

Recovery of Cortical Binocularity and Orientation Selectivity after the Critical Period for Ocular Dominance Plasticity

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Abstract

Cortical binocularity is abolished by monocular deprivation during a critical period of development lasting from approximately postnatal day (P) 35 to P70 in ferrets. Although this is one of the best-characterized models of neural plasticity and amblyopia, very few studies have examined the requirements for recovery of cortical binocularity and orientation selectivity of deprived eye responses. Recent studies indicating that different mechanisms regulate loss and recovery of binocularity raise the possibility that different sensitive periods characterize loss and recovery of deprived eye responses. In this report, we have examined whether the potential for recovery of binocularity and orientation selectivity is restricted to the critical period. Quantitative single unit recordings revealed recovery of cortical binocularity and full recovery of orientation selectivity of deprived eye responses following prolonged periods of monocular deprivation (i.e., longer than 3 weeks) starting at P49, near the peak of plasticity. Surprisingly, recovery was present when binocular vision was restored after the end of the critical period for ocular dominance plasticity, as late as P83. In contrast, ferrets that had never received visual experience through the deprived eye failed to recover binocularity even though normal binocular vision was restored at P50, halfway through the critical period. Collectively, these results indicate that there is potential for recovery of cortical binocularity and deprived eye orientation selectivity after the end of the critical period for ocular dominance plasticity.

Key words: ocular dominance plasticity, ferret visual cortex, monocular deprivation, orientation selectivity, amblyopia.

Introduction

One of the defining characteristics of the primary visual cortex is the convergence of monocular inputs at the single neuron level leading to the generation of binocular responses. Binocularity can be abolished by depriving the animal of patterned vision in one eye during a developmental window known as the critical period. The ensuing synaptic changes result in a cortex dominated by the non-deprived eye (Wiesel and Hubel 1965a). Decades of research have established monocular deprivation studies as a classic animal model of synaptic plasticity and human amblyopia. Yet, attempts to develop models in which cortical binocularity recovers following a period of monocular deprivation have met with limited success (Mitchell et al. 1977; Movshon 1976; Olson and Freeman 1978; Van Sluyters 1978; Wiesel and Hubel 1965b). Inducing recovery of deprived eye responses by reverse suture has been the recovery protocol most commonly used, but results in loss of responses from the newly deprived eye, precluding studies of binocular recovery. Systematic attempts to characterize recovery of deprived eye orientation selectivity are also lacking in the literature. For this reason, we have little information regarding the mechanisms that mediate recovery of binocularity or how recovery might be developmentally regulated, even though this information is highly relevant to understanding cortical plasticity and recovery from amblyopia.

Loss of binocularity following monocular deprivation has traditionally been regarded as the result of a competitive process. The deprived eye loses cortical representation to its more active, non-deprived counterpart. In contrast, binocular competition cannot drive recovery following deprivation because the previously deprived eye is unable to activate action potential activity in cortical neurons. The disparate nature

of afferent activity in these two situations suggests that each may rely on different signaling cascades. New evidence has pointed to a mechanistic dichotomy between loss and recovery of binocularity, with function of the cAMP/Ca⁺⁺ response element binding protein (CREB) being required for loss of binocularity (Mower et al. 2002) but not for recovery (Liao et al. 2002). Additionally, clinical studies indicate that recovery from amblyopia can occur after the end of the critical period for the effects of monocular deprivation (Birnbaum et al. 1977), or, paradoxically, may not occur when normal visual input is restored during the critical period (Birch and Stager 1988; Taylor et al., 2001; Williams et al., 2002). Collectively, these findings raise the possibility that different sensitive periods characterize loss and recovery of deprived eye responses. Furthermore, early deprivations, which seem to carry the worst prognosis for recovery, occur during development of crucial receptive field properties such as orientation selectivity. Thus, the potential for recovery may be related to the timing of deprivation because different receptive field properties mature during different stages of development (Daw 1998). In the present report we have examined whether there is potential for recovery of deprived eye responses beyond the critical period for ocular dominance plasticity and whether recovery is affected by the timing of deprivation.

Materials and Methods

Recovery was examined in three groups of ferrets deprived of patterned visual stimulation by monocular eyelid suture (Table I). In the first group (short-term deprivation, n=10 animals), ferrets were monocularly deprived starting at approximately P45, the peak of ocular dominance plasticity (Issa et al. 1999). After 5-7 days of monocular deprivation, ocular dominance was examined in some animals (n=5) while other animals (n=5) had ocular dominance and orientation selectivity examined following 3-7 days of binocular vision. In the second group of animals (late long-term deprivation, n=9), animals were deprived starting at approximately postnatal day (P) 49, near the peak of ocular dominance plasticity and when orientation selectivity is mature. Animals in this group were examined at the end of the period of deprivation (n=5), around P63, or following restoration of binocular vision starting at P73-P83 (n=4), after the end of the critical period for ocular dominance plasticity (Issa et al. 1999). To examine the time course of recovery, response properties were examined 3-19 days after binocular vision had been restored. In the third group (early long-term deprivation, n=9), recovery of cortical binocularity and orientation selectivity was examined in animals that had never received visual experience through one eye. In this group, the eyelid was sutured before eye opening (around P32 in ferrets) and monocular deprivation lasted three weeks, encompassing the period for development of orientation selectivity (Chapman and Stryker 1993). Some of these animals (n=4) were examined at the end of the period of deprivation while other animals (n=5) were examined following a period of binocular vision starting within the critical period for ocular dominance plasticity (Issa et al. 1999).

To examine the time course of recovery, animals were examined 5-24 days after restoration of normal vision. The Institutional Animal Care and Use Committee at Virginia Commonwealth University approved all procedures described in this paper.

Extracellular recordings in vivo: Animals were premedicated by subcutaneous injection of acepromazine (2mg/kg, i.p.) and methyl atropine bromide (0.2 mg/kg, i.p.), anesthetized with intraperitoneal sodium pentobarbital (35 mg/kg, Abbott Laboratories, North Chicago, IL), and placed in a stereotaxic frame. No procedures started until the animal was sufficiently anesthetized, as ascertained by the loss of withdrawal and cornea-blink reflexes. Body temperature, respiratory rate, and anesthesia level were monitored continuously during surgery. Surgery consisted of a craniotomy (3-5 mm in diameter) over the region in primary visual cortex where recordings were conducted. A tracheal cannulation was performed and the animal placed on a ventilator. Heart rate, expired CO₂ and O₂ were monitored continuously during the experiment and maintained at approximately 4.0% and above 90%, respectively. Body temperature was maintained at 38°C using a homeostatic blanket. The eyelids were opened, nictitating membranes were retracted using phenylephrine hydrochloride (2.5%), the pupils were dilated with atropine sulfate (1%), and contact lenses placed on the corneas. Animals were paralyzed using pancuronium bromide (0.2 mg/kg, i.p.) at the start of the recording session. Supplemental doses of pentobarbital (12 mg/kg, i.p.) and pancuronium bromide (0.1 mg/kg, i.p.) were given every hour throughout the experiment or when heart rate or expired CO₂ increased. Subcutaneous injections of 10% dextrose and 0.9% saline were given during the experiment as needed. Judicious supplementation of pentobarbital anesthesia preserves visual responses over time (Medina et al. 2003). To comply with

NIH guidelines for use of paralytic agents and certify that the animals were maintained at an appropriate level of anesthesia, use of muscle relaxants was omitted during the experiment and withdrawal reflexes were monitored in some animals. Similar procedures have been previously described and shown to be appropriate for visual physiology studies conducted in ferrets (Medina et al. 2003).

Single unit recordings were conducted using a tungsten-in-glass tungsten microelectrode lowered into the primary visual cortex through the craniotomy. All recordings were made within the binocular region of the ferret visual cortex (Law et al. 1988). After isolation of a single unit, its receptive field, ocular dominance, and preferred orientation, direction and velocity were determined qualitatively using a moving bar of light (0.5° wide and 20° long). Ocular dominance and/or orientation selectivity were then quantitatively determined under computer control. To assess orientation selectivity, the moving bar of light was presented to each eye separately at four orientations centered about the optimal. To assess ocular dominance only the optimal stimulus orientation was used. One stimulus presentation consists of the bar of light moving across the receptive field in one direction and then back across in the opposite direction. A computer collected spikes over 10 stimulus presentations at each orientation using Spike2 software (Cambridge Electronic Design, Cambridge, UK). Spontaneous activity was determined by recording in the absence of stimulation for 2 secs following each presentation. Repeated qualitative evaluation of receptive field position as well as examination of computer generated times of spike firing were used to examine eye movements during recordings of responses from each neuron. Upon the

conclusion of the experiment, the animal was sacrificed with Euthasol (125 mg/kg, Delmarva laboratories, Midlothian, VA).

To provide a quantitative estimate of response properties, an ocular dominance index and orientation selectivity index were calculated for each cell, as described in Results. Differences between experimental groups were determined by submitting these indices to a Wilcoxon Mann-Whitney test.

Results

We have examined whether recovery from the effects of monocular deprivation can occur after the end of the critical period for ocular dominance plasticity and whether the potential for recovery is related to the timing of deprivation. Recovery of binocularity and orientation selectivity of visual cortical neurons were examined following restoration of binocular vision in ferrets undergoing short (i.e. up to one week) and prolonged (i.e. longer than 3 weeks) periods of monocular deprivation (Table 1). The timing of deprivation and recovery in each group are schematically shown in Figure 1. Animals were subjected to prolonged deprivation either during the first half of the critical period, when orientation selectivity develops (early long-term deprivation group), or during the second half of the critical period after orientation selectivity had already matured (late long-term deprivation group). Binocular vision was restored during the critical period in the case of the short term and early long-term deprivation groups and after the critical period in the late long-term deprivation group. Marked differences in recovery were observed in the two groups of animals subjected to long-term deprivation.

Figure 1 near here

Full recovery from short-term monocular deprivation

To examine the full potential for recovery of binocularity and orientation selectivity in ferrets, first we characterized recovery in animals subjected to short-term monocular deprivation starting at P45, during the peak of ocular dominance plasticity (Issa et al. 1999). Animals were monocularly deprived 5-7 days, then had the eyelid opened to restore binocular vision. Quantitative *in vivo* electrophysiology was then conducted to assess cortical binocularity and orientation selectivity of primary visual cortical neurons following up to 7 days of binocular vision. To quantify ocular dominance, we calculated an ocular dominance index using the equation $EE/(EE+DE)$, where EE denotes the response to stimulation of the experienced eye (or left eye in normal ferrets) and DE for the deprived eye (or right eye for normal ferrets and recovering eye for recovering ferrets). An ocular dominance index of 1.0 indicates a cell responsive to only the experienced (or left) eye; an index of 0.0, a cell responsive only to the deprived (or recovering, or right) eye. Figure 2 shows that 5-7 days of MD induces an almost complete, saturating shift in ocular dominance towards a predominance of the non-deprived eye (Fig. 2B). In spite of this marked loss of responses to the deprived eye, binocular vision restored cortical binocularity so that the ocular dominance profile was similar to normal (compare A and C; $p>0.05$, Wilcoxon Mann-Whitney test).

Figure 2 near here

To examine recovery of orientation selectivity in these animals, an orientation selectivity index (OSI) was obtained for each cell by dividing the response at 45° and 90°

from the optimal by the response at the optimal orientation and subtracting the result from one. Figure 3 shows the cumulative percentage of cells plotted as a function of the OSI for two groups of animals: 1) ferrets that were monocularly deprived, then received binocular visual experience (n=61 cells activated by the deprived eye; filled symbols), and 2) normal animals (n=86 cells activated by the dominant eye, open symbols) studied at approximately the same age. Indices of 1.0 denote a high degree of selectivity and indices of 0.0 lack of selectivity. Therefore, cumulative curves that are shifted to the right indicate higher degree of selectivity while cumulative curves shifted to the left indicate decreased neuronal selectivity. The curves shown for both groups of cells overlap and are quite similar, and the orientation selectivity indices obtained for the normal and recovered groups are not different ($p>0.05$). This finding indicates that cortical response to stimulation of the previously deprived eye is highly selective to stimulus orientation, as in normal animals.

Figure 3 near here

Recovery after the critical period for ocular dominance plasticity

Having established that cortical binocularity fully recovers in animals subjected to short-term monocular deprivation, we examined whether binocularity can also recover after a prolonged period of deprivation. In the case of late long-term deprived animals specifically, we have asked whether recovery of normal responses can occur after the end of the critical period for ocular dominance plasticity.

Ferrets were monocularly deprived for at least 3 weeks starting around P49, near the peak of ocular dominance plasticity (Issa et al. 1999) and when orientation selectivity

is mature (Chapman and Stryker 1993). Following a prolonged period of deprivation, binocular visual experience was restored in animals ranging in age from P75 to P83, after the end of the critical period for ocular dominance plasticity (Issa et al. 1999). Prolonged monocular deprivation induced an almost complete shift in ocular dominance in favor of the non-deprived eye (Fig 4A). Nevertheless, binocularity was rescued and a majority of neurons (78% of 159 cells) recovered robust responses to the previously deprived eye ($ODI < 0.8$; Fig. 4B).

In order to characterize the rate of recovery of deprived eye responses, we have calculated a contralateral bias index (CBI) for each animal defined as $((P_{0.00-0.19} - P_{0.80-1.00}) + (P_{0.20-0.39} - P_{0.60-0.79}) / 2 + 100) / 200$ where P_{A-B} denotes the percentage of cells with binocular indices between A and B. Figure 4C shows rapid recovery of CBIs during the first week of binocular vision. Recovery of the normal pattern of cortical ocular dominance started as early as 3 days after restoration of binocular vision and was complete by 8 days, when a slight predominance of the contralateral eye was noticeable.

Figure 4 near here

To examine recovery of orientation selectivity following a prolonged period of monocular deprivation, we have compared OSIs to stimulation of the dominant eye in normal animals and the recovering eye in animals that had been monocularly deprived. Figure 5 shows that OSI distributions for the recovering (filled symbols, $n=41$ neurons) and normal (open symbols, $n=86$) eyes overlap ($p > 0.05$). This finding indicates that responses to the deprived eye fully recovered selectivity to stimulus orientation. Together, these results show a remarkable potential for recovery of deprived eye responses after the end of the critical period for ocular dominance plasticity.

Figure 5 near here

Lack of recovery from early MD

We examined whether recovery of binocularity and orientation selectivity can occur following early long-term monocular deprivation. Ferrets were monocularly deprived beginning one day before eye opening and binocular visual experience restored at P51, within the critical period for ocular dominance plasticity (Issa *et al.* 1999). This is approximately the same age at which we restored binocular vision to animals in the short-term monocular deprivation group (Table I). Animals were allowed binocular vision for periods of 7 to 40 days, and then examined for binocularity and orientation selectivity of cortical neurons. Figure 6 shows that monocular deprivation during this period induced a saturating shift in ocular dominance so that most neurons were dominated by the non-deprived eye (Fig 6A; n= 119 cells in 4 animals). Relatively little recovery of cortical binocularity was detected following restoration of binocular vision (Fig. 6B; n= 169 cells in 5 animals). Most cells responded preferentially to the experienced eye, indicating that recovery was substantially less pronounced following early long-term deprivation than short-term and late long-term deprivation. Moreover, recovery did not increase further following longer periods of binocular vision lasting up to 24 days (Fig.6C).

Figure 6 near here

Next, we examined whether responses to the previously deprived eye recover selectivity to stimulus orientation. Typically, neurons responsive to the previously deprived eye were not selective to stimulus orientation. To quantify this result, we have

calculated OSIs for neurons that were responsive to the recovering eye. The cumulative distribution curves are shown in Figure 7 (A, and B) of the responses of each neuron to stimulation of the previously deprived eye (open circles, n= 34 cells) and experienced eye (open triangles, n=62 cells) in the same animals. The results obtained for the dominant eye in normal animals (filled symbols, n=86) are also shown. The cumulative curves for the deprived eye are shifted to the left, indicating decreased selectivity to stimulus orientation for this eye relative to the experienced eye ($p < 0.01$) at both 45° and 90° from the optimal. In contrast, orientation selectivity for the experienced eye developed normally ($p > 0.05$), as indicated by cumulative distribution curves that overlap with the distributions for normal animals.

We have found that the most binocular neurons in recovering animals were also the least selective to stimulus orientation. This is shown in plots of the mean OSI as a function of the ocular dominance index (Fig 7C, and D). Cells with the lowest orientation selectivity indices (i.e., less than 0.6), indicative of reduced selectivity to stimulus orientation, were more binocular than cells with higher orientation selectivity indices ($p < 0.05$). In conclusion, animals that had never received normal visual stimulation through the deprived eye show very little recovery of cortical binocularity and orientation selectivity.

Figure 7 near here

Discussion

This study reports that ferrets can fully recover from the effects of 1-3 weeks of monocular deprivation if binocular vision is restored. This period of deprivation is sufficient to eliminate deprived eye responses and induce shrinkage of axon arbors serving the deprived eye (Antonini and Stryker 1996). In spite of the profound anatomical and functional effects of monocular deprivation, cortical binocularity and orientation selectivity in recovering animals were indistinguishable from normal. Especially remarkable is the finding of substantial recovery of deprived eye responses beyond the critical period for ocular dominance plasticity, which in ferrets ends around P65-P70 (Issa et al. 1999). Both orientation selectivity and binocularity recovered within a few days of binocular vision starting as late as P83, the oldest age examined. These findings demonstrate that recovery of deprived eye responses is not constrained by the closure of the critical period for ocular dominance plasticity, and are consistent with the idea that different mechanisms underlie loss and recovery of cortical binocularity (Liao et al. 2002).

This is the first time that substantial recovery of binocularity and orientation selectivity has been shown to occur after the end of the critical period. However, we have also found that recovery is affected by the timing of deprivation. Recovery of connections to highly selective cells, which presumably are an integral part of normal visual function, was not seen in animals that had never received normal visual stimulation through the deprived eye but was seen in animals subjected to late monocular deprivation.

Previous studies had shown recovery of influence from the deprived eye when reverse suture was conducted in kittens during the critical period (Blakemore and Van Sluyters 1974; Blakemore et al. 1981) but did not examine recovery of cortical binocularity and orientation selectivity. Furthermore, extreme manipulations such as enucleation of the nondeprived eye (Kratz and Spear, 1976) and blockade of intracortical inhibition (Burchfiel and Duffy, 1981) after the critical period were found to restore deprived eye responses in a minority of cortical neurons but the receptive field properties of cells responding to the deprived eye were abnormal. Collectively, the present results are the first to indicate that the potential for recovery of cortical binocularity and orientation selectivity is not directly linked to the critical period.

Different mechanisms for loss and recovery of cortical binocularity

We know considerably more about mechanisms regulating loss than recovery of deprived eye responses. Although a very large number of genes may be involved in loss of deprived eye responses (Prasad et al. 2002) and the mechanisms involved are likely to be complex, information has been obtained on some key factors that may be required for this type of plasticity. These include NMDA receptors (Bear et al. 1990; Roberts et al. 1998), GABA receptors (Hensch et al. 1998) and may also include neurotrophins (Galuske et al. 2000; Gillespie et al. 2000). Increased calcium influx through the NMDA receptor-associated channel and other membrane calcium channels activates protein kinases, including α calcium-calmodulin kinase type II (Taha et al. 2002), protein kinase A (Beaver et al. 2001) and extracellular signal-regulated kinase (Di Cristo et al. 2001). A common mechanism through which these kinases might act in ocular dominance

plasticity is phosphorylation of the cAMP response element binding protein (CREB; Mower et al. 2002; Pham et al. 1999), which binds to a consensus sequence known as CRE (cAMP response element; Montminy et al. 1990) to regulate the transcription of plasticity-related genes (Deisseroth et al. 1996; Finkbeiner et al. 1997).

The NMDA receptor and the CREB system of gene activation are also potentially interesting in the context of recovery from the effects of monocular deprivation. Contrary to expectations, however, a recent study has indicated that CREB activity is not necessary for recovery of cortical binocularity (Liao et al. 2002). Our finding that full recovery from the effects of monocular deprivation can occur after the end of the critical period for loss of deprived eye responses, when CREB is thought to be no longer activated by monocular deprivation (Pham et al., 1999), is consistent with the hypothesis that different mechanisms underlie loss and recovery of cortical binocularity. However, it should be noted that definition of the end of the critical period varies with the length of deprivation and that some weak residual ocular dominance plasticity can be observed after P70 in ferrets deprived for longer than two weeks (Issa et al., 1999). Furthermore, other forms of adult cortical plasticity different from classic ocular dominance plasticity have been observed in several species (Gilbert 1998; Issa et al. 1999; Sawtell et al. 2003).

Does recovery of binocularity require maturation of orientation selectivity?

Early lid suture is known to prevent the development of orientation maps (White et al. 2001) and maturation of orientation selectivity (Chapman and Stryker 1993) for the deprived eye. At the time when binocular vision was restored following the prolonged deprivations used in this study, orientation unselective inputs dominated by the deprived

eye were given the opportunity to re-establish functional connections with a relatively mature visual cortex in which approximately 75% of cells are orientation selective (Chapman and Stryker, 1993). Assuming that orientation selectivity is at least partly dependent on the spatial organization of geniculocortical afferents (Chapman et al. 1991; Ferster 1986; Reid and Alonso 1995), inputs from the deprived eye that were not allowed sufficient visual experience to develop fully were likely to be morphologically quite different from those of the experienced eye. For the majority of cortical neurons that are highly orientation selective, signals from the deprived eye that are outside of a relatively narrow orientation range would not be detected as coincident with signals from the experienced eye and no recovery would occur. Therefore, prolonged deprivation during the development of receptive field properties may destroy the ability of inputs from the deprived eye to reattach to the normal orientation scaffold that developed for the experienced eye.

These results raise the intriguing possibility that Hebbian mechanisms may actually prevent binocular recovery when responses elicited by the deprived eye are inappropriate for normal visual processing. This proposal is consistent with recent results showing that correlated binocular input is essential for recovery from monocular deprivation following restoration of binocular vision (Kind et al. 2002). Manipulations such as reverse suture following prolonged deprivation silence normal functional maps for the experienced eye, and may therefore allow recovering neurons to make inappropriate connections with deprived eye inputs. These binocular connections may generate abnormal receptive field properties that interfere with normal visual function, resulting in binocular amblyopia (Murphy and Mitchell 1986). While the present studies

introduce the ferret as a novel model of binocular recovery, they also call attention to the need for recovery of response properties for full functional recovery from monocular deprivation.

Potential clinical implications

The present results suggest a potential role for binocular vision in recovery from amblyopia. Although clinical experience indicates that patching the better eye of a child is required to improve spatial resolution in the amblyopic eye, binocular vision may also have an important role in recovery. This conclusion is supported by our findings and a recent study showing that initial recovery of form vision after MD is faster when both eyes are open than in reverse-deprived animals (Mitchell et al. 2001). Strong support for a role of binocular recovery in treatment of amblyopia was also obtained in a clinical study showing that most improvements in visual performance of the amblyopic eye occur following prescription of appropriate spectacles but prior to unilateral occlusion (Moseley et al. 1997).

Our findings that recovery of deprived eye responses is not tightly linked to the terminus of the critical period may also be relevant to understanding clinical reports dealing with the outcome of amblyopia therapy according to age. Although a large proportion of patients remain amblyopic following treatment (Flynn et al. 1999), a more favorable outcome has been shown in children treated before 3 years of age than in older children (Williams et al. 2002). Especially striking is the case of children born with congenital cataracts, who require surgery during the first 2 postnatal months in order to obtain improved deprived eye function (Birch and Stager 1988; Taylor et al. 2001). Our

finding that cortical binocularity as well as orientation selectivity failed to recover when normal vision was restored to the deprived eye halfway through the critical period may help explain why appropriate recovery of deprived eye responses requires very early intervention. The success of early treatment may be related to the existence of relatively early and narrow windows of opportunity for activity-dependent maturation of receptive field properties, especially orientation selectivity, in animals deprived from the time of eye opening.

In contrast to the finding that improvement of the amblyopic eye requires early intervention, other reports have shown clear improvement in some older children and even adults (Birnbaum et al 1977; Mintz-Hittner and Fernandez, 2000). Our finding that sufficient plasticity remains after the end of the critical period to allow recovery from monocular deprivation is consistent with the reports of successful treatment in adults. Our results suggest that recovery from amblyopia may occur in older patients that developed amblyopia relatively late, after orientation selectivity had already reached a mature state. There is an urgent need to elucidate the mechanisms regulating recovery of deprived eye responses and the ferret model described here presents a unique opportunity to achieve this goal.

Disclosures

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Table I. Monocular deprivation (MD) and recovery groups used in this study.

Animals used in this study were deprived according to 3 different protocols: i) a short period (i.e. 5-7 days) of monocular deprivation starting at P45, ii) a prolonged period (i.e., longer than 3 weeks) of late deprivation starting at P49, and iii) a prolonged period of early deprivation starting before eye opening. Recovery from the effects of monocular deprivation was examined following a period of binocular vision starting at different ages: i) P50-P52 for the short-term monocular deprivation group, ii) P73-P83 for the long-term late monocular deprivation group, and iii) P50 for the long-term early monocular deprivation group. An additional group of animals included in this study was composed of animals that were not deprived (normal).

Figure Legends

Figure 1. Schematic representation of the timing of monocular deprivation (MD) and restoration of normal binocular vision in 3 recovery protocols.

Figure 2. Full recovery of cortical binocularity after a short period of monocular deprivation (MD) followed by restoration of binocular input. Histograms with error bars show that while the normal ferret ocular dominance profile is characterized by a high degree of binocularity (A, n=119 neurons in 5 animals), approximately one week of monocular lid suture caused a dramatic loss of responses to the deprived eye (B, n=110 cells in 5 animals). Full recovery of cortical binocularity was present following 3-7 days of binocular vision in additional animals (C, n=228 cells in 5 animals).

Figure 3. Full recovery of cortical neuron orientation selectivity after a short period of monocular deprivation followed by restoration of binocular input. The cumulative percentage of cells is plotted as a function of the orientation selectivity index at 45° (A) and 90° (B) for responses to the dominant eye in normal animals (n=86 cells) and the recovered eye in animals that had been monocularly deprived and then allowed binocular vision (n=61 cells). Similar distributions of orientation selectivity indices are shown for the recovered eye in monocularly deprived animals and the dominant eye in normal animals.

Figure 4. Recovery of cortical binocularity after the critical period. Histograms with error bars show complete loss of cortical binocularity in animals deprived starting at approximately P49 (A). Restoration of binocular vision in additional animals at P75-P83, after the critical period, induced striking recovery of cortical binocularity (B). Most recovery was observed during the first week of binocular vision (C). Each point represents one animal.

Figure 5. Recovery of orientation selectivity after the critical period. In these experiments, animals had been monocularly deprived starting at approximately P49 until P75-P83 and then allowed binocular vision. The cumulative percentage of cells is plotted as a function of the orientation selectivity index at 45° (A) and 90° (B) for responses to the dominant eye in normal animals and the recovered eye in animals that had been monocularly deprived. Similar distributions of orientation selectivity are present in the two cases.

Figure 6. Lack of recovery from the effects of early long-term monocular deprivation. Ocular dominance histograms for animals that had their right eye lid sutured starting a few days before eye opening until approximately P51 (A), and for animals that were similarly deprived then allowed binocular vision (B). Comparison of histograms reveals very little recovery of cortical binocularity in the recovery animals, even though binocular vision was restored during the critical period for ocular dominance plasticity. Increasing duration of binocular vision up to 24 days did not enhance recovery of cortical binocularity (C). Each point represents one animal.

Figure 7. Orientation selectivity failed to recover following restoration of binocular vision to early-deprived animals. Quantitative analysis revealed that animals deprived during the period when orientation selectivity normally develops (early long-term deprivation, from P30 to P51) showed little recovery of orientation selectivity following restoration of binocular vision. Up to 24 days of binocular vision following the period of monocular deprivation did not restore deprived eye orientation selectivity to normal levels (A,B). In contrast, orientation selectivity for the experienced eye was indistinguishable from that seen in neurons (n=86) recorded from normal animals. Plots of average orientation selectivity indices with error bars as a function of ocular dominance indices reveal that binocular cells were much less selective to orientation than cells that showed little or no binocular recovery (C and D).

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Table I - Monocular deprivation and recovery groups

Group	Number of animals	Number of cells (ODI)	Number of cells (OSI)
Normal	5	119	86
Short-term MD	5	110	
Recovery from short MD	5	228	61
Late long-term MD	5	119	
Recovery from late MD	5	159	41
Early long-term MD	4	119	
Recovery from early MD	5	169	96
Total	33	1023	284

Figure 1

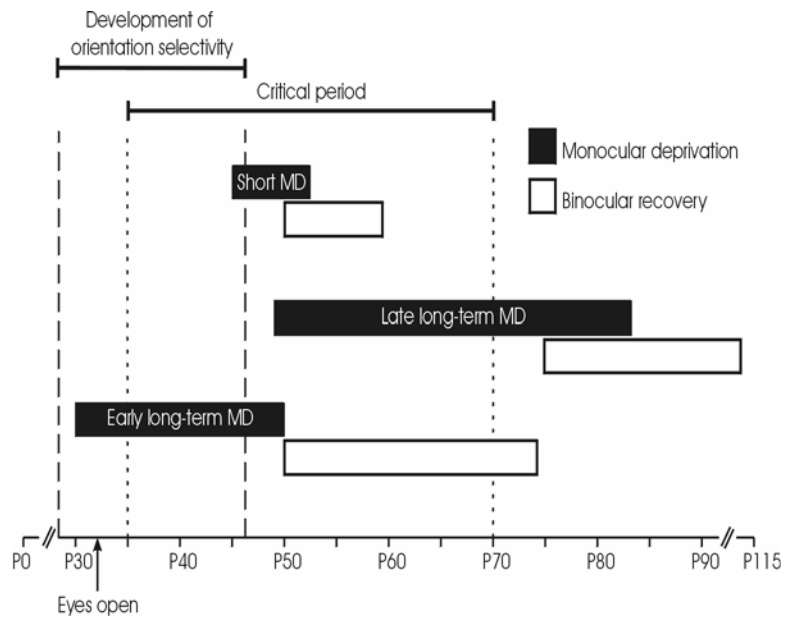


Figure 2

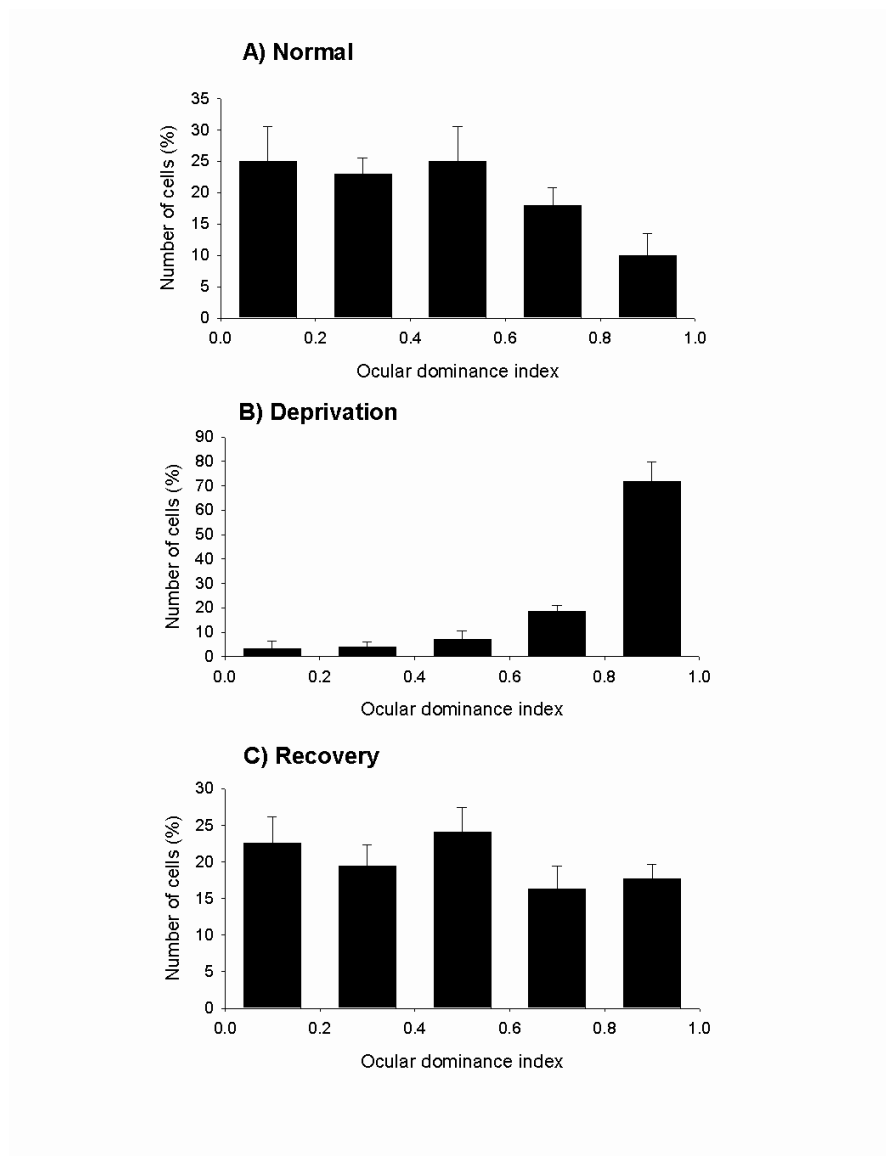


Figure 3

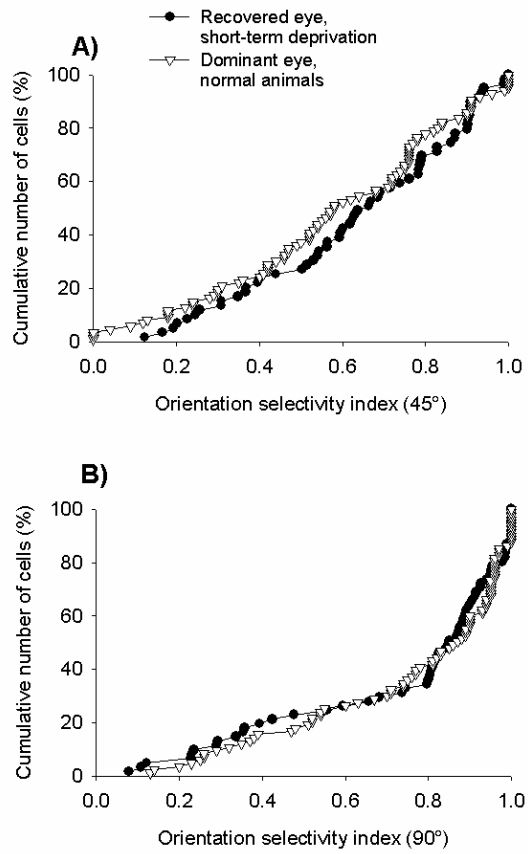


Figure 4

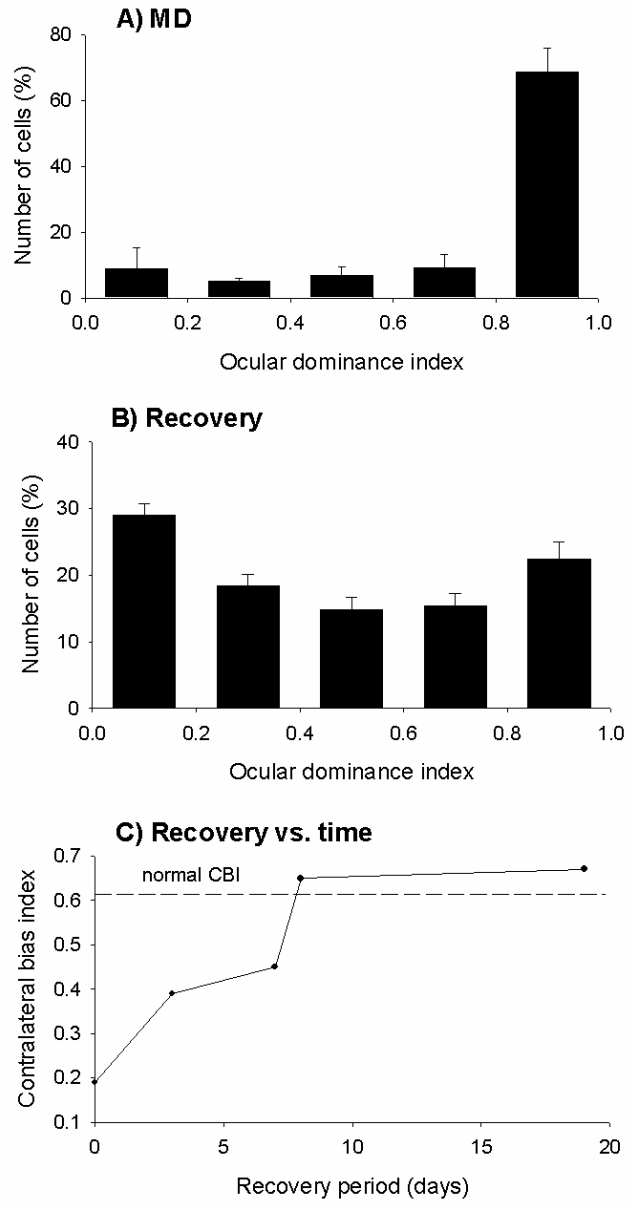


Figure 5

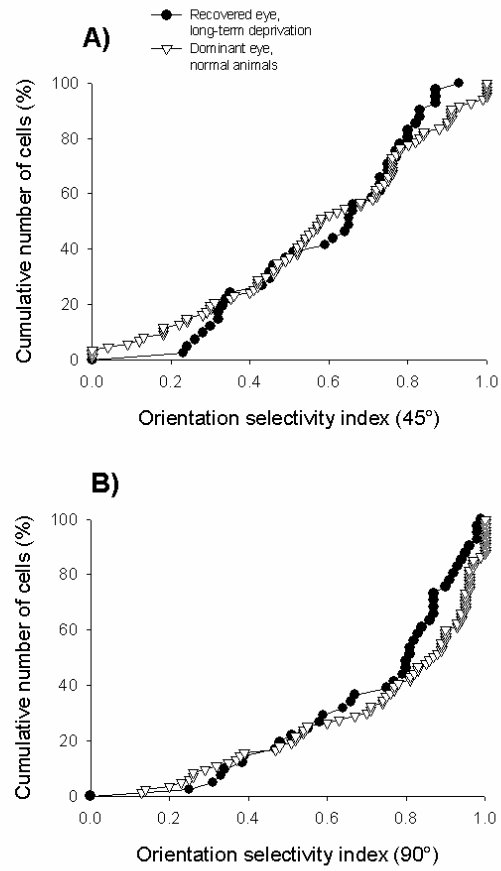


Figure 6

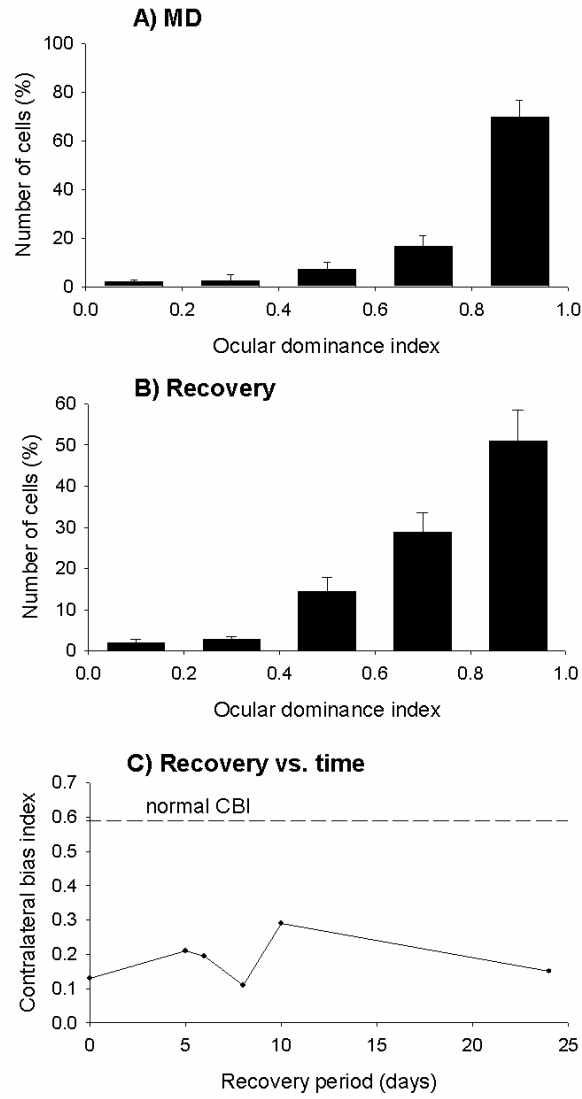


Figure 7

