

Bidirectional Modifications of Visual Acuity Induced by Monocular Deprivation in Juvenile and Adult Rats

Karen Iny*, Arnold J. Heynen*, Erik Sklar, and Mark F. Bear

Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Recent electrophysiological studies of rodent visual cortex suggest that, in addition to deprived-eye depression, monocular deprivation (MD) also shifts ocular dominance by potentiation of open-eye responses. We used computer-based, two-choice discrimination tasks to assess the behavioral significance of these findings in rats. As expected, prolonged MD, from postnatal day 21 until adulthood (>150 d) markedly decreased visual acuity through the deprived eye. However, we also found that the acuity through the nondeprived eye was significantly enhanced compared with normally reared controls. Interestingly, when the deprived eye was opened in adults, there was a gradual but incomplete recovery of acuity in the deprived eye preceded by a loss of the enhanced acuity in the nondeprived eye. These changes were reversed by again reclosing the eye. These findings suggest that the bidirectional changes in visually evoked responses after MD are behaviorally meaningful and that significant plasticity is exhibited well into adulthood.

Key words: acuity; visual cortex; monocular deprivation; critical period; metaplasticity; ocular dominance plasticity

Introduction

It is well established that a period of monocular deprivation (MD) during early postnatal life decreases the proportion of neurons in primary visual cortex that respond to stimuli presented to the deprived eye (Wiesel and Hubel, 1963, 1965; Hubel and Wiesel, 1970; Movshon and Dursteler, 1977; Blakemore et al., 1978). The consequences of deprivation are completely reversible if the period of MD is relatively brief (Malach et al., 1984); however, prolonged MD into adulthood has more dramatic and sustained effects on visual cortical function. After several months of MD in the cat and monkey, the vast majority of visual cortical neurons can be excited only by stimuli presented to the nondeprived eye (Wiesel and Hubel, 1965; Hubel and Wiesel, 1970; Hubel et al., 1977). This physiological change is accompanied by a profound impairment of visually guided behavior, such that subjects are described as being blind in the deprived eye (Wiesel and Hubel, 1965; Dews and Wiesel, 1970; Hubel and Wiesel, 1970; Mitchell, 1988). Although closure or removal of the initially open eye has been shown to enhance recovery of function of the initially deprived eye, the physiological and behavioral improvements described have been modest (Smith, 1981; Mitchell, 1988).

Similar physiological and behavioral manifestations of MD are also observed in rodent species that are well suited for mechanistic investigations (Fagiolini et al., 1994; Gordon and Stryker, 1996; Guire et al., 1999; Prusky et al., 2000a,b; Heynen et al., 2003;

Sawtell et al., 2003). Recently, chronic recordings in mice have shown that, in addition to causing rapid deprived-eye depression, MD also results in a progressive open-eye potentiation (Sawtell et al., 2003; Frenkel and Bear, 2004). It is notable that the visually evoked potentials (VEPs) through the open eye grow to values that are greater than those seen before deprivation. It has been suggested that this increase in VEP amplitude reflects an enhancement of excitatory synaptic transmission in visual cortex. However, VEPs reflect the summed activity of many synapses and neurons in visual cortex and are sensitive to changes in the timing as well as strength of responses. The fundamental question therefore remains as to whether the observed increase in VEP amplitude after MD is an indication of an alteration in visual function. The goal of the present study was to determine the functional significance of the increase in cortical responsiveness to the nondeprived eye after extended periods of MD in rodents. Because they are better suited than mice for behavioral experiments, we chose to use rats as subjects.

Here we show that long-term MD in rats is accompanied by an enhancement of visual function in the nondeprived eye: visual acuity as measured behaviorally is greater in the nondeprived eye after MD than that which is observed in normally reared (NR) control animals. This improvement of visual function is itself plastic. Opening the deprived eye in adults results, first, in a decrease in nondeprived eye acuity, followed by a modest recovery of visual acuity in the initially deprived eye. These changes are reversed by again closing the eye and restored by opening it.

Parts of this work have been presented previously in abstract form (Sklar et al., 2001).

Materials and Methods

Animals. Male Long–Evans (black-hooded) rats (Taconic Farms, Germantown, NY and Charles River, Cambridge, MA) were used for behav-

Received Jan. 11, 2006; revised June 5, 2006; accepted June 7, 2006.

This work was partly supported by grants from Howard Hughes Medical Institute and the National Institutes of Health. We thank Suzanne Meagher for assistance.

*K.I. and A.J.H. contributed equally to this work.

Correspondence should be addressed to Mark F. Bear, Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139. E-mail: mbear@mit.edu.

DOI:10.1523/JNEUROSCI.0124-06.2006

Copyright © 2006 Society for Neuroscience 0270-6474/06/267368-07\$15.00/0

ioral testing. Animals were housed in pairs, on a 12 h light/dark cycle with food and water available *ad libitum*.

Monocular deprivation. Monocular deprivation was performed by eyelid suture between postnatal day 18 (P18) and P21. Animals were anesthetized with inhaled isoflurane (IsoFlo; 2–3%) and placed under a surgical microscope. The area around the eye was cleaned with sterile Iodophor PVP antiseptic, and the upper and lower eyelid margins were removed. An ophthalmic antibiotic ointment (Vetropolylin; Pharmaderm, Melville, NY) was then applied to the eye. The full extent of the trimmed lids were then stitched in apposition using 5.0 or 6.0 surgical silk thread. Sterile Iodophor PVP antiseptic was applied over the eye once more. The health of the animal and the integrity of the suture were monitored daily to ensure that the sutured eye remained shut and free of infection. Animals whose eyelids did not fully seal were excluded from additional experimentation. When testing deprived-eye function, animals were reanesthetized at the end of the deprivation period, and the lid margins were separated using fine surgical scissors. The eye was then flushed with sterile saline and checked for clarity under magnification. Ophthalmic antibiotic ointment was then applied, and animals were monitored daily to ensure that the newly opened eye remained open and free of infection.

Monocular occlusion mask. A three-piece mask was designed to test monocular visual capabilities of MD and NR rats. The first piece, an elastic harness, rested behind the front legs of the animal. A T-shaped Velcro collar, secured through a small loop on the harness, was placed around the neck and extended midsagittally across the top of the head. A Velcro eye cover attached to the T-piece and covered the desired eye snugly without disturbing the vibrissae.

Apparatus. To test the visual acuity of freely behaving rats, we used two-alternative, forced choice, water-based discrimination tasks. Our initial experiments were conducted using visual water box 1 (supplemental Fig. 1A, available at www.jneurosci.org as supplemental material). During the course of these experiments, Prusky et al. (2000) introduced a water-based visual task that we adopted for the remainder of the study (supplemental Fig. 1B, available at www.jneurosci.org as supplemental material). Figure 1 demonstrates that, despite some task differences, both procedures resulted in comparable acuity measures from adult NR rats. We therefore established that the two tasks are both accurate and reliable methods to measure visual acuity in rodents, and no additional distinction between the two tasks will be made.

Visual water box 1 (supplemental Fig. 1A, available at www.jneurosci.org as supplemental material) consisted of a rectangular pool (150 × 60 × 46 cm), with the interior of the box painted flat black. Sony (Tokyo, Japan) Trinitron computer monitors (18 inches diagonally) located centrally at both ends of the box were used to present visual stimuli (100% contrast; 26.2 × 20.4° of visual angle), which consisted of a sinusoidal grating (positive stimulus) and a gray screen (negative stimulus). The stimuli, 26 × 25 cm, were drawn using NIH Image and were of equal luminance (mean stimulus luminance was 88.53 cd/m²; contrast range was linearized by gamma correction). An escape platform (Plexiglas, 11.4 × 11.4 × 1.2 cm), resting just below the surface of the water, was always located directly under the positive grating stimulus. Subjects viewed the monitors from a submergible platform positioned in the center of the pool. The design of the middle platform was based on the Atlantis Platform (Spooner et al., 1994). The surface of the platform was a square piece of Plexiglas (11.4 × 11.4 × 1.2 cm) with a collapsible support, which was held just above the surface of the water by an electromagnet. On release of the magnet, the platform submerged into the water, forcing the animal to begin swimming. The box was filled with 30 cm of water, and water temperature was kept at 20–22°C. Black curtains completely surrounded the box, thereby limiting all obvious visual cues other than the computer screens with which the stimuli were presented. The water box was dimly and indirectly illuminated by a 100 W lamp located outside the curtain. The viewing distance of the rat, from the edge of the middle platform to the computer screens, was 70 cm.

Visual water box 2, based on the design of Prusky et al. (2000), was a rectangular pool (152 × 90 × 74 cm) with two computer monitors placed side-by-side at one end (supplemental Fig. 1B, available at www.jneurosci.org as supplemental material). The pool was constructed

with three black sides and one transparent Plexiglas side, behind which two identical cathode ray tube computer monitors (Electron Blue III, 19 inches diagonally; LaCie, Beaverton, OR) were positioned. The floor of the box was painted flat black, and the entire pool was supported on a 46-cm-tall platform. Black acrylic dividers (74 cm height) of varying length rested in guides and extended between the two monitors into the pool. The length of the divider determined the choice point in the experiment, because it determined the proximity of the animals to the monitors before entering either arm. Black curtains completely surrounded the box, and the room was dimly illuminated with a 100 W lamp located outside the curtain. The box was filled with 30 cm of water maintained at 20–22°C. Visual stimuli (100% contrast; 29.9 × 23.4° of visual angle) were displayed on the two computer monitors that faced into the pool, with the bottoms of their displays at water level. The gamma measure, black luminance, white luminance, and color functions were calibrated using the LaCie Blue Eye calibration system (version 3.4) to ensure identical stimulus displays on both monitors. The monitors were also adjusted to maintain geometrically perfect shapes and corner purity. The mean luminance (55.53 cd/m²) was measured periodically to ensure consistent stimuli.

A computer program (Vista 2.2; Cerebral Mechanics, Lethbridge, Alberta, Canada) controlled the stimuli and organized the experiments. The spatial frequencies used were restricted to full cycles to eliminate edge effects and to maintain constant luminance between the two screens. Stimuli were randomized by the Vista software, and data were reported by the experimenter using a purpose-built pushbutton interface.

Training: visual water box 1. For 1 week before the onset of visual training, rats were brought directly into the testing room and were handled for 15 min daily. A training paradigm was designed so that the rats learned that swimming to the positive stimulus was associated with escape, whereas swimming to the negative stimulus was not. During training, the positive stimulus was a horizontal grating with a low spatial frequency [0.17 cycles per degree (cyc/°) and 100% contrast], and the negative stimulus was gray and of equal luminance to the grating stimulus. The side on which the positive stimulus and the escape platform were located was varied from trial to trial in a pseudorandom manner.

In step 1 of training, the rat was placed on the escape platform directly under the grating stimulus and were allowed to remain on the platform for 10–30 s. This was repeated on both sides of the water box, for five to six trials for 1–2 d.

In step 2 of training, the rat was placed in the water directly in front of the grating stimulus and were allowed to swim toward the stimulus, at which time the animal encountered the submerged escape platform and remained on the platform for 10–30 s. The distance from the grating stimulus from which the rat was released was increased gradually until the rat was swimming in a straight line from the middle of the pool to the escape platform. Shortly after arriving at the grating stimulus, the stimuli were turned off, and the rat was removed from the pool and returned to a holding cage.

In step 3 of training, the middle submerging platform was introduced. At the start of each trial, the rat was placed on the middle platform and was given 20–30 s in which to attend to both the stimuli. The stimuli were then turned off, the middle platform was submerged, and the rat was forced to swim. In a correct trial, the animal swam directly to the side with the grating stimulus and arrived at the escape platform, at which point the animal was removed from the pool. An error consisted of the animal swimming to the location of the gray negative stimulus. In this case, the animal was not only required to continue swimming until he encountered the escape platform located under the positive stimulus, but a correction trial began immediately after. During a correction trial, the animal was placed back on the middle platform, which was dropped 5 s later. Correction trials were repeated until the rat swam directly to the platform.

Training: visual water box 2. Habituation of animals to the testing room and introduction of visual stimuli and the escape platform (steps 1 and 2 above) were as described for visual water box 1. In step 3 of training using visual water box 2, animals were placed at the rear of the pool, at a middle point such that they were not biased to the left or right. A divider

(60 cm length) was placed between the two monitors so that the animal had to choose before it was within 60 cm of either monitor. In a correct trial, the animal swam directly to the grating stimulus and arrived at the escape platform, at which time the animal was removed from the pool. An incorrect trial consisted of the animal passing the 60 cm choice point on the side with the gray negative stimulus. In this case, the animal was forced to continue swimming until it swam to the other monitor and encountered the hidden platform below the grating stimulus. It was then immediately placed at the rear of the pool and required to perform an additional “correction” trial with the same stimulus configuration. Correction trials were repeated until the subject swam directly to the platform.

While being trained, some rats chose to adopt a spatial strategy to solve the task, such as a side bias (always swimming to one side of the pool regardless of the location of the positive stimulus) or an alternative side bias (always swimming to alternate sides of the pool). As demonstrated previously, these biases were easily corrected by early shaping (Prusky et al., 2000). Criterion for training was reached when the animals swam to the grating stimulus consistently (90% correct trials over 2–3 d).

Testing. Visual acuity was assayed using horizontally oriented grating stimuli. During acuity testing, the spatial frequency of the grating stimulus was increased in small increments until the ability of the animal to distinguish the grating stimulus from an equiluminant gray screen fell to chance. At low spatial frequencies, one cycle was added to the grating after each correct trial to minimize the number of trials spent far from the animal’s acuity threshold. To progress to a higher spatial frequency, animals were required to get three consecutive trials correct after error trials.

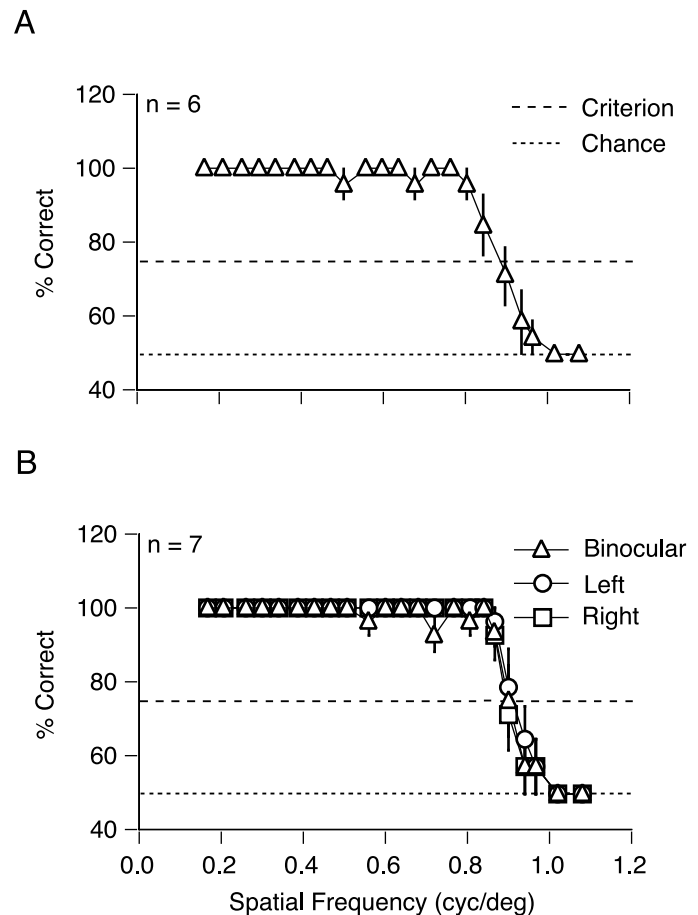
At higher spatial frequencies, animals were required to get 3 of 4 or 8 of 10 successive trials correct before another cycle was added. If an error was made because a spatial bias developed or the animal did not appear to be attending to the stimuli, a few training trials at a lower spatial frequency were given. An animal’s acuity threshold was defined as the highest spatial frequency at which performance was at or above criterion ($\geq 75\%$ trials correct). We reprobated each animal’s acuity threshold two to three times across consecutive days, always testing past the threshold until performance fell to chance (50% trials correct).

MD animals were trained and visual acuity was obtained using the nondeprived eye in the same manner as NR animals. To test the acuity of the deprived eye, MD animals were first habituated to wearing a mask that was designed to cover one eye at a time. Initially, the deprived eye was covered, and the rats demonstrated that performance using the nondeprived eye was comparable with that obtained without the mask. Then, the deprived eye was opened, and measures of deprived-eye acuity were obtained while the mask covered the nondeprived eye.

Statistical analyses. Group acuity data were fit to a four-parameter logistic equation (variable slope sigmoid; $R^2 > 0.95$; Prism 4.0; GraphPad Software, San Diego, CA), and acuity threshold was taken to be the V_{50} of the sigmoid (corresponding to 75% correct performance). Statistical analyses were performed using StatView 5.0 (Abacus Concepts, Berkeley, CA). Comparisons between deprived and nondeprived animals were done using a Mann–Whitney nonparametric U test. The effect of time on acuity was analyzed using a one-factor ANOVA, and relevant *post hoc* comparisons were made between time points using a Fischer’s protected least significant difference test. In all cases, significance was set at $p < 0.05$.

Results

Initially, we assessed the visual capabilities of NR adult rats (older than P150) using a custom-designed, forced-choice discrimination task (task 1). We subsequently used an automated variation introduced by Prusky et al. (2000a) (task 2). The visual acuity threshold for each subject was defined as the highest spatial frequency at which the animal performed at or above criterion ($\geq 75\%$ trials correct). The mean binocular acuity threshold of adult NR rats ($n = 6$) using task 1 was 0.89 cyc/° (Fig. 1A), and an identical acuity threshold of 0.89 cyc/° was obtained in seven additional subjects tested using task 2 (Fig. 1B). In this latter



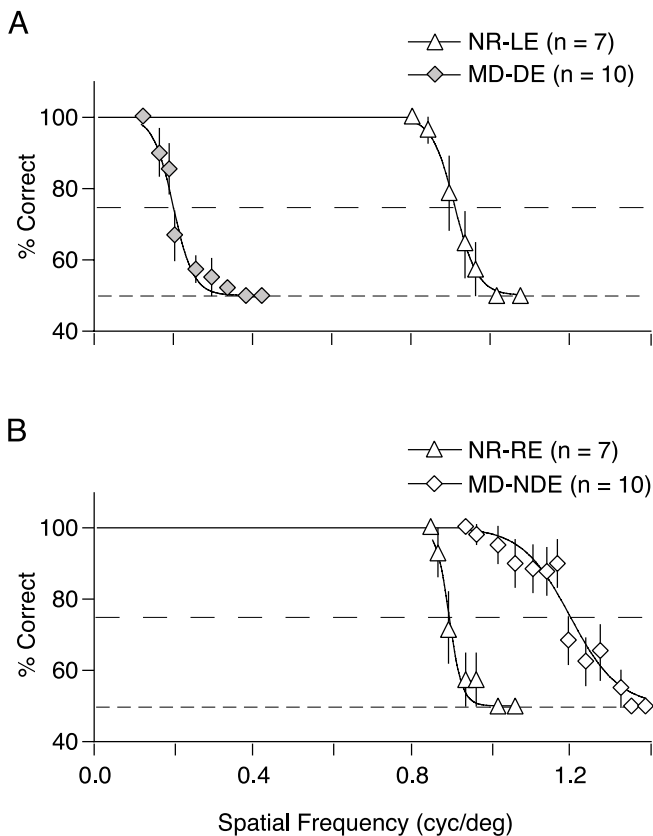


Figure 2. Long-term MD produces a profound decrease in deprived-eye acuity and an enhancement of nondeprived-eye function. **A**, Monocular deprivation beginning at P21 and maintained for >150 d results in a significant decrease in deprived-eye acuity (MD-DE; 0.20 cyc/°, $n = 10$) compared with the acuity obtained monocularly from normally reared animals of a comparable age (NR-LE; 0.91 cyc/°, $n = 7$). Data from normally reared animals is the same data as presented in Figure 1B (left eye). **B**, Visual acuity is enhanced in the nondeprived eye of long-term MD animals. Monocular visual acuity (MD-NDE; 1.20 cyc/°, $n = 10$) obtained before opening of the deprived eye of long-term MD animals is significantly greater than the monocular acuity of normally reared animals (NR-RE; 0.89 cyc/°, $n = 7$) of a comparable age. Data from normally reared animals is the same data as presented in Figure 1B (right eye).

initial eye opening, compared with the monocular acuity of NR animals. The deprived-eye acuity threshold of long-term MD animals (0.20 cyc/°) was significantly lower than the monocular acuity of NR animals (0.91 cyc/°; Mann–Whitney U test, $p < 0.001$).

Similar monocular testing through the nondeprived eye revealed that visual acuity thresholds (1.20 cyc/°) were actually significantly greater than those obtained monocularly in NR animals (0.89 cyc/°; Mann–Whitney U test, $p < 0.001$) (Fig. 2B). Thus, there are two responses to MD as measured behaviorally: deprived-eye impairment and open-eye enhancement.

As stated above, when testing the visual capabilities of the deprived eye, we noted that acuity threshold measurements were unobtainable for several weeks after initial eye opening (i.e., the animal performance never reached criterion). To establish a detailed time course for this modest recovery of function, in an additional six long-term MD animals, we closely monitored acuity thresholds at 3–4 d intervals for the deprived and nondeprived eye after deprived-eye opening (Fig. 3). These data demonstrate that the first measurable acuity threshold value for the previously deprived eye occurred 30–40 d after eye opening, with the increase in acuity of this eye reaching an asymptote of 0.32 cyc/° at 70–80 d. Interestingly, we observed that, before the onset of vi-

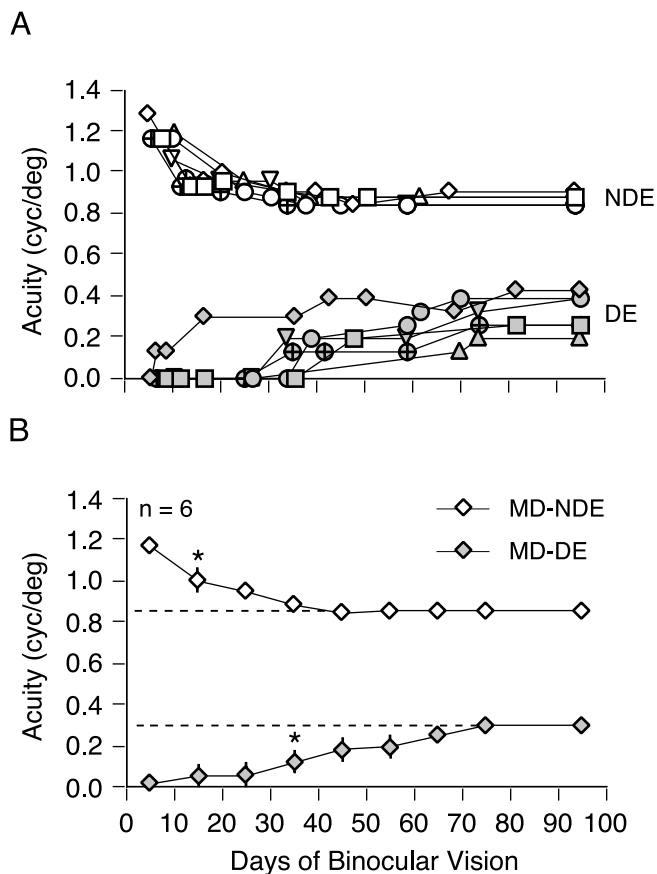


Figure 3. Enhanced visual acuity of the nondeprived eye of long-term MD animals decreases as acuity in newly opened eye increases. **A**, Individual data obtained from six long-term MD animals. **B**, Group summary of individual data presented in **A** demonstrating that acuity thresholds of the nondeprived eye decrease before the onset of visual recovery in the deprived eye. Asterisks indicate time at which a significant change in acuity threshold is first observed. NDE, Nondeprived eye; DE, deprived eye.

visual recovery in the deprived eye, acuity in the nondeprived eye first decreased rapidly from the augmented level of 1.17 cyc/° to near-normal levels. A significant decrease in acuity was readily observed 10–20 d after deprived-eye opening. Acuity thresholds in this eye stabilized at 0.86 cyc/°, ~20–30 d before the onset of visual recovery in the deprived eye.

Thus, a period of binocular visual experience after long-term MD is also accompanied by two responses: first, a reduction in nondeprived-eye acuity, which is followed by a delayed improvement of deprived-eye acuity. These data suggest that there is considerable plasticity of visual function in adult animals and that this plasticity is not limited to the eye of deprivation. We next wanted to determine in an additional group of animals whether this change in visual capabilities is bidirectional (Fig. 4). In accordance with our previous observations, we again found an enhancement of visual acuity thresholds of the nondeprived eye (1.15 cyc/°; $n = 4$) after an extended period of MD (~5 months). This enhanced visual acuity decreased to 0.86 cyc/°, whereas the acuity of the deprived eye increased from 0.25 to 0.44 cyc/° after opening of the deprived eye. These animals were then subjected to a second period of monocular deprivation, and acuity thresholds of the nondeprived eye were assessed. Within 1 week of eye closure, acuity in the nondeprived eye had begun to increase, and, by 7 weeks, acuity in this eye had equaled the original enhanced level (1.13 cyc/°; paired t test, $p > 0.72$). When binocular vision

was restored for a second and final time, visual capabilities of the nondeprived eye decreased to 0.87 cyc/deg, whereas those in the deprived eye once again improved. These data demonstrate plasticity in visual function of adult animals that is robust, bidirectional, and reversible.

Discussion

Our study supports two conclusions. First, MD initiates bidirectional changes in visual performance through the two eyes: the dramatic loss of visual acuity in the deprived eye is accompanied by a significant increase in acuity through the nondeprived eye. Second, the changes initiated by MD early in life can be partially reversed in adults by opening the deprived eye and then restored by closing it again. These findings are consistent with recent electrophysiological analyses of rodent visual cortex showing that there are two responses to MD and that substantial plasticity persists in adults (Sawtell et al., 2003; Frenkel and Bear, 2004; Pham et al., 2004; Tagawa et al., 2005; Hofer et al., 2006). The current findings extend these previous studies substantially, however, by demonstrating that such plasticity has a significant impact on vision.

The acuity thresholds obtained for normally reared adult animals (ranging from 0.81 to 0.97 cyc/deg, with a mean of 0.89 cyc/deg) are comparable with those reported by others using computer-generated visual stimuli (Keller et al., 2000; Prusky et al., 2000a,b), as well as studies using less sophisticated testing procedures (Lashley, 1930; Wiesenfeld and Branchek, 1976; Dean, 1981). Our behaviorally derived observations are also entirely consistent with acuity measurements obtained using electrophysiological procedures (Fagiolini et al., 1994).

Using identical testing methods, Prusky et al. (2000) studied the effects of varying lengths of MD during the critical period of rats and found that monocular deprivation from P13 to P40 or P13 to P60 resulted in comparable decreases in acuity of the deprived eye (to 0.67 and 0.71 cyc/deg, respectively). Because no significant difference in acuity between the two groups of animals was observed, these researchers concluded that a maximum amblyopic effect had been reached by P40. In the present study, we found that MD extending well into adulthood results in a more substantial decrease in acuity of the deprived eye. The mean deprived-eye acuity threshold of 0.20 cyc/deg was decreased by >70% compared with the acuity threshold of normally reared animals (0.89 cyc/deg) and by >80% compared with the mean threshold of the same-animal, nondeprived eye (1.20 cyc/deg). Our observation of a profound loss of visual function is consistent with cat and monkey studies in which extended periods of MD have been performed (von Noorden and Dowling, 1970; Smith, 1981; Smith and Holdefer, 1985; Sparks et al., 1986; Mitchell, 1988).

Our findings of a slowly developing recovery (over the course of several weeks) of deprived-eye function after reinstatement of binocular vision are reminiscent of observations made by Mitchell and colleagues (Mitchell et al., 1977, 1984a,b; Murphy and

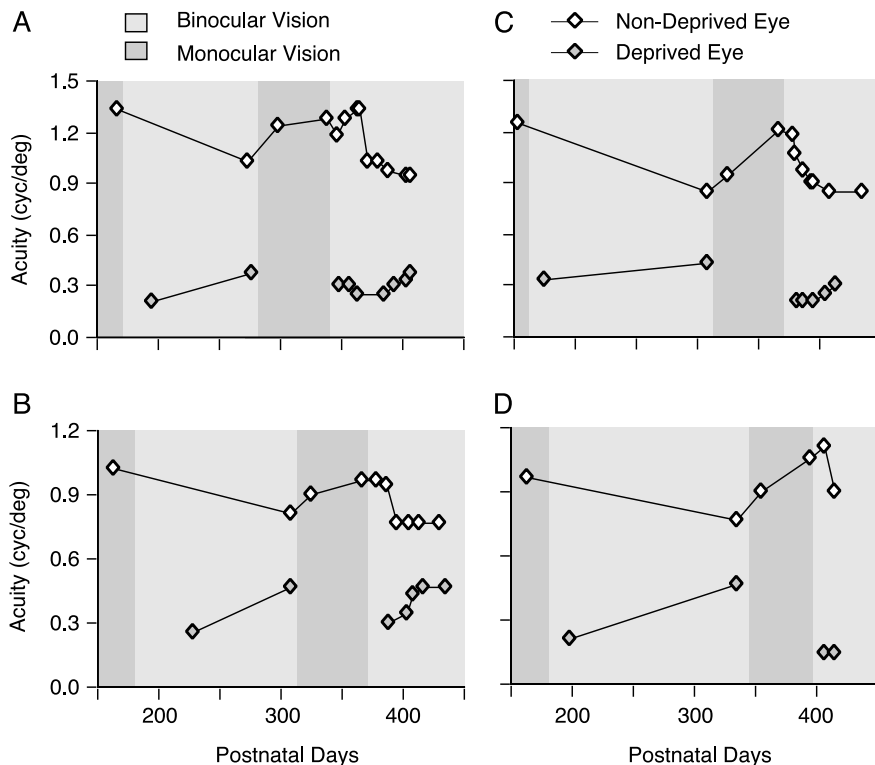


Figure 4. Changes in deprived and nondeprived eye acuity of long-term MD animals are bidirectional. **A–D**, Individual cases demonstrating that, after instatement of binocular vision, acuity thresholds of the nondeprived eye decrease as acuity thresholds of the deprived eye increase. Resuturing the initially deprived eye results in a return of enhanced visual acuity in the nondeprived eye, which once again declines after reinstatement of binocular vision. Data in **D** are abbreviated because of subject mortality.

Mitchell, 1986, 1987; Mitchell, 1988) who found that, after a period of reverse suture in the kitten, reinstatement of binocular vision results first in a reduction in nondeprived-eye acuity, which is followed by a delayed improvement of deprived-eye acuity. In the present study, the enhanced visual function of the nondeprived eye first returned to near control levels several days before a gradual but incomplete recovery of acuity in the deprived eye. It has been suggested that the ability of the deprived eye to regain some degree of visual function may reflect potentiation of weak subthreshold connections that persist despite prolonged periods of MD (Blakemore et al., 1982; Freeman and Ohzawa, 1988).

A novel finding in the present study was the enhancement of acuity observed in the nondeprived eye of long-term MD animals. Although numerous examples of the severe impairment of vision in the deprived eye of long-term MD animals have been documented, fewer studies have systematically tested visual function of the nondeprived eye, and vision through this eye has typically been described as normal (for review, see Odom, 1983). There are, however, examples in the human literature in which an enhancement of visual function is observed after early postnatal enucleation [particularly when compared with the monocular capabilities of “normal” binocular subjects (Freeman and Bradley, 1980; Blakemore et al., 1982; Reed et al., 1996, 1997; Gonzalez et al., 2002; Steeves et al., 2004)]. Moreover, in keeping with the present observations, in some instances, the enhancement in visual function in the remaining eye equals or surpasses that of binocularly viewing normal subjects (Nicholas et al., 1996). Although the functional outcome of the present study and these human studies appear complementary, the anatomical, physiological, and behavioral changes observed after prolonged MD are

substantially different from those resulting from the loss of an eye (for review, see Toldi et al., 1996). For example, in rodents, early monocular enucleation reduces the normal death of ganglion cells subserving the spared eye as well as enhances their subcortical and cortical connections (Lund et al., 1973; Rakic, 1986; Yee et al., 1987; Heywod et al., 1988). The enhancement of visual function in human enucleates has been attributed to a number of processes, such as a recruitment of cortical and subcortical visual areas by the remaining eye, years of monocular practice after enucleation, and/or the removal of inhibitory binocular interactions that are present in binocularly viewing subjects (Gonzalez et al., 2002). Our demonstration that an enhancement of nondeprived-eye capabilities need not be accompanied by removal of the partnering eye and that such enhancements are bidirectional in adult rodents may provide a starting point for future studies aimed at uncovering the physiological and molecular mechanisms contributing to supra-normal vision in humans.

An unexpected observation was the reversibility of the enhanced open-eye acuity. We found that open-eye acuity declined to control levels when the deprived eye was opened and then increased again when the deprived eye was reclosed, even in adults. The slow time course of these changes suggests that they reflect modifications of synaptic transmission. This finding of adult plasticity was not anticipated by previous electrophysiological studies. Unlike what has been observed in mice (Sawtell et al., 2003; Pham et al., 2004; Tagawa et al., 2005), both unit and VEP recordings have consistently failed to reveal an effect of MD in adult rats (Fagiolini et al., 1994; Guire et al., 1999; Pizzorusso et al., 2002). Very recent findings by Hofer et al. (2006) suggest the possibility that the plasticity of acuity we observe in adult rats might be a consequence of “priming” or metaplasticity caused by the initial period of MD. These authors reported that adult ocular dominance plasticity in mice is greatly enhanced in animals that had been monocularly deprived previously and allowed to recover. Because adult MD normally is without any effect in rats, this species might be particularly well suited for additional investigation of the mechanisms of priming of adult plasticity.

In conclusion, our studies suggest that previous findings of bidirectional plasticity of visual responses caused by MD in rodents are functionally significant. Rodent species hold particular promise for investigations of the synaptic mechanisms responsible for both juvenile and adult modifications of visual cortical function.

References

- Blakemore C, Garey LJ, Vital-Durand F (1978) The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *J Physiol (Lond)* 283:223–262.
- Blakemore C, Hawken MJ, Mark RF (1982) Brief monocular deprivation leaves subthreshold synaptic input on neurons of the cat's visual cortex. *J Physiol (Lond)* 327:489–505.
- Dean P (1981) Visual pathways and acuity hooded rats. *Behav Brain Res* 3:239–271.
- Dews PB, Wiesel TN (1970) Consequences of monocular deprivation on visual behaviour in kittens. *J Physiol (Lond)* 206:437–455.
- Fagiolini M, Pizzorusso T, Berardi N, Domenici L, Maffei L (1994) Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vision Res* 34:709–720.
- Freeman RD, Bradley A (1980) Monocularly deprived humans: nondeprived eye has supernormal vernier acuity. *J Neurophysiol* 43:1645–1653.
- Freeman RD, Ohzawa I (1988) Monocularly deprived cats: binocular tests of cortical cells reveal functional connections from the deprived eye. *J Neurosci* 8:2491–2506.
- Frenkel MY, Bear MF (2004) How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* 44:917–923.
- Gonzalez EG, Steeves JK, Kraft SP, Gallie BL, Steinbach MJ (2002) Foveal and eccentric acuity in one-eyed observers. *Behav Brain Res* 128:71–80.
- Gordon JA, Stryker MP (1996) Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J Neurosci* 16:3274–3286.
- Guire ES, Lickey ME, Gordon B (1999) Critical period for the monocular deprivation effect in rats: assessment with sweep visually evoked potentials. *J Neurophysiol* 81:121–128.
- Heynen AJ, Yoon BJ, Liu CH, Chung HJ, Haganir RL, Bear MF (2003) Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat Neurosci* 6:854–862.
- Heywod CA, Silveira LC, Cowey A (1988) Contrast sensitivity in rats with increased or decreased numbers of retinal ganglion cells. *Exp Brain Res* 70:513–526.
- Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hubener M (2006) Prior experience enhances plasticity in adult visual cortex. *Nat Neurosci* 9:127–132.
- Hubel DH, Wiesel TN (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol (Lond)* 206:419–436.
- Hubel DH, Wiesel TN, LeVay S (1977) Plasticity of ocular dominance columns in monkey striate cortex. *Philos Trans R Soc Lond B Biol Sci* 278:377–409.
- Keller J, Strasburger H, Cerutti DT, Sabel BA (2000) Assessing spatial vision: automated measurement of the contrast-sensitivity function in the hooded rat. *J Neurosci Methods* 97:103–110.
- Lashley KS (1930) The mechanism of vision. III. The comparative visual acuity of pigmented and albino rats. *J Genet Psychol* 37:481–484.
- Lashley KS (1938) The mechanism of vision. XV. Preliminary studies of the rat's capacity for detail vision. *J Genet Psychol* 18:123–193.
- Lund RD, Cunningham TJ, Lund JS (1973) Modified optic projections after unilateral eye removal in young rats. *Brain Behav Evol* 8:51–72.
- Malach R, Ebert R, Van SR (1984) Recovery from effects of brief monocular deprivation in the kitten. *J Neurophysiol* 51:538–551.
- Mitchell DE (1988) The extent of visual recovery from early monocular or binocular visual deprivation in kittens. *J Physiol (Lond)* 395:639–660.
- Mitchell DE, Cynader M, Movshon JA (1977) Recovery from the effects of monocular deprivation in kittens. *J Comp Neurol* 176:53–64.
- Mitchell DE, Murphy KM, Kaye MG (1984a) Labile nature of the visual recovery promoted by reverse occlusion in monocularly deprived kittens. *Proc Natl Acad Sci USA* 81:286–288.
- Mitchell DE, Murphy KM, Kaye MG (1984b) The permanence of the visual recovery that follows reverse occlusion of monocularly deprived kittens. *Invest Ophthalmol Vis Sci* 25:908–917.
- Movshon JA, Dursteler MR (1977) Effects of brief periods of unilateral eye closure on the kitten's visual system. *J Neurophysiol* 40:1255–1265.
- Murphy KM, Mitchell DE (1986) Bilateral amblyopia after a short period of reverse occlusion in kittens. *Nature* 323:536–538.
- Murphy KM, Mitchell DE (1987) Reduced visual acuity in both eyes of monocularly deprived kittens following a short or long period of reverse occlusion. *J Neurosci* 7:1526–1536.
- Nicholas JJ, Heywood CA, Cowey A (1996) Contrast sensitivity in one-eyed subjects. *Vision Res* 36:175–180.
- Odom JV (1983) Effects of visual deprivation on monocular acuities of humans and animals. *Am J Optom Physiol Opt* 60:472–480.
- Pham TA, Graham SJ, Suzuki S, Barco A, Kandel ER, Gordon B, Lickey ME (2004) A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB. *Learn Mem* 11:738–747.
- Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L (2002) Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 298:1248–1251.
- Prusky GT, West PW, Douglas RM (2000a) Behavioral assessment of visual acuity in mice and rats. *Vision Res* 40:2201–2209.
- Prusky GT, West PW, Douglas RM (2000b) Experience-dependent plasticity of visual acuity in rats. *Eur J Neurosci* 12:3781–3786.
- Rakic P (1986) Mechanisms of ocular dominance segregation in the lateral geniculate nucleus: competitive elimination hypothesis. *Trends Neurosci* 9:11–15.
- Reed MJ, Steeves JK, Steinbach MJ, Kraft S, Gallie B (1996) Contrast letter

- thresholds in the non-affected eye of strabismic and unilateral eye enucleated subjects. *Vision Res* 36:3011–3018.
- Reed MJ, Steeves JK, Steinbach MJ (1997) A comparison of contrast letter thresholds in unilateral eye enucleated subjects and binocular and monocular control subjects. *Vision Res* 37:2465–2469.
- Sawtell NB, Frenkel MY, Philpot BD, Nakazawa K, Tonegawa S, Bear MF (2003) NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* 38:977–985.
- Silveira LC, Heywood CA, Cowey A (1987) Contrast sensitivity and visual acuity of the pigmented rat determined electrophysiologically. *Vision Res* 27:1719–1731.
- Sklar E, Iny KJ, Heynen AJ, Bear MF (2001) Behavioral assessment of acuity and contrast thresholds in normally-reared and long-term monocularly deprived adult rats. *Soc Neurosci Abstr* 27:475.7.
- Smith DC (1981) Functional restoration of vision in the cat after long-term monocular deprivation. *Science* 213:1137–1139.
- Smith DC, Holdefer RN (1985) Binocular competitive interactions and recovery of visual acuity in long-term monocularly deprived cats. *Vision Res* 25:1783–1794.
- Sparks DL, Mays LE, Gurski MR, Hickey TL (1986) Long- and short-term monocular deprivation in the rhesus monkey: effects on visual fields and optokinetic nystagmus. *J Neurosci* 6:1771–1780.
- Spooner RI, Thomson A, Hall J, Morris RG, Salter SH (1994) The Atlantis platform: a new design and further developments of Buresova's on-demand platform for the water maze. *Learn Mem* 1:203–211.
- Steeves JK, Wilkinson F, Gonzalez EG, Wilson HR, Steinbach MJ (2004) Global shape discrimination at reduced contrast in enucleated observers. *Vision Res* 44:943–949.
- Tagawa Y, Kanold PO, Majdan M, Shatz CJ (2005) Multiple periods of functional ocular dominance plasticity in mouse visual cortex. *Nat Neurosci* 8:380–388.
- Toldi J, Feher O, Wolff JR (1996) Neuronal plasticity induced by neonatal monocular (and binocular) enucleation. *Prog Neurobiol* 48:191–218.
- von Noorden GK, Dowling JE (1970) Experimental amblyopia in monkeys. I. Behavioral studies of stimulus deprivation amblyopia. *Arch Ophthalmol* 84:206–214.
- Wiesel TN, Hubel DH (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26:1003–1017.
- Wiesel TN, Hubel DH (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol* 28:1060–1072.
- Wiesenfeld Z, Branchek T (1976) Refractive state and visual acuity in the hooded rat. *Vision Res* 16:823–827.
- Yee KT, Murphy KM, Van Sluyters RC (1987) Expansion of the ipsilateral primary visual pathway in rats monocularly enucleated at birth. *Invest Ophthalmol Vis Sci [Suppl]* 27:335.