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Topographic reorganization in area 18 of adult cats following circumscribed monocular retinal lesions in adolescence

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Circumscribed laser lesions were made in the nasal retinae of one eye in adolescent cats. Ten to sixteen months later, about 80 % of single neurones recorded in the lesion projection zone (LPZ) of contralateral area 18 (parastriate cortex, area V2) were binocular but when stimulated via the lesioned eye had ectopic discharge fields (displaced to normal retina in the vicinity of the lesion). Although the clear majority of binocular cells recorded from the LPZ responded with higher peak discharge rates to stimuli presented via the non-lesioned eye, the orientation and direction selectivities as well as preferred and upper cut-off velocities for stimuli presented through either eye were very similar. Furthermore, the sizes of the ectopic discharge fields of binocular cells recorded from the LPZ were not significantly different from those of their counterparts plotted via the non-lesioned eye. Thus, monocular retinal lesions performed in adolescent cats induce topographic reorganization in the LPZ of area 18. Although a similar reorganization occurs in area 17 (striate cortex, area V1) of cats in which monocular retinal lesions were made either in adulthood or adolescence, in view of the very different velocity response profiles of ectopic discharge fields in areas 17 and those in area 18, it appears that ectopic discharge fields in area 17 are largely independent of excitatory feedback input from area 18.

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In area 17 (striate cortex, area V1) of the cat and macaque visual cortices, neurones deprived of their principal visual input by a circumscribed retinal lesion 'develop' new 'ectopic' excitatory receptive fields (discharge fields or DFs) at loci bordering the lesion (for reviews see Chino, 1995; Darian-Smith & Gilbert, 1995; Dreher *et al.* 2001). A substantial effort has gone into elucidating the mechanism underlying development of these ectopic DFs (for review see Dreher *et al.* 2001). Recent anatomical (Darian-Smith & Gilbert, 1994) as well as functional (Wright *et al.* 1999) studies have provided strong evidence for the mediation of visual input to these partially deafferented neurones via intrinsic horizontal connections within area 17. However, several lines of evidence suggest that other visuotopically (retinotopically) organized cortical areas might contribute to the ectopic DFs of neurones in the lesion projection zone (LPZ) of area 17. In particular, another part of the primary visual cortices of carnivores, cytoarchitectonic area 18 (parastriate cortex, area V2), is often considered as a possible source of extrinsic excitatory input to neurones within the LPZ of area 17 (Chino, 1995; Darian-Smith & Gilbert, 1995). Thus, while area 18 has extensive visuotopically ordered interconnections with area 17 (cf. reviews Rosenquist, 1985; Dreher, 1986; Salin & Bullier, 1995) the response properties of area 18 neurones are only mildly affected by acute inactivation of area 17 (Dreher & Cottee, 1975; Sherk, 1978; Casanova *et al.* 1992; cf. however Donaldson & Nash, 1975 for effects of chronic deactivation of area 17). It appears, therefore, that area 18 works largely independently of area 17. Furthermore, at any given eccentricity the DFs of area 18 neurones are approximately three times the size of those of area 17 neurones (Hubel & Wiesel, 1962, 1965; Stone & Dreher, 1973; Tusa *et al.* 1978, 1979; Dreher *et al.* 1980; for review see Orban, 1984). Consistent with this finding at any given eccentricity (at optimal velocities and/or optimal temporal frequencies) area 18 cells prefer spatial frequencies on average one-third of those preferred by area 17 neurones (Movshon *et al.* 1978; Berardi *et al.* 1982; Bisti *et al.* 1985; Galli *et al.* 1988). Therefore, we would expect that very few neurones in the LPZ of area 18 would have their DFs totally eclipsed by a lesion of conventional size and thus could still provide effective excitatory input to their visuotopically corresponding counterparts in area 17 (cf. Chino, 1995; Darian-Smith & Gilbert, 1995). Indeed, in normal cats during reversible inactivation of visuotopically corresponding parts of lamina A of the dorsal lateral geniculate nucleus (LGNd), area 18 provides effective excitatory, contralateral eye input to area 17 neurones located in the supragranular layers (Mignard &

Malpeli, 1991). Furthermore, the responsiveness of area 17 cells to visual stimulation via the contralateral eye is not reduced by reversible inactivation of lamina A (Mignard & Malpeli, 1991).

We have previously published results demonstrating that circumscribed monocular retinal lesions either in adult (Calford *et al.* 2000) or adolescent (Burke *et al.* 2000; Dreher *et al.* 2000, cf. also Chino *et al.* 2001) cats result in topographic reorganization within the LPZ of area 17 (cf. for review Dreher *et al.* 2001). Topographically organized projections from the LGNd to both areas constituting the primary visual cortex, that is, areas 17 and 18, are already present in newborn kittens (Henderson, 1982). It is unlikely, therefore, that circumscribed monocular retinal lesions made in adolescent cats would affect the pattern of geniculo-cortical projections to primary visual cortices. At the same time, the proportion of neurones within the LPZ of area 17 for which DFs could be plotted reliably when stimuli were presented via the lesioned eye was substantially higher when the monocular retinal lesions were made in adolescence rather than in adulthood (Burke *et al.* 2000; Dreher *et al.* 2000, 2001). Thus, in the present study we have examined the binocular status of neurones in the LPZ of area 18 of adult cats, which received circumscribed monocular retinal lesions during their adolescence. Furthermore, we have compared the response properties (including position and size of excitatory receptive fields as well as selectivities for orientation, direction and velocity) of binocular neurones recorded from the LPZ of area 18 to stimuli presented via either eye. We have used these results to assess the validity of the proposal that cells in the LPZ of area 18 provide the principal excitatory ectopic visual input to cells in the LPZ of area 17 (cf. Chino, 1995; Darian-Smith & Gilbert, 1995). A preliminary report describing some of our findings has already been published in the form of an abstract (Young *et al.* 2001).

METHODS

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.

Retinal lesions and animal preparation

Discrete retinal lesions of approximately 5–9 deg diameter were placed in the left (two animals) or right (one animal) eye of adolescent (8 weeks old) kittens anaesthetized with ketamine (Ketalar; 40 mg kg^{-1}, I.M.) and xylazine (Rompun; 4 mg kg^{-1}, I.M.). Lesions of all neural layers in the near-upper nasal region of retina were produced with an argon-green laser focused to approximately 300 μm, at an intensity of 450–650 mW (for details of delivery system see Schmid *et al.* 1996). Lesions were achieved by continuous sweeping of the spot of laser light across the chosen region (each traverse lasting about 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, which lasted about 20 min, the kittens were returned to their mothers. No abnormal visual or behavioural traits were observed in any of the animals.

After 45–74 weeks of normal post-lesion visual experience, extracellular single neurone recordings were made from the part of area 18 corresponding in each case to and surrounding the projection zone of the lesion. On the day preceding the experiment the animals were given dexamethasone (0.3 mg kg^{-1}, I.M.) to reduce the possibility of brain oedema. During the experiment the animals were initially anaesthetized with ketamine (20 mg kg^{-1}, I.M.) and injected with atropine sulphate (0.1 mg kg^{-1}, I.M. to reduce mucous secretion) and dexamethasone (0.3 mg kg^{-1}, I.M.). Tracheal and cephalic vein cannulations were performed to allow artificial ventilation and infusion of drugs and nutrients. Eye movements were additionally minimized by bilateral sympathectomy.

During the recording sessions anaesthesia was maintained with a gaseous mixture of 67 % N_2O–33 % O_2) and halothane (0.4–0.7 %). Antibiotic (amoxycillin trihydrate, 75 mg), dexamethasone phosphate (3 mg) and atropine sulphate (0.3 mg) were injected I.M. on a daily basis. Neuromuscular blockade was induced with an intravenous injection of 40 mg of gallamine triethiodide in 1 ml sodium lactate (Hartmann's) solution and maintained with continuous injection of gallamine triethiodide (7.5 mg kg^{-1} h^{-1} 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 about 37.5 °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. Electroencephalogram (EEG) and the electrocardiogram (ECG) were also monitored continuously. By adjusting, when necessary, halothane levels in the gaseous mixture the EEG and heart rate were maintained respectively at the slow-wave synchronized activity and below 180 beats min^{-1}. Atropine sulphate (1–2 drops, 1 %) to dilate the pupils and 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 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.

Using a fibre optic light source (Pettigrew *et al.* 1979) we monitored rarely occurring small eye movements by projecting the optic discs (as well as the retinal lesion) onto a tangent screen every few hours. The positions of the areae centrales were plotted by reference to the optic discs. 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. Thus the lesion boundaries were easily plotted onto the tangent screen using a fibre optic light source.

Recording from area 18 and visual stimulation

For recordings from area 18, a plastic cylinder was mounted and glued around the craniotomy (Horsley-Clarke co-ordinates posterior 2 to anterior 5 and lateral 0 to 7) above the visual cortex contralateral to the lesioned retina. A smaller dural opening was made and a stainless-steel microelectrode (11 MΩ; FHC,

Brunswick, ME, USA) positioned just above the cortical surface and the cylinder was filled with 4 % agar gel and sealed with warm wax (melting point 40 °C). The microelectrode was advanced further with a hydraulic micromanipulator (Fig. 1*A* and *B*). Action potentials of single neurones were recorded extracellularly, conventionally amplified and then used to trigger standard pulses that were fed to a microcomputer for on-line analysis and data storage. The excitatory receptive fields (minimum discharge fields) of recorded neurones were plotted and assessed by at least two experimenters by listening to the cell's responses to moving light slits from a hand-held projector and hand-held black bars (cf. Barlow *et al.* 1967; Dreher *et al.* 1980). Although, the plots of the minimum DFs were based on subjective assessments there was always an excellent agreement between the DF plots made independently by two or more experimenters. Objective quantitative assessments of neural response properties (i.e. discharge rate, velocity, orientation and direction tunings), as well as the confirmation of the position of the centres of the DFs, were based on the peristimulus time histograms (PSTHs) of the responses of cells to light slits with a luminance of 15 cd m^{-2} against a background luminance of 0.9 cd m^{-2} 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). The PSTHs were constructed by summing the responses to 10–100 successive stimulus sweeps (number of sweeps related positively to stimulus velocity) at each test condition. The responses were then smoothed using a Gaussian weighted average over five neighbouring bins. Using elongated light slits (10 deg or more) we determined optimal orientations and optimal velocities and calculated the direction selectivity index (DI) by the following formula:

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

where R_p and R_np are the peak discharge rates at preferred and non-preferred directions, respectively.

Localization of recording sites

At the end of the recording sessions the animals were deeply anaesthetized (120 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 a 4 % solution of paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The electrode tracks were reconstructed from 50 μm coronal sections stained with cresyl violet.

Lesion projection zone and data analysis

The location and extent of each LPZ within area 18 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 that describes the extent of DF scatter for strictly radial electrode penetrations as a function of eccentricity. Schmid and colleagues (1996) used the radial value of the Albus (1975) point-spread function to define a region 1.4 mm, in cortical projection terms, inside the perimeter of the LPZ of area 17 in which cells may still receive direct input from the LGNd. This region, referred to as the fringe projection zone, was delineated in area 18 on a similar basis. One of the physical correlates of the cortical point-spread function is the arbor dimensions of geniculo-cortical afferents. Anatomical and physiological studies have shown that the arborization diameters of Y-type geniculate afferents in area 18 tend to be larger than those of X-type geniculate afferents in area 17 (Freund *et al.* 1985; Humphrey *et al.* 1985*a*,*b*). Furthermore, even if we use the point-spread radius defined for area 17, the lower cortical magnification in area 18 and the eccentricity of the retinal lesions make it necessary to define the entire representation of the lesion in area 18 as a fringe projection zone rather than a LPZ, for all the cats involved in this study. While we refer to the projection zone of the lesion in area 18 as LPZ it should be understood that the neurones in this area are not assumed to be completely deprived of geniculate afferents relaying information from the undamaged retina.

Values for normal DF incongruities (the distance between the two DF centres of a binocular neurone when the areae centrales are aligned) in the region of area 18 representing the visual field from 0 to 25 deg eccentricity and the so-called transition zone between areas 17 and 18, were derived from Ferster (1981) and Pettigrew & Dreher (1987), respectively.

Although the incongruity values of Ferster (1981) were derived from a population comprising exclusively cells with disparity-selective responses, we believe the values are indicative of the incongruity distribution in area 18 because Ferster's values for area 17, also restricted to disparity-selective cells, are very similar to previously published incongruity distributions for area 17 in which no such discrimination was made (Joshua & Bishop, 1970; von der Heydt *et al.* 1978).

Two non-parametric tests were used: the χ^2 test and the Wilcoxon's matched-pairs, signed-ranks test (Siegel, 1956) to assess statistical differences in the sample data. Statistical differences were considered significant when probability (P) at two-tailed criterion was < 0.05. Means are presented with S.D.

RESULTS

The DFs revealed by photic stimulation of either the lesioned or non-lesioned eye were plotted on a tangent screen relative to the optic disc and area centralis (AC) of each eye, the lesion, and the lesion's equivalent region in the non-lesioned eye (Fig. 1*C* and *D*).

Most neurones recorded in the LPZ (78 %; 25/32) were binocular, displaying DFs displaced to areas of the normal retina in the vicinity of the retinal lesion when the stimuli were presented via the lesioned eye. The proportion of neurones in our sample with displaced DFs may be even greater than 78 %, but we have no way of precisely verifying DF displacement for monocular neurones which were driven exclusively via the lesioned (contralateral) eye (class 1 neurones).

Of the 32 cells we recorded in the LPZ of area 18 only 17 possessed DFs that we could confidently plot via both eyes with hand-controlled stimuli. Of this plotted sample of 17 neurones, many of their non-lesioned eye DFs extended well beyond the region equivalent to the lesion. However, for 11 of these cells there was no spatial overlap in retinal co-ordinates between their DFs plotted via the lesioned and those plotted via the non-lesioned eye. Furthermore, the majority of the neurones (9/17; 53 %) in the plotted sample (with DF centres at eccentricities of 10–17 deg) had DF incongruities 0.6–17 deg greater than the largest value encountered by Ferster (1981) in a sub-population of area

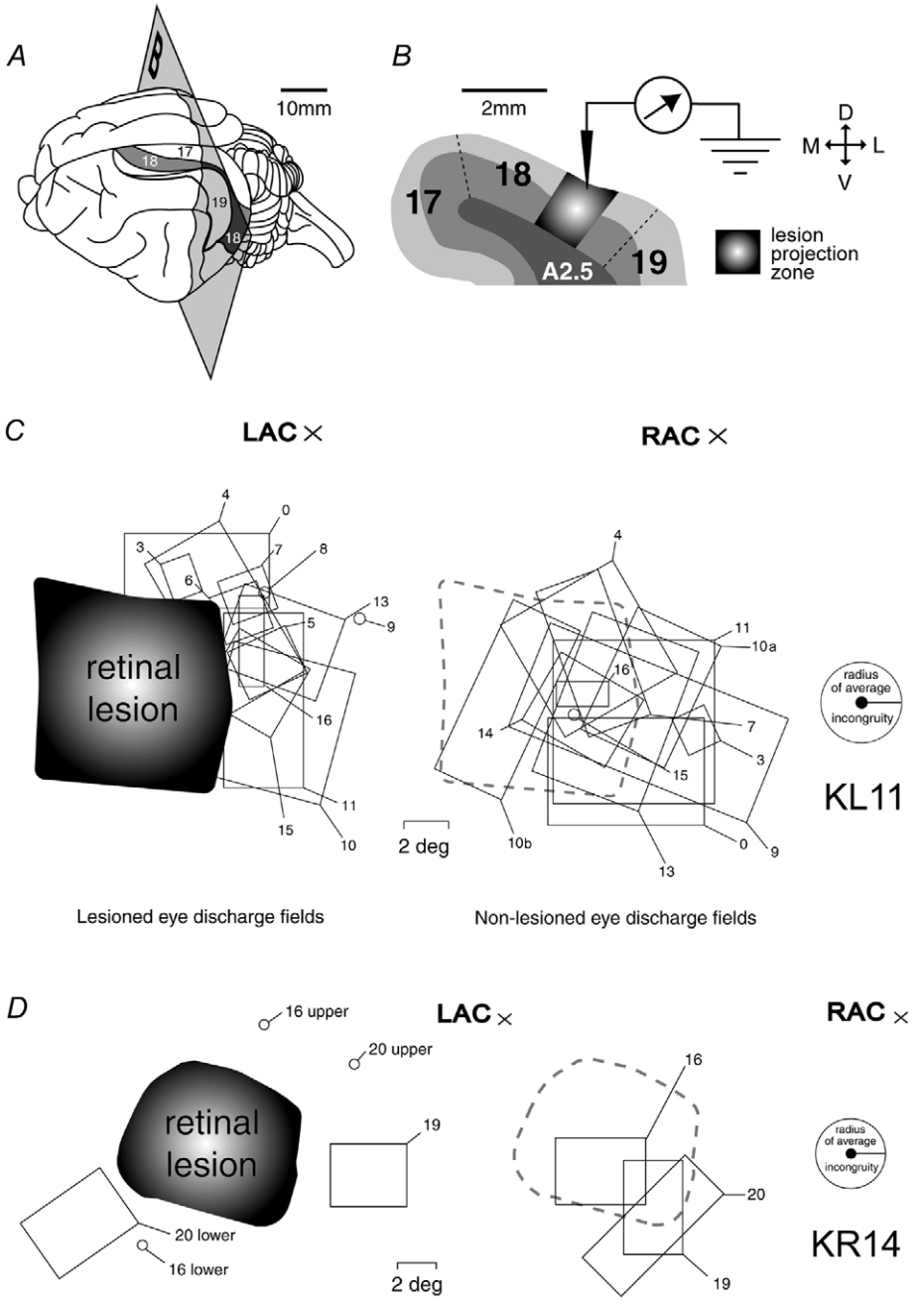

Figure 1. Discharge fields of neurones recorded from the LPZ of area 18

A, dorsolateral view of the cat brain with the locations of cytoarchitectonic areas 17, 18 and 19 indicated (after Tusa *et al.* 1978, 1979). *B*, average position of the LPZ in area 18 viewed in a coronal section (Horsley-Clarke anterior 2.5) through areas 17, 18 and 19. *C* and *D*, plots on the tangent screen of the outlines of ectopic and normal discharge fields (DFs) of binocular neurones recorded from the lesion projection zone (LPZ) in area 18 of the cat. *C*, left, the outline of the retinal lesion in the left eye of cat KL11 and the outlines of DFs (plotted via the lesioned eye) of single neurones recorded from the LPZ of area 18 of this cat. LAC; the left area centralis. Right, the outline of the retinal lesion in the left eye projected onto the right retina (grey dashed line) and the outlines of the normal corresponding DFs of single binocular neurones recorded from the LPZ of area 18 of cat KL11. RAC, the right area centralis. *D*, equivalent to *C* but for cat KR14. The smaller circles in both *C* and *D* indicate the approximate centres of DFs of neurones for which the signal-to-noise ratio of the response was not sufficient to plot the entire DF. Note that in *C*, cell 10 exhibited two spatially separated sub-fields (10a, ON discharge region and 10b, OFF discharge region) when stimulated via the non-lesioned (right) eye. These sub-fields were not apparent when the stimuli were presented via the lesioned (left) eye. By contrast, in *D* the DFs of units 16 and 20 consisted of two spatially distinct sub-fields when they were stimulated via the lesioned (left) eye and these sub-fields were not apparent when the cells were stimulated via the non-lesioned (right) eye. The radii of the larger circles on the right in both *C* and *D* indicate the expected average incongruity of DF positions, estimated from incongruity values of binocular cells recorded in area 18 of normal cats (cf. Ferster, 1981).

18 neurones recorded from normal cats (Fig. 2*A*). Of the remaining eight cells in the plotted sample, six had DF incongruities larger than the average value of 1.8 deg (derived from the data of Ferster, 1981; Fig. 2*A*) and three had DF incongruities larger than the average value of 2.2 deg (derived from the data of Pettigrew & Dreher, 1987). Finally, some binocular neurones in the LPZ, when stimulated via the lesioned eye, displayed split DFs with sub-regions on opposite sides of the lesion, again well beyond the dimensions of their corresponding DFs in the non-lesioned eye (Fig. 1*D*). On the other hand, one cell in our sample also displayed a split DF (with spatially separated ON and OFF discharge regions but in close proximity to each other) when stimuli were presented via the non-lesioned eye (see 10a and 10b in Fig. 1*C*).

Of the 17 cells recorded from the LPZ of area 18 and for which we plotted entire DFs via either eye, seven were identified as simple (S) cells since their DFs contained spatially distinct ON and OFF discharge regions when stationary flashing stimuli were employed and/or contained spatially distinct light and dark bar discharge regions when moving stimuli were employed (cf. Dreher & Cottee, 1975; Tretter *et al.* 1975; Orban & Callens, 1977; Harvey, 1980; for reviews see Stone *et al.* 1979; Orban, 1984; cf. also Pernberg *et al.* 1998). Another eight of these cells were classified as complex (C) cells since their DFs contained spatially overlapping ON and OFF discharge regions and/or spatially overlapping light and dark bar discharge regions (cf. Hubel & Wiesel, 1965; Stone & Dreher, 1973; Dreher & Cottee, 1975; Tretter *et al.* 1975; Orban & Callens, 1977; Harvey, 1980; for reviews see Stone *et al.* 1979; Orban, 1984; cf. also Pernberg *et al.* 1998). For all cells the designation as simple or complex did not depend on the eye via which the stimuli were presented. Despite differences in the relative magnitude of response to stimuli presented via the lesioned eye and via the normal eye (ocular dominance class, see below), most binocular

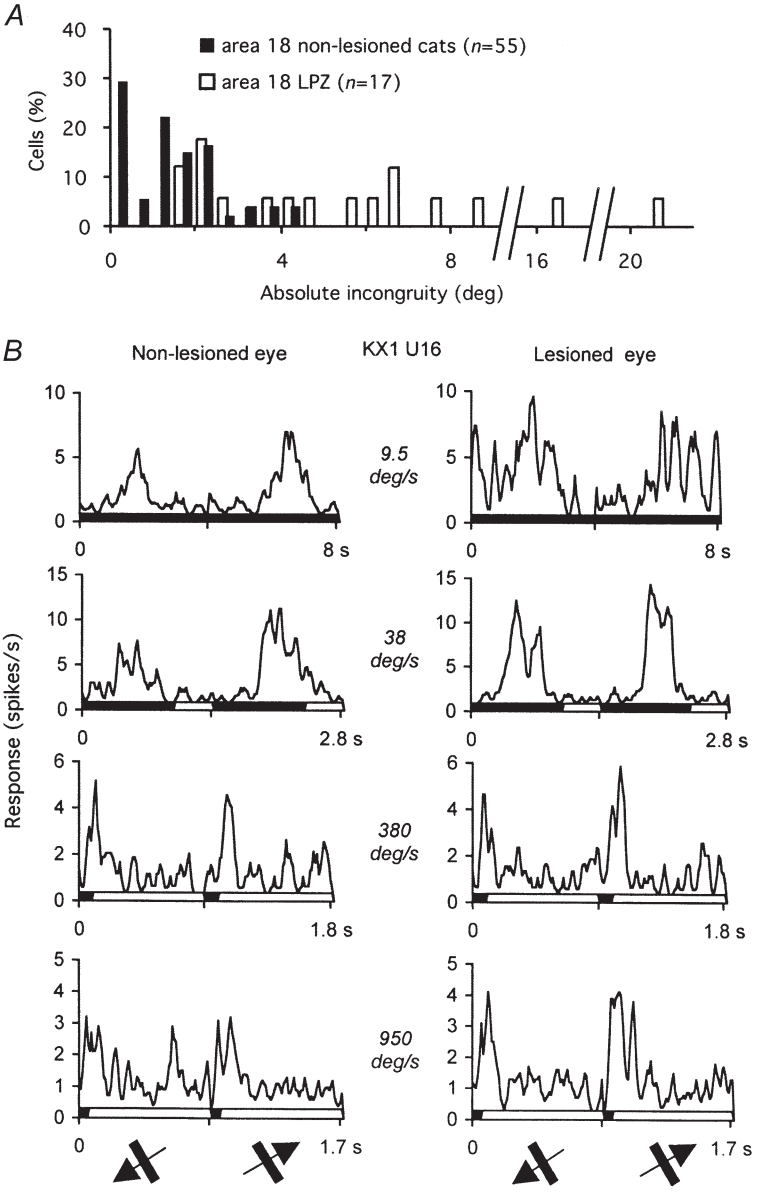

Figure 2. Discharge field incongruities and peristimulus time histograms of binocular cells in the LPZ of area 18

A, percentage histogram of discharge field incongruities of binocular neurones recorded from area 18 of normal cats (filled columns, modified from Ferster, 1981) and from the LPZ of area 18 following a monocular circumscribed retinal lesion (open columns, present study). *B*, peristimulus time histograms of a binocular neurone (KX1 16) recorded from the LPZ of area 18 to an optimally oriented light bar (7.4 deg × 1.4 deg) moving at the indicated velocities and presented via the non-lesioned (left, ipsilateral) or lesioned (right, contralateral) eye. The duration of recording is shown on the abscissa, the centre of which marks the change in stimulus direction. The period of stimulus movement is indicated (filled bar) as is the period when the stimulus remains stationary outside the discharge field (open bar), which was increased in proportion to the stimulus velocity. Note that the cell responds at a wide range of stimulus velocities irrespective of the eye through which the stimuli are presented. Furthermore, the cell is a class 2 cell since it responds more vigorously to stimuli presented via the contralateral eye.

cells recorded from the LPZ of area 18 responded over a wide range of stimulus velocities irrespective of the eye through which the optimally oriented stimuli were presented (Fig. 2*B*).

Figure 3*A* compares the distribution of ocular dominance classes of area 18 neurones recorded inside the LPZ with those of area 18 neurones recorded in normal animals in the approximate topographically corresponding region (cf. Dreher *et al.* 1992). Note that in both the control and LPZ samples most neurones were binocular (classes 2, 3 and 4: 65 and 78% in control and LPZ samples, respectively). However, while most of the neurones recorded in area 18 of normal animals were either dominated or driven exclusively by stimuli presented via the contralateral eye (class 2 and class 1 cells), most of the binocular neurones recorded from the LPZ of lesioned animals were dominated by the ipsilateral, that is, the non-lesioned eye (class 4 cells). Not surprisingly, the difference between these two populations was highly significant ($P < 0.002$ or $P < 0.02$, χ^2 test; for details see legend to Fig. 3*A*). Quantitative data concerning the magnitude of responses of 19 binocular cells recorded from the LPZ of area 18 indicated that indeed for most cells the peak

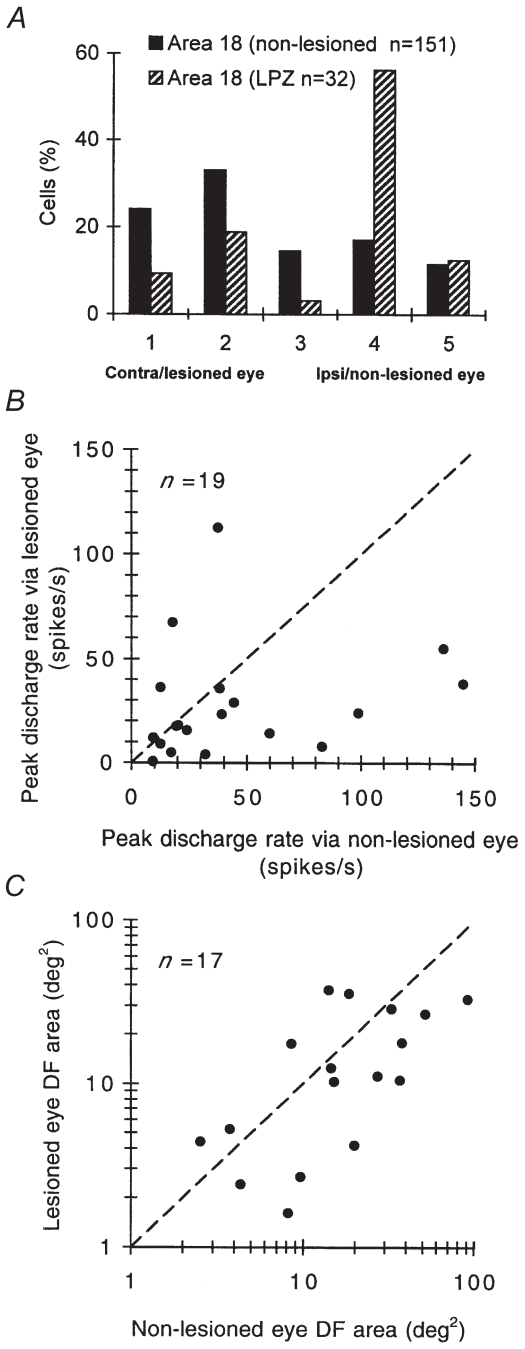

Figure 3. Ocular dominance, peak discharge rates and discharge field areas of binocular cells in the LPZ of area 18

A, percentage bar graph of eye dominance classes for single neurones recorded in either the LPZ of area 18 in monocularly lesioned cats (hatched columns) or the topographically corresponding region of area 18 in normal cats (filled columns). Data for non-lesioned cats were taken from Dreher *et al.* (1992). Monocular cells were classified as either class 1 or class 5 depending upon whether the excitatory responses could be evoked by stimuli presented via the contralateral (lesioned) eye or via the ipsilateral (non-lesioned) eye, respectively. Neurones categorized as class 2 or 4 were binocular cells dominated respectively by the contralateral (lesioned) or ipsilateral (non-lesioned) eye. Neurones that responded equally well to visual stimulation via either eye were categorized as class 3 cells. Note that in both populations the clear majority of neurones were binocular (classes 2, 3 and 4) . In view of the relatively small number of cells recorded from the LPZ of area 18, for the purpose of statistical analysis the neurones recorded from the LPZ of area 18 of lesioned animals and those recorded from area 18 of normal cats were divided into two rather than five eye dominance groups. One group consisted of all cells categorized as eye dominance class 1, 2 or 3 while the other group consisted of all cells categorized as eye dominance class 4 or 5. This division separates area 18 cells into those dominated or driven exclusively by the contralateral (lesioned eye) and those dominated or driven exclusively by the ipsilateral (non-lesioned) eye. Such grouping of eye dominance classes reveals a highly significant difference ($P < 0.002$; χ^2 test, two-tailed criterion) between the samples of area 18 cells recorded in normal animals and in the LPZ of area 18 of lesioned animals. An alternative grouping of eye dominance classes in which one eye dominance group consisted of all cells categorized as eye dominance class 1 or 2 while the other group consisted of all cells categorized as eye dominance class 3, 4 or 5 also reveals a significant difference between the sample of area 18 cells recorded in normal animals and that recorded from the LPZ of lesioned animals ($P < 0.02$; χ^2 test, two-tailed criterion). *B*, pairwise comparisons of the peak discharge rates of binocular neurones in the LPZ of area 18 in monocularly lesioned cats for stimuli presented via either eye. Note that for about half the neurones, the peak discharge rates for stimuli presented via the non-lesioned (ipsilateral) eye were substantially higher than those for stimuli presented via the lesioned (contralateral) eye and for only a small proportion of neurones the peak discharge rates for stimuli presented via lesioned eye were substantially higher than those for stimuli presented via the normal eye. The difference between the two populations is statistically significant ($P = 0.05$, Wilcoxon's matched-pairs, signed-ranks test). *C*, pairwise comparisons of the sizes of discharge fields (DFs) of binocular neurones in the LPZ of area 18 in monocularly lesioned cats for stimuli presented via either eye. Note that for the majority of binocular neurones recorded from the LPZ, the DFs were smaller when the stimuli were presented via the lesioned eye. The difference between the two populations was, however, not statistically significant ($P > 0.05$, Wilcoxon's matched-pairs, signed-ranks test).

discharge rate for stimuli presented via the non-lesioned (ipsilateral) eye was higher than that for stimuli presented via the lesioned (contralateral) eye (Fig. 3*B*). Overall, the mean peak discharge rate for stimuli presented via the lesioned (contralateral) eye at 27.8 ± 27.05 spikes s^{-1} was significantly lower ($P = 0.05$; Wilcoxon's matched-pairs, signed-ranks test) than that for stimuli presented via the non-lesioned (ipsilateral) eye (44.95 ± 41.5 spikes s^{-1}).

Although the DFs plotted via the lesioned eye tended to be smaller (Fig. 3*C*; mean 15.45 ± 12.5 deg^2) than those revealed by stimuli presented via the non-lesioned eye (Fig. 3*C*; mean 23.15 ± 22.25 deg^2) the difference in the size was not significant ($P > 0.05$, Wilcoxon's matched-pairs, signed-ranks test).

The orientation preferences of all binocular neurones recorded in area 18 were assessed subjectively while using hand-controlled stimuli to delineate their DFs via either eye. By listening to the sonic translation of the neural activity via an amplifier we concluded that each neurone exhibited a similar orientation preference to stimuli presented via either eye (lesioned or non-lesioned). Consistent with these subjective assessments, quantitative assessments of orientation selectivity in two binocular neurones within the LPZ also indicated that their orientation preferences and orientation tuning to stimuli presented via either eye were quite similar (Fig. 4*A*). Although for individual cells the direction selectivity indices (DI) for optimally oriented stimuli via each eye could be quite different (Fig. 4*B*), the difference between the mean DI (at optimal velocity) for stimuli presented via the normal eye (0.71 ± 0.24) and the mean optimal velocity DI (0.64 ± 0.33) for stimuli presented via the lesioned eye was not significant ($P > 0.05$; Wilcoxon's matched-pairs signed-ranks test).

The similarity of the velocity tuning to optimally oriented stimuli moving at different velocities across the receptive fields of the lesioned and non-lesioned eye illustrated in Fig. 2*B* echoes that of most of the cells recorded in the LPZ of area 18 (Fig. 4*C* and D). Indeed, for the whole population of binocular cells recorded from the LPZ the differences in preferred velocities (medians for both lesioned and non-lesioned eyes 19 deg s^{-1}) or upper cut-off velocities (median for lesioned eye 380 deg s^{-1}; median for non-lesioned eye 950 deg s^{-1}) to stimuli presented through either eye were not significant (Fig. 4*D*; $P > 0.05$, Wilcoxon's matched-pairs signed-ranks test). Furthermore, it is apparent from Fig. 4*D* that irrespective of the eye through which the stimuli were presented: (1) preferred velocities of almost 30 % of cells recorded in the LPZ were 95 deg s^{-1} or more and (2) upper cut-off velocities of over 70 % of cells recorded from the LPZ exceeded 95 deg s^{-1}.

DISCUSSION

Does topographic reorganization occur in area 18 of adult cats that undergo a monocular retinal lesion in adolescence? Two aspects of the data suggest that this is not the case. Principally, because of the size of the retinal lesions in this experiment and the arbor dimensions of geniculate axons projecting to area 18 (cf. Freund *et al.* 1985; Humphrey *et al.* 1985*b*), complete geniculate deafferentation of any neurone in the LPZ of area 18 could not be assured. Second, the responses of binocular cells recorded from the LPZ in area 18 were significantly weaker when stimuli were presented via the lesioned eye. Collectively these two facts might suggest that the contralateral (lesioned) eye DFs of area 18 LPZ neurones are remnants of the DFs that existed prior to lesioning.

Other aspects of the data, however, are at odds with the above conclusion. For example, in many cases the spatial shift of the lesioned eye DFs of neurones in the LPZ extended well beyond the boundaries of the corresponding DFs revealed by stimuli presented via the non-lesioned eye. In addition, over 90 % of binocular cells for which we were able to plot both DFs had DF incongruities larger than the normal average values determined by Ferster (1981) for up to 25 deg eccentricity (cf. also average incongruity values for the transitional area between areas 17 and 18; Pettigrew & Dreher, 1987). Furthermore, some binocular neurones in the LPZ of area 18 displayed split DFs with sub-fields on opposite sides of the lesion. To our knowledge there have been no published observations of neurones with split DFs in area 18 of normal cats. However, such neurones have been found in area 18 of non-lesioned cats that have undergone periods of restricted visual experience during adolescence or adulthood and the DFs of these neurones were similar to the split DFs found in the present study, with distances of up to 15 deg separating their excitatory sub-regions (Singer & Tretter, 1976*a*,*b*). Furthermore, in the present study one of the cells recorded from the LPZ exhibited a split DF (one ON and one OFF discharge region) when stimuli were presented via the non-lesioned eye (cell 10 in Fig. 1*C*).

It should also be pointed out that neurones within the LPZ of area 17 in cats in which retinal lesions were made in adulthood, binocular cells were clearly dominated by the non-lesioned eye (Calford *et al.* 2000). However, the ocular dominance distribution of cells recorded from the LPZ of area 17 appears to be critical-period-dependant. In particular, in adult cats in which retinal lesions were made in adolescence (8 weeks postnatal) the ocular dominance distribution of cells recorded from LPZ of area 17 was not significantly different from that of area 17 cells recorded in normal cats (Burke *et al.* 2000; Dreher *et al.* 2000, 2001). Thus, for cells recorded from the LPZ of area 18, the relative weakness of responses to stimuli presented via the lesioned eye may simply reflect a limitation of plasticity

determined by the age of lesioning relative to a developmental window that is similar, but temporally independent, to the one purported to exist in area 17 (for review see Dreher *et al.* 2001).

On the basis of the above evidence we conclude that within the LPZ of area 18 of adult animals that receive circumscribed monocular retinal lesions during adolescence, topographic reorganization occurs. This result appears to

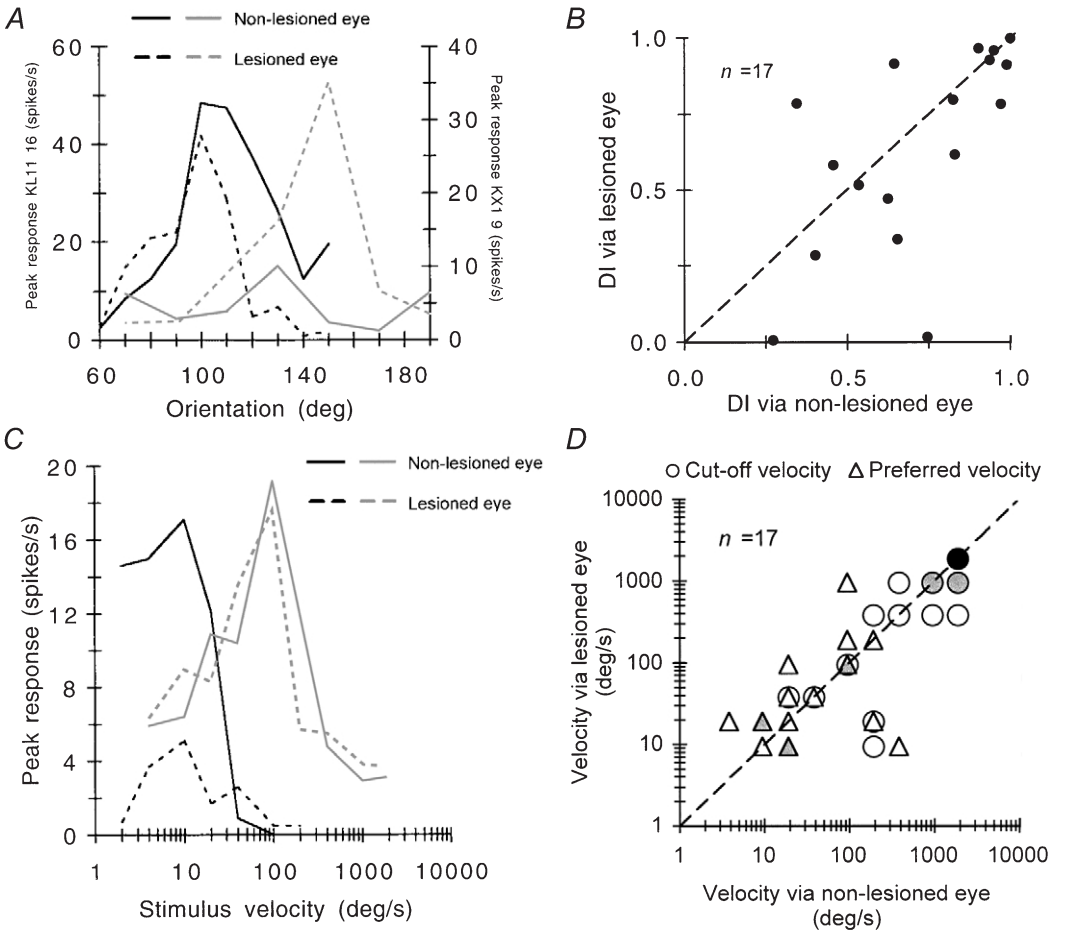

Figure 4. Orientation, direction and velocity-tuning of binocular cells in the LPZ of area 18

A, orientation tuning of LPZ neurones KL11 16 (black continuous and dashed lines, see Fig. 1*C*) and KX1 9 (grey continuous and dashed lines) for stimuli presented via the non-lesioned and lesioned eye. The peak response of each neurone to moving bars of preferred size and velocity at various orientations is shown. The specific orientations tested are indicated as the point at which each line deflects. Note that each neurone's orientation preference did not vary substantially depending on the eye to which the stimuli were presented. Note different scales for units KL11 16 (left) and KX1 9 (right). *B*, pairwise comparisons of the direction selectivity indices (DIs, measured at optimal velocities) of binocular neurones in the LPZ of area 18 in monocularly lesioned cats for stimuli presented via either eye. Note that for about half the cells there are substantial differences in the DIs for stimuli presented through either eye. The difference between the two populations is, however, not statistically significant ($P > 0.05$, Wilcoxon's matched-pairs, signed-ranks test). *C*, velocity tuning curves for neurones KL11 7 (black continuous and dashed lines, see Fig 1*C*) and KX1 16 (grey continuous and dashed lines). Note also that despite the substantially weaker responses of neurone KL11 7 to stimuli presented via the lesioned eye (class 4 cell) the velocity-tuning curves are almost identical, irrespective of the eye (lesioned or non-lesioned) through which the stimuli are presented. *D*, pairwise comparisons of preferred (triangles) and cut-off velocities (circles) of binocular neurones recorded from the LPZ/FPZ of area 18. Grey triangles indicate two cells with the same preferred velocities. Grey circles indicate two cells with the same cut-off velocities while the black circle indicates three cells with the same cut-off velocities. The preferred velocity was determined as the velocity at which an optimally oriented stimulus gave the maximum response (highest peak discharge rate). The cut-off velocity was defined as the upper velocity limit at which an optimally oriented stimulus gave an excitatory response. There was no significant difference between the preferred or cut-off stimulus velocities for stimuli presented via the lesioned (contralateral) eye and those for stimuli presented via the non-lesioned (ipsilateral) eye ($P > 0.05$, Wilcoxon's matched-pairs, signed-ranks test).

be consistent with a previously published claim of topographic reorganization in area 18 of adult-lesion-cats in response to monocular retinal lesions (Kaas *et al.* 1990). However, since Kaas and colleagues (1990) found it necessary to enucleate the non-lesioned eye in order to reveal the DFs of deafferented neurones in areas 17 and 18, they did not have the option of quantitatively comparing the responses of neurones in the LPZ to stimuli presented via either eye. Furthermore, Kaas and colleagues (1990), apart from the location and size of the ectopic DFs of cells recorded from the LPZ of area 18, did not perform a quantitative study of response properties of these cells. Therefore, at present, the extent of reorganization in area 18 and most of the receptive field properties (e.g. spatial organization, velocity response profiles, direction and orientation selectivities) of cells recorded from the LPZ of area 18 of adult and adolescent-lesion cats cannot be compared.

Is the reorganization in area 18 qualitatively similar to that in area 17? The orientation and velocity response properties of binocular LPZ neurones in area 18 suggest that this is the case. In animals without retinal lesions the orientation preferences of binocular neurones in areas 17 and 18 are virtually the same regardless of the eye via which the stimulus is presented (cf. Burke *et al.* 1992; Dreher *et al.* 1992). Remarkably, binocular neurones in the LPZ of area 17 retain this invariance of orientation preference despite the fact that their lesioned eye DFs are in a completely new location (Calford *et al.* 2000). Our present data (Fig. 4*A*) reveal that neurones in the LPZ of area 18 largely share this invariance of orientation preference. In area 17 and to a lesser extent in area 18 substantial morphological and functional evidence indicates that these preferences are significantly influenced by the activity of intrinsic horizontal associational connections that connect regions of iso-orientation preference (for review see Kisvárday *et al.* 1996). Furthermore, the overall receptive field organization (simple *vs.* complex) of cells recorded from the LPZ of area 18 was the same irrespective of the eye via which the stimuli were presented. This suggests to us that despite substantial local inhibitory processing contributing heavily to spatio-temporal receptive field properties of area 18 cells (Pernberg *et al.* 1998), excitatory horizontal associational connections might interconnect the cells sharing not only the same orientation preferences but also the same spatio-temporal receptive field organization.

Although areas 17 and 18 of the cat together constitute the primary visual cortex of this species, each area receives a quite distinct input from the LGNd and, presumably related to this difference, neurones in each area have very different velocity response profiles. In particular, area 17 is dominated by X-type geniculate input and most neurones in this area respond poorly to fast-moving stimuli (Stone & Dreher, 1973; Mitzdorf & Singer, 1978; Dreher *et al.* 1980; Freund *et al.* 1985, Humphrey *et al.* 1985*a*; Ferster, 1990*a*,*b*; Burke *et al.* 1992; for reviews see Stone *et al.* 1979; Orban, 1984). By contrast, area 18 is dominated by Y-type geniculate input and most neurones in this area respond well to fast-moving stimuli (Stone & Dreher, 1973; Mitzdorf & Singer, 1978; Dreher *et al.* 1980; Freund *et al.* 1985; Humphrey *et al.* 1985*a*; Ferster, 1990*a*,*b*; Dreher *et al.* 1992; for reviews see Stone *et al.* 1979; Orban, 1984).

Might the principal excitatory input to the ectopic DFs of area 17 neurones arise from associational excitatory input from the LPZ of area 18? Indeed, as we have mentioned in the Introduction, in normal cats, when lamina A of the LGNd is reversibly inactivated, cells in the supragranular layers of the visuotopically corresponding part of area 17 still respond to stimuli presented via the contralateral eye but the responses are dependant on cells in the visuotopically corresponding region of area 18 (Mignard & Malpeli, 1991). The main problem with the idea that the excitatory input to ectopic DFs of area 17 neurones arises from associational excitatory input from the LPZ of area 18 is that when stimulated via their ectopic DFs, the upper cut-off velocities of binocular neurones recorded from the LPZ of area 18 (median 380 deg s^{-1}; the present study) are significantly different from those of LPZ neurones recorded in area 17 of cats lesioned either in adulthood (median 38 deg s^{-1}; Calford *et al.* 2000) or adolescence (median 95 deg s^{-1}; Burke *et al.* 2000; Dreher *et al.* 2000). Furthermore, there is a similarity in velocity response profiles of area 17 cells recorded within the LPZ of animals lesioned in adolescence for stimuli presented via the non-lesioned eye and those presented via the lesioned eye (Burke *et al.* 2000; Dreher *et al.* 2000). Thus, in order to argue that in lesioned animals the LPZ of area 18 is providing ectopic drive to the LPZ cells of area 17 one would have to assume that: (1) excitatory associational connections from area 18 cells to area 17 cells act as a low velocity-pass filter and therefore selectively convey discharges evoked by low and moderate velocity stimuli but not discharges evoked by high velocity stimuli and (2) cells in the LPZ of area 18 provide principal excitatory input to the LPZ cells of area 17 irrespective of the eye (lesioned or non-lesioned) via which the visual stimuli are presented. These assumptions are challenged by the fact that: (1) reversible inactivation of layer 5 of area 18 in normal cats results in a dramatic increase in responsiveness to high-velocity stimuli (without a significant effect on responses to low and moderate velocities) of cells in layer 5 in the visuotopically corresponding part of area 17 (Alonso *et al.* 1993*a*) and (2) in normal cats reversible inactivation of layer 5 (Alonso *et al.* 1993*b*) or layers 2/3 (Martinez-Conde *et al.* 1999) of area 18 results only in minor changes in the orientation and/or direction selectivities of neurones in visuotopically corresponding parts of area 17. Overall therefore, we believe that the principal excitatory drive responsible for

the ectopic DFs of area 17 neurones is not conveyed by associational input from area 18 but rather from an intrinsic source, i.e. neurones outside the LPZ but within area 17 itself. Indeed, in adult cats with circumscribed monocular retinal lesions inactivation of a part of area 17 (without any involvement of area 18) topographically matched with the location of the ectopic DFs results in a dramatic reduction of the responses of cells in the LPZ to stimuli presented via the lesioned eye (Wright *et al.* 1999).

What about the possibility that the principal excitatory input to the ectopic DFs of area 18 neurones arises from associated excitatory input from the LPZ of area 17 (cf. Chino, 1995; Darian-Smith & Gilbert, 1995)? Again, there are a number of arguments against such a scenario. First, there is the similarity of velocity response profiles of area 18 cells recorded within the LPZ for stimuli presented via the non-lesioned eye and those presented via the lesioned eye (Figs 2*B*, 4*C* and *D*). Second, inactivation of area 17 results mainly in a reduction of responsiveness of area 18 neurones to slowly moving stimuli, but not to fast-moving stimuli (Dreher & Cottee, 1975; Sherk, 1978). Third, inactivation of area 17 exerts only a fairly minor effect on the orientation and direction selectivities of area 18 neurones (Sherk, 1978; Casanova *et al.* 1992). Combined, these results strongly suggest that the excitatory input underlying the ectopic DFs of area 18 cells stems mainly from an intrinsic source, i.e. neurones outside the LPZ but within area 18 rather than from area 17.

To our knowledge in both the cat (for review see Dreher *et al.* 2001) and macaque monkeys (Heinen & Skavenski, 1991; Gilbert & Wiesel, 1992; Darian-Smith & Gilbert, 1995; Murakami *et al.* 1997) the topographic reorganization that follows circumscribed retinal lesions has been tested only in the primary visual cortices. It remains to be examined if, following a circumscribed retinal lesion, topographic reorganization also occurs in 'higher-order' visual areas. If so, is such reorganization based on excitatory input from the LPZs of the primary visual cortices or rather on intrinsic associational connections within the higher order area? The recent study of Rosa and colleagues (2000) in which they observed ectopic DFs in the middle temporal cortices of New-World diurnal monkeys (common marmoset *Callithrix jacchus*) following lesions of their striate cortices, suggests to us that, if present, the reorganization in the higher-order visual cortices following retinal lesions, like the reorganization in area 18 revealed in the present study, would be based principally on neuronal activity conveyed by intrinsic associational connections.

Conclusion

The results of the present study suggest that topographic reorganization occurs in area 18 of the cat in response to deafferentation achieved by a monocular retinal lesion in adolescence. Considering that the orientation, direction and velocity tunings of neurones in the LPZ of area 18 cannot be distinguished on the basis of the eye via which the stimuli are presented, this reorganization appears qualitatively similar to the phenomenon that occurs in area 17 in response to the same perturbation (Calford *et al.* 2000; Dreher *et al.* 2001). Although the preferred and upper cut-off velocities of cells recorded from the LPZ of area 18 to stimuli presented via the lesioned and non-lesioned eye are very similar, the preferred and most importantly the upper cut-off velocities of cells recorded from the LPZ of area 18 are very different from those of cells recorded from the LPZ of area 17 (irrespective of the eye via which stimuli are presented). On the basis of this evidence we argue that the principal neural substrate underlying topographic reorganization in area 18 is analogous to that proposed for area 17, namely the horizontal long-range associated intrinsic connections of the cortex. Furthermore, we conclude it is unlikely that horizontal associational connections from area 18 provide the principal excitatory input responsible for the ectopic DFs of neurones in the LPZ of area 17, and vice versa.

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