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Research Note

Recovery of visual responses in foveal V1 neurons following bilateral foveal lesions in adult monkey

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Summary. Cells in the foveal representation of V1 cortex of adult primates became visually responsive after normal sensory input was removed. Immediately after foveae were lesioned bilaterally, a region was found where no cells' activity could be modulated by visual stimulation. Recordings made in that deafferented zone at > 2.5 months after lesions revealed that activity of over half of the cells could be modulated by visual stimuli presented to intact peripheral retina. Although response characteristics made cells with recovered driving quite unlike normal cells, the result suggests a level of visual cortical reorganization previously observed only in immature animals.

Key words: Plasticity – Primary visual cortex – Photocoagulation – Adult monkeys

Numerous studies have reported that selective visual deprivation dramatically modifies the type of visual stimulus required to elicit neuronal responses in the primary visual cortex (V1), but only if that deprivation is done during a critical period early in the animal's life, not after it. These results have led to the conclusion that neuronal connections in V1 are "hard-wired" in the adult and are, therefore, resistant to environmental manipulation (Blakemore and Cooper 1970; Hirsch and Spinelli 1971; Hubel and Wiesel 1970; Levay et al. 1980). However, recent work in both primary (S1) and secondary (S2) somatosensory cortex of adult monkeys has shown that neurons there become responsive to adjacent intact parts of the body when the finger normally providing sensory input to these cells is surgically removed in older animals (Merzenich et al. 1984; Pons et al. 1986). Earlier, Eysel et al. (1981) had demonstrated in adult cat that lateral geniculate neurons representing peripheral retina became responsive to other retinal areas when the normal input was lesioned. Combined, these results suggest that substantially more reorganization may take place in the central nervous system when the normal sensory input is completely removed than does when sensory stimulation is merely manipulated. Therefore, we asked whether the retinotopic mapping of the visual world onto cells in V1 responding to the central retina is similarly malleable in adult primates when retinal input to this area is selectively destroyed. We used bilateral fovea lesions to remove the input to foveal V1 neurons and found that about half of the cells we recorded did recover visual responsiveness by 75 days following the lesions, demonstrating a remarkable degree of plasticity in the adult animal. However, the response characteristics of these neurons were anomalous.

One nine-year old, and two five-year old, adult Macaca nemestrina monkeys were used. Each was implanted with a stain-less steel recording chamber over the right hemisphere foveal projection in V1 cortex using sterile surgical technique and Halothane-nitrous oxide anesthesia. Each was also implanted with a post to restrain head motion and a coil of wire was wound around the right eye to record eye position with the magnetic-field search-coil technique (Fuchs and Robinson 1966; Robinson 1963). The alert behaving animal preparation was chosen for this study to assess pre-lesion, immediate post-lesion, and later post-lesion, cell characteristics within the same animal, because an acute preparation would have required the use of many more animals to obtain the pre- and post-lesion data. Operant conditioning techniques were used to train each monkey to maintain stable fixation of a small red target rear projected on a tangent screen 65 cm away for intervals of 10 (Skavenski et al. 1975). Before each session, eye movements were recorded with the animal fixating a series of 10 deg arc eccentric targets in order to calibrate the coil and sta-

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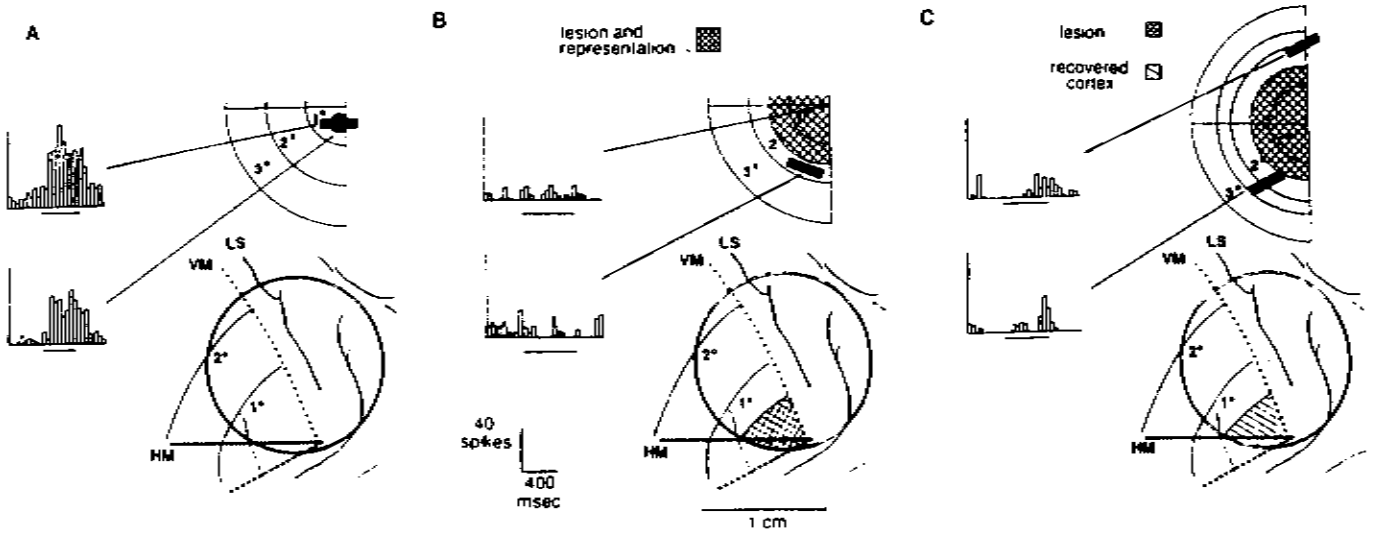

Fig. 1A–C. Visual field representation (top right) on V1 (bottom right) in recording chamber (heavy circle) at 3 recording intervals in M46. Peri-stimulus time histograms on the left of maps show representative cell responses to stimuli flashed 8 times at visual field locations indicated by lines from each histogram. **In A**, the top 2 histograms show vigorous discharge of a typical V1 neuron to a spot and bar flashed on its receptive field (RF). *Abbreviations:* LS, lunate sulcus; VM, vertical meridian; HM, Horizontal meridian. **In B**, histograms show responses of a representative cell in the same cortical location as the cell in **A** shortly after retinal lesions, showing only spontaneous activity to stimuli presented to the old RF (top) and outside lesion (bottom). Cross hatching shows representation of foveal lesions in the field map, and the non-responsive cortical zone. **In C**, histograms show responses of a neuron recorded at the same location as the cells in **A** and **B** at 3 weeks post-lesion. Stippling indicates visual field where stimuli modulated this cell, and light hatching shows cortex where cells were visually driven

bilization systems. After the lesion, it was possible to use the same procedure since fixation becomes quite stable in just a few days following foveal ablation (Heinen and Skavenski 1988). Visual receptive fields of neurons were mapped with small bright bars and spots (119 ft-cd) that were rear-projected onto the tangent screen and flashed with a shutter placed in the projection path. The mapping stimuli were retinally stabilized at selected positions by feeding horizontal and vertical eye position analogues into a pair of galvanometer driven mirrors. This precaution was taken to insure that the stimulus stayed on the same retinal locus across trials, since monkeys do not always use the same retinal locus to fixate (Snodderly and Kurtz 1985), as well as to compensate for increased fixation variability after the lesion. Mean position error before the lesion during good fixation was normal in these animals, typically 10 min arc over a 10 s trial. After the lesion, performance was poorer, but still good at 14 min arc for a typical trial (Heinen and Skavenski 1988). Cell responses were collected only when monkeys maintained fixation for the entire trial so that retinal slippage of the mapping stimulus had standard deviations of < 2 min arc. Recording of extracellular potentials of single and multiple neurons was done with stereotaxically positioned glass-insulated tungsten microelectrodes using conventional techniques (Evarts 1968). Eye and target position signals, as well as interspike intervals, were digitized by computer (PDP 11/23) and peristimulus time-histograms of spike activity were displayed on-line to facilitate mapping.

In the first phase of the experiment coarse sampling of the cortical surface was done to make an initial pre-lesion map of the visual field representation within the chamber. Receptive field location for each neuron was determined by flashing the small stimuli at different retinal locations and noting the retinal area where the neurons were driven by these stimuli. In all animals, the cortex in the chamber corresponded to a wedge of the lower left central visual field, with a radius extending from the central fovea to about 2.5 deg arc eccentricity. A representative map, along with histograms showing the response of a representative neuron, is shown in Fig. 1a.

After chamber position was verified, bilateral laser photocoagulation was administered to the foveae. In one animal (M46), 600 μ diameter lesions corresponding to 3 deg arc of visual field (de Monasterio et al. 1985) were made with a red krypton laser, which heats the retinal pigment epithelium and thereby destroys overlying neural elements. In the other two monkeys (M62 and M63), 400 μ diameter lesions were made removing two deg arc of the visual field, with a green argon laser, which destroys neural tissue directly. The effectiveness and spatial extent of the lesions were verified by fundus photography, and by a 1.5 deg arc upward shift in fixation in the living animals. Retinal histology, performed after recording was complete, revealed a total absence of functional photoreceptors and other cells in the area of the lesion.

A second mapping was performed over several weeks, beginning immediately after retinal lesions, to determine the cortical area that was completely deafferented. In all three monkeys, an area of cortex was found in which all neurons were unresponsive to any of our visual stimuli presented anywhere within five deg arc of the center of the visual field. This region roughly

corresponded to the stereotaxic coordinates of the cortical projection of the ablated retinae. Figure 1b shows the extent of the retinal lesion in the visual field of monkey M46, along with the cortical representation of the lesion where no cells were visually responsive. Also shown in Fig. 1b is the lack of visual response of a representative neuron isolated in this region. This cortical area where no visual response could be obtained was notably smaller than the visual field loss in all animals. However, electrodes lowered into a 1 to 2 mm wide area bordering this unresponsive zone encountered some cells which could be driven, and some which could not, on every penetration. This partially responsive area was most likely composed of columns having cells with receptive fields completely in the retinal lesion and cells with larger receptive fields that may have included intact retina (Dow et al. 1981; Hubel and Wiesel 1974).

When the totally unresponsive zone was clearly delineated, recording was suspended until 75 days after retinal lesions during which time the animals were kept in their home cages where they received no unusual visual stimulation. In the last phase of the experiment, a third mapping was made in the previously completely unresponsive visual cortex, and more than half of the cells could once again be driven by visual stimuli. Figure 1c shows the receptive field and response of a representative cell which was recorded from the same cortical area as the nonresponsive cell in Fig. 1b. Figure 2 summarizes the number of single and multiple cell samples obtained in all animals, and the number of these samples which responded to visual stimuli in each mapping.

There were interesting differences in the receptive field characteristics of cells measured before and after deafferentation. For example, some of the "recovered" neurons had large, abnormally shaped, receptive fields. Normal foveal striate neurons have small (less than one deg arc), elongated, receptive fields which often have antagonistic sub-fields (Hubel and Wiesel 1962, 1968). The "recovered" neurons had excitatory receptive fields as long as 5 deg arc, which were commonly circular, or crescent shaped, like the field in Fig. 1c, and which had no antagonistic subregions. Unlike normal cells, many of the recovered cells had receptive fields with diffuse borders that were difficult to map precisely. Overall, responses of cells with recovered driving to flashed stimuli seemed weaker, and a sample of cells from the first mapping had a mean peak firing rate of 58 spikes/s to the optimum stimulus, whereas a sample of cells in recovered cortex responded with a mean peak rate of only 44 spikes/s; however, this difference was not statistically reliable. Recovered driving also had a longer latency to peak response to the best stimulus we could find, with a mean latency to peak firing rate of 285 ms compared to the mean latency of 137 ms in normal neurons ($p < 0.01$, student two-tailed t test).

Anatomical results also support the notion that this recovered area is different from normal cortex. Cytochrome oxidase staining performed after recording ended in the striate cortex of 2 of the recovered animals revealed depressed activity in the foveal region, especially in layers IVa and IVc compared to surrounding cortex with intact retinal input. Changes were also found in the lateral geniculate nucleus (LGN); specifically, cytochrome oxidase levels were lower, and cells were smaller (as revealed by Nissl staining) in the parvocellular layer foveal representation (Skavenski and Sikes 1989). These results appear somewhat different from those of Kaas et al. (1990) who reported a similar recovery of visual responding of V1 and V2 neurons in adult cats after the cells were deafferented with 5–10 degree diameter retinal lesions placed peripheral to area centralis. However, they noted that recovered receptive fields had sizes and response characteristics that appeared similar to normal cells (note 9).

Despite these important differences that make recovered V1 cells unlike normal V1 cells or recovered S1

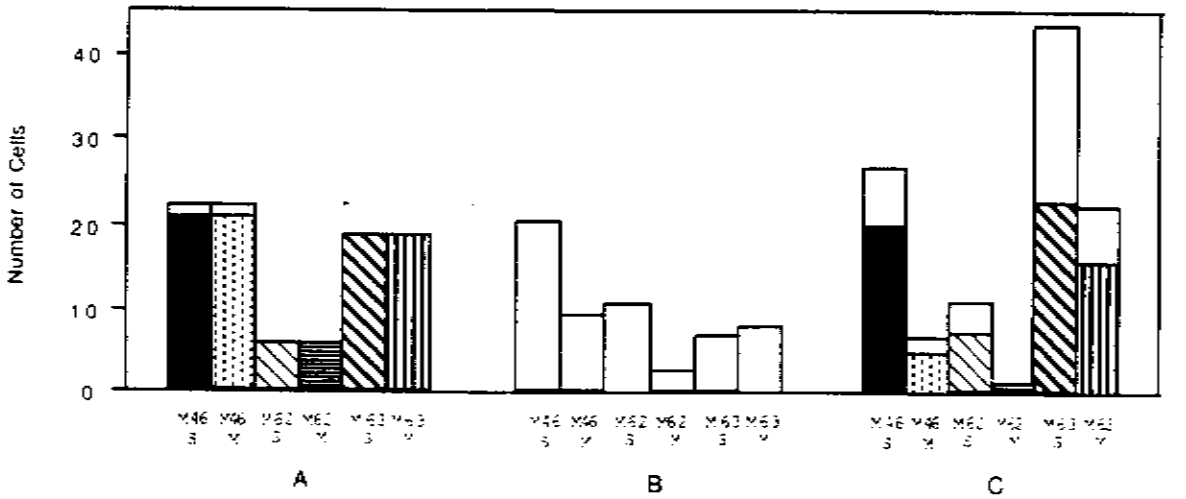

Fig. 2A–C. Bar graphs showing the total number of cells recorded (full bar height) recorded before (**A**), immediately after (**B**) and at > 2.5 months after (**C**) monkeys were given bilateral foveal lesions. Shaded areas show the number of cells out of the total whose activity could be modulated by visual stimulation. A–C Are further broken down into single and multiple unit responses for each monkey; e.g., M46, S. refers to the single unit responding in one animal. M refers to the multiple unit responding in that same animal. Only recordings made within the shaded portion of the chamber map in B and C of Fig. 1 are reported for the 2 periods after lesions.

cells, it was clear that the location and size of receptive fields of V1 cells had changed drastically in animals well past their critical developmental period. How might these results be reconciled with previous studies that failed to find visual cortex plasticity in adult animals? It is unlikely that the retinal lesions merely "unmasked" contributions that pre-existing connections from a broad region made to the normal receptive field. If unmasking were the case, then the second mapping done immediately after the lesion should have encountered visually responsive cells. In fact, no visually responsive cells were found in the cortical projection of the lesion for a time interval of more than 1 month. If the recovery utilized pre-existing connections, they must have initially been quite weak, and after the retinal lesion, strengthened gradually over time. Eysel et al. (1981) also argued against unmasking as an explanation of the recovered visual driving they observed in cat LGN because the process took up to one week.

A more likely reason for the recovery is that the bilateral lesion completely removed all visual input from a discrete area, leaving visual input intact at the border of that locus. Monocular enucleation, a paradigm which produces maximum ocular dominance shifts in the critical period of animals (LeVay et al. 1980) similarly results in complete deafferentation of a discrete cortical region, and could be expected to optimize the ability of this deafferented area to modify response characteristics. In this study, LeVay et al. also found that the anatomical labelling of ocular dominance columns followed an "entirely normal pattern" when done in an adult enucleated animal, implying that the enucleated eye was still represented in the cortex. However, it was a surprise when these authors found only two visually unresponsive zones in a second enucleated adult studied physiologically. The latter result suggested that the normal eye had come to drive cells previously driven by the enucleated eye, evidence that some reorganization had occurred in the adult animal.

This explanation does not however resolve the issue of what changes actually take place, or where in the visual system these changes occur. It is unlikely that retinal reorganization was the substrate for the renewed cortical activity, since all retinal cells in the area of the lesion were functionally destroyed. Some evidence does exist, however, for involvement of the LGN in this recovery. Eysel et al. (1981), in a similar preparation in cats, found a recovery of driving in an area of LGN representing lesions made at 20 deg arc eccentricity. The area of LGN filling-in found in this study was on the order of 200 μ which encompassed somewhat more than 1 deg arc in the visual field. Furthermore, Eysel et al. (1981) found that area centralis lesions did not reveal such a remapping, possibly because 200 μ of filling-in of the area centralis LGN would result in a visual receptive field shift of only a fraction of a degree: a shift that was too small to be detected by their technique. Kaas et al. (1990) observed that the reorganization of visual cortex representing the periphery extended over several degrees (to encompass 5 deg or more) which cannot be accounted for solely by the extent of LGN filling-in Eysel et al. observed. In the monkey, we observed that the recovery of visual responsiveness extends over several millimeters of visual cortex and corresponds to more than one degree in the visual field. It seems unlikely that LGN changes could be the sole explanation for that recovery. Also, the fact that we observed a lowered cytochrome oxidase level and shrunken cells in foveal LGN suggests that the cortical reorganization may play a more central role in recovery from central retinal lesions.

Studies of cortical reorganization following monocular lid suture during the critical period support this contention providing evidence for synaptic changes at the geniculo-cortical synapses in layer IVc (LeVay et al. 1980; Shatz and Stryker 1978). Sprouting of stellate cell dendritic arbors in layer IVc have also been demonstrated in deprivation studies (Lund and Holbach 1988). In normal animals there is also evidence of divergent axonal arborizations and long-range intracortical connections, which can extend for several millimeters (Gilbert and Wiesel 1989; Rockland and Lund 1983; Tso et al. 1986). There is a possibility that these connections are weak, and strengthen when retinal input is removed from the area which they innervate, a situation which our unanesthetized preparation might allow us to more easily monitor. Whatever the cause, our results suggest that cortical maps in the primate visual system remain malleable well past the critical developmental period when a cortical area within these maps is completely deafferented. Although the site(s) and mechanisms for the reorganization remain unresolved, such change seems reasonable given the amount of compensation humans show for retinal damage incurred not only during, but also well beyond, the first few years of life. For example, these physiological changes might well accompany the perceptual filling-in experienced by many scotoma patients (Gerrits and Timmerman 1969) who often do not even notice the sometimes quite large blind spots in their visual fields.

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References

Blakemore C, Cooper GF (1970) Development of the brain depends on the visual environment. Nature 228:477–78

Dow BM, Snyder AZ, Vautin RG, Bauer R (1981) Magnification factor and receptive field size in foveal striate cortex of the monkey. Exp Brain Res 44:213–228

Evarts EV (1968) A technique for recording activity of sub-cortical neurons in moving animals. Electroenceph Clin Neurophys 24:83–86

Eysel UT, Gonzalez-Aguilar F, Mayer U (1981) Time-dependent decrease in the extent of visual deafferentation in the lateral geniculate nucleus of adult cats with small retinal lesions. Exp Brain Res 41:256–263

Fuchs AF, Robinson DA (1966) A method for measuring horizontal and vertical eye movement chronically in the monkey. Appl Physiol 21:1068–1070

Gerrits HJ, Timmerman GJ (1969) The filling-in process in patients with retinal scotomata. Vis Res 9:439–442

Gilbert CD, Wiesel TN (1989) Columnar specificity of intrinsic

horizontal and corticocortical connections in cat visual cortex. J Neurosci 9:2432–2442

Heinen SJ, Skavenski AA (1988) Recovery of eye movements after bilateral fovea lesions in monkeys. Soc Neurosci Abstr 14:796

Hirsch VB, Spinelli DN (1971) Modification of the distribution of receptive field orientation in cats by selective visual exposure during development. Exp Brain Res 13:509–527

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154

Hubel DH, Wiesel TN (1968) Receptive fields and functional architecture of monkey striate cortex. J Physiol 195:215–243

Hubel DH, Wiesel TN (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol 206:419–463

Hubel DH, Wiesel TN (1974b) Uniformity of monkey striate cortex: a parallel relationship between field size, scatter, and magnification factor. J Comp Neurol 158:295–306

Kaas JH, Krubitzer LA, Chino YM, Langston AL, Polley EH, Blair N (1990) Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. Science 248:229–231

LeVay S, Wiesel TN, Hubel DH (1980) The development of ocular dominance columns in normal and visually deprived monkeys. J Comp Neurol 191:1–51

Lund JS, Holbach SM (1988) Effects of visual deprivation on dendritic maturation of spiny stellate neurons in monkey primary visual cortex. Soc Neurosci Abstr 14:1112

Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM (1984) Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 224:591–605

de Monasterio FM, McCrane JK, Newlander JK, Schein SJ (1985) Density profile of blue-sensitive cones along the horizontal meridian of macaque retina. Invest Ophthalmol Vis Sci 26:289–302

Pons TP, Garraghty PE, Mishkin M (1986) Topographical reorganization in the second somatosenesory area (SII) after removal of selected protions of postcentral cortex. Soc Neurosci Abstr 13:1234

Rockland KS, Lund JS (1983) Intrinsic laminar lattice connections in primate visual cortex. J Comp Neurol 216:303–318

Robinson DA (1963) A method of measuring eye movement using a scleral search coil in a magnetic field. IEEE Trans Bio-Med Eng BME-10:137–145

Shatz CJ, Stryker MP (1978) Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. J Physiol 281:267–283

Skavenski AA, Robinson DA, Steinman RM, Timberlake GT (1975) Miniature eye movements of fixation in rhesus monkey. Vision Res 15:1269–1273

Skavenski AA, Sikes RW (1989) Cytochrome oxidase activity in the adult primate visual system after recovery from bilateral foveal ablations. Soc Neurosci Abstr 15–794

Snodderly DM, Kurtz D (1985) Eye position during fixation tasks: comparison of macaque and human. Vision Res 25:83–98

Tso DY, Gilbert CD, Wiesel TN (1986) Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. J Neurosci 6:1160–1170