Abnormal early visual experience often leads to poor vision, a condition called amblyopia. Two recent approaches to treating amblyopia include binocular therapies and intensive visual training. These reflect the emerging view that amblyopia is a binocular deficit caused by increased neural noise and poor signal-to-noise integration. Most perceptual learning studies have used monocular training; however, a recent study has shown that binocular training is effective for improving acuity in adult human amblyopes. We used an animal model of amblyopia, based on monocular deprivation, to compare the effect of binocular training either during or after the critical period for ocular dominance plasticity (early binocular training vs. late binocular training). We used a high-contrast, orientation-in-noise stimulus to drive the visual cortex because neurophysiological findings suggest that binocular training may allow the nondeprived eye to teach the deprived eye's circuits to function. We found that both early and late binocular training promoted good visual recovery. Surprisingly, we found that monocular deprivation caused a permanent deficit in the vision of both eyes, which became evident only as a sleeper effect following many weeks of visual training.

Introduction

Lazy eye (amblyopia) is caused by abnormal visual experience during early postnatal development. In the laboratory, the neural basis of amblyopia and its treatment are studied using monocular deprivation (Antonini & Stryker, 1993; Horton & Hocking, 1997; Hubel & Wiesel, 1970; Le Vay, Wiesel, & Hubel, 1980; Swindale, Vital-Durand, & Blakemore, 1981; Wiesel & Hubel, 1963, 1965). The changes in the visual cortex caused by monocular deprivation are not permanent if the occlusion is reversed during the critical period (Movshon, 1976; Movshon & Van Sluyters, 1981). The visual recovery, however, is often not permanent and is...
rapidly lost when binocular vision is restored (Murphy & Mitchell, 1986, 1987). Similar findings of residual and recurrent visual deficits have been reported after patching therapy in human amblyopes (Allen, Speedwell, & Russell-Eggitt, 2010; Birch & Stager, 2006; Levertovsky, Oliver, Gottesman, & Shimshoni, 1995; Ohlsson, Baumann, Sjöstrand, & Abrahamsson, 2002). This transient recovery after reverse occlusion has been a puzzle because it does not fit the classic idea that patching gives a competitive advantage to the amblyopic eye and the physiological findings of normal ocular dominance (Murphy & Mitchell, 1986) and orientation maps (Gödecke & Bonhoeffer, 1996) in the visual cortex. These results have motivated a search for alternative approaches for treating amblyopia.

A number of animal studies have shown permanent recovery of acuity when binocular vision is part of the treatment. For example, part-time patching therapy that included a few hours of binocular vision each day led to permanent recovery of visual acuity (Mitchell, 1991). In addition, simply restoring binocular vision to monocularly deprived cats caused faster initial recovery of acuity in the deprived eye (Mitchell, Gingras, & Kind, 2001) and better physiological recovery in the visual cortex (Kind et al., 2002). The theory behind these paradigms is that the nondeprived eye acts as a “teacher” to the deprived eye and cooperatively guides recovery (Kind et al., 2002; Smith & Trachtenberg, 2007). Together these results show that binocular vision plays a special role during recovery from visual deprivation. Furthermore, new clinical therapies that employ binocular approaches are achieving better outcomes for human amblyopes (Birch, 2013).

Intensive visual training is another approach used to improve vision in human amblyopes (Levi & Polat, 1996; Zhou et al., 2006). Many of these studies use stimuli with added visual noise to challenge the amblyopic visual system and promote adaptive visual plasticity. These noise stimuli are used because the visual deficits in amblyopia can be attributed to increased neural noise and poor signal-in-noise processing (Hess, Wang, Demanins, Wilkinson, & Wilson, 1999; Kiorpes & Movshon, 1998; Levi & Klein, 2003; Levi, Klein, & Chen, 2007). The visual training improves vision by driving adaptive plasticity to reduce neural noise and improve signal-in-noise processing for visual information.

Recent studies have combined binocular vision and intensive visual training designed to reduce suppression of the amblyopic eye in order to achieve good visual recovery with adult amblyopes (Hess, Mansour, & Thompson, 2010; Ooi, Su, Natale, & He, 2013). Both studies used techniques aimed at reducing visual drive through the dominant eye to achieve binocular balance. We chose a related but different approach aimed at maximally driving nondeprived eye responses in the visual cortex because neurophysiological results suggest that the effectiveness of binocular recovery may be due to the nondeprived eye teaching the deprived eye circuits to function (Kind et al., 2002; Smith & Trachtenberg, 2007). We used an orientation-in-noise discrimination task (Anderson, Murphy, & Jones, 2007; Jones, Anderson, & Murphy, 2003) because neurons in the visual cortex are tuned for orientation. Also, the stimulus is high contrast and broadband in spatial frequency, which makes it easy to see the target. Yet, the addition of visual noise makes it perceptually challenging to discriminate the orientation.

Most human amblyopes receive some patching therapy, which leaves open the question of whether binocular training alone is sufficient to promote good recovery. We used an animal model of monocular deprivation to study visual recovery promoted by only binocular training with the high-contrast orientation-in-noise stimulus. We compared the effectiveness of this intensive binocular training when it was started either during or after the peak of the critical period for ocular dominance plasticity in the visual cortex.

### Materials and method

#### Animals and rearing conditions

We used 12 cats to study the effect of binocular training with an orientation-in-noise stimulus on recovery from early monocular deprivation. All experimental procedures were in compliance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision research and were approved by the McMaster University Animal Research Ethics Board. The animals were reared with either normal vision and early (n = 2) or late (n = 2) training or monocular deprivation for 2 weeks during the critical period and early (n = 4) or late (n = 4) training (Figure 1). The early-training group received intensive daily training on an orientation-in-noise discrimination task starting at 5 to 6 weeks of age. The late-training group also began behavioral testing at 5 to 6 weeks of age but started with intensive daily training on grating acuity. At 6 months of age, the late-training group was switched to intensive training on the orientation-in-noise discrimination task.

#### Surgical procedures

Following procedures that have been described in detail previously (Murphy & Mitchell, 1987), eyelids were sutured closed with 5-0 vicryl using aseptic surgical techniques, and gaseous anesthetic (isoﬂurane,
1.5%–5%, in oxygen) was used for induction and maintenance of anesthesia. Sutured eyes were checked daily to ensure that the margins were completely fused closed. At the end of the 2 weeks of monocular deprivation, the lid margins were carefully parted using the aseptic surgical techniques described for closing the eye. Because the lid margins were not removed, the reopened eye had a normal palpebral aperture.

Visual testing apparatus and stimuli

Daily testing of either orientation-in-noise discrimination or grating acuity was done using the jumping stand (Giffin & Mitchell, 1978; Murphy & Mitchell, 1987, 1991). The visual stimuli were generated on an Apple G4 computer (Apple Inc., Cupertino, CA) using custom software written in Matlab (MathWorks Inc., Natick, MA) and the Psychophysics Toolbox (Brainard, 1997). The stimuli were displayed on a 24-in. computer monitor (Sony GDMFW900, Sony, Tokyo, Japan) with 0.23-mm dot pitch, spatial resolution of 2304 × 1440 pixels, 8-bit gamma correction lookup table, 80-Hz frame rate, and luminance of approximately 40 cd/m². The monitor was placed under a thick glass landing platform with a center divider. Stimuli were presented in a large circular aperture with a diameter of approximately 16'. For each trial, two stimuli—the target and a 100% noise stimulus—were displayed, one to the left of the center divider and the other to the right. Cats viewed the stimuli from the jumping stand above the glass landing platform and jumped down to the right or left side of the landing platform to indicate their selection. The viewing distance was approximately 60 cm.

We used an orientation-in-noise stimulus (Figure 2) developed in our laboratory to measure orientation discrimination in human observers (Anderson et al., 2007; Jones et al., 2003). The orientation-in-noise stimulus was a high-contrast gray-level pattern containing a broad range of spatial frequencies, with an independently variable amount of orientation signal in the presence of unoriented noise (Anderson et al., 2007; Jones et al., 2003). This stimulus was chosen because it is easy to see yet perceptually challenging. Pixel values were selected from a uniform random distribution of 256 gray levels. When generating the stimuli, the parameter P represents the strength of the orientation signal—namely, the percentage of pixels carrying the orientation signal versus noise pixels. When P = 100%, the stimulus was a vertical, one-dimensional white noise grating; when P = 0%, the stimulus was uniform, random noise with no dominant orientation. The orientation-in-noise stimulus resembles an oriented pattern of gray streaks with variable average length (Figure 2).

To measure grating acuity, we used a high-contrast (Michelson contrast = 0.86), vertically oriented sine-wave grating as the target stimulus and a spatially scrambled version of the same grating as the negative
Both were presented in a large circular aperture approximately 16° in diameter. We chose to use the scrambled grating instead of a uniform gray field to control for any slight variations in luminance between the grating (target) and the alternative (negative) stimuli.

Visual testing procedures

A two-alternative forced-choice paradigm and modified staircase procedure were used to measure the visual thresholds. The procedure has been described previously for measuring grating and vernier acuity (Murphy & Mitchell, 1987, 1991). Training began at 5 to 6 weeks of age for all cats and continued until they were over 1 year of age. The early-training group started with the orientation-in-noise stimulus, whereas the late-training group started with grating acuity and was switched to orientation in noise at 6 months of age. The testing procedure was the same for both groups.

Cats learned the tasks by viewing an easy target stimulus (80% orientation in noise or 0.1 cycles/deg sine-wave grating) and were trained to jump to the target stimulus (Figure 3). Correct jumps were rewarded with food (chicken liver) and petting, whereas incorrect jumps resulted in withholding the rewards and immediately repeating the trial. Animals learned to jump toward the target stimulus and met the learning criteria of 10 consecutive correct jumps to the easy stimulus in just a few (typically three to five) sessions. After this brief learning period, the cats received daily training sessions. These sessions were about 45 to 60 min long when the cats did approximately 45 to 60 trials to obtain a threshold for either orientation in noise or grating acuity.

The training was done binocularly and each session began with an easy target and the negative stimulus (Figure 3). The position of the two stimuli was interchanged from left to right in a pseudorandom order. Thresholds were determined using a modified staircase procedure where the target stimulus was made more difficult in small steps. The amount of signal for the orientation-in-noise stimulus was reduced by 16 steps per octave. The spatial frequency of the grating was increased by 16 steps per octave. Using these small step sizes enabled the cats to perform the tasks nearly
error free until the stimulus approached the threshold level. Typically, performance fell from flawless to chance in just two steps, showing that this method allowed us to confidently measure the visual thresholds. Usually cats received only one trial for the easy stimuli unless an error was made. When an error was made, additional trials were given until the cat made either five consecutively correct responses or seven correct responses in a maximum of 10 trials. Within about an octave of the estimated threshold, the minimum number of trials was increased to two or three consecutive correct. This minimum number of trials was increased again to three to five for stimuli close to the threshold. Sessions ended when the cat no longer achieved criterion within 10 trials. The last stimulus level that the animal passed was taken as the threshold. This gave the lowest percentage signal for the orientation in noise or the highest spatial frequency for the sine-wave grating as the threshold for the session.

Once the binocular orientation-in-noise threshold had been stable for more than 3 months, we measured thresholds separately for each eye. An opaque soft contact lens (EyeTech Optics, Coquitlam, British Columbia, Canada) was placed in one eye and the orientation-in-noise threshold was measured for the other eye. These monocular thresholds were measured on alternate days for 2 to 3 weeks until at least three consistent thresholds were measured for each eye. Monocular thresholds were not measured for grating acuity with the late-training group because it was important to ensure that all phases of the training were done binocularly and that the deprived eye did not have a competitive advantage at any time before training with the orientation-in-noise stimulus.

### Curve fitting of visual thresholds

The trajectories for the improvement in orientation-in-noise thresholds were quantified by fitting exponential decay functions to the results from each animal. The tau (τ) decay values were converted to half-life (τ½ = τ ln 2), and we calculated the number of days for the orientation-in-noise threshold to improve to 90% of its final asymptotic level (τ90 = τ ln 10). The τ90 was used to define the number of training days needed to reach the optimal threshold. The standard deviation and standard error of the mean (SEM) were corrected for the small sample sizes using the equation and tables from Gurland and Tripathi (1971).

### Statistical analyses

We used a bootstrapping test to evaluate visual thresholds among the groups. Bootstrapping is a common statistical method for small sample sizes. We used Matlab to simulate a normally distributed data set with the same mean and standard deviation as the thresholds for the comparative group. To determine if there were differences between early training and late training on binocular or deprived eye thresholds, we compared the simulated early-training data set with average thresholds for the late-training group. We ran Monte Carlo analyses that randomly sampled from the simulated early-training distribution N times, where N was the number of animals in a group (N = 4). This random sampling was repeated 1,000,000 times to create the early-training distribution expected for that sample size. We used those simulations to calculate the probability that the orientation-in-noise thresholds of the late-training group were from that early-training distribution. We also ran bootstrapping analyses to...
compare thresholds (binocular, deprived eye—monocular, nondeprived eye—monocular) between deprived and normal animals. Probabilities less than 0.025 were used to identify significant differences.

Results

Early binocular training with orientation in noise

We first asked if a short period (2 weeks) of monocular deprivation at the peak of the critical period affects the developmental trajectory and optimal threshold for binocular orientation-in-noise discrimination. To address this question, normal and monocularly deprived cats began daily binocular training on the orientation-in-noise discrimination at 60 days of age. Cats learned to make the discrimination prior to starting the daily training so that by 60 days of age we were able to measure reliable visual thresholds. The developmental trajectories and final thresholds for the binocular orientation-in-noise discrimination for each cat in the early-training group are shown in Figure 4. At the start of training, the cats needed 70% to 100% orientation signal to make the discrimination. Over the next 20 days of training the thresholds for both normal (Figure 4A, B) and monocularly deprived (Figure 4C through F) animals gradually improved at a similar rate. After that, however, thresholds for the deprived animals stopped developing, whereas the normal animals continued to develop for about 1 week before reaching their optimal (τ90) levels.

The developmental trajectories and final thresholds after early training can be compared by plotting each of the exponential decay curves fit to the binocular thresholds on a single graph (Figure 5). All of the curve fits were significant, with R values of 0.93 or greater (R range 0.93–0.98, p < 0.000001). The initial portion of the curves overlapped, suggesting similar rates of improvement until about 20 days of training, when they separated and the thresholds of deprived animals stopped improving (average τ90 = 18 days, SEM = 2 days) while normal animals continued to improve for about 1 week (average τ90 = 24 days, SEM = 6 days). We quantified the rate of improvement during the developmental trajectories by comparing the τ½ values calculated for each animal. The τ½ values were not significantly different between normal (average τ½ = 7.22 days, SEM = 1.94) and deprived (average τ½ = 5.56 days, SEM = 0.53) animals, indicating similar developmental trajectories. In contrast, final binocular orientation-in-noise thresholds were modestly different. The deprived animals required slightly more orientation signal (average threshold = 27.52%, SEM = 2.22%) than normal animals (average threshold = 18.94%, SEM = 0.14%) to make the discrimination. Even after more than 300 days of training, binocular thresholds for deprived animals remained slightly worse than those for normals. We describe these results as a “sleeper effect” of the short period of visual deprivation since the initial developmental trajectory was not affected but the final optimal binocular threshold for orientation-in-noise discrimination was affected, leaving the deprived animals with binocular thresholds that were worse than normal.

The poor binocular performance of the deprived cats was unexpected because one eye had never been deprived and had experienced normal vision during development. One possible explanation for the poor binocular orientation-in-noise thresholds was that some type of binocular suppression was limiting the binocular threshold. To address that, we measured thresholds for each eye individually (Figure 6). Most cats had one eye that was better than the other. For normals, the best monocular threshold was equivalent to the animal’s binocular performance (best monocular to binocular threshold, not significant [n.s.]). This suggests that binocular performance on the orientation-in-noise stimulus was limited by the vision of the better eye. For three of the four deprived cats, the nondeprived eye’s thresholds were slightly better than those of the deprived eye, and although the difference was small, as a group the nondeprived eye was significantly better than the deprived eye (p < 0.0001; Figure 6). Furthermore, nondeprived eye thresholds were not different from binocular performance (n.s.) and were consistently worse than either eye of normal animals (p < 0.0001). Taken together, these results show that poor binocular performance of deprived cats was not a simple case of binocular suppression reducing vision of the nondeprived eye.

Late binocular training with orientation in noise

While thresholds of the deprived animals improved over the course of early training with the orientation-in-noise stimulus, we cannot separate normal developmental improvements from the benefits of early daily training with the noise stimulus. To address this, we tested a second group of cats in which daily binocular training on the orientation-in-noise stimulus was started at a later age (180 days).

The rearing conditions for the late-training group were the same as those for the early group—the deprived animals had 2 weeks of monocular deprivation during the peak of the critical period (Figure 1)—but the initial visual testing was with grating acuity (between 50 and 180 days of age). This ensured that the late-training group received the same daily experience with the laboratory and performance of a visual
discrimination task during development but with a large noise-free stimulus (sine-wave grating). Cats quickly learned the grating acuity task (within three to five sessions) and were able to measure reliable grating acuity thresholds by 50 days of age (Figure 7). The development of binocular grating acuity for both normal and deprived animals improved together. By 98 days of age ($SEM = 3$ days) binocular grating acuity
had reached 10 to 11 cycles/deg—approximately 90% of the optimal grating acuity. Grating acuity leveled off about 14 days after the early group reached optimal orientation-in-noise thresholds. Interestingly, grating acuity appeared to plateau at approximately 6 cycles/deg at 70 to 85 days of age but then showed another phase of developmental improvement. In contrast with orientation in noise, the binocular grating acuity thresholds were not different between normal and deprived animals.

Next, the late-training group switched to training on the orientation-in-noise task. It is important to remember that all of the grating acuity testing was done binocularly so the deprived eye was not given a competitive advantage prior to starting late training with orientation in noise. The training started at about 6 months of age, when the late-training cats had passed the onset of puberty (Tsutsui, Nakagawa, Hirano, & Nagakubo, 2004) and normal development of orientation-in-noise had plateaued (Figure 4).

The procedure for training with the orientation-in-noise stimulus was the same for the late-training group as for the early-training group. Within five sessions all cats had learned the orientation-in-noise task, and then daily training consisted of measurement of the binocular threshold for discriminating the orientation-in-noise stimulus (Figure 8). The normal animals showed rapid improvement, reaching optimal orientation-in-noise threshold of 17.7% signal after an average of 24 days ($\tau_{90}$ range 21–26 days) of binocular training (Figure 8A, B). The deprived cats improved at a slower rate (Figure 8C through F), and optimal thresholds (range 23%–32% signal) were not reached until after 63 to 195 days ($\tau_{90}$; average $\tau_{90} = 114$ days, $SEM = 34$ days) of binocular training. Even though binocular grating acuities were similar for normal and deprived animals.

Figure 5. Developmental trajectories of normal and deprived animals for binocular orientation in noise. Exponential curves were fit to binocular thresholds for each animal ($R$ range 0.93–0.98, $p < 0.000001$). Rate of improvement was quantified by comparing the $\frac{1}{2}$ $\tau$ values for each animal. Both normal (dashed lines) and deprived (solid lines) animals started early training at 60 days of age and developed at similar rates for almost 20 days of training. After that time, deprived animal thresholds stopped improving, while the normal animals continued improving for another week.

Figure 6. Monocular testing of orientation-in-noise detection after early training. Average thresholds obtained from the assessment of the deprived (black bars) and nondeprived (white bars) eyes are displayed individually for each animal. For normal animals ($n = 2$), neither eye was deprived of vision during development, and thus both bars represent the threshold from an unaffected eye. Orientation signal is presented logarithmically on the y-axis. Error bars represent the standard error of thresholds obtained from monocular training sessions.
cats, that did not transfer to performance on the orientation-in-noise task.

Often the vision of human amblyopes is described as having poor integration of visual signals (Hess et al., 1999; Levi et al., 2007; Levi & Klein, 2003). To test whether the performance of normal animals could be made to look like that of deprived animals, we trained the normal cat using a coarse version of the orienta-

Figure 8. Late orientation-in-noise training thresholds. Training results are presented individually for each animal in this group (A–F). Graphs are presented in the same way as those in Figure 4. Filled triangles at the right side of each graph represent the mean final thresholds of the early-trained deprived animals (n = 4), and open triangles represent the threshold of the early-trained normal animals (n = 2). One of the late-trained normal animals (B) also received training with the “coarse” version of the orientation-in-noise stimulus (dotted area). Filled squares represent the thresholds obtained from complete training sessions with the coarse stimulus. Open squares represent thresholds from interrupted sessions where the cat still received training.
tion-in-noise stimulus. The coarse stimulus had larger pixels, so it had about one-fifth the number of samples as the fine stimulus, but it still had the same range of orientation signal as the fine stimulus (Figure 3). Using the coarse stimulus, thresholds for the normal animal (Figure 8B) dropped to about 30% orientation-in-noise signal—a level that was similar to the thresholds of deprived animals using the fine stimulus. This suggests that deprived animals have either undersampling or greater internal noise.

Although the rate of improvement for deprived animals was slower, they continued to improve with prolonged training. This improvement was found for both thresholds (Figure 8) and day-to-day variability (Figure 9). The threshold variance as a proportion of the mean was calculated for each animal in the late-training group. We determined the threshold variance by calculating the difference between the observed value and the value predicted based on the slope of the six surrounding orientation-in-noise thresholds. The variance of these differences was calculated in a running box and then relative to the box mean. The final value of this calculation for each animal is presented logarithmically on the y-axis. Red shaded symbols represent data collected from deprived animals (n = 4), which are fit by solid lines. Green shaded symbols represent data obtained from the normal animals, which are fit by dashed lines. Curves were fit based on an exponential decay.

The final binocular and monocular orientation-in-noise thresholds were plotted for each rearing condition (Figure 10A, C) and for average thresholds (normal or deprived animals) after early versus late training (Figure 10B, D). There was a range of final binocular orientation-in-noise thresholds among deprived animals after both early (23%–30% signal) and late (23%–32% signal) training (Figure 10A), but there was no difference in binocular thresholds between early and late training for either normal or deprived animals (n.s.; Figure 10B). Deprived animals, however, did not achieve normal binocular thresholds and continued to require about 10% more signal than normal animals (early training, p < 0.001; late training, p < 0.001) to make the orientation discrimination.

We plotted orientation-in-noise thresholds after early and late training for the deprived eye and one eye of normals (Figure 10C, D). Compared with normals, the deprived eye thresholds were slightly worse and needed about 15% to 20% more orientation signal after early (p < 0.0001) and late (p < 0.0001) training, respectively. We compared monocular and deprived eye thresholds after early versus late training (Figure 10D) and found no significant difference for normal animals but an extremely small difference for deprived animals (p < 0.001), suggesting that early training
might give a slight advantage for recovery of the deprived eye.

**Discussion**

The results of this study show that binocular visual training can be effective in promoting recovery after early monocular deprivation. We also uncovered a latent binocular vision deficit caused by monocular deprivation. We have drawn two main conclusions from the results. First, correlated patterns of activity stimulated by binocular visual training drive plasticity mechanisms in the central visual pathway that affect recovery of vision for both eyes. Our results complement previous studies in human amblyopes that used procedures to reduce suppression during binocular training (Hess et al., 2010) and together show that different binocular training approaches can support recovery in the amblyopic visual system (Birch, 2013).

Second, we were surprised to find that monocular deprivation impaired the vision of both eyes since the traditional view is that acuity of the nondeprived eye is normal (Dews & Wiesel, 1970). Although no reverse occlusion was used, the orientation-in-noise thresholds for the nondeprived eye were impaired, providing evidence that early monocular deprivation can affect the vision of both eyes. We describe this as a sleeper effect because the impact of monocular deprivation on binocular vision was not apparent until many weeks after the end of deprivation, at a time when maturation of orientation-in-noise thresholds had stopped improving. We did not find a deficit for binocular grating acuity, and this dissociation between acuity and orientation in noise points to different sensitivities for the mechanisms that process noise-free versus noise stimuli. On one hand, grating acuity depends on local processing of spatial frequency tuning (Parker & Hawken, 1985), and normal grating thresholds indicate that there was sufficient development of those receptive field properties to support normal acuity. On the other hand, modeling of orientation-in-noise thresholds shows a dependence on global processing to integrate information from a large number of visual samples (Jones et al., 2003) and suggests that the mechanisms that underlie integration are more sensitive to abnormal visual experience (Hamm, Black, Dai, & Thompson, 2014; Kiorpes, 2006). Early monocular deprivation causes a lack of lateral inhibitory interactions among neurons in the visual cortex but similar spatial frequency and contrast sensitivity potentials for stimuli presented to deprived or nondeprived eyes (Kasamatsu, Kitano, Sutter, & Norcia, 1998). Furthermore, anisometropic and strabismic monkeys often have poor contour integration in both eyes (Kozma & Kiorpes, 2003). Those physiological and behavior findings, plus the current orientation-in-noise losses, suggest that there is less recovery of lateral interaction needed for integration of neural signals to support noise-limited global processing.

**Methodological considerations**

A number of methodological factors were taken into consideration in designing this study: the use of the orientation-in-noise stimulus, exclusive use of binocular training, and the use of the cat as the model system. There is an emerging view that correlated binocular activity and balanced synaptic input are critical for recovery of vision in amblyopia (Birch, 2013; Faulkner, Vorobyov, & Sengpiel, 2006; Hess et al., 2010; Kind et al., 2002; Mitchell, Kind, Sengpiel, & Murphy, 2003, 2006). However, even with binocular training, correlated binocular activity can be difficult to achieve if the deprived eye is unable to see or be effectively driven by the stimulus. We chose to use the orientation-in-noise stimulus for daily training because it is high contrast and broadband in spatial frequency yet perceptually challenging (Jones et al., 2003). While there are other ways to introduce visual noise (e.g., Pelli, Levi, & Chung, 2004), our stimulus provides some advantages for studying developmental changes after visual deprivation. The broadband spatial frequency composition made the stimulus equally visible throughout development as grating acuity matured or for deprived animals, where it was impaired by monocular deprivation. The high contrast made the stimulus visible even if deprivation had reduced contrast sensitivity. Our approach is an alternative to recent work with human amblyopes in which the contrast level presented to the “good eye” was reduced to match the sensitivity of the amblyopic eye (Hess et al., 2010). We chose to use a high-contrast stimulus because we wanted to provide strong excitatory drive for both eyes; work from our laboratory and others has shown that even briefly reducing visual input causes downregulation of synaptic proteins necessary for optimal plasticity (Beston, Jones, & Murphy, 2010; Jaffer, Vorobyov, Kind, & Sengpiel, 2012; Murphy, Duffy, & Jones, 2004). Finally, we have previously demonstrated that performance on the orientation-in-noise task can be accurately described by a computational model that pools local responses of low-level neural mechanisms and is limited by intrinsic neural noise (Jones et al., 2003). That model provides a framework for considering potential mechanisms influenced by deprivation and intensive training. Together, these make the orientation-in-noise stimulus a good tool for assessing vision during development, visual training, and recovery from visual deprivation.
Only binocular training was used to test if noncompetitive mechanisms help promote recovery of good vision. The limitation of this approach is that we were not able to follow development of acuity in the deprived eye. Instead, we measured performance of the deprived eye at the end of training. With this binocular protocol we were able to remove the impact of patching therapy from interpretation of the results.

The cat has high-resolution spatial vision, and using the jumping stand to measure visual acuity allowed for an accurate titration of thresholds (Giffin & Mitchell, 1978; Murphy & Mitchell, 1987, 1991) with acuities that were close to those predicted by spacing of receptors in the retina (Campbell, Maffei, & Piccolino, 1973; Cleland, Harding, & Tulunay-Keesey, 1979; Cleland, Mitchell, & Gillard-Crewther, 1980; Jacobson, Franklin, & McDonald, 1976; Robson & Enroth-Cugell, 1978; Steinberg, Reid, & Lacy, 1973). The jumping stand required the cats to make a decision rather than passively view the stimuli, so the task was active and physical and depended on the cats attending to the stimuli. Physical activity is known to have positive effects on plasticity, neurogenesis, and recovery of cognitive function after acquired brain injury (Cotman & Berchtold, 2002; Devine & Zafonte, 2009), and physical activity has rescued both visual acuity and ocular dominance in monocularly deprived rats (Baroncelli et al., 2012). Furthermore, attentional factors are important for improvements in adult amblyopes that were induced by playing video games (Li, Ngo, Nguyen, & Levi, 2011). Perhaps the combination of physical activity and attentional demands associated with the jumping stand has a positive effect on visual training.

Binocular training promotes recovery of both eyes

Intensive monocular visual training with perceptually challenging stimuli has been used to promote the recovery of vision in human amblyopes (Levi & Li, 2009; Li et al., 2011; Liu, Zhang, Jia, Wang, & Yu, 2011; Polat, Ma-Naim, & Belkin, 2004; Zhou et al., 2006), and recent studies have found that binocular training promotes good recovery (Hess et al., 2010; Ooi et al., 2013). In our study cats had binocular training, and although the deprived eye never received a competitive advantage, both eyes demonstrated good vision after the intensive training. This good vision depended on training with the visually challenging stimulus because initially the orientation-in-noise thresholds for the late-training group were worse than the thresholds for the early-training group at the same age. Even late binocular training (during adolescence) was able to promote improvements in visual thresholds of both eyes. These observations add to a growing body of behavioral (Birch, 2013; Mitchell, 1991; Mitchell et al., 2001, 2003, 2006; Ooi et al., 2013) and physiological (Kind et al., 2002) evidence that points to concordant binocular vision as an essential ingredient for good—and permanent—recovery of vision after early abnormal vision. The current results are consistent with a model in which the good eye acts as a "teacher" to the deprived eye ("student") to cooperatively guide recovery (Kind et al., 2002; Smith & Trachtenberg, 2007).

We found slightly better deprived eye thresholds after early training (that started during the critical period) versus late training (during adolescence). There is a widely held view that treatment of amblyopia during the critical period is necessary to achieve good visual outcomes. Although early training started at the peak of the critical period, the benefit was extremely small—much smaller than expected from physiological and behavioral studies characterizing plasticity in the cat visual system (Mitchell, 1991; Olson & Freeman, 1980). The most direct way to determine if early training provides an extra benefit is to compare animals that never received visual training with ones that had early or late training. That approach, however, is not practical in animal studies because measuring just one visual threshold, especially on a perceptually challenging task, requires days or weeks of training. Previous studies using reverse occlusion to promote recovery from monocular deprivation have shown that there is substantial physiological (Movshon, 1976), anatomical (Antonini, Gillespie, Crair, & Stryker, 1998), and behavioral (Mitchell, 1991) recovery of the deprived eye, but that recovery is often not maintained once binocular vision is introduced (Murphy & Mitchell, 1986, 1987). Here we found that the deprived eye recovery promoted by binocular training was maintained after both early and late training.

Monocular deprivation affects the vision of both eyes, emerging as a sleeper effect

An unexpected outcome of our study was that 2 weeks of monocular deprivation impaired orientation-in-noise thresholds for both eyes, and those deficits emerged only later in development (sleeper effect). Several authors have observed visual deficits in the fellow eye of human amblyopes (Birch, 2013; Chatzistefanou et al., 2005; Kandel, Bedell, & Fallon, 1976; Kelly & Buckingham, 1998; Leguire, Rogers, & Bremer, 1990; Levi & Klein, 1985; Lewis, Maurer, Tytla, & Bowering, 1992; Rentschler & Hilz, 1979), but they have not been able to rule out patching of that eye as the cause of the deficit. Our experiment provides clear evidence that early monocular deprivation can affect the vision of the nondeprived eye, extending previous studies of anisometropic and strabismic monkeys that found fellow eye deficits (Kozma &
Kiorpes, 2003). No reverse occlusion or patching was used in our study, and yet vision in the nondeprived eye was still impaired. Furthermore, the deficit was not a simple form of binocular interference or suppression because thresholds did not suddenly get better when the nondeprived eye was tested monocularly. This binocular deficit may result from changes in the region of the visual cortex that supports binocular vision since that region is particularly vulnerable to abnormal visual experience (Beston et al., 2010; Kiorpes & Movshon, 1998; Murphy et al., 2004).

We describe the late onset of deprivation-induced visual deficits as a sleeper effect similar to that found by Maurer, Mondloch, and Lewis (2007). They found that amblyopia caused by congenital cataracts leads to deficits in both low- (contrast sensitivity) and high-level (e.g., face processing) visual perception that do not emerge until childhood. That delayed emergence of visual deficits in human amblyopes is similar to the time course found in the current study and may have at least two potential biological mechanisms. First, monocular deprivation accelerates the maturation of synaptic plasticity mechanisms in the visual cortex (Beston et al., 2010), which may effectively shorten the length of the critical period in deprived animals. The consequences of a shorter critical period may be that visual development simply ends earlier. Furthermore, those synaptic changes are greatest in the central visual field representation in the visual cortex, where high-resolution spatial vision is processed (Beston et al., 2010; Murphy et al., 2004). Our current understanding is that a long-term potentiation (LTP)-like mechanism underlies perceptual learning (Cooke & Bear, 2010; Frenkel, Sawtell, Diogo, Yoon, & Neve, 2006; Gagolewicz & Dringenberg, 2011; Sale, DePasquale, Bonaccorsi, & Pietra, 2011), and that mechanism depends on excitatory receptors (Cooke & Bear, 2010; Frenkel et al., 2006). The loss of those receptors after monocular deprivation (Beston et al., 2010; Murphy et al., 2004) may limit the potential for experience-dependent plasticity and, therefore, the degree of visual recovery.

A second explanation is that there are two stages in the development of the visual cortex: an early phase characterized by the refinement of local circuit properties and emergence of normal spatial frequency tuning of individual neurons, and later improvement of intra- and intercortical integration of information beyond the classic receptive field properties. Because we observed that binocular gratings acuity was not affected by monocular deprivation (Figure 8), deficits cannot be the result of uncertainty in local circuits. Therefore, development likely continues normally through the first stage but breaks down at the integration stage, which is critical for orientation in noise. Here, we have demonstrated that monocular deprivation disrupts the emergence of optimal visual function by impairing signal in noise.

How might the cortex support recovery?

Improvement of visual function through intensive training was originally thought to occur through one of two mechanisms: the sharpening of neuronal receptive field properties in the visual cortex or an increase in the number of neurons devoted to the training task (e.g., Gilbert, Li, & Piech, 2009; Recanzone, Schreiner, & Merzenich, 1993; Schoups, Vogels, Qian, & Orban, 2001). Other studies indicated that perceptual learning works by improving the way visual information is integrated and promoting task-specific tuning of neuronal templates or receptive fields (Gilbert et al., 2009; Li, Klein, & Levi, 2008; Li, Levi, & Klein, 2004). This interpretation is interesting in the context of the current experiment because success on the orientation-in-noise task depends on signal integration and the number of samples available for integration (Jones et al., 2003). We observed that reducing the number of orientation samples available for integration (by increasing pixel size) reduced the performance of a normal animal to that of deprived animals (Figure 8B). This suggests that monocular deprivation affects neural signal-to-noise by decreasing the number of spatial samples available for accurate integration of visual information. This would have less impact on grating acuity but significantly impair orientation-in-noise perception. This may result from the disruption of anatomical connections to or within the visual cortex (Antonini, Fagiolini, & Stryker, 1999; Antonini & Stryker, 1996) or synaptic changes that would affect optimal integration of neural signals (Beston et al., 2010; Murphy et al., 2004). Alternatively, training may promote recovery by driving more efficient use of less affected areas in the visual cortex (Li et al., 2004; Lu & Dosher, 2004). Physiological, anatomical, and molecular studies have shown that the visual periphery in the visual cortex is relatively spared from the effects of abnormal visual experience (Beston et al., 2010; Kiorpes & Movshon, 1998; Murphy et al., 2004). Perhaps intensive binocular training engages plasticity mechanisms in that portion of the visual cortex, so the amblyopic cortex integrates visual information by using both central and peripheral visual fields.

Our observations suggest that monocular deprivation during the critical period leaves a permanent trace that impairs the integration of information in the visual cortex. We have also demonstrated that this impairment affects both eyes and that prolonged binocular visual training can promote improvement of visual thresholds. We have highlighted several biological mechanisms, especially plasticity differences between
the center of vision and the visual periphery, to explain both the lasting deficits and recovery after binocular training. Future experiments addressing binocular training as a treatment for amblyopia will be able to use this animal model to explore the neurobiological mechanisms. It will be important to understand the effects of deprivation on the visual cortex in order to tease apart how cortical changes support or limit the potential for binocular training to drive recovery.

Keywords: perceptual learning, amblyopia, binocular vision, monocular deprivation, orientation in noise

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