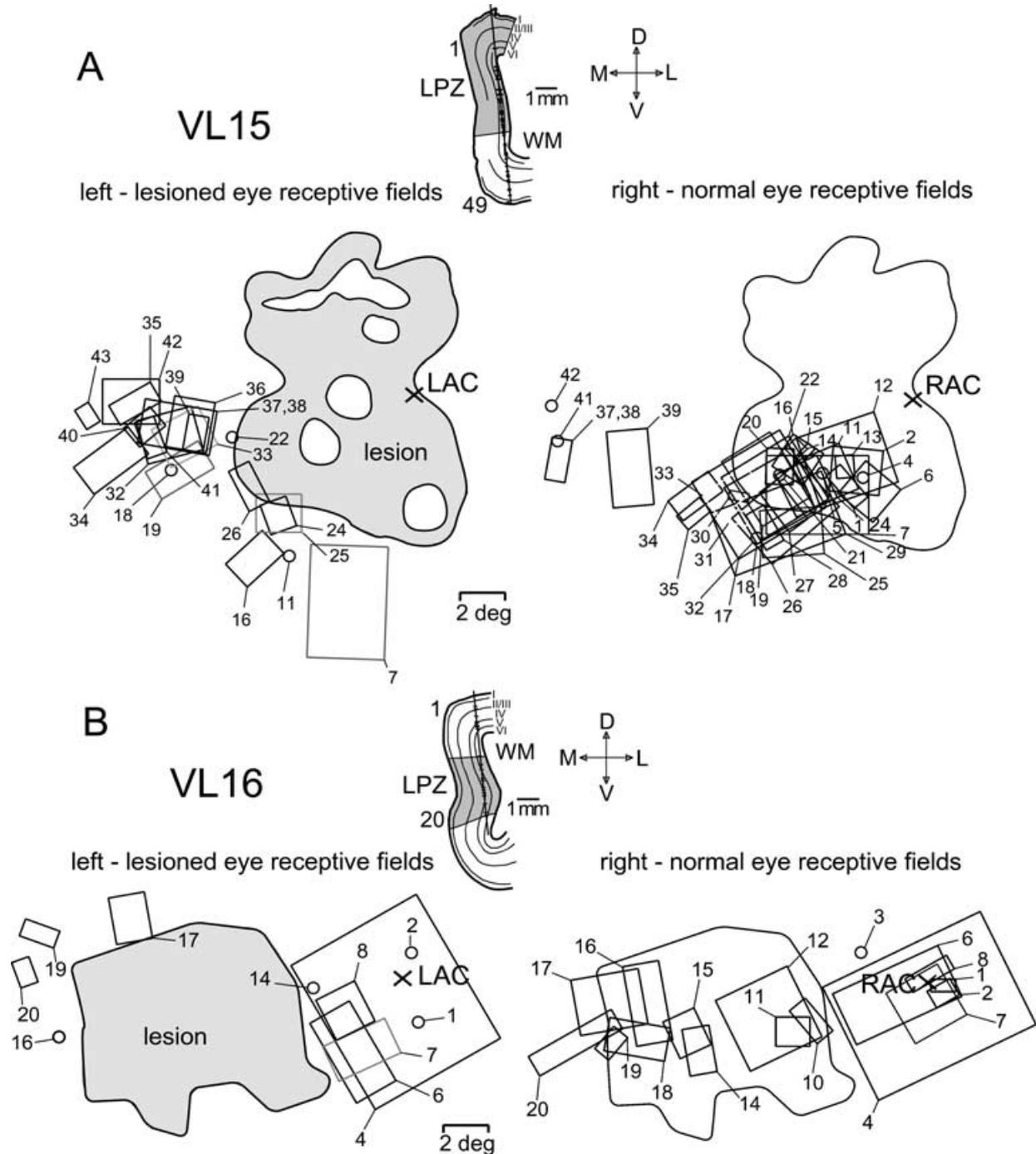


FIG. 3. Examples of normal and ectopic RFs in cats lesioned in adulthood. Outlines of RFs of single neurons recorded in area 17 of two cats lesioned in adulthood, (A) VL15 and (B) VL16. Recordings took place, respectively, 53 and 45 months later. RFs of neurons recorded in only one track are shown. The outline of the lesion, the positions of RFs revealed by stimulation of the lesioned left eye and the position of the left *area centralis* (LAC) are shown in the left panel. The right panel illustrates the 'reference position of the lesion' in the right eye, the positions of RFs revealed by stimulation of the normal right eye and the position of the right *area centralis* (RAC). Note that the lesion in VL15 (A) contains five islands of intact retina (white patches). Insets in A and B show outline drawings of frontal sections through occipital cortex and the reconstructed positions at which recordings were made. For other details see Fig. 2.

Wilcoxon test, two-tailed criterion). This result is clearly consistent with our qualitative assessment of ocular dominance (Fig. 7A).

Cats lesioned in adulthood vs. normal cats or cats lesioned as kittens

In the case of AL cats also most cells recorded from the LPZ were binocular although the proportion of such cells was lower (18/31;

58.1%) than that in the visuotopically corresponding part of area 17 of normal cats (Fig. 7C) or that in the LPZ in area 17 of KL cats (cf. Fig. 7C and A). Furthermore, the responses of a clear majority of binocular LPZ cells recorded in AL cats (14/18; 77.8%) to stimuli presented via the lesioned eye were weaker than those to stimuli presented via the normal nonlesioned eye (class 4 cells) and almost 40% of LPZ cells (12/31; 38.7%) could be activated only by stimuli

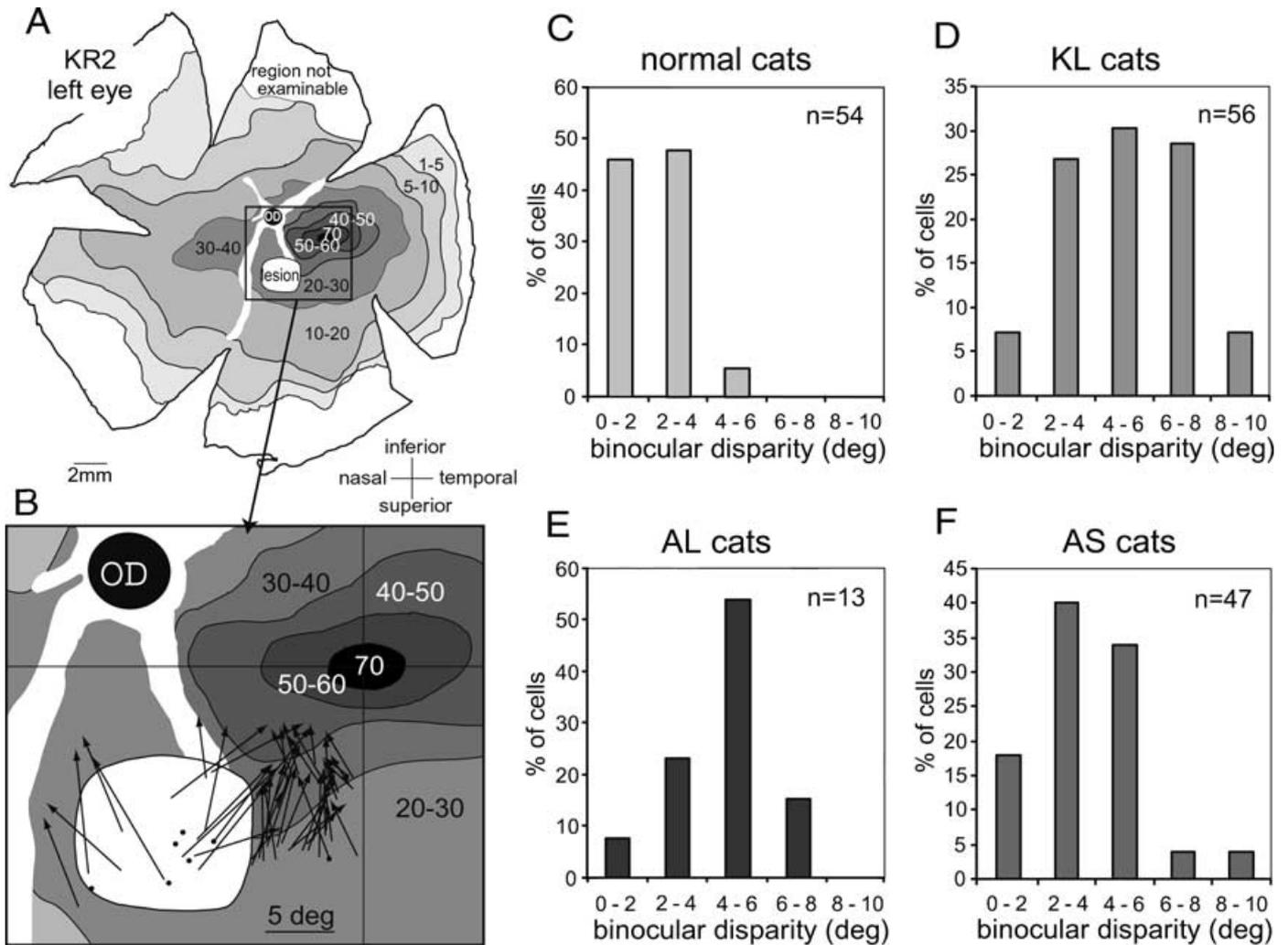


Fig. 4. RF displacements and distribution of binocular disparities for LPZ neurons. (A) Density map of α -ganglion cells (per mm^2) for the wholemount of the left-lesioned retina of cat KR2. The region of central retina with the lesioned area is enlarged in B to show displacement of RFs of area 17 neurons recorded from two penetrations crossing the LPZ. Arrows extend from the position of the RF centres obtained with stimulation of the right (normal) eye to centres of RFs determined with stimulation of the left (lesioned) eye. Note that although there was no radial degeneration of ganglion cells (due to the damage of fibres passing through the lesioned area) the RFs of cells located outside the LPZ (revealed by stimuli presented via the lesioned eye) were also displaced. Black dots show the centres of the RFs determined for the right eye for monocular units not responding to stimulation of the left eye (class 5 cells). Note the relatively high proportion of monocular class 5 cells in the central region of the LPZ. (C) Distribution of binocular disparities of neurons recorded in area 17 of normal cats. Disparity was defined as the distance between the centres of the RFs of a binocular neuron when the *areae centrales* of the left and right retinas were superimposed. Note that only a very small proportion of cells exhibited disparities $>4^\circ$. (D) Distribution of binocular disparities of neurons recorded in the LPZ of kitten-lesioned (KL) cats. Note that about two thirds of cells exhibited disparities $>4^\circ$. (E,F) Distributions of binocular disparities of area 17 neurons recorded in the LPZ of adult-lesioned (AL and AS) cats. Note that in both AL and AS cats high proportions of cells exhibited disparities $>4^\circ$.

presented via the ipsilateral, that is, nonlesioned eye (class 5 cells; Fig. 7C). Finally, in a substantial proportion of binocular LPZ cells (4/18, 22.2%) the ectopic RFs plotted via the lesioned eye could not be clearly delineated (cf. Figs 3A and B, and 8B).

In view of the small number of LPZ cells recorded from AL cats we subdivided the cells into two rather than five ocular dominance classes when considering the statistical significance of the results. One group comprised cells receiving marked input from the contralateral (lesioned) eye (class 1, class 2 and class 3 cells) while the other group comprised cells which received predominant or exclusive input from the ipsilateral (nonlesioned) eye (class 4 and class 5 cells). Thus compared, the ocular dominance distribution of LPZ cells of AL cats was significantly different from that of cells recorded in area 17 of normal cats ($P < 0.002$, $\chi^2 = 15.673$, d.f. = 1; two-tailed criterion) or that of LPZ cells recorded in KL cats ($P < 0.02$, $\chi^2 = 6.816$, d.f. = 1; two-tailed criterion).

The percentage of binocular neurons among the cells recorded from the LPZ of AS cats (86/122; 70.5%; Fig. 7E) was very similar to that in the visuotopically corresponding part of area 17 of normal cats or that (56/80; 70%) among cells recorded from the LPZ of KL cats (cf. Fig. 7A and E). However, unlike area 17 cells recorded in normal cats, the clear majority of the LPZ cells recorded from both AS and AL cats were either dominated by the nonlesioned (ipsilateral) eye (class 4 cells) or could be activated only by stimuli presented via this eye (class 5 cells). Furthermore, in over a quarter of binocular LPZ cells (23/86; 26.5%) recorded in AS cats the ectopic RFs had poorly defined boundaries (Calford *et al.*, 2000; cf. also Fig. 8A and B). The ocular dominance distribution of the LPZ cells recorded in area 17 of AS cats was not only significantly different from that of cells recorded from area 17 cells of normal cats ($P < 0.001$, $\chi^2 = 34.4$, d.f. = 4; two-tailed criterion) but also from

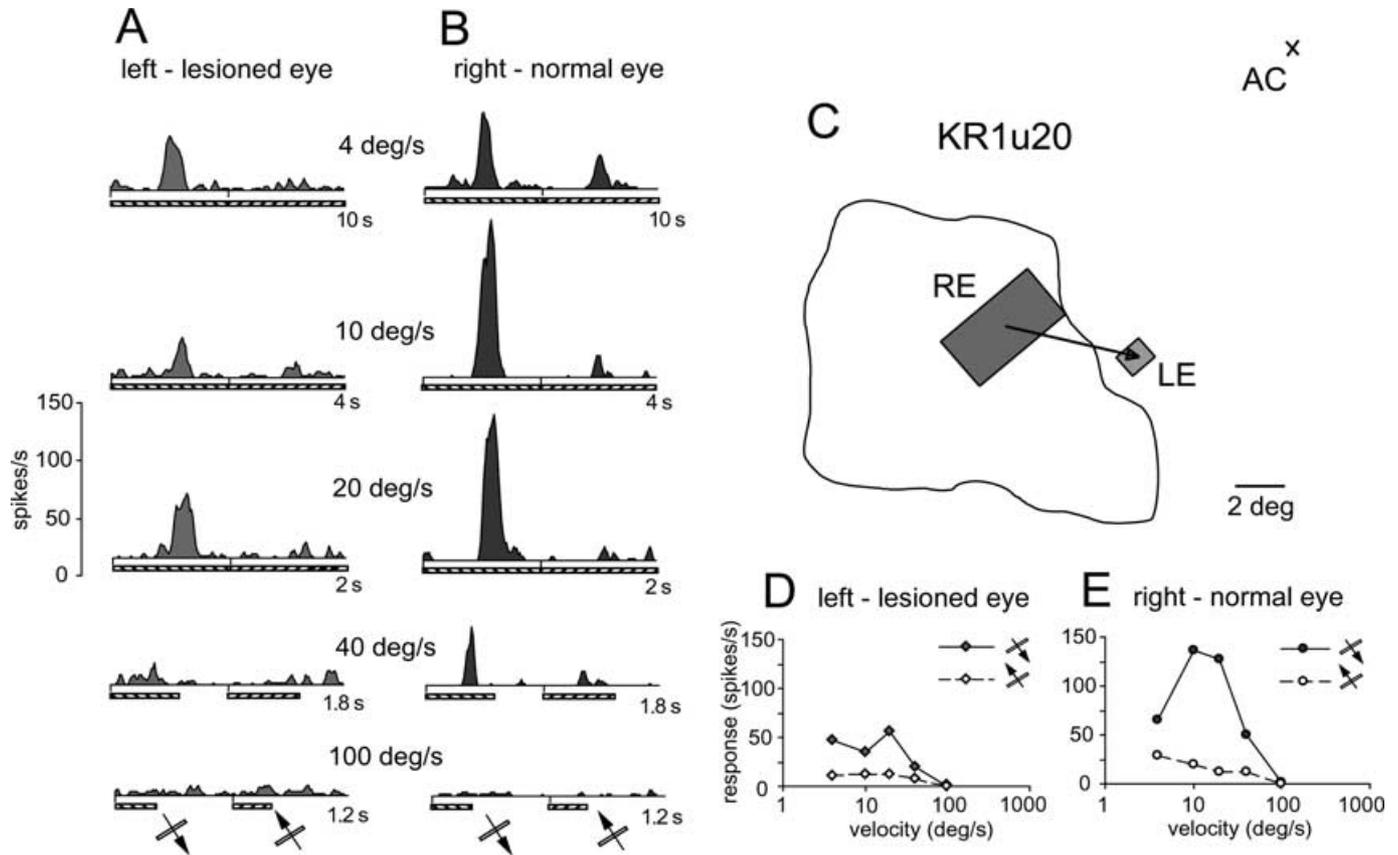


FIG. 5. Example of responses of a binocular (class 4) neuron recorded in the LPZ of area 17 of adult cat (KR1) lesioned at 8 weeks. Peristimulus time histograms (PSTH) of the responses to an obliquely orientated light bar ($8.5 \times 0.5^\circ$) moving across the cell's RF at indicated velocities. Stimuli were presented via either (A) the left (lesioned, contralateral) eye or (B) the right (normal, ipsilateral) eye. Hatched lines under the timebases indicate the duration of the photic stimuli. PSTHs were compiled from responses to successive 10–50 stimulus sweeps. Note that the cell was direction-selective irrespective of the eye through which the stimuli were presented. (C) The large irregular outline represents the lesion boundary (as projected onto a tangent screen) in left retina in relation to the position of the *area centralis* (AC, centre indicated by \times). Note that the RF revealed by visual stimuli presented via the normal right eye (dark rectangle; RE) was located in the region topographically corresponding to part of the lesioned region of the left retina. By contrast, the ectopic RF revealed by visual stimuli presented via the left (lesioned) eye (light rectangle; LE) was displaced to the region just outside the lesion. The displacement of the ectopic RF indicated by the arrow between the centres of the RFs was 6° . Note that in this case the RF plotted via the nonlesioned eye is substantially larger than that plotted via the lesioned eye. (D and E) Velocity tuning curves for the peak responses (averaged over five bins centred at the bin with the highest number of spikes), for the same neuronal responses shown in A and B. Because the cell was direction-selective irrespective of the eye through which the stimuli were presented the magnitudes of the peak responses to stimuli moving downward and those to stimuli moving upward are indicated separately. Note that the response magnitude to a slowly moving stimulus ($4^\circ/s$) presented via the normal eye was not that much greater than that to slowly moving stimulus presented via the lesioned eye. By contrast, the magnitudes of peak responses to faster moving stimuli (10 – $40^\circ/s$) were much greater when the stimuli were presented via the normal eye. Note also that the upper cut-off velocities were the same irrespective of the eye through which the stimuli were presented.

that of the LPZ cells recorded from KL cats ($P < 0.05$, $\chi^2 = 10.51$, d.f. = 4; two-tailed criterion).

The pairwise comparisons of peak discharge rate of responses to stimuli presented via the lesioned eye and those to stimuli presented via the normal eye are shown in Fig. 7D and F for AL and AS cats, respectively. Consistent with the qualitative assessment of ocular dominance in these groups the peak discharge rates of responses to stimulation via the lesioned eye were in both cases significantly lower ($P < 0.05$, Wilcoxon test, two-tailed criterion) than those to stimulation via the normal eye.

Ocular dominance vs. laminar location

Supragranular layers

Figure 8 shows the relationship between the laminar location and ocular dominance class for cells recorded from the LPZ in the three groups of lesioned cats. As indicated in Fig. 8A, the majority of LPZ cells recorded from the supragranular layers II and III of area 17 in KL cats ($14/24$; 58.3%) were assigned to binocular classes 2 or 3 or monocular class 1, and the RFs of all binocular cells could be hand-plotted with stimuli presented via either eye.

The proportion of cells receiving strong input from the contralateral (lesioned) eye ($11/26$; 45.8%) among the LPZ cells recorded from the supragranular layers of a subpopulation of AS cats (CRS series of Calford *et al.*, 2000) was smaller than that among the supragranular LPZ cells recorded in KL cats. Furthermore, in a proportion ($3/26$; 11.5%) of these cells we were unable to hand-plot the ectopic RFs. Nevertheless, the difference between the LPZ cells recorded from supragranular layers of area 17 of KL and AS cats was not significant ($0.2 < P < 0.3$, $\chi^2 = 1.28$, d.f. = 1; one-tailed criterion). Because none of the LPZ cells recorded in AL animals was located in the supragranular layers we do not have information concerning the effect of prolonged postlesion experience on the ocular dominance of cells in the supragranular layers.

We do not have our own control data concerning the ocular dominance distribution of cells recorded from the supragranular layers of area 17 of normal cats. However, when we analysed the data of Shatz & Stryker (1978) we discovered that the ocular dominance distribution of cells recorded from the supragranular layers of area 17 of normal cats was not significantly different from that of cells

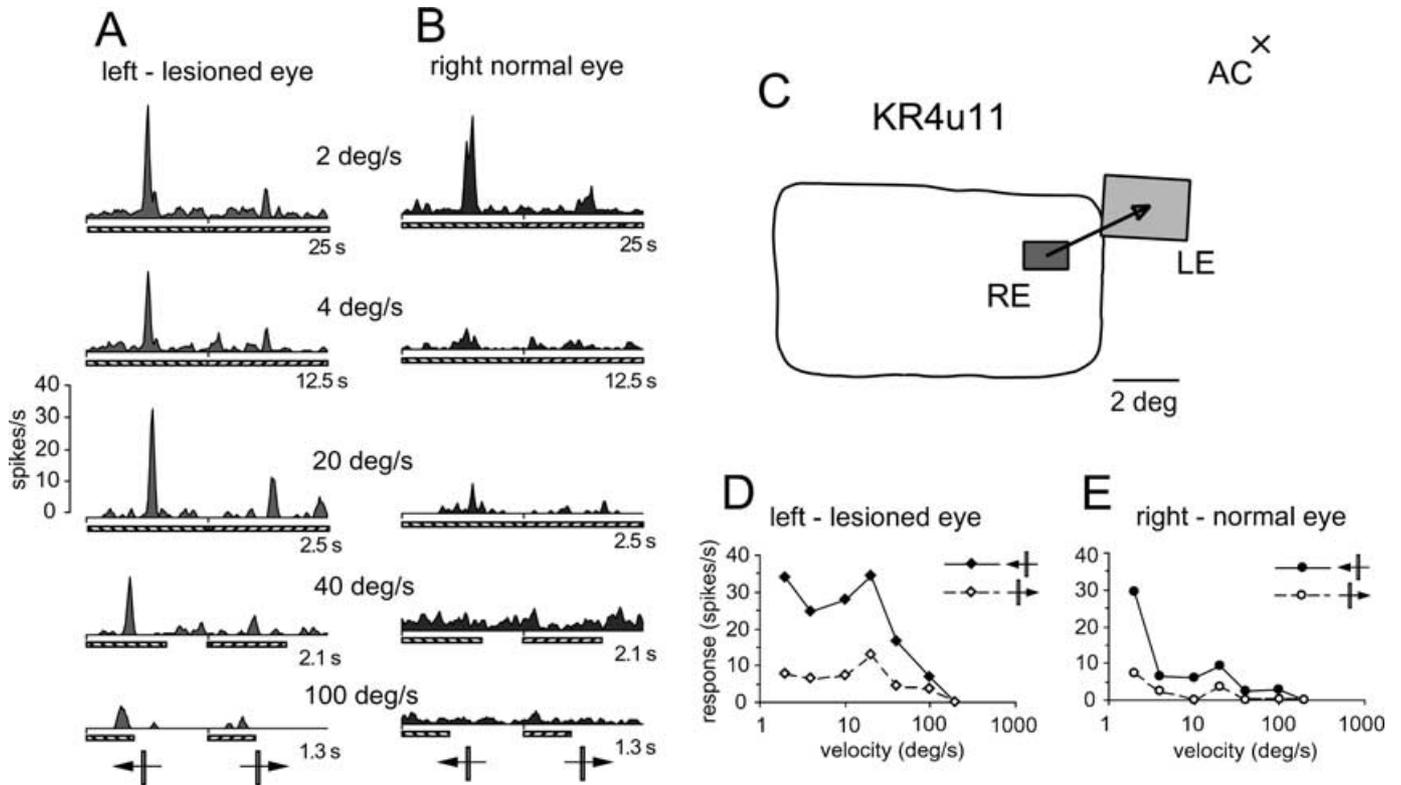


FIG. 6. Example of responses of a binocular (class 2) neuron recorded in the LPZ of area 17 of adult cat (KR4) lesioned at 8 weeks. PSTHs of the responses to a vertically orientated light bar ($8.5 \times 0.5^\circ$) moving across the cell's RF at the indicated velocities. Stimuli were presented via either (A) the left (lesioned, contralateral), eye or (B) the right (normal, ipsilateral) eye. Hatched lines under the timebases indicate the duration of the photic stimuli. Note that, like the cell whose responses are illustrated in Fig. 5, this cell was strongly direction-selective irrespective of the eye through which the stimuli were presented. (C) The large empty rectangle represents an outline of the lesion (as projected onto a tangent screen) in the left retina in relation to the position of the *area centralis* (AC, centre indicated by \times). Note that the RF revealed by visual stimuli presented via the normal right eye (dark rectangle; RE) was located in the region topographically corresponding to part of the lesioned region of the left retina. By contrast, the ectopic RF revealed by visual stimuli presented via the left eye (light rectangle; LE) was displaced to the region just outside the lesion. The displacement of the ectopic RF indicated by the arrow between the centres of the RFs was 3.5° . Note that the RF plotted via the nonlesioned eye (RE) is substantially smaller than the ectopic RF plotted via the lesioned eye (LE). (D and E) Velocity tuning curves for the peak responses (averaged over five bins centred at the bin with the highest number of spikes), for the same neuronal responses shown in A and B. For other details see legend to Fig. 5. Note that the response magnitude to slowly moving stimuli ($2^\circ/s$) was fairly similar irrespective of the eye through which the stimuli were presented. By contrast, the magnitudes of peak responses to faster moving stimuli ($4\text{--}40^\circ/s$) were much greater when the stimuli were presented via the lesioned eye. Note also that the upper cut-off velocities were the same irrespective of the eye through which the stimuli were presented. (Modified from Dreher *et al.*, 2001, with permission).

recorded from granular layer IV and infragranular layers V or VI ($0.3 < P < 0.5$, $\chi^2 = 3.174$, d.f. = 4; one-tailed criterion). Thus it is legitimate to compare the ocular dominance distributions of LPZ cells recorded from the supragranular layers of area 17 of KL cats or AS cats with the ocular dominance distribution of our sample of cells recorded from the visuotopically corresponding parts of area 17 of normal cats even though the laminar location of these cells was not known (cf. Fig. 7A, C and E). Due to the small size of our samples of LPZ cells recorded from the supragranular layers of KL or AS cats we again divided cells into two rather than five eye dominance groups (classes 1, 2 and 3 vs. classes 4 and 5). Thus compared, the ocular dominance distribution of the LPZ cells recorded from the supragranular layers of KL cats ($0.5 < P < 0.7$, $\chi^2 = 0.176$, d.f. = 1; two-tailed criterion) or AS cats ($0.1 < P < 0.2$, $\chi^2 = 1.76$, d.f. = 1; two-tailed criterion) was not significantly different from that of cells recorded from the visuotopically corresponding part of area 17 of normal cats.

Granular and infragranular layers

As indicated in Fig. 8B, the responses of most neurons recorded from the granular (layer IV) and infragranular (layers V and VI) layers of the LPZ were dominated by the nonlesioned (ipsilateral) eye. The ocular dominance distribution of such cells recorded in KL cats differed only

marginally ($0.05 < P < 0.1$, $\chi^2 = 8.754$, d.f. = 4; one-tailed criterion) from that of cells recorded from the visuotopically corresponding part of area 17 of normal cats (cf. Fig. 7A). However, a highly significant difference was found when the comparison was done with LPZ cells recorded from the granular and infragranular layers of AL cats ($P < 0.002$, $\chi^2 = 15.673$, d.f. = 1; two-tailed criterion) or AS cats ($P < 0.002$, $\chi^2 = 22.333$, d.f. = 4; two-tailed criterion). Nevertheless, for both KL and AS cats ocular dominance distributions of cells recorded from the granular and infragranular layers did not differ significantly from those of neurons recorded from the supragranular layers ($0.2 < P < 0.4$, $\chi^2 = 3.56$ or 3.62 for KL and AS cats, respectively, d.f. = 2; two-tailed criterion; see legend to Fig. 8B).

In kitten-lesioned cats the RFs of all but one class 4 cell (23/24; 95.8%) recorded from the granular and infragranular layers could be reliably plotted when the stimuli were presented via the lesioned eye. By contrast, in adult-lesioned cats, the proportion of cells with 'non-plottable' ectopic RFs was either substantial (4/14; 28.6%; AL cats) or they constituted a majority of class 4 cells (15/28; 53.6%; AS cats).

Ocular dominance distributions of granular and infragranular cells recorded from the LPZ of areas 17 of AL and AS animals did not differ significantly from each other ($0.7 < P < 0.8$, $\chi^2 = 0.6$, d.f. = 2; one-

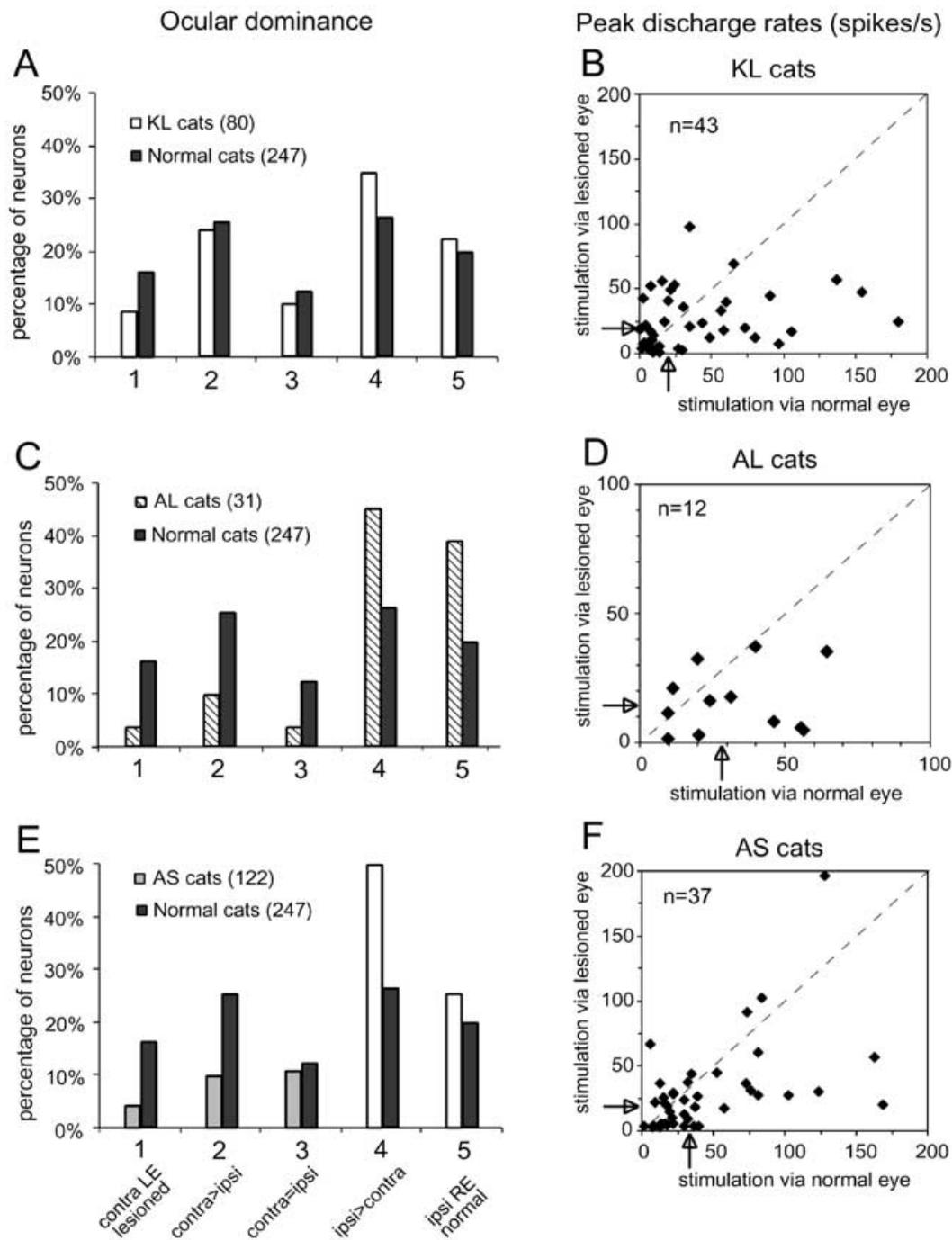


FIG. 7. Comparison of ocular dominance and peak discharge rates in different groups of cats. (A) Comparison of ocular dominance distribution for neurons recorded in area 17 of normal cats (dark bars; our unpublished data added to those of Burke *et al.*, 1992) and the LPZ cells recorded in kitten lesioned- KL cats (open bars). Cells classified as class 1 or 5 were monocular cells and could be only driven via the contralateral (lesioned) or ipsilateral (normal) eye, respectively. Class 3 cells responded equally well to stimuli presented via either eye. Class 2 and class 4 cells were binocular cells which responded more strongly to stimuli presented via the contralateral (class 2) or ipsilateral (class 4) eye. The ocular dominance distributions in A were not significantly different ($0.2 < P < 0.3$, χ^2 test). (B) Pairwise comparison of peak discharge rates at optimal stimulus conditions to stimulation of each eye for binocular LPZ neurons recorded in kitten-lesioned cats. (C) Comparison of ocular dominance distribution for neurons recorded in area 17 of normal cats (dark bars) and the LPZ cells recorded in AL cats (hatched bars). Ocular dominance classes as in A. The ocular dominance distributions in C were significantly different from each other ($P < 0.002$, χ^2 test). (D) Pairwise comparison of peak discharge rates at optimal stimulus conditions to stimulation of each eye for binocular LPZ neurons recorded in AL cats. (E) Comparison of ocular dominance distribution for neurons recorded in area 17 of normal cats (dark bars) and the LPZ cells recorded in AS cats (grey bars). The ocular dominance distributions in E were significantly different from each other ($P < 0.001$, χ^2 test). (F) Pairwise comparison of peak discharge rates at optimal stimulus conditions to stimulation via each eye for binocular LPZ neurons recorded in AS cats. Parts E and F are modified from Calford *et al.* (2000), with permission. Arrows in B, D and F point to the median values of peak discharge rates for stimuli presented via the lesioned and via the nonlesioned eye. Although in B the mean peak discharge rate to stimuli presented via the lesioned eye (24.7 ± 3.3 spikes/s) was lower than that (38.1 ± 6.7 spikes/s) for stimuli presented via the nonlesioned eye the difference was not significant ($P = 0.144$, Wilcoxon test). By contrast, in both groups of cats lesioned in adulthood (AL and AS cats) peak discharge rates to stimuli presented via the lesioned eye were significantly lower ($P < 0.05$, Wilcoxon test) than those for stimuli presented via the nonlesioned eye.

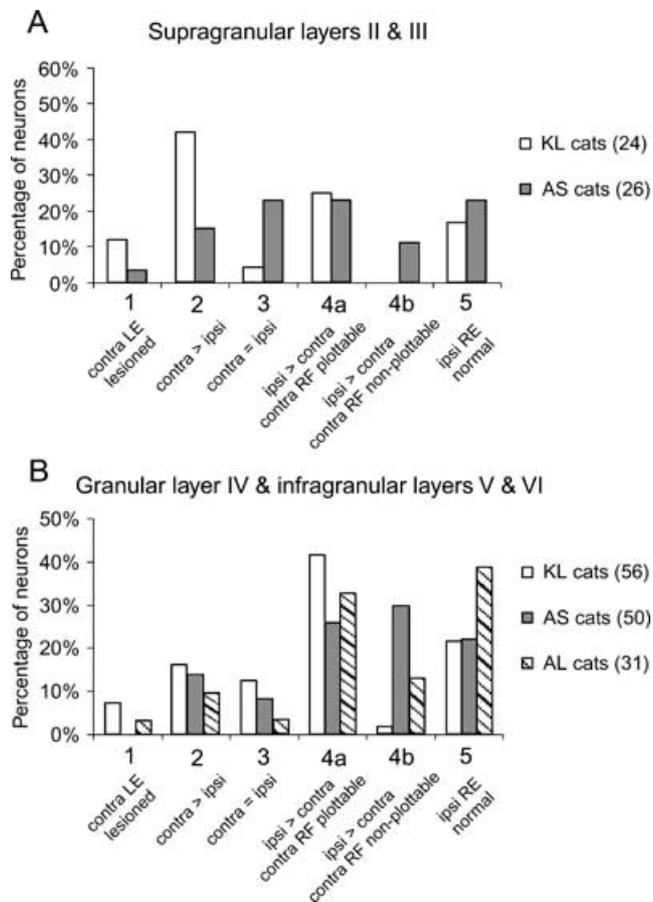


FIG. 8. Comparison of ocular dominance distribution of LPZ cells recorded from different layers. (A and B) Ocular dominance distributions of cells recorded from supragranular layers II and III and granular and infragranular layers IV, V and VI, respectively. Note that there are six rather than five (as in Fig. 7A) eye dominance groups. In particular, we have subdivided class 4 cells, that is, binocular cells dominated by the nonlesioned (ipsilateral) eye, into two groups. One of these subgroups (4a) comprises class 4 cells whose RFs could be clearly outlined by stimuli presented via either eye. The second subgroup (4b) comprises class 4 cells whose RFs could not be clearly delineated when hand-held stimuli were presented via the lesioned (contralateral) eye. (A) In view of the sample size of LPZ cells recorded from the supragranular layers, for statistical purposes we divided the populations into three rather than five eye dominance groups. One group combined classes 1, 2 and 3, that is, the cells with exclusive or relatively strong input from the lesioned (contralateral) eye. The second group comprised class 4 cells (binocular cells dominated by the nonlesioned ipsilateral eye) whose RFs could be hand-plotted with stimuli presented via either eye (4a group). Finally, the third group combined class 4 cells whose RFs could not be hand-plotted with stimuli presented via the lesioned eye (4b group) and monocular class 5 cells, that is, cells which could be activated only by stimuli presented via the nonlesioned eye. The difference between KL and AS cats was not significant ($0.3 < P < 0.5$; χ^2 test, one-tailed criterion). (B) LPZ cells recorded from the granular and infragranular layers were also divided into three rather than five ocular dominance groups. Ocular dominance distributions of granular and infragranular cells recorded from the LPZ of AL and AS animals did not differ significantly from each other ($0.7 < P < 0.8$; χ^2 test, one-tailed criterion). By contrast, the ocular dominance distribution of granular and infragranular cells recorded from the LPZ of KL cats differed significantly from that of AL cats ($P < 0.04$; χ^2 test, two-tailed criterion) or that of AS cats ($P < 0.02$; χ^2 test, two-tailed criterion).

tailed criterion). By contrast, the ocular dominance distribution of granular and infragranular cells recorded from the LPZ of area 17 in KL cats was significantly different from that of AL cats ($P < 0.04$, $\chi^2 = 7.9$, d.f. = 2; two-tailed criterion) or that of AS cats ($P < 0.02$, $\chi^2 = 9.41$, d.f. = 2; two-tailed criterion).

Receptive field properties of neurons recorded from the LPZ

Spatial organization and size of RFs

As previously reported for AS cats (Calford *et al.*, 2000) in both kitten-lesioned (KL) and adult-lesioned (AL) cats all binocular LPZ cells examined for C- (complex) type or S- (simple) type response characteristics were found to conform to the same type (S or C) irrespective of the eye (lesioned or nonlesioned) through which the stimuli were presented.

Whereas in AS cats $\approx 15\%$ of ectopic RFs contained two or three widely separated excitatory discharge regions (Calford *et al.*, 2000; cf. also Kaas *et al.*, 1990; Chino *et al.*, 1992, 1995; Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995), spatially distinct multiple excitatory RFs were not found in KL or AL cats. Although the areas of the normal and ectopic RFs of binocular neurons recorded from the LPZ of kitten-lesioned animals were often substantially different (Figs 2, 5, 6 and 9A) the difference was not significant (Fig. 9A; $P = 0.23$, Wilcoxon test, one-tailed criterion). Similarly, although the sizes of ectopic RFs of binocular cells recorded in cats lesioned in adulthood were often quite different from those of their normal counterparts (Figs 3 and 9B) the differences were not significant (cf. Calford *et al.*, 2000 for AS cats).

Direction selectivity indices

It is well established that the direction selectivity in cat's primary visual cortices (areas 17 and 18) tend to vary with stimulus velocity (cf. Burke *et al.*, 1992; Dreher *et al.*, 1992). As in AS cats (cf. Fig. 5 of Calford *et al.*, 2000) in KL cats this variation was apparent not only for stimuli presented via the normal RFs but also for the stimuli presented via the ectopic RFs (cf. Figs 5 and 6). Furthermore, even at optimal velocities binocular LPZ cells recorded in area 17 of KL cats can exhibit substantial differences in the direction selectivity indices (DI) to optimally orientated stimuli presented via the normal RFs and those presented via the ectopic RFs (Figs 5, 6 and 9C; cf. for AS cats Figs 5 and 8 of Calford *et al.*, 2000.). Nevertheless, for the sample of quantitatively tested binocular LPZ cells recorded in KL cats, the DIs for stimuli presented via the lesioned eye and the DIs for stimuli presented via the nonlesioned eye were highly correlated (Pearson's correlation coefficient $r = 0.755$, $P < 0.001$; two-tailed criterion). Furthermore, the mean DI for optimally orientated stimuli moving at optimal velocities presented via the nonlesioned eye ($59.6 \pm 5.2\%$) was virtually identical to that ($60.2 \pm 5.0\%$) for stimuli presented via the lesioned eye ($P = 0.73$; Wilcoxon test, two-tailed criterion; $n = 38$).

We were also able to measure the DIs for a very small sample of binocular LPZ cells recorded in AL cats ($n = 5$; Fig. 9D). Again, the mean direction selectivity index for stimuli presented via the nonlesioned eye ($74.6 \pm 8.6\%$) was virtually identical to that ($74.5 \pm 11.0\%$) for stimuli presented via the lesioned eye.

Finally, for AS cats at optimal velocities the DIs for stimuli presented via the lesioned eye were also positively correlated with the DIs for stimuli presented via the nonlesioned eye (Pearson's correlation coefficient $r = 0.406$, $P < 0.05$; two-tailed criterion). On the other hand, as reported earlier (Calford *et al.*, 2000 and Fig. 9D) the mean DI for optimally orientated stimuli presented via the lesioned eye ($49.3 \pm 5.5\%$) was significantly greater than that ($40.0 \pm 5.2\%$) for stimuli presented via the nonlesioned eye ($P < 0.05$ Wilcoxon test, two-tailed criterion).

Orientation preferences and tuning in kitten-lesioned animals

For binocular LPZ neurons of kitten-lesioned animals (KL cats) as for the LPZ neurons in cats lesioned in adulthood (AL and AS cats; see

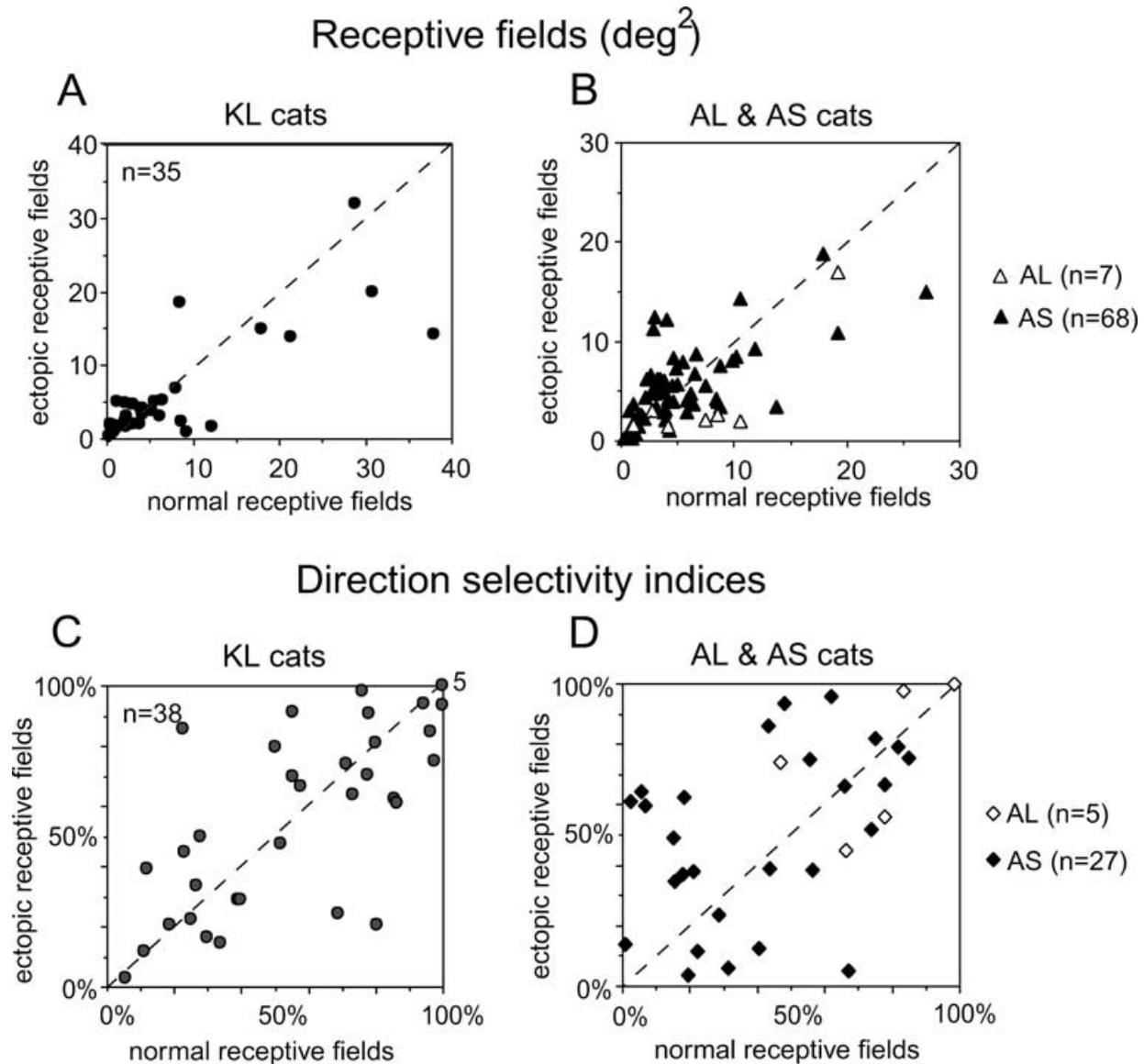


FIG. 9. (A and B) Pairwise comparisons of the areas of RFs for binocular neurons recorded from the LPZ of kitten-lesioned (KL) or adult-lesioned animals (AL and AS cats after Calford *et al.*, 2000). For both groups the areas of the ectopic and normal RFs were not significantly different from each other ($P > 0.05$; Wilcoxon test). (C and D) Pairwise comparisons of the direction selectivity indices (DIs) of binocular LPZ cells recorded in the same cats. For KL cats the mean DIs for optimally orientated stimuli moving at optimal velocities were very similar irrespective of the eye through which the stimuli were presented ($60.2 \pm 5.0\%$ for stimuli presented via the lesioned eye and $59.6 \pm 5.2\%$ for stimuli presented via the nonlesioned eye) and the difference was not statistically significant ($P = 0.73$; Wilcoxon test). Note that in five cells DIs were 100% when the stimuli were presented through either eye. Similarly, for AL cats the mean DI for stimuli presented via the nonlesioned eye ($74.6 \pm 8.6\%$) was virtually identical to that ($74.5 \pm 11.0\%$) for stimuli presented via the lesioned eye. By contrast, for AS cats the mean DI for stimuli presented via the lesioned eye ($49.3 \pm 5.5\%$) was significantly different ($P < 0.05$ Wilcoxon test, after Calford *et al.*, 2000) from that ($40.0 \pm 5.2\%$) for stimuli presented via the nonlesioned eye.

Calford *et al.*, 2000), the optimal orientation for stimuli presented via the lesioned eye tended to be very similar to that for stimuli presented via the nonlesioned eye (Fig. 10A). Indeed, the preferred orientations for moving bars presented separately via the normal and the ectopic RFs were significantly correlated in both KL cats (Pearson correlation coefficient $r^2 = 0.98$, $P < 0.001$; two-tailed criterion; Fig. 10A) and AL cats (Pearson correlation coefficient $r^2 = 1$, $P < 0.001$; two-tailed criterion; Fig. 10A). Although some LPZ cells recorded in kitten-lesioned cats were more sharply tuned for orientation when the stimuli were presented via the lesioned eye (Fig. 10B and C) most cells had broader tuning curves and overall the mean width of orientation tuning ($81.4 \pm 25.3^\circ$) for stimuli presented via the

lesioned eye was significantly broader ($P < 0.05$, Wilcoxon test, two-tailed criterion) than the mean width of orientation tuning for stimuli presented via the nonlesioned eye ($61.8 \pm 30.7^\circ$). Furthermore, a substantial proportion of cells with broader orientation tuning for stimuli presented via the lesioned eye (4/9; 44.5%) exhibited preferences for more than one orientation when stimuli were presented via the ectopic RFs (Fig. 10D and E).

Velocity sensitivity: preferred velocities

All but two of 34 binocular LPZ cells recorded from area 17 of kitten-lesioned cats (KL group) and tested quantitatively for velocity selectivity exhibited a preferred velocity not exceeding $50^\circ/\text{s}$ for stimuli

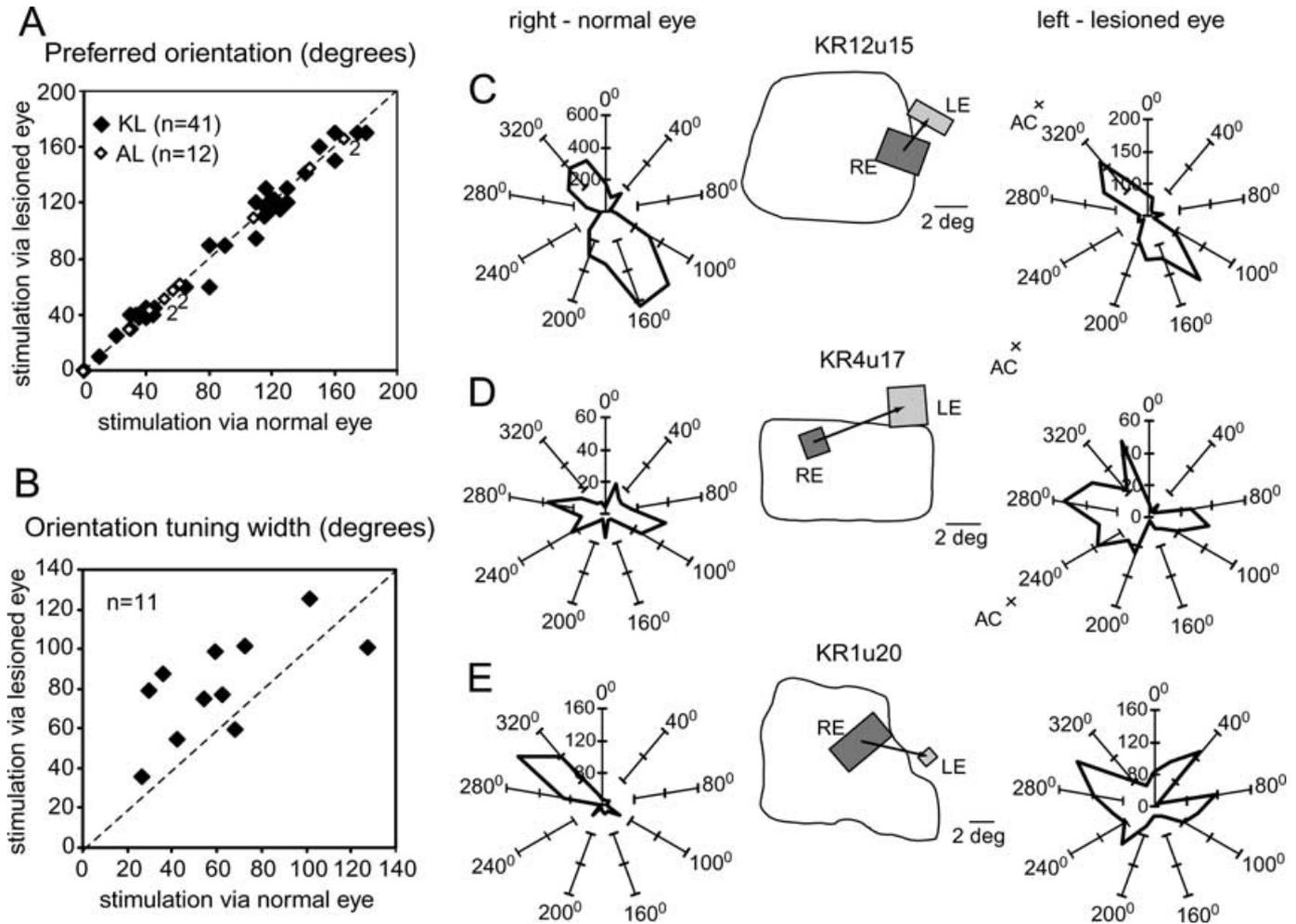


Fig. 10. Orientation tuning for LPZ cells recorded from area 17 of kitten-lesioned (KL) animals. (A) Comparison of preferred orientations for a sample of binocular cells (recorded from LPZ of KL and AL cats), stimulated via each eye separately. Note that the preferred orientations for normal and ectopic RFs were significantly correlated ($r^2 = 0.98$, $P < 0.0001$). (B) Comparison of orientation tuning width at half-height for a sample of binocular cells when stimuli were presented through either eye. Note that all but two cells showed substantially broader width of orientation tuning for stimuli presented via the lesioned eye ($P < 0.05$, Wilcoxon test). (C–E) Polar plots of the orientation tuning of responses of three neurons to stimulation of each eye with a moving bar of optimal size at preferred velocity. Insets show the positions of RFs obtained during stimulation of each eye in relation to the lesion and *area centralis* (AC, centre indicated by \times); the arrow connecting the centres of the RFs shows the displacement (ectopicity) of the position of the RF revealed by stimuli presented via the lesioned eye. In all three examples preferred orientations were similar for normal and lesioned eye RFs. (C) Note that for KR12u15 cell the orientation tuning width is narrower for stimuli presented via the lesioned eye (width at half-height for ectopic RF 59.3° vs. 67.9° for normal RF). Two other neurons, (D) KR4u17 and (E) KR1u20 showed much broader orientation tuning for stimuli presented via the lesioned eye. In the case of neuron KR4u17 the width at half-height for the ectopic RF was 87.2° vs. 36.1° for the normal RF. Neuron KR1u20, apart from broadening of orientation tuning for the main orientation for stimuli presented via the lesioned eye (54.4° vs. 42°), showed responses for two additional orientations when stimulated via the lesioned eye.

presented through either eye (Fig. 11A); the preferred velocities for stimuli presented through either eye were not significantly different ($P > 0.05$; Wilcoxon test, two-tailed criterion) and their median preferred velocities were the same ($9.5^\circ/s$).

None of 12 binocular LPZ neurons recorded from area 17 of AL cats and tested quantitatively for velocity selectivity exhibited a preferred velocity exceeding $50^\circ/s$ (Fig. 11B); the preferred velocities to stimuli presented via the two eyes were very similar (Fig. 11B; median preferred velocity $7^\circ/s$ and $10^\circ/s$ for lesioned and nonlesioned eye, respectively) and the difference between the lesioned and nonlesioned eyes was not significant ($P > 0.05$; Wilcoxon test, two-tailed criterion).

In the case of binocular LPZ cells recorded in area 17 of AS cats none of the tested cells exhibited a preferred velocity exceeding $100^\circ/s$ (Fig. 11C; after Calford *et al.*, 2000). For almost a third of these (9/31;

29%; Fig. 11C) the preferred velocities were virtually the same irrespective of the eye through which the stimuli were presented. Although for the majority of the remainder of the sample (13/31; 41.95%; Fig. 11C) the preferred velocities for stimuli presented via the normal eye were higher, the median preferred velocity for the two eyes was the same ($9.8^\circ/s$) and the difference between them was not significant ($P > 0.322$; Wilcoxon test, two-tailed criterion).

Upper cut-off velocities

It is apparent from Fig. 11D that the upper velocity limits (upper cut-off velocities) for binocular LPZ cells recorded in area 17 of KL cats are often very similar for stimuli presented via each eye. Furthermore, the similarities in upper cut-off velocities were apparent irrespective of the eye dominance class of the neuron (Figs 5 and 6). Overall, for the whole population of LPZ cells tested quantitatively in KL cats the

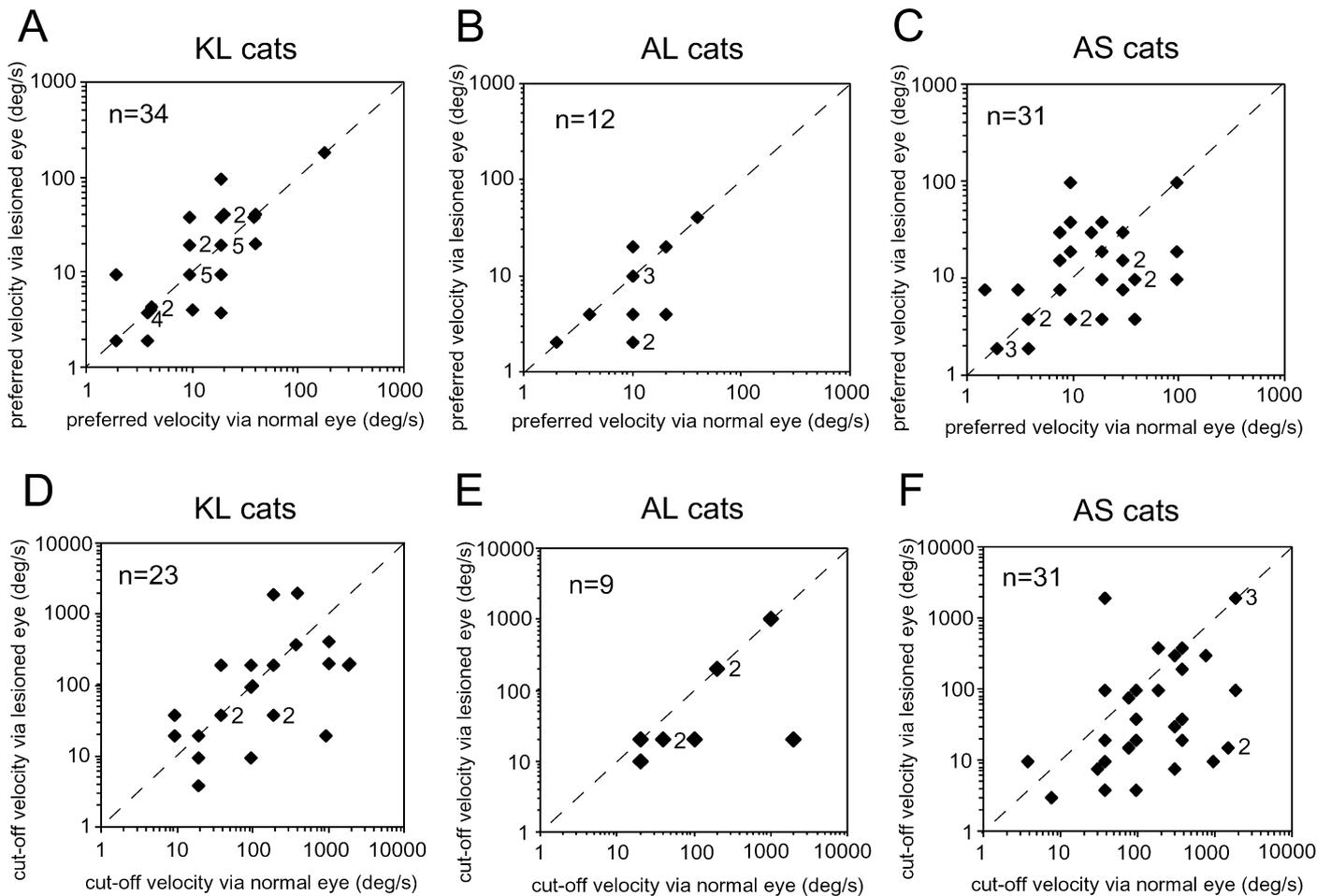


FIG. 11. Pairwise comparisons of the velocity sensitivity of binocular LPZ neurons for stimuli presented via either eye. (A–C) Velocity giving the maximal response for stimulation of each eye (preferred velocity) for neurons recorded in the LPZ of kitten-lesioned (KL) or adult-lesioned (AL and AS) animals. Moving stimuli were at the optimal orientation in each case. The pairwise comparison reveals the difference between the distributions of preferred velocities for the lesioned and the nonlesioned eye to be insignificant for all three groups ($P > 0.05$; Wilcoxon test). (D–F) Upper velocity limit of excitatory responsiveness to stimulation of each eye (cut-off velocity) for neurons recorded in LPZ of KL, AL and AS cats. In the kitten-lesioned animals there was no statistically significant difference ($P > 0.05$; Wilcoxon test) between the upper velocity limits to stimuli presented via the lesioned eye and those presented via the nonlesioned eye. By contrast, for both adult-lesioned groups (AL and AS cats) the upper cut-off velocities for stimuli presented via the nonlesioned eye were significantly higher ($P < 0.05$ for AL cats and $P < 0.004$ for AS cats; Wilcoxon test). Parts C and F are modified from Calford *et al.* (2000), with permission.

median cut-off velocities for stimuli presented via normal RFs and those for stimuli presented via ectopic RFs were the same ($145^\circ/\text{s}$), and there was no significant difference between the two sets of values ($P > 0.05$; Wilcoxon test, two-tailed criterion).

By contrast, as indicated in Fig. 11E, the upper cut-off velocities of most (5/9; 55.5%) of the small sample of binocular LPZ cells (all of them in the granular and infragranular layers) recorded in area 17 of AL cats were not only lower for stimuli presented via the lesioned eye but the difference between the upper cut-off velocities for stimuli presented via the lesioned eye (median $20^\circ/\text{s}$) and those presented via the nonlesioned eye (median $100^\circ/\text{s}$) was significant ($P < 0.05$; Wilcoxon test, two-tailed criterion).

As illustrated in Fig. 11F, for most LPZ cells (20/31; 64.5%) recorded in area 17 of AS cats the upper cut-off velocities for stimuli presented via the ectopic RFs tended to be substantially lower than those for stimuli presented via the normal RFs. Although in over a third (11/31; 35.5%) of the cells the upper cut-off velocities for stimuli presented via the lesioned eye were either the same as or higher than those for stimuli presented via the nonlesioned eye, the majority of these (7/11; 63.6%) were encountered in the supragranular layers. Overall, in

AS cats not only was the median upper cut-off velocity for stimuli presented via the lesioned eye substantially lower ($38^\circ/\text{s}$ vs. $190^\circ/\text{s}$) but the difference between the two populations was highly significant ($P < 0.004$; Wilcoxon test, two-tailed criterion; Calford *et al.*, 2000).

Discussion

Neural basis of the ectopic receptive fields

We have found that in adult cats in which monocular retinal lesions were made when they were 8-week-old kittens (KL cats) as in cats in which monocular retinal lesions were made in adulthood (Calford *et al.*, 2000; the present study) the majority of cells recorded from the lesion projection zone (LPZ) of contralateral area 17 were binocular but the RFs plotted via the lesioned eye were ectopic, that is, displaced to normal retina in the vicinity of the lesion.

The fact that in adult-lesioned cats sprouting of the retino-geniculate terminals into the LPZ of the LGNd is absent (Darian-Smith & Gilbert, 1995) or only very minor (at most $250\ \mu\text{m}$ inside the LPZ; Eysel *et al.*, 1980; Eysel, 1982; Eysel & Neubacher, 1984; Eysel & Wolfhard, 1984) combined with paucity of sprouting of geniculocortical projec-

tions to area 17 (Darian-Smith & Gilbert, 1995) suggests that these phenomena could not substantially account for the topographically widespread reorganization observed in area 17. Indeed, several functional studies (Das & Gilbert, 1995; Wright *et al.*, 1999; Calford *et al.*, 2003) have provided strong evidence that, in adult-lesioned cats, several months after the lesion the visual input from the lesioned retina to neurons in the LPZ is largely mediated via intrinsic horizontal connections within area 17. Given that the topographically organized projection from the LGNd to areas 17 and 18 is already established in newborn kittens (Henderson, 1982), it is unlikely that topographically widespread reorganization of the geniculo-cortical projection occurred in kitten-lesioned animals. It is likely therefore that the generation of ectopic RFs of neurons in area 17 of kitten-lesioned animals is also based, anatomically, mainly on widespread horizontal cortico-cortical connections.

It has been reported that in adult cats, largely irrespective of the amount of time (a few hours or two months) which elapses between the creation of a monocular lesion and recording from area 17, ectopic RFs can be plotted almost immediately after enucleation of the nonlesioned eye (Chino *et al.*, 1992). It has therefore been argued that the observed topographic reorganization must be based largely on existing connections. Indeed, there is substantial functional evidence indicating that cortico-cortical connections in normal cats allow integration of signals over wide areas of striate cortex (Kitano *et al.*, 1994; Bringuier *et al.*, 1999). Consistent with this, stimulating the visual field for a few minutes with a pattern of moving lines or dots while masking out the discharge regions ('artificial scotoma') of neurons located in the supragranular layers of area 17 of normal adult cats results in a dramatic (≈ 5 -fold), albeit transient, expansion of their discharge fields (Pettet & Gilbert, 1992; Das & Gilbert, 1995; Volchan & Gilbert, 1995).

Although ectopic RFs of area 17 neurons in the affected cortical projection zone observed within a few hours of a monocular retinal detachment (Schmid *et al.*, 1995), monocular retinal lesion (Calford *et al.*, 1999) or topographically matching binocular retinal lesion (Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995) tend to be 2–10 times larger than their normal counterpart, the reorganization of area 17 appears to be limited to 0.5–1 to 2–3 mm (Chino *et al.*, 1992; Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995; cf. however, Calford *et al.*, 1999), that is, a distance much smaller than the spatial extent of existing cortico-cortical connections within area 17. Furthermore, the responses of LPZ cells to visual stimuli presented via the lesioned eye tend to be sluggish and habituate easily (Darian-Smith & Gilbert, 1995; see however, Calford *et al.*, 1999). Consistent with this, in area 17 of adult cats even 2 weeks after matched bilateral retinal lesions the neurons recorded from the central part of the LPZ are characterized by reduced levels of both visually evoked and spontaneous activity and by reduced (15–26%) levels of glutamate immunoreactivity (Eysel *et al.*, 1999).

There are clear indications that in adult animals cortico-cortical interactions are strengthened and reshaped over time and/or with postlesion visual experience. Indeed, the long-term topographic reorganization following homonymous binocular retinal lesions in adult cats is accompanied by axonal sprouting of intrinsic connections in the supragranular and to a lesser extent infragranular but not in the granular layers (Darian-Smith & Gilbert, 1994). Although the axons spreading from the injection sites in the LPZ, like those in normal cats, never extended further than 4–4.3 mm, axonal sprouting within the LPZ was indicated by a substantial (57–88%) increase in fibre density (Darian-Smith & Gilbert, 1994).

We do not know the time-course of topographic reorganization in the LPZ of area 17 following circumscribed monocular retinal lesions in 8-week-old kittens. However, the present data indicate that several months after the retinal lesions the spatial limit of cortical reorganization in kitten-lesioned animals is about the same as that (5–6 mm) observed in adult-lesioned cats and macaques (Kaas *et al.*, 1990; Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995; Schmid *et al.*, 1996; Calford *et al.*, 2000; the present study). This result is consistent with the fact that long-range horizontal connections in cat's area 17 reach their maximal extent by the end of the fourth postnatal week (cf. Luhmann *et al.*, 1990; Galuske & Singer, 1996).

In both adult- and kitten-lesioned animals a further factor, but one not yet properly evaluated, is the contribution to topographic reorganization of area 17 made by feedback projections from extrastriate cortices.

Receptive field properties of ectopic receptive fields vs. normal receptive fields

In both adult- and kitten-lesioned animals months or years after the monocular or topographically matching binocular retinal lesions the sizes of the ectopic RFs are either virtually the same (Kaas *et al.*, 1990; Calford *et al.*, 2000; the present study) or only slightly larger (Chino *et al.*, 1995; Darian-Smith & Gilbert, 1995) than those of their normal counterparts. Consistent with this, it was reported recently that for the LPZ cells recorded from area 17 of adult cats whose retinas were lesioned monocularly when they were 8-week-old kittens (>3 years earlier) there are no significant interocular differences in the optimal spatial frequencies, spatial resolutions or spatial frequency bandwidths (Matsuura *et al.*, 2002). Presumably, a dynamic balance between excitatory inputs tending to enlarge RFs and more localized inhibitory interconnections via GABAergic interneurons (cf. Albus & Wahle, 1994) tending to restrict RFs accounts for the fact that normally the RF of a visual cortical cell is restricted to an area much less than might be inferred from the extent of horizontal connections (e.g. Gilbert *et al.*, 1990).

In the studies in which bilateral homonymous retinal lesions were made in adulthood (Gilbert & Wiesel, 1992; Chino *et al.*, 1995; Chino, 1995; Darian-Smith & Gilbert, 1995) as well as in the studies in which the monocular retinal lesions were made in adulthood (Calford *et al.*, 2000) or in kittens (the present study; Chino *et al.*, 2001; Matsuura *et al.*, 2002), the ectopic RFs of neurons recorded from the LPZ of area 17 are reported to exhibit a normal range of orientation selectivities. Thus, normal orientation selectivity of cortical neurons can be based on the cortico-cortical interactions. Close matching of orientation preferences and selectivities of ectopic and normal receptive fields in animals lesioned monocularly (Calford *et al.*, 2000; Matsuura *et al.*, 2002; the present study) suggests an important role of demonstrated substantial interconnections between columns of similar orientation selectivity across wide expanses of striate cortex. Substantial morphological and functional evidence indicates that in primary visual cortices of the cat (areas 17 and 18) these preferences are significantly influenced by the activity of intrinsic horizontal associational connections that connect regions of iso-orientation preference (see for reviews Kisvárdy *et al.*, 1996; Vidyasagar *et al.*, 1996). Indeed, in the cat injection of retrograde tracers demonstrated connections between iso-orientation columns across 8 mm of area 17 (Gilbert & Wiesel, 1989; see for reviews LeVay & Nelson, 1991; Gilbert, 1998; see also Matsubara *et al.*, 1985). Broader orientation tuning to stimuli presented via ectopic RFs (the present study; see, however, Matsuura *et al.*, 2002) is consistent with the proposal that the excitatory convergence of the LGNd input neurons on

cortical cells makes an important contribution to their orientation selectivity (Hubel & Wiesel, 1959, 1962; for recent review see Miller, 2003). The fact that the direction selectivities and the overall receptive field organization (simple vs. complex) of cells recorded from the LPZ were very similar irrespective of the eye via which the stimuli were presented suggests to us that excitatory horizontal associational connections might interconnect the cells sharing not only the same orientation preferences but also the same directional preferences and spatio-temporal RF organization. Alternatively, the fact that close matching of direction selectivity indices is apparent only in animals with long postlesion visual experience (KL and AL cats) but not in animals with shorter postlesion experience (Calford *et al.*, 2000) suggests a role of time and/or visual experience in matching direction selectivities of ectopic RFs with those of their normal counterparts.

Topographic reorganization of the LPZ in area 17 of adult cats: binocular vs. monocular retinal lesions

It has been reported in the past that: (i) following monocular circumscribed retinal lesions the ectopic receptive fields of the cells recorded from the LPZ of the primary visual cortices of adult cats to stimuli presented via the lesioned eye become apparent only when the other (nonlesioned) eye is enucleated (Kaas *et al.*, 1990; Chino *et al.*, 1992); (ii) several months after circumscribed monocular retinal lesions all cells recorded from the LPZ in striate cortex of adult macaque monkey could be activated only by stimuli presented via the nonlesioned eye (Murakami *et al.*, 1997); and (iii) the ectopic receptive fields of cells recorded from the LPZ in striate cortices of cats or macaque monkeys were, however, apparent when the retinal lesions were made in homonymous parts of the two retinæ (Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Chino *et al.*, 1995; Chino, 1995; Darian-Smith & Gilbert, 1995). It has been suggested, therefore, that reorganization of visual cortex following spatially circumscribed retinal deafferentation is masked by an inhibitory process dependant on the input from the topographically corresponding part of the intact retina. Indeed, a substantial amount of data indicates that, in cats monocularly deprived of pattern vision during the critical period of development, the nondeprived eye exerts a powerful inhibitory influence on the responses to stimuli presented via the deprived eye (see for recent review Dreher *et al.*, 2001). Similarly, in adult cats in which convergent or divergent strabismus was surgically induced in the first 12 weeks of postnatal life, the inhibition exerted by the nondeviating (normal) eye on the deviating eye appears to be stronger and longer-lasting than the reverse (Singer *et al.*, 1980).

On the other hand, several studies reported that ectopic RFs of neurons within the LPZ in area 17 of adult cats could be revealed following a circumscribed monocular retinal lesion (Rosa *et al.*, 1995; Schmid *et al.*, 1996; Calford *et al.*, 1999, 2000) or monocular detachment of part of the retina (Schmid *et al.*, 1995) without removal of the nonlesioned eye or additional retinal lesion in the homonymous part of the retina of the other eye.

Several factors contribute to this apparent discrepancy between the results obtained by Kaas, Chino and their colleagues (Kaas *et al.*, 1990; Chino *et al.*, 1992; paucity of ectopic RFs in monocularly lesioned adult cats) and those obtained in our laboratories (numerous ectopic RFs in monocularly lesioned adult cats). Thus, consistent with a suppressive effect emanating from the topographically corresponding part of the intact retina in both AS and AL cats, many of the responses of the LPZ cells recorded from the granular and infragranular layers to stimuli presented via the lesioned eye tended to be rather weak and frequently the ectopic RFs were not

'plottable' using hand-operated stimuli presented via the lesioned eye. Clearly without extensive testing it would be quite easy to miss their ectopic RFs. Second, most binocular LPZ cells located in the granular and infragranular layers of monocularly lesioned adult cats exhibited substantially lower upper cut-off velocities for stimuli presented via the lesioned eye. Third, in cats lesioned in adulthood ocular dominance distribution of cells recorded from the supragranular layers of the LPZ region were not significantly different from the ocular dominance distribution of cells recorded from the visuotopically corresponding part of area 17 of normal cats (see, however, Schmid *et al.*, 1996). The proportion of LPZ cells recorded from the supragranular layers in our studies was, however, either fairly low (data collected by Calford *et al.*, 2000 and re-analysed in the present study) or there was a complete paucity of such cells (AL cats in the present study).

The low proportion or paucity of supragranular LPZ cells in our samples is due to a specific spatial arrangement of topographic representation of the contralateral visual field in cat's striate cortex. Thus, in order to reach the LPZ region of area 17 in animals in which the retinal lesions were made in the upper nasal retinas one has to advance the electrode along the marginal gyrus on the medial bank of the cerebral hemisphere (Tusa *et al.*, 1978; see also inserts in Figs 2 and 3). When the electrode is directed vertically to the cortical surface along the medial bank of the hemisphere >600–700 µm from the medial edge of the cortex, by the time it reaches the LPZ it is restricted to the granular and infragranular layers. Indeed, the reconstructions of the electrode tracks presented by Chino and colleagues suggest that their recordings from the LPZ were very strongly biased in favour of the granular and infragranular layers (see Fig. 3A and B in Chino *et al.*, 1992; cf. also fig. 3 in Chino *et al.*, 1995).

Ectopic receptive fields in monocularly lesioned cats: granular–infragranular vs. supragranular layers

In both kitten-lesioned (KL) cats and adult-lesioned (AS and AL) cats the LPZ cells recorded from the granular and infragranular layers tended to be dominated by the input from the nonlesioned, ipsilateral eye. However, the ocular dominance distributions of the LPZ cells recorded from the granular and infragranular layers of AL and AS cats were significantly different from those in the visuotopically corresponding parts of area 17 of normal cats, whereas in the KL cats there was no significant difference. Furthermore, in adult-lesioned cats, unlike in kitten-lesioned cats, substantial proportions of class 4 LPZ cells recorded from granular and infragranular layers were not 'plottable' with hand-held stimuli when stimuli were presented via the lesioned eye. Finally, in kitten-lesioned cats, unlike in adult-lesioned cats, the upper cut-off velocities of binocular LPZ cells recorded from the granular and infragranular layers tended to be very similar irrespective of the eye through which the stimuli were presented.

In view of the fact that the differences in the properties of granular and infragranular LPZ cells in kitten-lesioned and adult-lesioned cats are largely independent of the length of postlesion experience it appears that there are substantial differences in the degree of cortical plasticity between adult and adolescent cats. Indeed, consistent with our present observations, it has been reported recently that following a long (>3 years) postlesion experience period after monocular retinal lesions in young (8-week-old) kittens, most of the LPZ cells in area 17 respond 'nearly as robustly to optimal stimuli in new as in retained receptive fields' despite the substantially higher contrast thresholds for stimuli presented via the lesioned eye (Chino *et al.*, 2001; Matsuura *et al.*, 2002). Furthermore, the LPZ neurons recorded from the parastriate cortex (cytoarchitectonic area 18; area V2) of adult cats whose retinas were lesioned when they were 8-week-old kittens

exhibited the upper cut-off velocities to stimuli presented via the lesioned eye which were virtually indistinguishable from those to stimuli presented via the nonlesioned eye (Young *et al.*, 2002).

Cortical plasticity and NMDA receptors

In the visual cortices of both cats and ferrets, apparent disconnection of primary visual cortices from the eye deprived of visual pattern experience during the critical period of development (activity-dependent plasticity) is largely mediated by the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor (see for reviews Rauschecker, 1991; Daw, 1994; see also Roberts *et al.*, 1998; Daw *et al.*, 1999; see, however, Kasamatsu *et al.*, 1998). Hence, the difference in responsiveness to stimuli presented via the lesioned eye between the LPZ cells in the supragranular layers and those in the granular and infragranular layers of area 17 of adult-lesioned cats might be related to prominence in the supragranular layers vs. the paucity in the granular and infragranular layers of NMDA receptors (Fox *et al.*, 1989; see also Bode-Greuel & Singer, 1989; Shirokawa *et al.*, 1989; cf. Rosier *et al.*, 1993).

The differences between adult-lesioned cats and kitten-lesioned cats can also be related to the difference in the laminar distribution of NMDA receptors. Thus, the density of NMDA receptors in the supragranular layers of visual cortices becomes high in 4-week-old kittens and remains high throughout the rest of the cat's life (Bode-Greuel & Singer, 1989; cf. Rosier *et al.*, 1993). By contrast, the density of NMDA receptors in the granular and infragranular layers drops dramatically between postnatal weeks 12 and 17 and remains low throughout the rest of the cat's life (Bode-Greuel & Singer, 1989; cf. Rosier *et al.*, 1993; see, however, Gordon *et al.*, 1996). If indeed there is a causal relationship between the expression of NMDA receptors and cortical plasticity following monocular retinal lesions one would expect that, for LPZ cells in granular and infragranular layers, the period of heightened plasticity would be largely over by postnatal week 17. Whether this is so or not it is clear that there is a marked difference between the supragranular layers and the granular/infragranular layers. Plasticity in the latter is marked in the early stages of postnatal cat's life and is generally reduced in adulthood. By contrast, plasticity in the supragranular layers seems to be undiminished in adulthood.

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Abbreviations

AL cats, cats whose retinas were lesioned in adulthood (long postlesion visual experience); AS cats, cats whose retinas were lesioned in adulthood (relatively short postlesion visual experience); DI, direction selectivity index; KL cats, adult cats whose retinas were lesioned when they were 8-week-old kittens (long postlesion visual experience); LGNd, dorsal lateral geniculate nucleus; LPZ, lesion projection zone; NMDA, *N*-methyl-D-aspartate; PSTH, peristimulus time histogram; RF, excitatory receptive field (minimum discharge field); Rnp, peak discharge rates in the nonpreferred direction; Rp, peak discharge rates at the preferred direction.

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