Monocularly Deprived Cats: Binocular Tests of Cortical Cells Reveal Functional Connections from the Deprived Eye

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Animals that are deprived of vision in one eye during a vulnerable phase of development lose visual function of the eye. Although this phenomenon has been studied extensively, little is known about the mechanism of disconnection of the deprived eye from visual cortex. One fundamental question is whether input remains from that eye. We have examined the hypothesis that there is functional input from a deprived eye to visual cortex that cannot be observed with standard alternate tests of each eye. We have employed a robust visual stimulation procedure in which large sinusoidal gratings are presented to each eye, as well as to both eyes together, at varying relative phases or retinal disparities.

Monocular and binocular stimulation was used to test kittens unilaterally deprived for brief, intermediate, or long periods. A fourth group of kittens was studied as normal controls. Standard methods were used to record from single cells in the striate cortex. After initial qualitative exploration of receptive fields, all testing and analysis were quantitative. As expected, monocular tests revealed that, for most cells, the deprived eye was ineffective, i.e., did not activate the unit. This effect was increasingly pronounced as the length of deprivation was increased. However, binocular tests revealed that a large fraction of these cells (30–40%) was clearly influenced by and therefore functionally connected to the deprived eye. This interaction was phase-selective, or suppressive and not selective for phase. There was no indication that the connections that remained were of a specific type, i.e., excitatory or inhibitory. Therefore, excitation and inhibition appear equally resistant to the effects of monocular deprivation. However, with long-term deprivation, we find minimal evidence of functional input from the deprived eye. We conclude that the effects of monocular deprivation occur over a considerably longer time period than was previously thought.

Monocular deprivation (MD) is an important model for the study of visual development, and it has been examined extensively from physiological, anatomical, and behavioral aspects (see recent reviews by Frégnac and Imbert, 1984; Mitchell and Timney, 1984). In spite of the considerable body of information available, the mechanism by which afferent input from one eye is functionally disconnected from neurons in the visual cortex remains unclear. One of the central questions is: Do afferent

pathways from the deprived eye remain intact or do they atrophy? This question has obvious significance in that attempts to restore visual function to a deprived eye tacitly assume that some form of input remains.

The evidence relevant to this question is largely indirect, somewhat controversial, and generally qualitative. During the period sensitive to visual deprivation (Hubel and Wiesel, 1970; Olson and Freeman, 1980), if the deprived eye is opened and the normal eye closed (Movshon, 1976), or if both eyes are opened following monocular deprivation (Olson and Freeman, 1978), some functional recovery is found, but it is mainly limited to monocular pathways. A more direct approach, which has been explored in monocularly deprived cats, examines the assumption that spontaneous activity from the normal eye blocks input, in some way, from the deprived eye to the visual cortex. Enucleation of the experienced eye results in substantial recovery of activity from the deprived eye (Kratz et al., 1976). However, the extent of this effect appears to vary considerably, and it may depend on when deprivation was initiated and how long it was carried out (Blakemore and Hawken, 1982).

The design of most of these previous studies has been restrictive, in that reliable sampling was required of cell populations in order to estimate proportions of neurons driven by each eye before and after the condition under investigation. However, there is considerable variability between results from different electrode tracks. Intra- and interanimal variability can also be extensive. To partly compensate for this problem, large populations of neurons may be sampled, but, once again, this poses limits on the investigation. Another limit of previous studies is the way by which they address questions on the binocularity of neurons. Surprisingly, most previous investigations test the *binocularity* of neurons with *monocular* tests alone. Instead of using binocular stimulation, studies have dealt mainly with the effectiveness of each eye in driving a cell under study, and characterizing it primarily by ocular dominance alone. Finally, these difficulties emphasize the need for techniques that are capable of examining binocular responses quantitatively.

In the investigation reported here, we have used an alternative approach in order to study the process of afferent disconnection from a deprived eye to visual cortex. Following a period of monocular deprivation, we record quantitatively from cortical neurons while stimulating left, right, or both eyes in quasirandom order. This experimental design has a distinct advantage in that it does not require a population study before and after a given rearing condition. We are able to address directly the question of whether input is present from a deprived eye to visual cortex. A somewhat surprising finding of this study is that an eye that does not elicit a response when activated mon-

Received July 27, 1987; revised Nov. 13, 1987; accepted Nov. 13, 1987.

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Figure 1. The experimental setup illustrated schematically. A cat faces a tangent screen on which bars of light of variable size and shape may be flashed or swept. Gratings are presented to each eye via beam-splitters. Stimulus control and spike acquisition are under control of a computer.

ocularly can exert a clear influence on cortical cells under conditions of binocular stimulation.

Materials and Methods

Rearing conditions. Four groups of kittens from a closed colony were used for these experiments. Three groups were deprived of vision in one eye by suture of the eyelids, using procedures described previously (Freeman and Olson, 1982). The groups were deprived of vision for 3–4 d, 8 weeks, or 10–35 months, beginning at postnatal weeks 5, 8, or 3, respectively. During the entire rearing period, all animals were monitored closely. There were no problems associated with the lid suture procedure.

A fourth group of kittens, aged 5 weeks, was used to obtain control data. These animals were also inspected regularly during rearing to ensure that there were no obvious problems associated with vision.

Physiological study. Kittens were prepared for physiological study with the use of standard procedures for single-unit recording. Following initial delivery of a tranquilizing agent (Acepromazine; $1 \text{ mg} \cdot \text{kg}^{-1}$) and atropine ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), an animal is anesthetized with halothane. Canulas are placed in a vein and the trachea, electrocardiogram leads are fixed, electroencephalogram screws are positioned, and a rectal temperature probe is inserted. Halothane is discontinued and anesthesia maintained with venous delivery of sodium thiamylal (Surital).

The skull is exposed and bone and dura are removed around a small area centered approximately at Horsley-Clarke coordinates P3, L2, which is generally a few millimeters anterior to lambda suture. A tungsten-in-glass electrode (Levick, 1972) is inserted into cortex at an angle of 10° – 15° , pointing medially from vertical, and the chamber is sealed with agar followed by melted wax. The animal is paralyzed with gallamine triethiodide (Flaxedil), which is then infused continuously at a rate of $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ in a lactated Ringer's solution. A ventilator is run at 25 strokes/min and stroke volume is adjusted in accordance with body weight and expired CO_2 levels, which are maintained at around 4.5%. The respiration pump delivers a mixture of gas consisting of N_2O (30%) and O_2 (70%), and CO_2 (1–2%) is sometimes added.

During the experiment, the following are monitored: electrocardiogram (ECG), heart rate, temperature, and intratracheal pressure. Electroencephalogram (EEG) is also monitored in an attempt to estimate anesthesia levels. When required, Surital is added to the Flaxedil infusion mixture.

Apparatus. We have described the apparatus in detail in another paper (Ohzawa and Freeman, 1986a). As Figure 1 shows, the cat faces a rear-projection screen on which manually controlled stimuli (mainly bars of light of variable size and shape) are presented to estimate receptive-field position and characteristics. A pair of beam splitters, positioned

in front of the 2 eyes, are used to present stimuli from 2 CRT's. In this way, large (30°), bright ($250 \text{ cd} \cdot \text{m}^{-2}$) grating stimuli with sinusoidal luminance distributions can be delivered to each eye. Orientation, contrast, drift rate, phase, and spatial frequency may be varied independently for tests of left, right, and both eyes. A micropositioning device is used to advance the electrode, and standard electronic components are employed to amplify signals, display and separate action potentials from individual neurons, and observe peristimulus time (PST) histograms. It is important to note that the action potential is recorded with respect to time of occurrence, and that it is coded and transmitted to a buffer that can be read out during a test. This allows data collection to be monitored in real time, which is critical in this type of experiment (see Discussion).

The entire test procedure and data collection process are under the control of a minicomputer system. This system permits collection of hard-copy data following tests of each cell.

Recording procedure. Using suitable topical and systemic anesthesia, the sutured eye of the kitten is opened carefully. Corneas are cleaned and contact lenses with 4 mm artificial pupils are positioned after atropine and neosynephrine are applied topically. Optic disks are projected by using a reversible ophthalmoscope, and we also try to estimate projections of the areae centrales. The electrode is lowered, while a bar of light is moved through the expected visual-field region. Once a cell is isolated, subjective observations are made about receptive-field characteristics, and CRTs are positioned so that fields are approximately centered.

Next, under computer control, optimal parameters are determined for the gratings presented to each eye. A binocular test is then run as follows: Spatial phase of the grating is fixed to one eye and varied in 30° steps to the other, so that 12 phase values constitute a complete set. Monocular conditions are interleaved with binocular tests. If one eye does not respond during initial monocular tests, the optimal parameters for the other eye are used for the binocular sequence. Finally, in the binocular testing sequence, we also include presentation of a blank screen to monitor spontaneous discharge levels. All conditions are quasirandomly interleaved to minimize the effects of potential adaptation and fluctuations of responsiveness (Henry et al., 1969; Ohzawa and Freeman, 1986a). We sometimes repeat the main binocular run to estimate stability.

Histological procedures. Small lesions are made at the end of each electrode track and additional lesions are made as the electrode is raised to the surface. The electrode is removed slowly, in an attempt to minimize tissue drag. At the completion of each experiment, the animal is killed after it is deeply anesthetized with Nembutal, and standard perfusion and fixation techniques are used. Frozen cortical tissue is cut in $40 \mu\text{m}$ sections and thionin is used for staining. Electrode tracks are reconstructed, lamina are noted, and each recorded cell is identified with respect to cortical layer.

Results

Altogether, we studied 12 cats, 3 from each group, and recorded from 278 cells, of which 209 were held long enough for complete data collection. We first consider results from normal kittens and then provide data for comparison from each group of monocularly deprived animals.

Normal kittens

Data from a typical cell are shown in Figure 2. Using manually controlled stimuli, we classed this cell as simple on the basis of standard criteria (Hubel and Wiesel, 1962), primarily the presence of adjacent regions which gave ON and OFF responses, respectively. Monocular tests with grating stimuli, under computer control, gave modulated responses, as shown in Figure 2C, that are typical of simple cells (Schiller et al., 1976; Movshon et al., 1978; De Valois et al., 1982). After determining optimal parameters by manually varying spatial frequency, orientation, and drift rate, objective data are obtained from monocular tests of orientation and spatial frequency tuning. The resulting functions are shown in Figure 2, A, B. In this case, each eye drives the cell, and the pathway from the right eye is slightly dominant.

Figure 2. Responses of a simple cell from a 5-week-old kitten. Monocular and binocular stimulation is produced by drifting sinusoidal gratings. *A, B*, Orientation and spatial frequency tuning curves, respectively, for each eye (open circle, left; asterisk, right). Optimal orientation and spatial frequency were determined from these runs as 285° and 0.6 cycles/deg. These values were used for subsequent binocular experiments. *C*, PST histograms from a binocular run in which the relative stimulus phase of the gratings presented to left and right eyes was varied over 360°. Monocular conditions and the null (zero-contrast) stimulus were also included in the stimulus set. These conditions are depicted to the left of the histograms. Each histogram is the cumulative result of a total of 20 sec of stimulation presented in 5 blocks. Harmonic analyses are performed on these histograms, and the results (first harmonic) are plotted in *D* as a function of relative stimulus phase (open circles). Monocular responses for left and right eyes are indicated by asterisks and plus signs, respectively, in the column at the right (*M*). The curve with no data marks shows responses when the orientation of the gratings presented to the left eye was made orthogonal to the optimal. Monocular responses for this condition are shown by open and filled squares for left and right eyes, respectively. For the spatial frequency used, 0.6 cycle/deg, a 90° shift in stimulus phase has a corresponding shift in position of 25' of arc, as shown above the abscissa. For this and all subsequent results from other cells, temporal frequency (drift rate) was 2 Hz, and contrast was 50% unless otherwise noted.

These orientation and spatial frequency tuning functions are relatively narrow. Although we have not made explicit comparisons, our impression is that these tuning functions are typical of those found in adult animals.

Results of the binocular run from this cell are shown in Figure 2, *C, D*. The left-hand column of Figure 2*C* indicates the relative phase-shift of one grating with respect to the other. Temporal phase also changes, of course, but we have determined that the response pattern is due to spatial phase-shifts (Ohzawa and Freeman, 1986a). Note from the PST histogram data of Figure 2*C* that, with a relative phase-shift of around 120°, the cell is suppressed markedly and there is only a minimal response. On the other hand, with a relative phase-shift of about 300°, the response is considerably stronger than either monocular result. These findings are presented quantitatively in Figure 2*D*, which shows the amplitude of the fundamental frequency component at the drift rate of the stimulus (first harmonic of the PST histogram of Fig. 2*C*) as a function of relative phase-shift between

the gratings presented to the 2 eyes. The right-hand column of Figure 2*D* contains results of interleaved monocular tests (shown in Fig. 2*C* as RE and LE). The angular magnitude of the phase-shift is also indicated along the abscissa. The resulting function is clearly phase-specific and, once again, the behavior of this cell is typical of that found in adult cats (Ohzawa and Freeman, 1986a). An implication of this finding is that the binocular organization of cells in young kittens is indistinguishable from that of adults, but, of course, more data are required to permit this conclusion.

An additional test was performed to determine whether binocular interaction occurs when one grating is oriented orthogonal to optimal. In this case, the result is presented as the continuous line of Figure 2*D*. Monocular test results are also shown (filled and unfilled squares). Clearly, binocular interaction is eliminated under these conditions, and this result was confirmed from tests of several additional units.

The results of Figure 2 are typical for the population of units

Figure 3. Results of binocular phase-shift experiments for 4 additional cells from 5-week-old kittens. The format is similar to that of Figure 2D, and response amplitudes are plotted as a function of phase. The column at the right depicts responses to monocular stimulation interleaved with binocular conditions. *A*, Results from a simple cell. For this cell and that in *D*, the first harmonics are plotted. The 2 curves (open and filled circles) are from 2 repeated runs taken 20 min apart. The curve without data marks shows the results for a binocular phase run when the left grating was rotated 90° from the optimal orientation. For this and all other figures of this format, an asterisk and a plus sign show monocular responses for the left and right eyes, respectively, measured concurrently with binocular presentations, shown by open circles. Open and filled squares also represent responses of the left and right eyes, respectively, but for the second curve. *B*, Results from a complex cell that also had phase-specific interaction. In this case, the cell appeared essentially monocular by alternate tests of each eye. *C*, A complex cell that was clearly binocular, as shown by monocular tests of each eye, but that did not show any phase-specific interaction. For these complex cells, the average discharge rates (DC components) are plotted as functions of relative stimulus phase. *D*, A case of non-phase-specific suppression for a simple cell. The cell was apparently monocular, but responses from the left eye were suppressed when the gratings were presented to the right eye simultaneously. Spatial frequencies and orientation for these runs were (*A*) 0.6 cycle/deg, 357°; (*B*) 0.3 cycle/deg, 305°; (*C*) 0.5 cycle/deg, 70°; (*D*) 0.4 cycle/deg, 84°.

we studied. Of 41 cells recorded from 3 normal kittens, 26 were classified as simple and the remainder as complex. We did not study length-tuned cells. Of the simple cells, 19 out of 27 exhibited phase-specific binocular interaction. For complex cells, assuming similarity between kitten and adult cats, we expect that nearly half should exhibit phase-specific binocular interaction (Ohzawa and Freeman, 1986b). Of 14 complex cells studied in the normal kittens, 9 exhibited phase-specific binocular interaction.

Data from binocular interaction tests of 4 representative cells from the normal kittens are shown in Figure 3. Results from a simple cell are shown in Figure 3A. Note the extensive phase-specific binocular interaction, such that a relative phase difference of 90°–150° causes complete suppression of discharge of the cell. Similarly, at around 0° and 270°, response is substantially greater than that from monocular tests (right-hand column). Once again, if one grating is rotated orthogonally to optimal, interaction is eliminated (continuous line).

Phase-specific binocular interaction is shown for a complex cell in Figure 3B. As in the previous example, the cell is silenced at one relative phase (30°) and fires vigorously at another (170°). Once again, binocular interaction appears to require optimal orientation of both gratings, since 90° rotation of one (continuous line) prevents interaction. One additional feature of these data should be noted. The monocular tests, run concurrently with the binocular presentations, show that one eye (the left) was virtually silent when tested alone (right-hand column). However, in the binocular mode, this eye exerted a clear and substantial influence on the activity of the neuron. This pattern of subthreshold input from the silent eye, revealed through binocular stimulation, is seen frequently in the monocularly deprived kittens, as discussed below.

As with normal adult animals, a second type of complex cell is also found in kittens. Figure 3C shows the results from a cell that exhibits no apparent binocular interaction in spite of the fact that this unit responds to stimulation of either eye (see right-

hand column). Binocularity of the cell is also demonstrated clearly by separate measurements of tuning for spatial frequency and orientation for each eye (not shown).

Another type of binocular interaction, non-phase-specific suppression, is also found in kittens. Figure 3D shows an example from a simple cell that does not exhibit any phase-specific tuning. Note, however, that in 2 successive runs, the eye that does not respond when tested monocularly (see right-hand column) has a clear influence in the binocular case. It suppresses the cell's response nearly uniformly as the relative phase is altered. The response patterns of Figure 3, *B*, *D*, demonstrate clearly that afferent pathways that do not produce a response monocularly are intact and functional under binocular conditions.

Brief monocular deprivation

In a previous study, we looked for, but did not find, evidence of binocular interaction in monocularly deprived cats (Freeman and Robson, 1982). Our methods were similar to those used in this investigation. To pursue this issue, we decided to maximize the chance of observing functional binocular pathways in monocularly deprived animals by using brief periods of lid closure, which, we knew from previous work, would result in clear abnormalities of ocular dominance histograms (Olson and Freeman, 1975; Movshon and Dursteler, 1977; Freeman and Olson, 1982). We imposed 3 d of monocular deprivation at postnatal week 5 and recorded from animals immediately thereafter.

Results from this group of kittens in terms of ocular dominance distributions are shown in Figure 4. For comparison, results from a normal kitten of the same age are shown in Figure 4A. The pattern of the other histograms is typical of that found for short-term monocular deprivation (Freeman and Olson, 1982). This includes a severe reduction in the number of cells that can be activated through both eyes, tested separately (groups 2–6), and a predominance of neurons that are dominated by the open eye (group 7). It is not our purpose here to define precisely the effects of monocular deprivation on ocular dominance histograms, a topic that has been covered in numerous previous studies (see Mitchell and Timney, 1984). The data in Figure 4 are included to point out that the brief monocular deprivation protocol we have used causes clear abnormalities.

Results from a cell from this group of kittens that exhibits a normal response pattern are shown in Figure 5. The response of one eye is greater than that of the other, but the cell is clearly activated by stimulation of either eye. Once again, there is pronounced binocular interaction that is phase-specific such that the unit is turned off at relative phases of 210°–240° and fires maximally at values of 30°–60°. An additional question addressed here is whether the response is stable. Since we are not attempting to specify absolute phase and do not monitor eye position in a precise way, it is important to estimate stability of the response. For a number of cells, including the one whose results are illustrated in Figure 5, we ran a complete second test of binocular interaction. As the second curve (filled symbols) shows, the main result is quite stable over time. We found this level of stability to hold in general for nearly all the second runs. Since our method includes the analysis of data in real time, we are able to monitor histograms as they are accumulated. It is thus possible to detect a change in the phase-dependent response pattern during a run, and, if this happens, the test is terminated until stability is again achieved. We have experienced this problem only rarely.

Figure 4. Ocular dominance histograms for 3 kittens that were monocularly deprived for 3 d at the age of 5 weeks (*B–D*). For the purpose of comparison, a histogram from a normal kitten of this age is shown in *A*. Groups 1 and 7 represent monocular cells driven exclusively by the eye, which is contralateral or ipsilateral, respectively, to the hemisphere containing the electrode. Groups 2–6 represent cells that are binocular and are influenced to varying degrees by each eye (Hubel and Wiesel, 1962).

The most interesting result of this study is illustrated in Figure 6. In this case, findings are shown from a moderately responsive cell of a short-term monocularly deprived kitten. The monocular tests demonstrate a clear lack of response from the deprived eye (Fig. 6, *A–C*). But with binocular phase-variable stimulation, a pronounced influence is seen from the deprived eye, and in this case the interaction is phase-specific. To verify that the interaction is a consistent property of the cell, a second complete binocular run was carried out, and the result shown in Figure 6D closely resembles that of the first test. This, then, is a clear situation in which a cell would be classified unequivocally, on the basis of monocular tests, as lacking binocular input. This input is only demonstrated under conditions of binocular testing. What is striking about this result is that the interaction must be due to highly organized bilateral input. In this case, it appears that linear mechanisms of the receptive-field structure of the deprived eye are clearly functional under binocular, but not monocular, stimulation. The implications of this result are considered in the Discussion.

The result illustrated above was not atypical. Of 59 cells recorded in the short-term monocularly deprived kittens, 38 were classed as monocular on the basis of tests of each eye in turn. Clear binocular input was demonstrated in 17 of these 38 under conditions of relative phase-varying binocular testing. Examples of results from the binocular tests for this group of kittens are shown in Figure 7. In *A* and *B*, the findings show clear phase-specific binocular interaction. For the cell of Figure 7A, the maximum response is close to that of the nondeprived eye when tested alone. A relative phase-shift of 30°–60° results in a total

Figure 5. Results of binocular phase-shift experiments are shown for a cell from a kitten monocularly deprived (left eye closed) for 3 d at the age of 5 weeks postnatal. This cell was binocular and the results are shown in the same format as that of Figure 2. Optimal spatial frequency and orientation were 0.65 cycle/deg and 70°, respectively.

silencing of the cell, and a smooth response transition is observed for the other phase positions. The result in Figure 7*B* differs in that a very small response is evident from the deprived eye. However, the major difference is that the maximum binocular response is substantially higher than that of either eye alone. Different patterns of binocular interaction are observed in the remaining examples of Figure 7. In both cases (*C*, *D*), the deprived eye exerts a strong suppressive effect on the output of the cell under conditions of binocular stimulation. Note that for each example, the deprived eye is totally silent when tested monocularly. With binocular stimulation, a non-phase-specific suppressive effect is strong and consistent. The cells of Figure 7 were classed as simple (*A*, *B*) or complex (*C*, *D*) on the basis of standard criteria (Hubel and Wiesel, 1962). For the briefly monocularly deprived group, there was no apparent difference between these types in the tendency to exhibit binocular interaction in cells for which one eye was ineffective during monocular tests. Of 34 and 25 simple and complex cells, 24 and 14,

respectively, were binocular, according to the results of monocular and binocular tests.

Late-onset monocular deprivation

A second group of kittens were monocularly deprived relatively late (8 weeks after birth), but for a longer period than the first group (8 weeks). From previous work, we knew that this protocol would produce abnormal cortical binocular patterns (Olson and Freeman, 1980), and the ocular dominance histograms that illustrate this are shown in Figure 8. For 2 of the 3 cats, the proportion of binocular neurons (groups 2–6) is clearly low (46 and 33%, Fig. 8, *A* and *B*, respectively), while the distribution for the third is unusual. These compare to values of around 80% or more for normal cats (Hubel and Wiesel, 1962).

The behavior of cells from this group of kittens is generally similar to that of the short-term deprived animals described above. We have the impression that tuning characteristics of the cells in this group may be somewhat sharper than those of

Figure 6. Results of binocular phase-shift experiments for a cell from a kitten whose left eye was monocularly deprived for 3 d at 5 weeks of age. The cell was apparently monocular when each eye was tested alternately, but clear binocular interaction is demonstrated in *C* and *D*. The format of the figure is identical to that of Figure 2. Optimal spatial frequency and orientation were 0.2 cycle/deg and 170°, respectively.

previously studied kittens, but there are insufficient data to make a meaningful comparison. Results from a cell in a cat with late-onset deprivation are depicted in Figure 9. The data and presentation are of the same form shown previously and, in this case, vigorous responses are observed from each eye under conditions of monocular testing (Fig. 9, *A, B*). When monocular tests are interleaved with phase-varying binocular runs (Fig. 9, *C, D*), responses of each eye when tested alone are substantially reduced. We have observed this behavior for a number of cells in normal adults (Ohzawa and Freeman, 1986a) and have the impression that it may be due to a type of adaptation that occurs in the predominantly binocular test sequence. In any case, the data in Figure 9*D* show a clear phase-specific binocular interaction in which facilitation is substantial.

Results from another cell in this group are shown in Figure 10. In this case, the cell is heavily dominated by the one eye (the nondeprived eye), but there is a clear small response to stimulation of the other eye. Once again, the binocular stimu-

lation mode shows highly phase-tuned binocular interaction, indicating that the eye that barely responds when tested monocularly exerts a substantial influence under binocular stimulation. Note that if the gratings presented to the 2 eyes are orthogonal to each other (continuous curve, Fig. 10*D*), phase-specific interaction is eliminated.

Several examples of results from binocular tests in this group of kittens are shown in Figure 11. In every case, the neuron is nearly completely monocular when each eye is tested alone (see right-hand columns of Fig. 11). However, for all the cells, evidence of organized input from the "silent" eye is clear during binocular tests. In 3 of the 4 cases shown, the interaction is phase-specific (Fig. 11, *A–C*). In the fourth case, a non-phase-specific suppression is observed, which is so potent that it nearly shuts off the cell's activity completely (Fig. 11*D*). Of the examples shown here, 2 are simple cells (*A, B*) and the other 2 are classed as complex (*C, D*). Note that phase-specific interaction is clearly present in Fig. 11*C*. We have observed this type of

Figure 7. Results of binocular phase-shift experiments for 4 additional cells from monocularly deprived kittens whose left eye was closed for 3–4 d at the age of 5 weeks. The 2 curves in *A–D* are from repeated runs. The format is identical to that of Figure 3. *A, B*, Phase-specific binocular interactions. *C, D*, Cases of non-phase-specific suppression. Optimal spatial frequencies and orientations were (*A*) 0.5 cycle/deg, 292°; (*B*) 0.7 cycle/deg, 64°; (*C*) 0.7 cycle/deg, 170°; (*D*) 0.4 cycle/deg, 305°.

behavior frequently for complex cells from normal adult cats (Ohzawa and Freeman, 1986b).

Long-term monocular deprivation

In a previous study, we searched for, but did not find, evidence of input from the deprived eye to visual cortex in cats that had

been monocularly deprived for long periods of 1 year or more (Freeman and Robson, 1982). However, our techniques in that study were not as refined as those used here. In addition, it is of obvious importance to establish whether the pathways we have demonstrated to be intact in the cases described above remain functional over extended periods. On the basis of the previous experiments, we anticipated a negative answer, but it was appropriate to determine this directly. Ideally, the same animal could be recorded several times in the hope of sampling the same region of cortex after varying periods of deprivation. Variability, however, and the problem of histological identification suggest that separate preparations are preferable. We therefore recorded from cats that had been monocularly deprived for extended periods (from 3 weeks postnatal to 11 months or more), using the same techniques as described above. Ocular dominance distributions for these cats, shown in Figure 12, confirm that the effects of extended monocular deprivation are severe.

Our results are similar to those of the previous study (Freeman and Robson, 1982), in that very little evidence was found to suggest that pathways from the deprived eye remain intact. However, for a few cells, there was clear functional input from the deprived eye; an example of this is shown in Figure 13. With monocular testing, the right (nondeprived) eye is completely ineffective in driving the cell (Fig. 13, *A–C*). But under binocular conditions, this eye causes suppressed output of the cell to such an extent that there is almost a cessation of activity (Fig. 13*D*). This suppression is non-phase-specific.

Another interesting result from this group of cats is shown in

Figure 8. Ocular dominance histograms for cats that had been monocularly deprived for 8 weeks starting at the age of 8 weeks. Categories are the same as those defined in Figure 4.

Figure 9. Results of binocular phase-shift experiments for a cell from a cat whose left eye was monocularly deprived for 8 weeks, starting from the age of 8 weeks. This cell was binocular, as shown by orientation and spatial frequency tuning curves, illustrated in *A* and *B*, respectively (open circle, left; asterisk, right). The format is identical to that of Figure 2. The optimal spatial frequency and orientation were 0.7 cycle/deg and 80°, respectively.

Figure 14. There are 2 aspects of the data from this cell that are unusual. First, the monocular tests of orientation tuning show that one eye is nearly nonresponsive and the other is bidirectional and tuned for orientation, but also responds to some extent at all stimulus orientations. Spatial frequency tuning appears normal. The second feature of interest is that no binocular interaction is observed when harmonic analysis is used to display the average discharge rate (i.e., DC component), but for the fundamental frequency component (first harmonic), a clear phase-specific binocular interaction is indicated (see Fig. 14, *D*, *E*). This suggests that the convergence of signals from the 2 eyes is nonlinear and nonantagonistic, as opposed to the case with simple cells in the normal cat (Ohzawa and Freeman, 1986a). The pattern of Figure 14, *D*, *E*, suggests nonlinear convergence as follows. Suppose the input to the cell in question arrives from a pair of LGN cells in layers A and A1, which therefore have receptive fields in separate eyes. Also suppose that there is no intracortical input to this cell, providing inhibition through which antagonism and linear spatial summation are achieved. As we

vary the relative phase of the gratings shown to the 2 eyes, the arrival times (or relative temporal phase) of bursts of spikes from the 2 LGN cells also vary. At one relative phase of the stimulus, these bursts will coincide, resulting in a large modulation of the response at the temporal frequency of the stimuli (first harmonic). On the other hand, if the relative phase is 180° away from the above condition, the bursts from the 2 cells will be interleaved in time, filling in each other's nonactive periods. Therefore, at this phase, the first harmonic component takes a minimum value. This condition may produce a response modulation at twice the temporal frequency of the stimulus if bursts are crisp, but it will otherwise be smoothed out in the response, as perhaps is the case for the cell of Figure 14. Note, however, that the DC component of the response is not dependent on the relative phase, because the time-average of the sum of the bursts from the 2 LGN cells is constant and independent of the relative phase of the stimulus. If one assumes that impulse activity of the cortical cell occurs only above a minimal threshold, the scheme described above would produce an apparent phase-spe-

Figure 10. Results of binocular phase-shift experiments for a cell from a cat that had been monocularly deprived for 8 weeks, starting at the age of 8 weeks (left eye closed). This cell was determined to be monocular (group 7) by an initial subjective test using a bar of light. Quantitative measurements reveal a weak excitatory input from the left eye. The format is identical to that of Figure 2. The optimal spatial frequency and orientation were 0.4 cycle/deg and 309°, respectively.

cific binocular interaction for the first harmonic component of the response, but not for the DC component, as shown in Figure 14, *D*, *E*. This is the only cell we recorded that exhibited these properties, but this type of behavior is observed frequently in the perigeniculate nucleus (PGN) of the cat (Xue et al., 1988).

Results for all the cells recorded in this investigation are summarized in Figure 15. As the distributions show, the relative proportions of binocular and monocular cells change markedly from the normal (top) to long-term monocular deprivation (bottom) groups. All shaded regions represent cells that appear monocular by alternate tests of each eye. However, substantial proportions of these cells are not truly monocular. Although the numbers of monocular cells increase in the brief and late-onset monocular groups, the proportions of cells that reveal binocular interaction despite their apparent monocularity remain approximately constant. These cells exhibit suppressive or phase-specific behavior. In each group, except for the long-term MD cats, 25–30% of the cells are clearly influenced by pathways from

each eye. These cells would have been classed as monocular if conventional techniques were employed. Although cells with residual binocular input did not appear to be limited to a given type in the brief and late-onset groups, all 7 binocular cells in the long-term group were complex. In addition, they were classed as group 6 in terms of ocular dominance and did not exhibit any apparent binocular interaction.

Are any of the cells that exhibit binocular connectivity when tested with 2 simultaneous gratings distinguished by morphological, laminar, or other physiological features? The answer appears to be negative. Complex cells are considered to be more binocular in general than are simple cells (Gilbert, 1977), and we compared the relative proportions of each class, in our present sample, that exhibited binocular interaction or were binocular with monocular tests. There was very little difference (for brief and late-onset MD groups, 60 and 69% for complex and simple cells, respectively). We next sought differences that might be associated with cortical lamina, and, as Figure 16 shows,

Figure 11. Results of binocular phase-shift experiments for 4 additional cells from cats whose left eye was closed for 8 weeks, starting at the age of 8 weeks. *A–C* indicate phase-specific binocular interactions, while *D* shows the case of non-phase-specific suppression. The format is identical to that of Figure 3. The optimal spatial frequency and orientation for each cell was (*A*) 0.3 cycle/deg, 87°; (*B*) 1.2 cycles/deg, 289°; (*C*) 1.2 cycles/deg, 185° (nearly horizontal); (*D*) 0.9 cycles/deg, 136°.

there are no obvious patterns related to laminar distribution. It might be noted, however, that of the 7 cells with binocular input (including the suppression type) in the long-term monocular groups, 5 are located in the layers that receive direct input from the LGN (layers 4 and 6). Cells in these layers are thought to be relatively more resistant to the effects of monocular deprivation than neurons in other layers (Shatz and Stryker, 1978).

Discussion

To provide data for comparison, we have examined binocular interaction in cortical cells of normal kittens at 5 weeks of age. The results show that the majority of these cells are binocular and display response properties that are indistinguishable from those of adult cats (Ohzawa and Freeman, 1986a, b). In particular, most of these cells exhibit phase-specific binocular interaction, with tuning characteristics similar to those of adults, although we have not made a quantitative comparison. Orientation, spatial frequency tuning, and directional preferences also approximate adult characteristics. However, there are 2 differences between the samples from these kittens and those of adult cats. First, the kittens have a relatively large proportion of cells that appear monocular from tests of each eye alone, but exhibit binocular interaction (see Fig. 15). It is possible that this reflects a maturational process and that these neurons might develop full binocular status over time. The other point of in-

Figure 12. Ocular dominance histograms for 3 cats that were monocularly deprived for more than 10 months from the age of 3 weeks until the day of the recording. Categories of ocular dominance are the same as for Figure 4.

Figure 13. Results of binocular phase-shift experiments for a cell from a cat whose left eye had been deprived for 35 months, starting at the age of 3 weeks. This cell was driven by stimulation of the left eye (deprived eye), while the right eye was unresponsive. *A, B*, Orientation and spatial frequency tuning curves for each eye (open circle, left; asterisk, right). *C*, PST histograms for the binocular run. *D*, Plots of response amplitude (DC component) obtained by harmonic analyses of the histograms in *C* as a function of relative phase (open circles). The second curve (filled circles) represents results of a binocular run in which the gratings for the right eye were rotated 90° from the optimal orientation for the left eye. The suppression persisted at the orthogonal orientation. The optimal spatial frequency and orientation for the left eye were 0.6 cycle/deg and 230°, respectively.

terest here is that phase-specificity appears finely tuned in these kittens and, if one thinks of this interaction as a disparity-selective process, then it is important to know how early in postnatal maturation this facility is developed (Pettigrew, 1974). Although we have only preliminary data from younger kittens, our current impression is that binocular phase-specificity is present at the postnatal age of 3 weeks.

Results for the 2 groups of kittens reared with brief or late-onset monocular deprivation are quite similar. In both cases, around 60–70% of the cells appear to be monocular from tests of each eye alone. With binocular phase-varying stimulation, however, a substantial proportion (25–30% of the total) of these units display clear input from the deprived eye. This latter group of cells is remarkable in that, for most cases, the influence through the deprived eye pathway is clear and robust, even though no response is obtained upon unilateral stimulation of that eye. There were 2 kinds of interaction, phase-specific and overall

suppression. Each type occurs with about the same frequency. Since complex cells are more binocular than simple cells (Gilbert, 1977), it might be expected that the former type would be more likely to retain input from a deprived eye, but we have not found this to be the case. Of 78 cells that exhibited functional input from the deprived eye, 46 and 32, respectively, were classed as simple and complex. Finally, it should be noted that the phase-specific interactions observed for the cells of the monocularly deprived kittens appear indistinguishable from those we find in normal kittens or cats. Although we have not made a quantitative comparison, the amplitudes and tuning characteristics of the interaction patterns appear to be the same in these groups of cats.

Concerning the nature of residual binocular interaction, it is of interest to know whether monocular deprivation causes any differential effects on excitatory or inhibitory connections. In previous studies that have addressed this question, evidence has

Figure 14. Results of binocular phase-shift experiments for a cell from a cat that had been monocularly deprived for 23 months, starting at the age of 3 weeks. *A*, Orientation tuning of the cell. The left eye (open circles) appears unresponsive, while tuning for the right eye (asterisks) is abnormal in that tuning width is broad and responses are present at troughs of the tuning. *B*, Spatial frequency tuning for the cell, but no obvious abnormality is seen. *C*, PST histograms for the binocular run in the same format as that of Figure 2*C*. Results of harmonic analyses on these histograms are shown in *D* (DC component) and *E* (first harmonic). While no interaction is observed with the DC components, strong effects of relative stimulus phase are observed in the first harmonic components. The 2 curves in *D* and *E* are results from repeated runs.

been found of excitatory connections from the deprived eye (Tsumoto and Suda, 1978). On the other hand, inhibitory pathways have been reported to remain intact (Singer, 1977). Although our data are insufficient for drawing definite conclusions, there is no obvious trend that shows that either excitation or inhibition is more resistant to monocular deprivation. Specifically, many apparently monocular cells that show phase-specific binocular interaction clearly retain both excitation and inhibition. This is demonstrated by the fact that the monocular response of the dominant eye is smaller than the peak and larger than the trough of the binocular phase-tuning curve (see Figs. 6; 7, *A*, *B*; 10; 11*A*). Excitation is necessary to raise the binocular response at the peak beyond the monocular level. Conversely, inhibition is required to bring the response level below the monocular excitation level. The other group of apparently monocular cells, the non-phase-specific suppression type, seems to show inhibition from the silent eye. However, there is no apparent

increase in the proportion of these cells for monocularly deprived cats. Normal 5-week-old kittens have as many of these cells as deprived ones (Fig. 15).

One additional observation should be made concerning the findings from these groups of kittens. We have mentioned only results that show a functional input from the deprived eye expressed during binocular stimulation. This result has also been obtained with the opposite combination of factors. In these cases, the nondeprived eye fails to respond under the condition of monocular testing, but exerts a substantial influence on the activity elicited by the stimulation of the deprived eye. We found 3 cases like this in the groups of brief and late-onset monocularly deprived kittens, compared to 29 neurons that behaved in the opposite (i.e., obvious) way. This finding suggests what has been noted in previous work (Hubel and Wiesel, 1970; Olson and Freeman, 1975), i.e., that the most fragile component of the postsynaptic pathway in visual cortex is binocularity. The first

Figure 15. Proportions of different types of cells in 4 groups of animals. Neurons identified as binocular by monocular tests of each eye are indicated by *white spaces*. Some apparently monocular cells showed binocular interaction, either in the form of phase-specific tuning (*dotted areas*) or in the form of suppression (*hatched areas*). Thus, these 2 types of cells were not really monocular, but would have been missed by conventional techniques. Truly monocular cells are shown as *cross-hatched areas*. Some cells whose ocular dominance could be determined by initial tests were lost before complete quantitative runs were performed, and are not included.

effect of interference with binocular vision is a failure of effective stimulation through either eye, and it is not necessarily the deprived eye that fails first (Hubel and Wiesel, 1970; Olson and Freeman, 1975; Freeman and Olson, 1982).

In either case, most of the connections that are functional in these kittens eventually become silent. This is shown clearly by the experiments in which long-term monocular deprivation is imposed prior to physiological study. Since we had previously examined the case of extended deprivation (Freeman and Robson, 1982), we had not anticipated much evidence of retained input from the deprived eye. However, in 2 cells from the long-term deprivation group, there was clear evidence of such input, as noted in Figures 13 and 14. In each of these examples, the 2 cells were located in direct input layers (4 and 6) from the lateral geniculate body. The remaining 5 cells, which are shown

Figure 17. Possible schemes of binocular convergence for cells that are apparently monocular, but exhibit binocular interaction. *A-D*, Illustrations of how a threshold mechanism may cause apparent monocularly, and yet allow phase-specific binocular interaction to occur. *A, B*, Monocular responses as functions of time for the silent and dominant eyes, respectively. *Th*, Threshold level; the *filled area* above this level indicates responses observable as spike discharge. *C*, The condition where these monocular inputs are combined in *antiphase*, causing cancellation of the response. *D*, The condition where inputs are summed *in-phase*, resulting in apparent facilitation. *E*, Another possible scheme for convergence, where inhibition is exerted from the silent eye within the LGN, or presynaptically in the cortex.

as binocular in Figure 15, were located in layers 2 + 3, 4, and 6. The unique form of binocular interaction exhibited by the cell of Figure 14 suggests that the binocular combination of signals from the 2 eyes can occur in an unusual way. In any case, binocular survival is almost certainly an anomaly under conditions of long-term monocular deprivation.

On the other hand, the process of functional disconnection of the deprived eye pathway to visual cortex appears to take much longer than was previously thought. The results from the brief and late-onset deprived kittens show that a substantial proportion of cells that appear to be monocular on the basis of alternate tests of each eye alone have, in fact, intact binocular

Figure 16. Laminar distributions of cells are shown for (*A*) normal control, (*B*) brief monocular deprivation, and (*C*) late-onset monocular deprivation. In all cases, *white areas* indicate cells that were identified as binocular by alternate tests of each eye. *Dotted* and *hatched areas* denote apparently monocular cells that showed binocular interactions in the form of phase-specific interaction and suppression, respectively. *Cross-hatched areas* indicate cells that were monocular in all of the tests performed.

inputs. This has also been noted for a small population of cells ($n = 16$) by the use of DL-homocysteic acid, which is iontophoretically applied to cortical neurons (Blakemore et al., 1982). Another study suggests that use of many stimulus presentations also can lead to a detectable response from the deprived eye (Fiorentini and Maffei, 1979).

These latter results should be considered together with the finding of the current study that some cells appear monocular but can, under the right conditions, be shown to have functional binocular input. What is of interest here is that the proportions of neurons that show this property are approximately the same in both groups of deprived kittens and in the control group of normal kittens (Fig. 15). This suggests that the apparent monocular of cells that show phase-specific interactions may be due to a difference in threshold of the cells rather than to the deprivation procedure itself (see below). However, the effect of monocular deprivation is evident, as shown by the differences in proportions of truly monocular neurons between deprived and control groups. In addition, since the phenomenon of binocular function in apparently monocular cells also occurs in normal kittens, but appears relatively rare in normal adults, there could be a maturation component involved, in which increased myelination and other changes that occur during normal development (Cragg, 1972, 1975; Mitchell and Timney, 1984) act to strengthen pathways to above threshold for any visual stimulation.

There are several possibilities as to how these apparently monocular cells may exhibit input from the silent eye either as phase-specific binocular interaction or as non-phase-specific suppression. A likely possibility that would account for phase-specific interaction in these cells is illustrated in Figure 17, *A–D*. It is based on the assumption that the spike-generation mechanism of a cell has a threshold. In this case, the cell cannot generate spikes unless the transmembrane potential exceeds threshold, even if some excitation is present (Ohzawa and Freeman, 1986a). Figure 17, *A, B*, shows monocular responses from the silent and dominant eyes, respectively. Note that the silent eye does not elicit any response, because excitation is subthreshold. However, this apparently silent eye influences the binocular response in a phase-specific manner, as is shown in Figure 17, *C, D*. Adding input from the 2 eyes in the *antiphase* condition causes suppression of the response, while addition in the *in-phase* condition facilitates the response. Another scheme, likely for the non-phase-specific suppression observed in apparently monocular cells, is illustrated in Figure 17*E*. Here, inhibition may be exerted from the silent eye subcortically, within the LGN or from the PGN, or it may inhibit presynaptically the pathway from the dominant eye at the cortex. It is conceivable that this type of presynaptic cross-inhibitory pathway may persist even after disconnection of the excitatory pathway from the deprived eye. Although evidence for the latter type of connection has not been reported, several studies have shown inhibition of the dominant eye response from the nondominant eye in LGN (e.g., Sanderson et al., 1969; Kato et al., 1981). Xue et al. (1987), using a technique similar to that employed in the present study, also show that this inhibition is non-phase-specific. Although contributions from a corticofugal pathway may play a role, intrinsic interlaminar inhibition appears to be specific to LGN (Schmielau and Singer, 1977).

In conclusion, we have shown that many cells that appear monocular in monocularly deprived kittens maintain functional connections from both eyes. It is interesting to note that the

binocular interaction observed in these cases shows that the input from the deprived (as well as the nondeprived) eye is highly organized despite apparent monocular. In the case of long-term monocular deprivation, the cells that can be driven generally have irregular or diffuse receptive fields. Our present results suggest that this disorganization and complete disconnection of deprived-eye input must take considerable time to develop.

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