Effects of Perceptual Learning on Local Stereopsis and Neuronal Responses of V1 and V2 in Prism-Reared Monkeys

C. Nakatsuka, B. Zhang, I. Watanabe, J. Zheng, H. Bi, L. Ganz, E. L. Smith, R. S. Harwerth and Y. M. Chino

J Neurophysiol 97:2612-2626, 2007. First published Jan 31, 2007; doi:10.1152/jn.01001.2006

J Neurophysiol 97: 2612–2626, 2007.
First published January 31, 2007; doi:10.1152/jn.01001.2006.

Effects of Perceptual Learning on Local Stereopsis and Neuronal Responses of V1 and V2 in Prism-Reared Monkeys

C. Nakatsuka,[1] B. Zhang,[1] I. Watanabe,[2] J. Zheng,[1] H. Bi,[1] L. Ganz,[1] E. L. Smith,[1] R. S. Harwerth,[1] and Y. M. Chino[1]

[1]*College of Optometry, University of Houston, Houston, Texas; and* [2]*Department of Ophthalmology, Kawasaki Medical University, Okayama, Japan*

Submitted 21 September 2006; accepted in final form 23 January 2007

Nakatsuka C, Zhang B, Watanabe I, Zheng J, Bi H, Ganz L, Smith EL, Harwerth RS, Chino YM. Effects of perceptual learning on local stereopsis and neuronal responses of V1 and V2 in prism-reared monkeys. *J Neurophysiol* 97: 2612–2626, 2007. First published January 31, 2007; doi:10.1152/jn.01001.2006. Visual performance improves with practice (perceptual learning). In this study, we sought to determine whether or not adult monkeys reared with early abnormal visual experience improve their stereoacuity by extensive psychophysical training and testing, and if so, whether alterations of neuronal responses in the primary visual cortex (V1) and/or visual area 2 (V2) are involved in such improvement. Strabismus was optically simulated in five macaque monkeys using a prism-rearing procedure between 4 and 14 wk of age. Around 2 yr of age, three of the prism-reared monkeys ("trained" monkeys) were tested for their spatial contrast sensitivity and stereoacuity. Two other prism-reared monkeys received no training or testing ("untrained" monkeys). Microelectrode experiments were conducted around 4 yr of age. All three prism-reared trained monkeys showed improvement in stereoacuity by a factor of 7 or better. However, final stereothresholds were still ~10–20 times worse than those in normal monkeys. In V1, disparity sensitivity was drastically reduced in both the trained and untrained prism-reared monkeys and behavioral training had no obvious effect. In V2, the disparity sensitivity in the trained monkeys was better by a factor of ~2.0 compared with that in the untrained monkeys. These data suggest that the observed improvement in stereoacuity of the trained prism-reared monkeys may have resulted from better retention of disparity sensitivity in V2 and/or from "learning" by upstream neurons to more efficiently attend to residual local disparity information in V1 and V2.

INTRODUCTION

Perceptual learning is a highly complex phenomenon that has been widely investigated and documented in primate sensory systems (for review, see Goldstone 1998; Fine and Jacobs 2002). The neural basis for perceptual learning, which presumably reflects plasticity in adult visual brain, has become a matter of considerable debate lately. One of the most frequently debated issues is whether plastic changes in the adult visual brain occur in the early stages of cortical processing (e.g., V1) or whether they are restricted to specialized extrastriate mechanisms (Crist et al. 2001; Dosher and Lu 1998; Ghose et al. 2002; Gilbert et al. 2001; Jagadeesh et al. 2001; Komatsu 2006; Li et al. 2004; Schoups et al. 2001; Smirnakis et al. 2005; Yang and Maunsell 2004).

Another key issue associated with perceptual learning is whether adult subjects that experience reduced visual capacities (acute or developmental) can improve their visual performance by training. This is important because cortical plasticity in mature subjects has many enthusiastic proponents in vision care that specialize in rehabilitation of "reduced" vision in adults. However, many of the claims of "functional recovery" or "improved" performance after visual training in human patients have been challenged because improvements associated with practice are typically small and/or not supported by solid scientific evidence (Helveston 2005; Horton 2005). Consequently, the extent to which perceptual learning is involved in such rehabilitation and the potential extent of functional recoveries for visually impaired adult subjects has become a matter of debate.

Monkeys that experience early strabismus exhibit binocular vision deficits that are similar to those in humans (for review, see Chino et al. 2004; Crawford et al. 1996; Kiorpes et al. 1996; Kiorpes and Movshon 2003). For example, strabismic monkeys exhibit a lack of binocular summation for contrast detection thresholds, severe stereodeficiencies, and/or binocular suppression (Harwerth et al. 1997). Although stereoacuity in normal adult humans can be improved by practice (Fendick and Westheimer 1983; O'Toole and Kersten 1992), there is no comparable data for stereodeficient subjects. Also neurons in V1 of strabismic monkeys show a significant loss of binocularity, reduced disparity sensitivity, and/or increased interocular suppression (Crawford and von Noorden 1978, 1981; Kiorpes et al. 1998; Kumagami et al. 2000; Mori et al. 2002; Smith et al. 1997a; Zhang et al. 2005a).

However, it is also not known whether perceptual learning has any impact on these neuronal responses in adult strabismic monkeys. Therefore in this study, we examined whether extensive training and testing can improve the stereoacuity of adult monkeys that are stereodeficient due to early strabismus, and if so, whether the disparity tuning and other response properties of V1 and V2 neurons in those monkeys show changes that parallel these behavioral improvements. Preliminary data appeared in abstract form (Watanabe et al. 2005).

METHODS

All experimental procedures conformed to the National Institute of Health guidelines for the use of animals in research and were approved by the University of Houston's Institutional Animal Care and Use Committee.

Address for correspondence: Y. Chino, College of Optometry, University of Houston, 505 J. Davis Armistead Bldg., Houston, TX 77204-2020 (E-mail: ychino@uh.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Subjects

The details of the rearing regimen to simulate strabismus are described elsewhere (Crawford and von Noorden 1980; Smith et al. 1997a). Briefly, five infant monkeys (*Macaca mulatta*) wore a lightweight helmet that held 15 diopter prisms oriented base-in in front of the left and right eyes. The total prismatic deviation exceeded the fusional vergence ranges of normal monkeys. The rearing regimen began at 4 wk of age and continued until 14 wk of age, after which the monkeys were reared with unrestricted vision until ~2 yr of age.

Three prism-reared monkeys (*MK-2, MK-3,* and *MK-4*) and one age-matched normal monkey (*MK-1*) were trained to behaviorally perform spatial contrast sensitivity and stereoacuity tasks (*trained prism-reared*). Two prism-reared monkeys did not undergo any behavioral training or testing (*untrained prism-reared*). All prism-reared monkeys exhibited normal alignment (Hirschberg test). Prior to the start of the training for stereo tasks, the monkey's fusional vergence was assessed by measuring dichoptic nonius alignment thresholds and fixation disparities as a function of prism-induced disparity vergence (see Fredenburg and Harwerth 2001; Harwerth et al. 1997 for the details of the experimental methods). The disparity vergence of our prism-reared monkeys was indistinguishable from that in normal monkeys (Fig. 1*A*). Specifically, the psychometric functions for dichoptic nonius alignment to determine vergence responses in our prism-reared monkeys were not different from that in a typical normal monkey (see Herwerth et al. 1997 for more data on disparity vergence and stereopsis in strabismic and normal monkeys). Thus although objective methods were not used to monitor eye position, it is likely that the fusional vergence of our prism-reared monkeys during stereo tasks was also not different from that in normal monkeys. None of the monkey's refractive errors were significant. Spatial contrast sensitivity functions were determined for monocular and binocular viewing (Harwerth et al. 1980; Smith et al. 1985). The spatial contrast sensitivity functions of the three trained prism-reared monkeys demonstrated that these subjects were not amblyopic but lacked binocular summation of contrast detection (Fig. 1*B*). Around 4 yr of age, microelectrode recording experiments were conducted in V1 and V2 of all monkeys to characterize the monocular and binocular receptive field properties of individual neurons. In addition to the normal monkey (*MK-1*) that was trained in stereo tasks (*trained normal*), two normally reared monkeys that had not been trained in stereo tasks served as normal controls for the physiology experiments (*untrained normal*).

Behavioral testing

PRETRAINING. All subjects received the "pretraining" sessions for the operant conditioning specific to the measurement of spatial contrast sensitivity. After the completion of the contrast sensitivity measurements, the monkeys received the pretraining sessions for the stereoacuity measurements. The pretraining for stereo tasks consisted of the use of a Gabor patch for test stimuli with concordant spatial-frequency and contrast monocular depth cues in addition to disparity

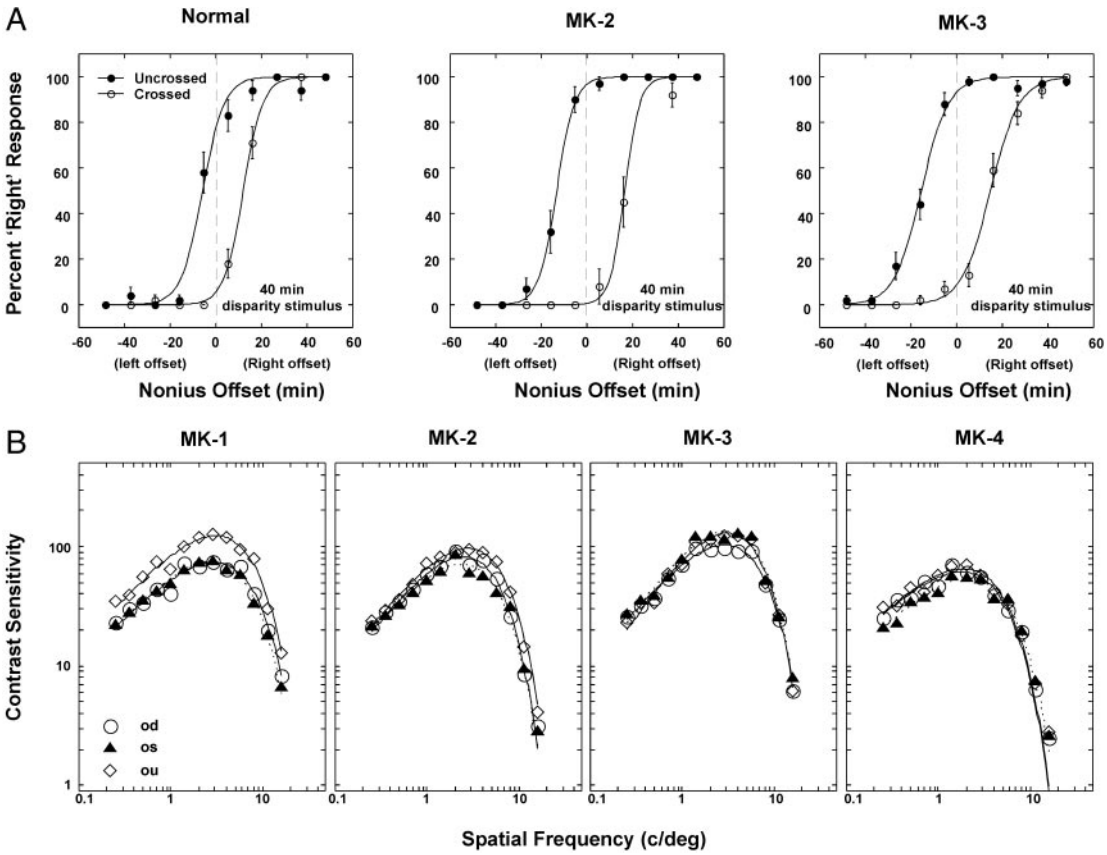

FIG. 1. *A*: disparity vergence response functions of a normal and 2 prism-reared monkeys (*MK-2* and *MK-3*). Examples of psychometric functions for dichoptic nonius alignment to determine vergence responses are illustrated (see Fredenberg and Harwerth 2001; Harwerth et al. 1997 for details). Disparity vergence responses to crossed (○) and uncrossed (●) disparities were expressed by the proportion of responses for which the dichoptic test stimuli appeared to be offset to the right of the reference stimulus. Leftward offsets signify a relative divergence, and rightward offsets indicate a relative convergence. The point of subjective alignment (i.e., 50% correct) on the psychometric functions defines the direction and magnitude of the vergence response. Note that the psychometric functions for *MK-2* and *MK-3* were very similar to that obtained in a normal monkey. *B*: spatial contrast sensitivity functions of normal (*MK-1*) and 3 trained prism-reared monkeys (*MK-2, MK-3,* and *MK-4*). Note that none of the prism-reared monkeys exhibited amblyopia, but these monkeys did not have binocular summation of contrast detection. od, right eye; os, left eye; ou, both eyes.

cues. Monocular cues were faded over 5−10 sessions before disparity cues in isolation of all other cues were used for testing. The pretraining ended when we obtained reliable psychometric functions with disparity cues alone. The duration of the pretraining for each task varied considerably among subjects.

VISUAL STIMULI. The methods used to measure stereoacuity have been described in detail elsewhere (Harwerth et al. 1995, 1997; Harwerth and Fredonburg 2003). Briefly, the visual stimuli were Gabor patches or random-dots stereograms generated by computer graphics (VSG 2/3, Cambridge Research Systems, Cambridge, UK) and presented on video monitors (model HL7955SETK, Mitsubishi, Tokyo, Japan). Dichoptic viewing was achieved by displaying alternate, noninterlaced frames to each eye at 60 Hz using a ferroelectric liquid-crystal shutter system (LV100P, Display Tech, Longmont, CO) that was synchronized to the video monitor.

In most of the local stereopsis experiments, monkeys were trained to compare two Gabor patches consisting of the reference and test patches that were vertically separated by 4 arc deg (Fig. 2*A*). The upper reference stimulus was a static Gabor patch of 3 c/deg, 50% contrast, and zero disparity, and the lower test stimulus was a static Gabor patch of variable spatial frequency, contrast, and binocular disparity. The Gabor patches were composed of vertical sine-wave carrier gratings that were windowed by two-dimensional Gaussian envelopes. The SD of the vertical filter was constant (2 arc deg), and the SD for the horizontal filter varied with the spatial frequency of the carrier (2 spatial periods of the carrier grating to produce stimulus bandwidths of ~1.0 octave). The phase of carrier was not varied but the position of test Gabor pattern was jittered across trials to eliminate monocular alignment cues. Also we had monocular control sessions in which disparity was absent and the monkeys showed chance performance.

In one experimental and one normal monkey, global stereopsis was measured with dynamic random-dots stereograms after the measurement of local stereopsis. The dynamic random-dots stereograms were squares of 13 arc deg per side in overall size with a central square of 4.3 arc deg presented with stereoscopic depth. The individual dot-elements, 6.7 × 6.7 ft in size, were correlated between the two half-views of the stereogram, but each dot changed from dark to light with a probability of 0.5 between successive views at 60 Hz. Stereoacuity levels of binocular disparities were obtained by disparity averaging from displacement of a portion of the dot elements in the test area (Harwerth and Fredenberg 2003; Mallot et al. 1996; Popple et al. 1998).

PROCEDURES. Each trial began with the presentation of binocular fusion stimuli (3.0 × 3.0 arc min), which in the experiments with Gabor patches were small dichoptic squares presented at the center of the monitor screen between the upper (reference) and lower (test) stimuli. The fusion stimuli disappeared prior to the onset of the stereoscopic viewing interval. In the experiments with random-dots stimuli, dynamic, correlated random-dot patterns without a disparity-defined contour served as the fusion stimuli. As mentioned in the preceding text, we did not use an objective method (e.g., eye coil or eye tracker) to monitor eye position, and thus it is not clear exactly where the monkeys were fixating during the stereo tasks. However, the stereo acuity and disparity vergence data obtained in this and previous studies (e.g., Harwerth et al. 1995, 1997) indicate that trained monkeys in this study learned a fixation strategy that results in stereoacuity comparable to human observers that were instructed on fixation (see Fig. 3).

The depth discrimination functions were obtained by a two-alternative forced-choice paradigm (Harwerth et al. 1995, 1997). Briefly, an auditory cue was given to indicate the beginning of a trial. Depression of a response switch by the subjects initiated the trial. The initiation response was followed by an orienting interval of 500 ms and presentation of the stereoscopic stimulus for 500 ms with a coincidence response interval of 1,000 ms. During the response interval, the monkey's alternatives were a release of the response switch during the observe-response interval if the test stimulus appeared to be nearer than the reference stimulus or a maintained depression of the response switch during the observation-response interval if the test stimulus appeared to be farther than the reference stimulus. A high-frequency tone provided feedback for responses that were appropriately correlated with the sign of binocular disparity. For monkeys, a reward (a small amount of juice) was given probabilistically for correct responses. At the end of the observation-response interval, a short intertrial interval was given during which the video screen was blanked. Crossed and uncrossed disparities in stereoscopic stimuli were distributed across five disparity magnitudes and presented randomly with equal probability. Each session lasted 2 h or until the monkeys became satiated with orange juice.

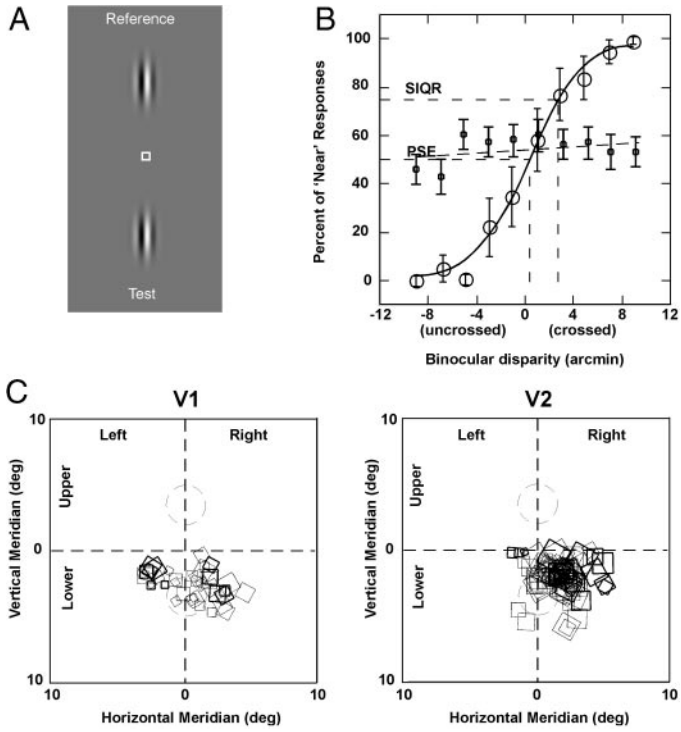

FIG. 2. *A*: schematic illustration of stereodiscrimination tasks. Monkeys were trained to compare 2 Gabor patches, consisting of the reference (*top*) and test (*bottom*) patches that were vertically separated by 4 arc deg after the disappearance of a fusion stimulus (□). The upper reference stimulus was a static Gabor patch of 3 c/deg, 50% contrast, and zero disparity, and the lower test stimulus was a static Gabor patch of variable crossed and uncrossed disparity with respect to the reference. Monkeys performed a "go/no-go" discrimination in which correct behavior was defined as a lever release (a go response) if the test stimulus was offset in crossed disparity or maintained lever press (a no-go response) if the test stimulus was offset in uncrossed disparity. *B*: psychometric function from a prism-reared monkey (*MK-4*) derived from the percentage of responses of "near" as a function of stimulus magnitude with negative values arbitrarily assigned to uncrossed disparities. The depth discrimination data were fit with a logistic function (Berkson 1953) to determine the psychophysical stereothreshold, taken as the semi-intraquartile range (SIQR) of the psychometric function. PSE, point of subjective equality. Monocular control data are also plotted (□). *C*: maps of receptive fields of V1 (*left*) and V2 (*right*) neurons. Each field may represent several units recorded consecutively. Receptive fields drawn with thick lines were from trained prism-reared monkeys. The location of the test and reference stimuli during stereo tasks are indicated (○). It is assumed that during stereo tasks the monkeys were fixating on the location of the fixation target or, more likely, on the test stimuli.

DATA ANALYSIS. For each session, the psychometric function for depth discrimination was derived from the percentage of responses of "near" as a function of stimulus magnitude with negative values

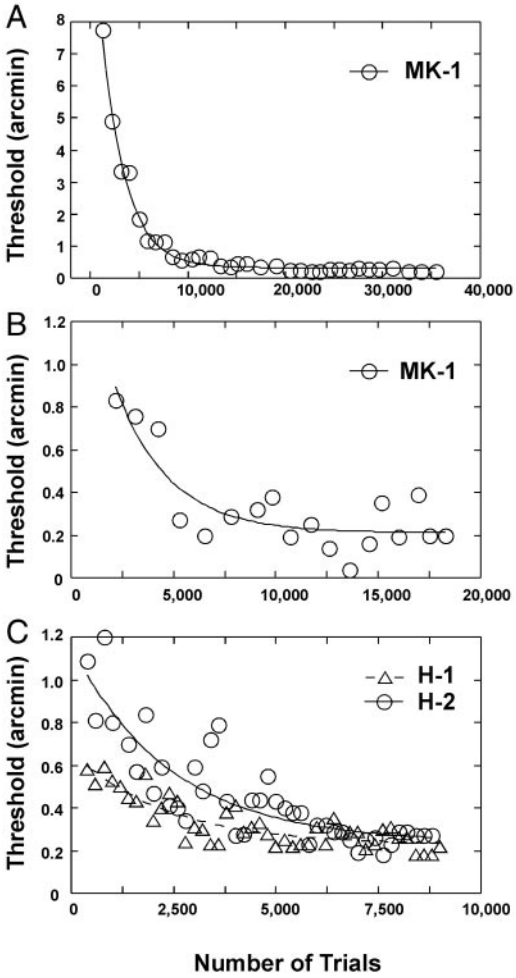

FIG. 3. Stereothresholds as a function of training and testing. *A*: improvement in stereothresholds with Gabor stimuli in a normal monkey (*MK-1*). Data points were fit with a single exponential. Asymptotic threshold = 0.34 arc min. τ = 2,339. *B*: learning transfer in *MK-1*. Stereothresholds measured with random-dots stimuli. Asymptotic threshold = 0.21 arc min. τ = 2,940. *C*: improvement in stereothresholds in 2 normal human subjects measured with random-dots stimuli. Asymptotic thresholds = 0.23 arc min for *H-1* and 0.29 for *H-2*. τ = 2,472 for *H-1* and 1,639 for *H-2*.

arbitrarily assigned to uncrossed disparities (Fig. 2*B*). Using this method, the psychometric function varied from zero "near" responses associated with the largest uncrossed disparities to 100% "near" responses for the largest crossed disparities. The depth discrimination data were fit with a logistic function (Berkson 1953) to determine the psychophysical stereothreshold, taken as the semi-intraquartile range of the psychometric function (Harwerth et al. 1995, 1997).

Electrophysiological recording

PREPARATION. The surgical preparation and recording procedures have been described in detail elsewhere (Chino et al. 1997; Smith et al. 1997b). Briefly, the monkeys were anesthetized initially with an intramuscular injection of ketamine hydrochloride (15–20 mg/kg) and acepromazine maleate (0.15–0.2 mg/kg). A superficial vein was canulated, and all subsequent surgical procedures were carried out under sodium thiopental anesthesia. A tracheotomy was performed to facilitate artificial respiration, and after securing the subjects in a stereotaxic instrument, a small craniotomy and durotomy were made over the operculum of V1. After all surgical procedures were completed, the animals were paralyzed by an intravenous injection of pancuronium bromide (a loading dose of 0.1 – 0.2 mg/kg followed by a continuous infusion of 0.1–0.2 $mg \cdot kg^{-1} \cdot h$) and artificially ventilated with a mixture of 59% N_2O-39% O_2-2% CO_2. Anesthesia was maintained by the continuous infusion of a mixture of Propofol (4 $mg \cdot kg^{-1} \cdot h^{-1}$) and Sufentanyl sodium (0.05 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Core body temperature was kept at 37.6°C. Cycloplegia was produced by the topical instillation of 1% atropin, and the animals' corneas were protected with rigid gas-permeable, extended-wear contact lenses. Retinoscopy was used to determine the contact lens parameters required to focus the eyes on the stimulus screens.

RECORDING AND VISUAL STIMULATION. Tungsten-in-glass microelectrodes were used to isolate the activity from individual cortical neurons. Action potentials were extracellularly recorded and amplified using conventional technology. For each isolated neuron, the receptive fields for both eyes were mapped, and its ocular dominance was initially determined using hand held stimuli (Hubel and Wiesel 1962). All receptive fields were located within 5.0° of the center of the fovea (Fig. 2*C*). In anesthetized and paralyzed monkeys, it is not always possible to determine the exact location of each receptive field in relation to the location of psychophysical test stimuli when these monkeys were awake and behaving. Due to eye rotations and drifts and the nature of the methods used to determine the center of the fovea, an error of few degrees must be considered. However, the majority of receptive fields of V1 and V2 neurons including those from our trained prism-reared monkeys were located in or around the region of the visual field where the test stereoscopic stimuli were presented during the behavioral testing.

All visual stimuli for the physiology experiments were sine wave gratings generated by using Vision Research Graphics (VRG) software on a monochrome monitor (frame rate = 140 Hz; 800 × 600 pixels, mean luminance 50 cd/m^2). Responses to drifting sine wave gratings (3.1 Hz, 80% contrast) were measured to determine the orientation and spatial frequency tuning functions for each unit. Cells were classified as simple or complex on the basis of the temporal characteristics of their responses to a drifting sine wave grating of the optimal spatial frequency and orientation (Skottun et al. 1991).

Data analysis

ORIENTATION TUNING. The optimal orientation and orientation bandwidth for each receptive field were determined by fitting the orientation tuning functions with wrapped Gaussian functions (Swindale 1998)

$$G(\theta) = m_1 \sum_{n=-\alpha}^{n=\alpha} \exp[-(\theta - m_2 + 180n)^2/(2m_3^2)]$$

Where θ = orientation, m_1 = amplitude, m_2 = preferred orientation, and m_3 = SD of the Gaussian function.

SPATIAL FREQUENCY TUNING. To determine each cell's optimal spatial frequency and spatial resolution, the spatial frequency response data were fitted with Gaussian functions (DeAngelis et al. 1993)

$$G(m_0) = m_1 \exp[-(m_0 - m_2)^2/(2m_3^2)]$$

Where m_0 = spatial frequency, m_1 = amplitude, m_2 = optimal spatial frequency, and m_3 = SD of the Gaussian function. Spatial resolution of each unit was determined by locating the highest spatial frequency that evoked responses significantly higher than the average spontaneous firing of the unit (i.e., more than ±2 SD).

OCULAR DOMINANCE. The ocular dominance index (ODI) of a neuron was calculated using the following formula (Chino et al. 1997;

Smith et al. 1997b): ODI = (R_i – noise)/(R_c – noise) + (R_i – noise), where R_i is the peak response amplitude for ipsilateral eye stimulation, R_c is the peak response amplitude for contralateral eye stimulation, and *noise* is the spontaneous activity. ODI values range from 0.0 (contralateral response alone) to 1.0 (ipsilateral response alone) with 0.5 indicating perfect binocular balance.

BINOCULAR INTERACTIONS. To determine the strength and the nature of binocular interactions, responses were collected for dichoptic sine wave gratings of the optimal spatial frequency and orientation as a function of the relative interocular spatial phase disparity of the grating pair. The sensitivity to relative interocular spatial phase disparities was quantified using a *binocular interaction index* that was calculated from the sine function fit to the binocular phase tuning data (BII = amplitude of the fitted sine wave/the average binocular response amplitude) (Ohzawa and Freeman 1986; Smith et al. 1997b). To characterize whether binocular signal interactions were facilitatory or suppressive in nature, the *peak binocular response amplitude/dominant monocular response amplitude* ratios (peak B/M ratios) were calculated for each unit and expressed in terms of relative strength (db), i.e., 10 log peak B/M. Negative peak B/M values signify binocular suppression, and positive values indicate binocular facilitation.

Histology

At the end of each penetration, small electrolytic lesions (5 μA, 5 s, electrode negative) were made at three points along the track in V1 for later reconstruction. Experiments were terminated by administering an overdose of sodium pentobarbital (100 mg/kg), and the animals were killed by perfusion through the heart with an aldehyde fixative. Frozen sections were stained for Nissl substance and cytochrome oxidase.

RESULTS

Perceptual learning

NORMAL SUBJECTS. *Gabor stimuli.* A typical normal monkey (*MK-1*) learned to discriminate stereoscopic cues after ~1,000 training trials (Fig. 3*A*) and stereoacuity at this time was 7.7 arc min. Perceptual learning occurred in two phases, an initial rapid phase followed by a slow extended phase as reported for nearly all monocular visual tasks (e.g., Ghose et al. 2002; Yang and Maunsell 2004). Specifically, a threshold of 0.5 arc min was rapidly reached after over additional 8,000–9,000 trials, but the final threshold value of 0.34 arc min was not obtained until after 35,000 trials. The performance of *MK-1* shows 20-fold improvement with practice, and the learning curve for this monkey is well described by a single exponential.

Random-dots stimuli. The same normal monkey (*MK-1*) was tested with random-dots stereograms (RSD) to determine the extent of learning transfer. The ability of this monkey to discriminate stereoscopic cues was well retained and learning transfer was remarkably efficient (Fig. 3*B*). After ~1,500 training trials, the first measured stereothreshold was 0.83 arc min (compared with 7.7 arc min with Gabor stimuli for the initial trials), and the thresholds dropped rapidly to 0.3–0.4 arc min after additional 3,000 trials. The final value of 0.29 arc min was achieved with only 10,000 additional trials.

Learning curves of two normal human subjects are illustrated in Fig. 3*C* for comparison. Measurements were made with the same random-dots stimuli and testing procedures as those employed for our monkeys (*MK-1* and *MK-3*). Human subjects exhibited learning curves that were similar to that for the normal monkey (*MK-1*), i.e., stereoacuity at the beginning of trials ranged between 0.6 (*H-1*) and 1.2 (*H-2*) arc min. Their performance improved after additional 3,000 trials and then after 9,000 additional trials, the final threshold values (0.23 arc min for *H-1* and 0.29 for *H-2*) were reached. These improvements in thresholds can be best described with single exponentials for both subjects and are similar to the previously reported learning curves for normal human subjects (Fendick and Westheimer 1983; O'Toole and Kersten 1992).

PRISM-REARED MONKEYS. In two of the three trained prism-reared monkeys (*MK-2* and *MK-3*), successful depth discrimination of test stimuli strictly based on disparity cues occurred after ~6,000 training trials (Fig. 4) compared with 1,500 trials for the normal monkey (*MK-1*). At this time stereoacuity was 41 arc min for *MK-2* and 46 arc min for *MK-3*. These values were five to six times worse than that of a normal monkey prior to practice-induced improvement in discrimination. However, rapid improvement in performance followed and their stereothresholds decreased to ~6–7 arc min after 10,000 trials. Small but gradual decreases in thresholds followed in both subjects with additional 20,000 trials and their final thresholds were 4.9 and 4.4 arc min, respectively. As in normal subjects, these improvements are best described by single exponentials.

The observed improvement in disparity thresholds resulted from changes in the slope of psychometric functions, i.e., the slope became steeper with training (Fig. 5). Our experimental monkeys were producing 100% correct responses for larger disparities during a relatively early period of training and with more trials, their psychometric functions steepened. However, in the monocular control trials in which one eye was occluded, these monkeys showed a chance performance. Thus the observed improvement in performance largely reflects improved binocular vision. Also because these monkeys initially received training for both contrast sensitivity and nonius alignment tasks followed by the pretraining for stereo tasks, the "cognitive" component of perceptual leaning is likely to have completed prior to stereothreshold measurements.

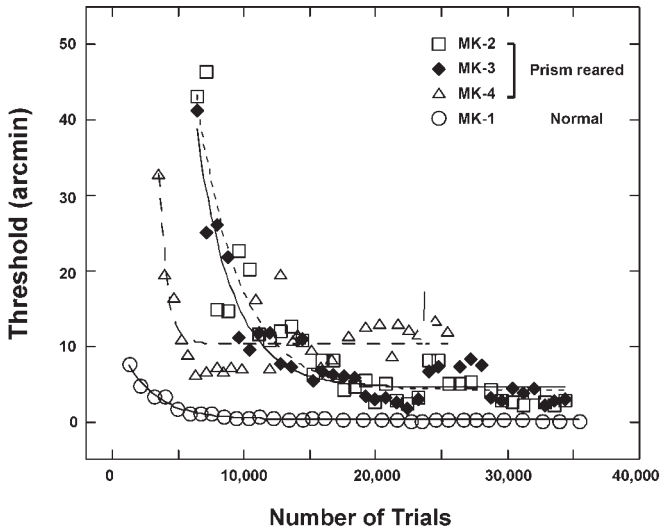

FIG. 4. Improvement in stereothresholds as a function of training and testing in 3 prism-reared monkeys (*MK-2, MK-3,* and *MK-4*). Data from a normal monkey (*MK-1*) are shown for comparisons. Asymptotic thresholds = 4.9 arc min for *MK-2* and 4.4 arc min *MK-3* and 10.4 arc min for *MK-4.* τ = 2,236 for *MK-2,* 2958 for *MK-3* and 618 for *MK-4.* ↓, thresholds for *MK-2* and *MK-3* after a period of no training in stereotasks for 3 mo.

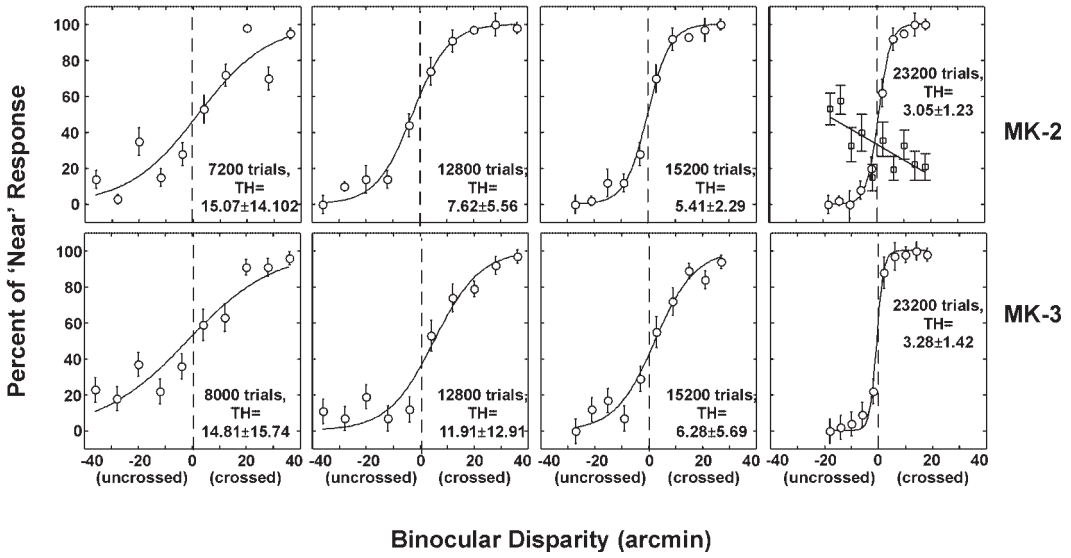

FIG. 5. Improvement in stereothresholds with training. Psychometric functions of *MK-2* and *MK-3* at an early (7,000–8,000 trials), middle (12,000–15,000 trials), and late (23,000 trials) stages of training. Note that the slope of the functions became steeper with the amount of training. Disparity thresholds in arc min are shown inside each panel (TH). An example of monocular control data are illustrated for *MK-2* (□).

The rate and magnitude of perceptual learning varied considerably among stereodeficient subjects (Fig. 4). In the third trained prism-reared monkey (*MK-4*), the first successful discrimination with Gabor stimuli occurred only after 3,000 trials, much earlier than in *MK-2* or *MK-3*. Threshold stereoacuity improved at a much faster rate down to ~7 arc minutes. However, the performance was not consistent after 10,000 trials, and as a result, stereothresholds tended to rise and the final threshold value was around 10.4 arc min after 25,000 trials, twice as high as thresholds for *MK-2* and *MK-3* and nearly 30 times higher than that for normal subjects.

It is important to know how long these positive effects of perceptual learning may last. Although we did not specifically investigate this issue, we found that in *MK-2* and *MK-3,* the improvement due to practice continue to be present for ≥3 mo. Specifically, the measurement of stereoacuity was discontinued after 24,000 trails, and for ~3 mo, testing was switched to measurements of monocular functions. When the monkeys were tested for stereoacuity again, a slight elevation of stereothresholds was found for both monkeys (see the big arrow for *MK-2* and *MK-3* in Fig. 4). However, continuing with the stereothreshold measurements, their performance rapidly improved to the previous level (4.9 and 4.2 arc min, respectively).

How efficient is learning transfer of depth discrimination in prism-reared monkeys? In *MK-3,* the ability to discriminate depth with Gabor stimuli was remarkably well transferred to performance measured with random-dots stimuli (Fig. 6). The first successful discrimination occurred after 3,000 training trials compared with 6,000 trials with Gabor stimuli. However, stereothresholds dropped to near the final value of 4 arc min after only 3,000 trials (i.e., <5 days) instead of >20,000 trials in the initial training with Gabor stimuli. This transfer of learning effects in this prism-reared monkey was as nearly efficient as in normal monkeys, although unlike in the normal monkey (*MK-1*), the initial threshold value for random dot stimuli was elevated to 43 arc min.

Electrophysiology

Binocular responses were analyzed for a population of 167 individual V1 and 252 V2 neurons in five prism-reared monkeys (92 V1 and 181 V2 units in 3 trained monkeys) and 153 V1 and 253 V2 neurons in three normal monkeys (50 V1 and 84 V2 neurons in 1 trained monkey). Although the normal control group had both the trained and untrained normal monkeys, the sample size for the trained normal monkey (both the number of subjects and sample units) was too small for a comprehensive analysis of "learning effects" on cortical neurons in normal monkeys. Nevertheless, the data on binocular responses from these two control groups are separately illustrated for qualitative comparisons but were combined for statistical analyses.

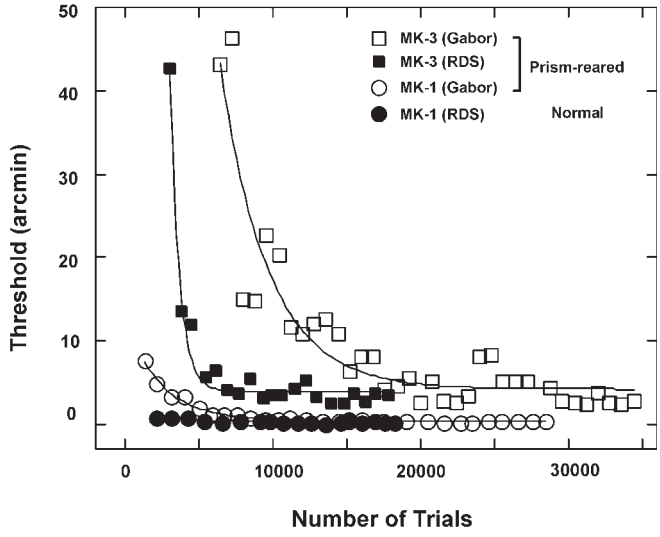

FIG. 6. Transfer of learning in a strabismic (*MK-3*) and normal (*MK-1*) monkey. ○ and □, performance with Gabor stimuli in initial trials; ● and ■, performance improvement measured with random-dots stimuli after the initial trials. Asymptotic thresholds = 4.4 arc min for Gabor stimuli and 4.0 arc min for random dots stimuli. τ = 2,958 trials for Gabor and 621 trials for random dots.

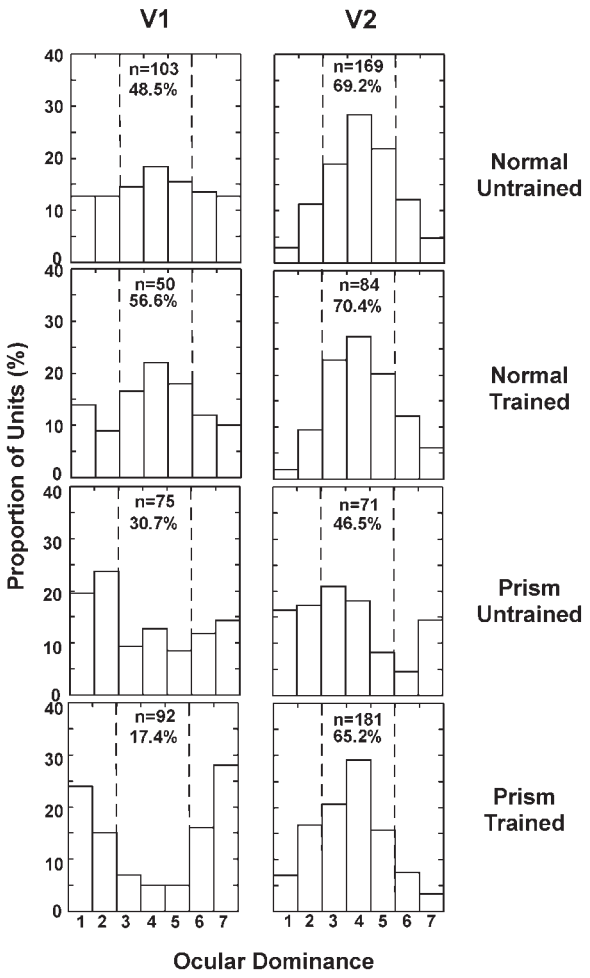

FIG. 7. Effects of training on ocular dominance distribution of V1 (*top*) and V2 neurons (*bottom*). Based on unit's ocular dominance index (ODI) value each unit was placed in 1 of the traditional 7 categories (Hubel and Wiesel 1962). Percentages indicate the proportion of binocularly balanced units (OD = 3–5).

OCULAR DOMINANCE. Previous studies in cats and monkeys have demonstrated that abnormal visual experience from early strabismus reduces the percentage of V1 cells that can be activated by either eye (Movshon and Kiorpes 1993; Smith et al. 1997a; von Noorden and Crawford 1978, 1981). In both trained and untrained prism-reared monkeys, we found reductions in cortical binocularity relative to trained or untrained normal monkeys (Fig. 7). Ocular dominance of each unit was determined using seven-category scheme based on its ODI values. The proportion of binocularly balanced units (i.e., OD = 3–5) relative to the percentage of monocularly dominated units (OD = 1–2 and 6–7) was significantly lower in both trained (17.4%) and untrained (30.7%) strabismic monkeys in comparison to trained (56.6%) and untrained normal monkeys (48.5%; χ^2, $P < 0.001$).

In contrast, there were no measurable alterations in the ocular dominance distribution of V2 neurons in the trained prism-reared monkeys. Instead, we found that 65.2% of V2 units in the trained prism-reared monkeys to be binocularly balanced, similar to the percentage in normal V2 (69.2% in untrained and 70.4% in trained normal monkeys; χ^2, $P > 0.1$; Fig. 7). However, the proportion of binocularly balanced V2 cells was reduced in the untrained prism-reared monkeys (46.5%) compared with trained and untrained normal or trained prism-reared monkeys. As a result, there were significant differences in the ocular dominance distributions of V2 neurons between the untrained and trained prism-reared monkeys and between the untrained prism-reared monkeys and the trained and untrained normal monkeys (χ^2 test, $P < 0.01$).

DISPARITY TUNING. Ocular dominance provides limited information on the functional status of cortical mechanisms that support stereoscopic vision. One of the most fundamental requirements for fusion and stereopsis is the presence of disparity-sensitive neurons in the early stages of cortical processing (Held 1993; Poggio et al. 1988). Therefore we wanted to know how severe the disparity-sensitivity losses were in our strabismic monkeys and more importantly, whether or not the visual training and testing that improved stereoacuity reflected better retention of disparity sensitivity in V1 and/or V2.

Figure 8 illustrates the disparity tuning functions of representative V1 and V2 neurons in the untrained normal, trained normal, untrained prism-reared, and trained prism-reared monkeys. The disparity sensitivity of the representative V1 unit was substantially reduced in both the untrained (BII = 0.14) and trained prism-reared monkeys (BII = 0.16) compared with the unit from an untrained normal monkey (BII = 0.54) or a trained normal monkey (BII = 0.61). The representative V2 neuron from the trained prism-reared monkey exhibited better disparity sensitivity (BII = 0.35) than the V2 unit from the untrained prism-reared monkey (BII = 0.12) although it was still subnormal (BII of the normal units = 0.46 and 0.48).

The population data demonstrate that the disparity sensitivity of V1 neurons was substantially reduced in prism-reared monkeys and that the extensive training and testing had little effects on the average disparity sensitivity of V1 neurons (Fig. 9*A, left*). The average BII (0.17 ± 0.021) for the trained monkeys was not different from that for the untrained monkeys (0.14 ± 0.02, 1-way ANOVA, $P > 0.3$). However, the differences between the normal (0.42 ± 0.03 for the untrained and 0.44 ± 0.04 for the trained) and prism-reared monkeys were highly significant (1-way ANOVA, $P < 0.0001$).

Only 8.9% of V1 neurons in untrained monkeys compared with 56.7 and 50.8% in normal controls were disparity sensitive (i.e., BII >0.3; Fig. 9*A, left*). Interestingly, the proportion of disparity-sensitive V1 units in the trained monkeys was substantially higher (21.5%) than in the untrained prism-reared monkeys. This difference between the trained and untrained monkeys was marginally significant (χ^2 test, $P < 0.05$).

In V2, the reduction in disparity sensitivity was similar to that observed in V1 and much lower than that found for the untrained monkeys (mean BII = 0.12 ± 0.01; disparity-sensitive units = 5.9%) compared with untrained normal (mean BII = 0.48 ± 0.03, disparity-sensitive units = 68.0%) or trained normal monkeys (mean BII = 0.55 ± 0.04, disparity-sensitive units = 72.1%; Fig. 9*A, right*). However, the trained prism-reared monkeys exhibited significantly higher disparity sensitivities (mean BII = 0.24 ± 0.021; 1-way of ANOVA, $P < 0.001$) and a higher proportion of disparity-sensitive units (29.9%) than the untrained prism-reared monkeys (χ^2 test, $P < 0.001$). The average disparity sensitivity and the proportion of disparity-sensitive units in both trained and untrained prism-reared monkeys, however, were substantially

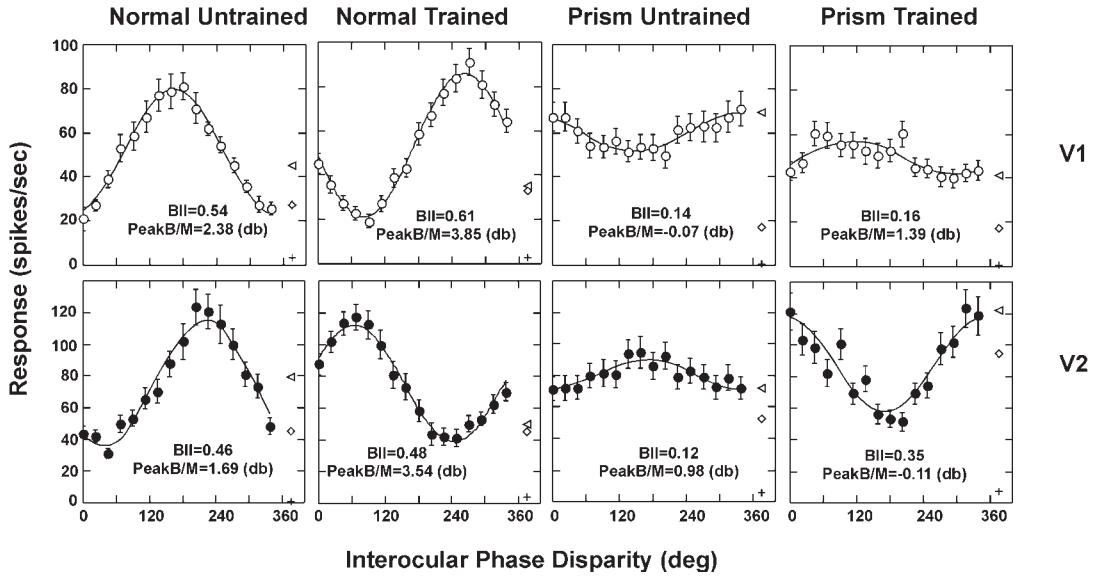

FIG. 8. Representative binocular spatial phase disparity functions of V1 (*top*) and V2 neurons (*bottom*) in normal and prism-reared monkeys. Error bar indicates SE. △, dominant monocular response amplitude; ◇, nondominant monocular amplitude; +, noise level.

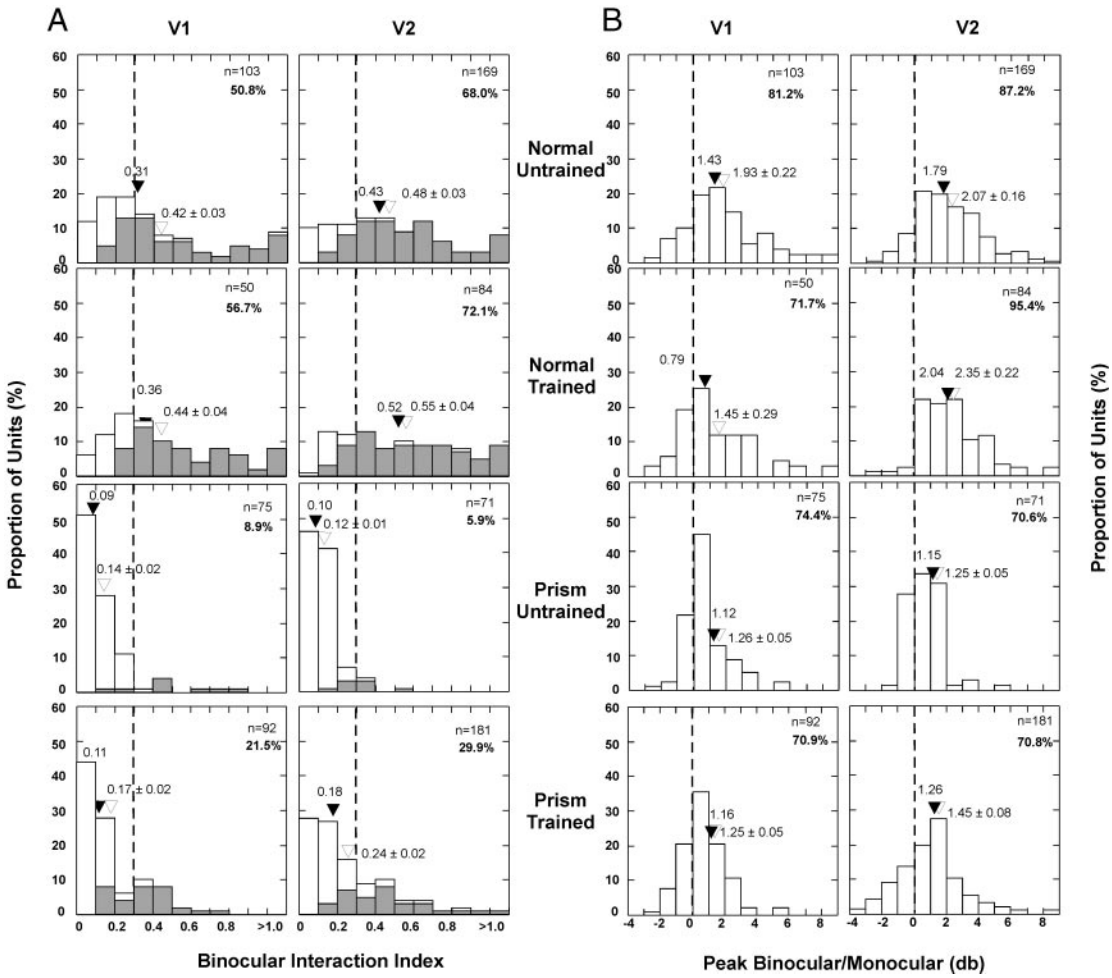

FIG. 9. Effects of training on binocular disparity sensitivity of V1 and V2 neurons. *A*: histograms showing the distribution of BII values of V1 (*left*) and V2 neurons (*right*). ▲, median; △, mean. ■, proportion of neurons that had statistically significant disparity tuning (1-way ANOVA, $P < 0.05$) (Prince et al. 2002). The percentages of disparity-sensitive units (i.e., BII > 0.3) are also indicated. *B*: histograms illustrating the distribution of the peak binocular/monocular response ratios of V1 (*left*) and V2 (*right*) neurons. ···, border between excitatory (>0.0 db) and inhibitory (<0.0 db) binocular interactions. ▲, median; △, mean.

lower than the comparable values for normal monkeys (1-way ANOVA, $P < 0.001$; χ^2 tests, $P < 0.001$). It is worthwhile to note that regardless of subject groups, the great majority of V1 and V2 neurons with the BII value >0.3 exhibited a statistically significant disparity tuning (i.e., 1-way ANOVA, $P < 0.05$) (Prince et al. 2002).

In the visual cortices of monkeys that experienced strabismus early in life, facilitatory binocular interactions are reduced and suppressive binocular interactions are abnormally increased (e.g., Kumagami et al. 2000; Mori et al. 2002; Smith et al. 1997a; Zhang et al. 2005a). In this study, the peak binocular/monocular ratios of V1 and V2 neurons were also significantly reduced in both trained and untrained prism-reared monkeys compared with those in normal monkeys (1-way ANOVA, $P < 0.01$; Fig. 9*B*). However, in trained prism-reared monkeys, the peak binocular/monocular ratios of V2 neurons were significantly better and there were more V2 units with higher binocular/monocular ratios (e.g., >2.0 db; 25%) than in untrained prism-reared monkeys (6%; χ^2 test, $P < 0.01$).

Based on the BII values of individual neurons, we estimated the ability of each neuron to discriminate fine disparity differences (defined here as *normalized optimal disparity sensitivity*) by taking its optimal spatial frequency and response variability into account (for a similar analysis, see Nover et al. 2005; Yang and Maunsell 2004). To consider the effects of optimal spatial frequency, the changes in cell's absolute firing rate per unit of angular disparity (spike·s^{-1}·arc min^{-1}) were calculated for the phase disparity tuning function (Fig. 10*A*, - - -) including that at the steepest slope of the function (indicated by an arrow). To estimate the effects of response variance, the relationship between the mean discharge rate and the response variance for the same unit was first determined by plotting its mean response rate as a function of response variance (Fig. 10*B*). Based on the best linear fit for these data points (—), the response variance of this unit was estimated for the steepest point of its phase tuning function (the - - -). The *normalized optimal disparity sensitivity* of this neuron was, then, calculated by taking the ratio of cell's *firing rate per unit of angular disparity/SD*.

Figure 10*C* demonstrates that V2 neurons, but not V1 neurons, of trained prism-reared monkeys had significantly higher normalized optimal disparity sensitivity than did un-

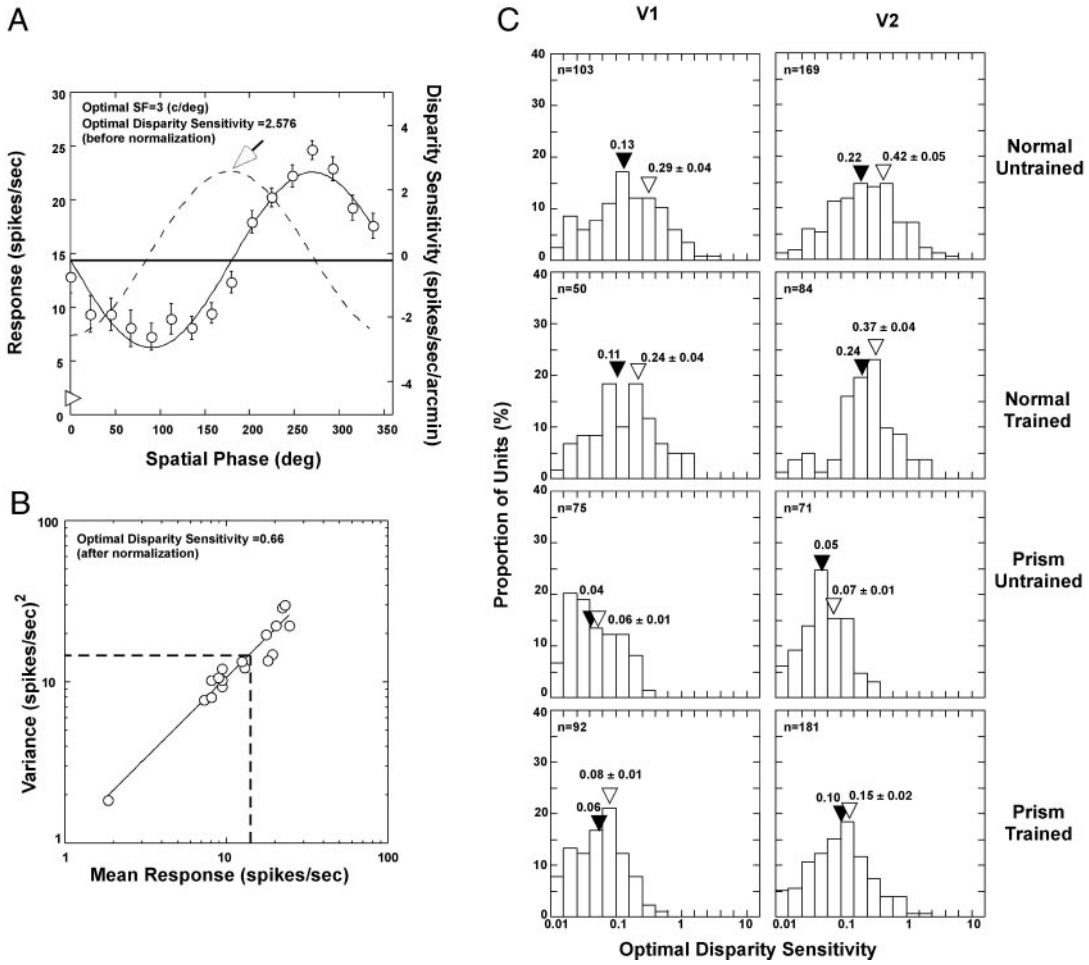

FIG. 10. Effects of training on the "optimal" disparity sensitivity of V1 and V2 neurons. *A*: disparity tuning curve of a V2 neuron from a normal monkey (— with data points) from which the *optimal disparity sensitivity* of the cell was determined by taking its optimal spatial frequency (3 c/deg) into account (- - -). The optimal disparity sensitivity at the steepest portion of the tuning function (2.58 spike·s^{-1}·arc min^{-1}) is indicated (→). *B*: mean response is plotted as a function of response variance for the same neuron in *A*. Each data point indicates 1 spatial phase disparity including spontaneous firing (the lowest data point). —, best linear fit. The response variance was estimated from the fit function for the steepest portion of the phase tuning function (- - -). The optimal disparity sensitivity of this neuron was then normalized with its SD of responses. *C*: frequency histograms illustrating the distribution of the *normalized optimal disparity sensitivity* of V1 (*left*) and V2 (*right*) neurons. ▲, median; △, mean.

trained prism-reared monkeys (*t*-test, $P = 0.003$). Not surprisingly normal monkeys exhibited much better optimal disparity sensitivity than either trained or untrained prism-reared monkeys (*t*-test, $P = 0.001$). Together the ability of V2 neurons in the trained prism-reared monkeys to discriminate fine binocular disparities was better by a factor of ~2.0 compared with that in the untrained monkeys.

Was the observed improvement of the normalized optimal disparity sensitivity for the trained prism-reared monkeys specific to those neurons that preferred vertical orientation? To answer this question, we divided all units into two groups; those neurons having preferred orientation within ±45° of vertical orientation (0–45°) and those within ±45° of horizontal orientation (45–90°). Figure 11*A* shows that vertically tuned V2 neurons in our trained prism-reared monkeys indeed exhibited greater disparity sensitivity than those in the untrained monkeys but that this superior neuronal performance was also found for those V2 neurons that preferred horizontal orientations.

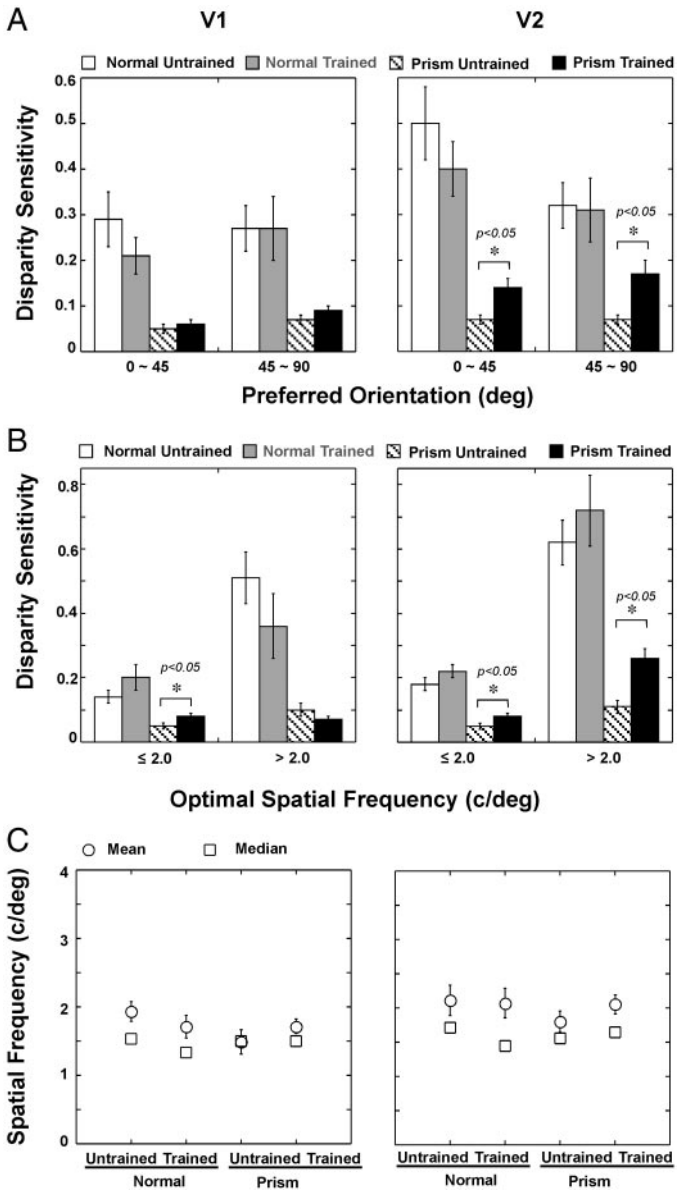

FIG. 11. *A*: effects of preferred orientations of individual neurons on the mean (±SE) normalized optimal disparity sensitivity. Neurons were divided into vertically and horizontally tuned according to their preferred orientations. *P* values are shown when there is a significant difference between groups. *B*: effects of optimal spatial frequencies on mean (±SE) optimal disparity sensitivity. Neurons were divided into low-frequency (≤2.0 c/deg) and high-frequency (>2.0 c/deg) groups according to their optimal spatial frequencies. *P* values are shown when there is a significant difference between groups. *C*: comparisons of the mean (±SE) and median optimal spatial frequencies of V1 and V2 neurons. Note that the mean values are ~2.0 c/deg for all subject groups.

Not surprisingly, the normalized optimal disparity sensitivity of V1 and V2 neurons was generally better for those neurons tuned to higher spatial frequencies in all monkey groups (Fig. 11*B*). More importantly, the optimal disparity sensitivity of V2 neurons in the trained prism-reared monkeys was much better than that in untrained monkeys for those units tuned to spatial frequencies higher than their mean optimal spatial frequencies (~2.0 c/deg; Fig. 11, *B* and *C*). Interestingly, V1 and V2 neurons that were tuned to lower spatial frequencies (i.e., ≤2.0 c/deg) in the trained prism-reared monkeys had marginally but significantly better disparity sensitivity than those in the untrained prism-reared monkeys. The functional significance of such small differences in the low frequency range is not clear.

Another variable that may substantially influence the disparity sensitivity of V1 or V2 neurons is the responsiveness (i.e., firing rate) of individual units. Figure 12 illustrates scatter plots of BII values of individual units as a function of their mean firing rates (i.e., average of binocular response amplitudes at all binocular spatial phases). The average firing rates of V1 and V2 neurons were very similar in normal monkeys and trained or untrained prism-reared monkeys (~30 spike/s). More importantly, those disparity-sensitive V2 neurons (e.g., >0.3) in trained prism-reared monkeys had a broad range of firing rate as in normal monkeys.

Next we examined whether or not our sampling method somehow biased the results. Figure 13 illustrates the BII value of each unit as a function of recording distance from the beginning of each penetration. Because V2 neurons were sampled with nearly identical manners in each penetration, there were no systematic differences in the distribution of BII values across the entire penetration distance between the normal and experimental monkeys, i.e., those V2 neurons with higher BII values were evenly distributed across the entire penetration. Thus the observed superior disparity sensitivity of V2 neurons in trained prism-reared monkeys over that in untrained prism-reared monkeys was unlikely to have resulted from a sampling bias.

DISCUSSION

The main findings of this study were that adult monkeys that experienced strabismus early in life substantially improved their stereoacuity by visual training and testing and that V2, but not V1, neurons in our trained monkeys retained significantly better disparity sensitivity than neurons in untrained monkeys.

Comparisons to previous studies

Although improvement with practice in stereoacuity has been reported for normal adult humans (Fendick and Westheimer 1983; O'Toole and Kersten 1992; Ramachandran and

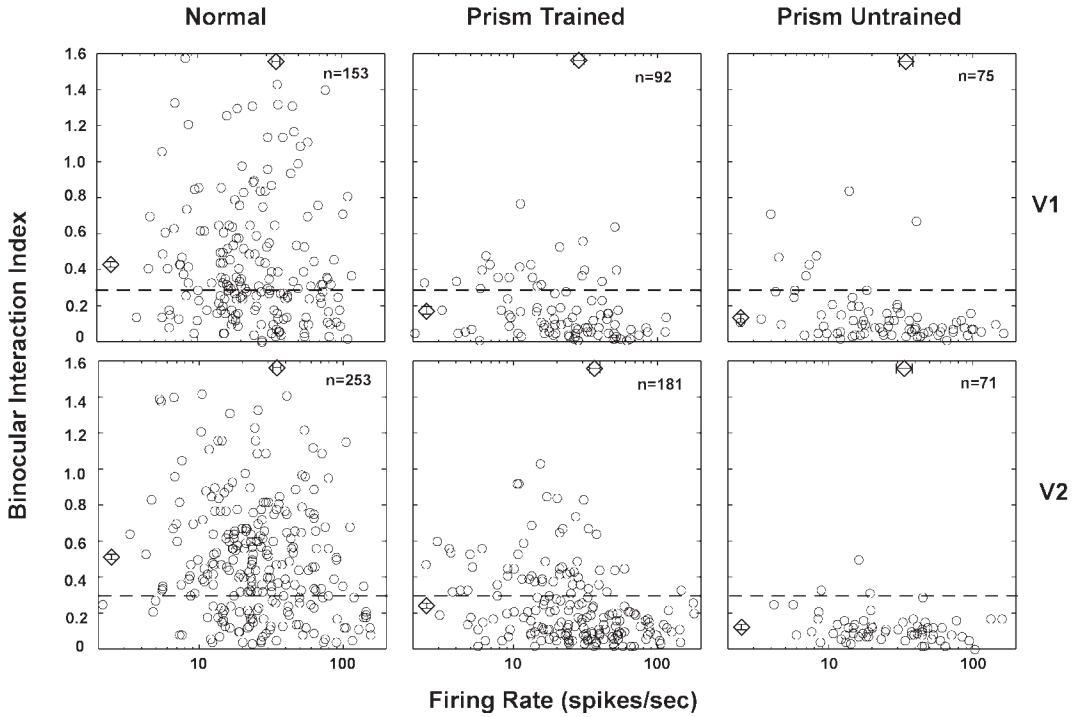

FIG. 12. Analysis of disparity sensitivity (BII) of V1 (*top*) and V2 (*bottom*) neurons as a function of unit's mean binocular response amplitude for normal (*left*), trained prism-reared (*middle*), and untrained prism-reared (*right*) monkeys. ◇, mean values (±SE) for BII and firing rate; ···, BII value of 0.3.

Braddick 1973), there is no documentation for comparable improvement of binocular functions in humans who experienced strabismus early in life. Also the present results represent the first and only demonstration of perceptual learning in binocular visual tasks in normal monkeys or in monkeys that experienced early abnormal binocular vision. The overall shapes of the learning curves for our normal and prism-reared monkeys were similar to those recently reported for monocular orientation discrimination tasks in normal monkeys (Ghose et al. 2002; Yang and Maunsell 2004). In these studies of monocular practice effects, a rapid drop in orientation difference thresholds occurred during the first 50,000 trials followed by a small, prolonged improvement over an additional 50,000–100,000 trials. Thus the total number of trials required to

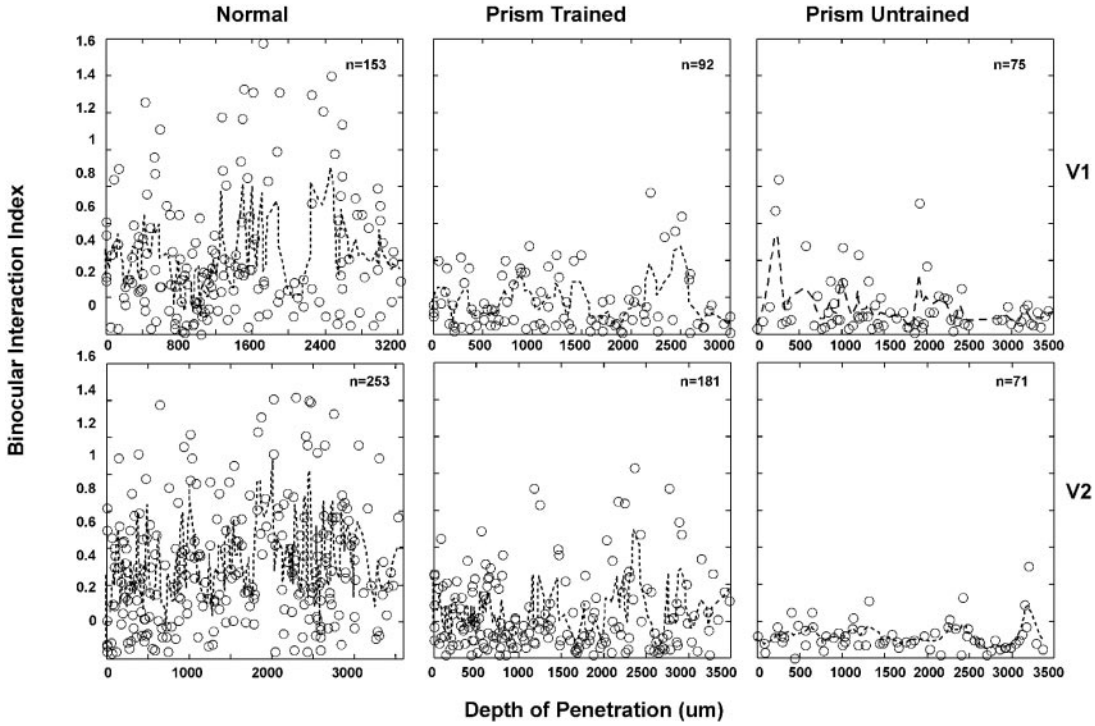

FIG. 13. Disparity sensitivity (BII) of V1 (*top*) and V2 (*bottom*) neurons as a function of recording depths. ···, running means.

achieve their final thresholds appeared to be far greater than that in our study. This apparent discrepancy probably arises from procedural differences between the studies. Prior to stereothreshold measurements, our monkeys received an initial training period of ~10,000 trials in which each monkey learned to fixate and detect the presence of contrast-threshold level stimuli. This training was followed by the measurement of spatial contrast sensitivity functions for each eye and for the two eyes together, and stereo pretraining was given prior to the stereo tasks. The total number of trials typically required for these tasks was ~40,000–50,000. In the study of Yang and Maunsell (2004), monkeys were trained for fixation and orientation discrimination tasks (match to sample) without prior experience in psychophysical tests. Considered together, there is a remarkable similarity in the time course of perceptual learning in monkeys between monocular and binocular tasks.

Although our prism-reared monkeys retained their ability to improve stereoacuity with practice, their stereothresholds were still abnormally elevated at the end of the training and testing (i.e., 5−10 arc min compared with 0.34 arc min in the normal monkey). Also it is important to mention that in separate studies, there were prism-reared monkeys that could not be tested for their stereoscopic vision because their stereodeficiency was presumably much more severe. Specifically, although they learned all of the behavioral tasks required for measuring stereoacuity, they could not learn to use disparity cues in isolation of all other cues. Therefore it must be concluded that they lacked disparity-sensitive mechanisms for the detection of depth from even coarse disparity. Thus there is a clear limit to how much perceptual learning can improve stereoacuity in stereodeficient subjects.

What was learned?

It is a matter of considerable interest as to what is learned by practice, what are the underlying neural mechanisms for perceptual learning or where in the visual brain major changes occur to support learning (Dosher and Lu 1999; Ghose et al. 2002; Gilbert et al. 2001; Goldstone 1998; Karni and Bertini 1997; Li et al. 2004; Yang and Maunsell 2004). A consensus view is that perceptual learning is achieved by multiple processes and that learning to pay selective attention to relevant features of stimuli is one of the most critical processes. This selective attention is highly dependent on becoming familiar with stimulus features and also increasing the ability to discriminate features by altering the efficiency of "functional detectors" (Ghose et al. 2002; Goldstone 1998).

With respect to the neural mechanisms for perceptual learning, two major ideas have been proposed. Specifically, performance in monocular tasks (e.g., orientation discrimination) may improve with practice because the ability of individual neurons ("detectors") to discriminate specific features in visual stimuli (e.g., orientation differences) increases (more efficient detectors) following the training (in V1, Schoups et al. 2001; in V4, Yang and Maunsell 2004). Alternatively, neurons in higher-order visual areas may "learn" to give greater or selective "attention" to V1 or V2 units (low-level detectors) that are more or less sharply tuned to stimulus features (i.e., changes in "pooling" patterns) (Dosher and Lu 1998; Ghose et al. 2002). Obviously, these two ideas are not mutually exclusive.

In the majority of cases where improvement in monocular visual performance was found, learning effects were localized to the trained location (Ball and Sekuler 1987; Kani and Sagi 1991; Schoups et al. 2001), and specific to the training stimuli (Karni and Bertini 1997; Sagi and Tanne 1994). As a result, it was argued that the neural mechanisms underlying these perceptual improvements reside in the earliest stage of cortical processing (i.e., V1). This idea was initially collaborated by electrophysiological studies on orientation discrimination in macaque monkeys (e.g., Schoups et al. 2001). However, more comprehensive investigations on the neural basis of improved orientation discrimination challenged this prevalent idea by demonstrating that the sharpness of orientation tuning of V1 and V2 neurons were largely unchanged by the same training (Ghose et al. 2002). Instead, these investigators found that V4 neurons exhibited relatively modest but significant sharpening of orientation tuning that correlated with the behavioral improvement in orientation discrimination (Yang and Maunsell 2004).

In line with the data on V4, substantial changes in the neuronal responses of inferior-temporal cortex (IT) have been documented after behavioral training for a variety of monocular tasks (DiCarlo and Maunsell 2000; Jagadeesh et al. 2001; Logothetis and Pauls 1995; Sakai and Miyashita 1994; Sigala and Logothetis 2002). Together, an emerging view is that higher-order visual cortical areas exhibit greater plasticity than does V1 in mature monkeys and thus likely to be more involved in perceptual learning (Gilbert 2001; Yang and Maunsell 2004).

What is, then, the neural basis of the observed improvement in stereoacuity after training? In normal monkeys, stereoscopic vision depends on disparity detectors in V1 that are sensitive to absolute binocular disparity (low-level processing) (Cumming and Parker 1999) and stereoneurons that are sensitive to relative disparity in extrastriate visual areas such as V2 (Thomas et al. 2002) and V4 (Neri et al. 2004; Tanabe et al. 2005) (mid-level processing), although MT neurons are apparently insensitive to relative disparities (Uka and DeAngelis 2006). Consistent with the previous results from the experiments on monocular orientation discrimination (Ghose et al. 2002), we found that extensive visual training had marginal effects on the prevalence of binocularly driven neurons or the overall disparity sensitivity in V1

In V2 of our trained prism-reared monkeys, however, the proportion of binocularly driven units was similar to that in normal monkeys, and the average disparity sensitivity was twice as high as that in V2 of the untrained prism-reared monkeys. Also, there were five times as many disparity-tuned V2 units in our trained prism-reared monkeys compared with that in the untrained prism-reared monkeys. More importantly, those V2 units in the trained prism-reared monkeys are capable of discriminating finer disparities than those in the untrained prism-reared monkeys (Fig. 10). Thus the higher disparity sensitivity of V2 neurons in our trained prism-reared monkeys was likely to have contributed to the observed improvement in stereoacuity. However, the disparity sensitivity of V2 neurons in the trained prism-reared monkeys was better by a factor of only 2.0 compared with that in the untrained prism-reared monkeys, whereas stereoacuity improved, on the average, by a factor of 7 or better during the course of training. Hence additional learning processes were likely to have played a large

role, e.g., learning by upstream neurons to more efficiently utilize residual disparity information that was maintained by V1 and, to a greater extent, by V2 neurons.

Why was the disparity sensitivity of V2 neurons in the trained prism-reared monkeys better than that in the untrained monkeys? The behaviorally determined plastic period for binocular vision in monkeys continues beyond 2 yr of age, although the relative degree of such plasticity drops rapidly during the first 6 mo of life and becomes relatively low by 2 yr of age (Harwerth et al. 1986). The present results suggest that the functional connections necessary for disparity tuning in V2 remain sufficiently plastic after 2 yr of age, which allows the residual binocular connections in many V2 neurons to be strengthened or reorganized by repeated use during the course of training and testing.

This interpretation of our results, however, must be taken with considerable caution for a couple of reasons. For example, it is widely thought that V1 neurons tuned to vertically oriented stimuli are most sensitive to horizontal disparities (e.g., DeAngelis et al. 1991; Gonzales and Perez 1998; Ohzawa et al. 1990), and the stimuli used in our stereo tasks were vertically oriented Gabor patches. Therefore those V2 neurons preferring vertical orientations in the trained prism-reared monkeys may be expected to show the largest training effect. Vertically tuned V2 neurons in our trained monkeys indeed exhibited greater disparity sensitivity than those in the untrained monkeys, but this superior neuronal performance was not restricted to those V2 neurons that preferred vertical orientations. However, training with vertical-oriented Gabor stimuli potentially could improve the disparity sensitivity of V2 neurons with a considerable range of preferred orientations if we consider that encoding horizontal disparities may depend on the disparity pooling mechanisms beyond V1 consisting of individual cortical neurons (e.g., V2 neurons) and their subunits that are tuned to a broad range of preferred orientations (Cumming 2002; Morgan and Castet 1997; Patel et al. 2003, 2006; Read and Cumming 2004).

As previously mentioned, we did not use physiological means to monitor eye position during the behavioral training and testing, and in anesthetized and paralyzed preparations, the location of projected reference targets (e.g., the fovea and the optic disks) on the tangent screen could be off by as much as a few degrees. Thus it is not entirely clear whether the receptive fields of all V2 neurons with higher or improved disparity sensitivity of our trained monkeys were localized to the trained zone, although many were located within the trained area, and if not, they were located within 1–2° (Fig. 2*C*). Despite these technical limitations, the majority of our sample V2 units were likely to have been frequently activated by stimuli used for stereo tasks, and thus the better disparity sensitivity of V2 neurons in trained monkeys may have resulted from their experience in stereo tasks. Alternatively, the superior disparity sensitivity of V2 neurons in the trained monkeys may have little to do with the stereo training but simply reflect a consequence of an unknown sampling bias. However, such bias is unlikely considering the sample size and our sampling methods (see also Figs. 2*C* and 13).

Regardless, the present results are consistent with the emerging view that normal functional maturation of the visual brain proceeds in a hierarchical order (Barone et al. 1995; Harwerth et al. 1986; Kiorpes and Bassin 2003; Zhang et al. 2005b) and that plasticity in adults persists longer at higher cortical levels (Yang and Maunsell 2004). However, it is important to keep in mind that long-term neural adaptation is known to emerge in mature V1 of multiple species in response to more drastic changes in the environment, e.g., cortical map reorganization in V1 in response to complete removal of feed forward inputs by small retinal lesions (see Chino et al. 1992, 1995; Collins and Kaas 2004; Gilbert and Wiesel 1992; Kaas et al. 1990; Komatsu 2006; but see Smirnakis et al. 2005).

Clinical implications

Learning effects in prism-reared monkeys were relatively long-lasting (≥3 mo). Unlike in some cases of monocular tasks, what was learned (i.e., discriminate depth purely based on binocular disparity) was readily transferred between binocular tests with very different stimuli (i.e., Gabor vs. random dots). These findings suggest that perceptual learning in stereothresholds have considerable therapeutic values for binocular vision disorders as reported in amblyopic patients (see Levi 2005, 2006 for review).

However, there are also considerable limits to this therapeutic value because our prism-reared monkeys exhibited relatively mild stereodeficiencies at the onset of training. Also as previously mentioned, we had several other prism-reared monkeys with much more severe deficits (e.g., no response to depth cues), and consequently we could not train them for stereoacuity measurements. Moreover, two of three trained prism-reared monkeys (*MK-2* and *MK-4*) could not be trained for depth discrimination with random-dots stimuli. Perceptual learning allows recovery to some limit set by the residual disparity mechanisms that were not so severely affected by early strabismus.

Equally important is that normal alignment was restored at 14 wk of age (roughly equivalent to 14 mo of age in humans) and unrestricted vision was given for >1 year before testing, thus providing more favorable conditions for maintaining (or not loosing altogether) the functional binocular connections in V2. Also our previous study showed that the average disparity sensitivity of V1 neurons in adult prism-reared monkeys was significantly better if prism removal occurred at 8 wk rather than 12 wk of age (Mori et al. 2002, Fig. 6a). Considered together, the present results provide additional evidence in support of the clinical view that alignment at the earliest possible age is important for not only preserving stereopsis but also *improving* stereoscopic vision in stereodeficient subjects (Birch et al. 2004; Kumagami et al. 2000; Mori et al. 2002; Tychsen and Scott 2003; Tychsen et al. 2004; Wong et al. 2003).

ACKNOWLEDGMENTS

We thank H. Bedell for comments on the manuscript and H. Queener and Y. Lin for software development.

Present address of C. Nakatsuka: Dept. of Ophthalmology, Okayama University school of Medicine, Okayama, Japan.

GRANTS

This work was supported by National Institutes of Health Grants EY-08128 to Y. M. Chino, EY-03611 to E. L. Smith, EY-01139 to R. S. Harwerth, and RR-07146.

REFERENCES

Ball K, Sekuler R. Direction-specific improvement in motion discrimination. *Vision Res* 27: 953–965, 1987.

Barone P, Dehay C, Berland M, Bullier J, Kennedy H. Developmental remodeling of primate visual cortical pathways. *Cereb Cortex* 5: 22–38, 1995.

Bennett RG, Westheimer G. The effect of training on visual alignment discrimination and grating resolution. *Percept Psychophys* 49: 541–546, 1991.

Berkson J. A statistically precise and relatively simple method of estimating the bioassay with quantal response, based on the logistic function. *J Am Stat Assoc* 48: 565–599, 1953.

Birch EE, Stager DR, Sr, Berry P, Leffler J. Stereopsis and long-term stability of alignment in esotropia. *J Amer Assoc Ped Ophthal Strab* 8: 146–150, 2004.

Chino YM, Bi H, Zhang B. The postnatal development of the neuronal response properties in primate visual cortex. In: *Primate Vision,* edited by Kaas J, Collins C. Boca Raton, FL: CRC, 2004, p. 81–108.

Chino YM, Kaas JH, Smith EL 3rd, Langston AL, Cheng H. Rapid reorganization of cortical maps in adult cats following restricted deafferentation in retina. *Vision Res* 32: 789–796, 1992.

Chino YM, Smith EL 3rd, Hatta S, Cheng H. Postnatal development of binocular disparity sensitivity in neurons of the primate visual cortex. *J Neurosci* 17: 296–307.

Chino Y, Smith EL 3rd, Kaas J, Sasaki Y, Cheng H. Receptive-field properties of deafferented visual cortical neurons after topographic map reorganization. *J Neurosci* 15: 2417–2433, 1995.

Collins CE, Kaas JH. Plasticity of visual cortex in adult primate. In: *Primate Vision,* edited by Kaas J, Collins C. Boca Raton, FL: CRC, 2004, p. 161–180.

Crawford ML, Harwerth RS, Chino YM, Smith EL 3rd. Binocularity in prism-reared monkeys. *Eye* 10: 161–166, 1996.

Crawford MLJ, von Noorden GK. The effects of short-term experimental strabismus on the visual system of *M. mulatta. Invest Ophthalmol Vis Sci* 18: 396–404, 1979.

Crawford ML, von Noorden GK. Optically induced concomitant strabismus in monkeys. *Invest Ophthalmol Vis Sci* 19: 1105–1109, 1980.

Crist RE, Li W, Gilbert CD. Learning to see: experience and attention in primary visual cortex. *Nat Neurosci* 4: 519–525, 2001.

Cumming BG. An unexpected spacialization for horizontal disparity in primate primary visual cortex. *Nature*, 418: 633–636, 2002.

Cumming BG, Parker AJ. Binocular neurons in V1 of awake monkeys are selective for absolute, not relative, disparity. *J Neurosci* 19: 5602–5618, 1999.

DeAngelis GC, Newsome WT. Perceptual "read-out" of conjoined direction and disparity maps in extrastriate area MT. *P Lo S Biol* 2: E77, 2004.

DeAngelis GC, Ohzawa I, Freeman RD. Depth is encoded in the visual cortexby a specialized receptive field structure. *Nature* 352: 156–159, 1991.

DeAngelis GC, Ohzawa I, Freeman RD. Spatiotemporal organization of simple-cell receptive fields in the cat's striate cortex. Linearity of temporal and spatial summation. *J Neurophysiol* 69: 1118–1135, 1993.

DiCarlo JJ, Maunsell JH. Form representation in monkey inferotemporal cortex is virtually unaltered by free viewing. *Nat Neurosci* 3: 814–821, 2000.

Dosher BA, Lu ZL. Perceptual learning reflects external noise filtering and internal noise reduction through channel reweighting. *Proc Natl Acad Sci USA* 95: 13988–13993, 1998.

Dosher BA, Lu ZL. Mechanisms of perceptual learning. *Vision Res* 39: 3197–3221, 1999.

Fendick M, Westheimer G. Effects of practice and the separation of test targets on foveal and peripheral stereoacuity. *Vision Res* 23: 145–150, 1983.

Fine I, Jacobs RA. Comparing perceptual learning tasks. *J Vis* 2: 190–203, 2002.

Fredenberg P, Harwerth RS. The relative sensitivities of sensory and motor fusion to small binocular disparities. *Vision Res* 41: 1969–1979, 2001.

Ghose GM, Maunsell J. Specialized representations in visual cortex: a role for binding? *Neuron* 24: 79- 85, 111–125, 1999.

Ghose GM, Yang T, Maunsell JH. Physiological correlates of perceptual learning in monkey V1 and V2. *J Neurophysiol* 87: 1867–1888, 2002.

Gilbert C, Wiesel T. Receptive field dynamics in adult primary visual cortex. *Nature* 356: 150–152, 1992.

Gilbert CD, Sigman M, Crist RE. The neural basis of perceptual learning. *Neuron* 31: 681–697, 2001.

Goldstone RL. Perceptual learning. *Annu Rev Psychol* 49: 585–612, 1998.

Gonzalez F, Perez R. Neural mechanisms underlying stereoscopic vision. *Prog Neurobiol* 55: 191–224, 1998.

Harwerth RS, Boltz RL, Smith EL 3rd. Psychophysical evidence for sustained and transient channels in the monkey visual system. *Vision Res* 20: 15–22, 1980.

Harwerth RS, Smith EL 3rd, Duncan GC, Crawford ML, von Noorden GK. Multiple sensitive periods in the development of the primate visual system. *Science* 232: 235–238, 1986.

Harwerth RS, Smith EL 3rd, Siderov J. Behavioral studies of local stereopsis and disparity vergence in monkeys. *Vision Res* 35: 1755–1770, 1995.

Harwerth RS, Smith EL 3rd, Crawford ML, von Noorden GK. Stereopsis and disparity vergence in monkeys with subnormal binocular vision. *Vision Res* 37: 483–493, 1997.

Harwerth RS, Fredenburg PM. Binocular vision with primary microstrabismus. *Invest Ophthalmol Vis Sci* 44: 4293–4306, 2003.

Held R. Two stages in the development of binocular vision and alignment. In: *Early Visual Development: Normal and Abnormal*, edited by Simons K. New York: Oxford University Press, 1993, p. 250–257.

Helveston EM. Visual training: current status in ophthalmology. *Am J Ophthalmol* 140: 903–910, 2005.

Horton JC. Disappointing results from Nova Vision's visual restoration therapy. *Br J Ophthalmol* 89: 1–2, 2005.

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

Jagadeesh B, Chelazzi L, Mishkin M, Desimone R. Learning increases stimulus salience in anterior inferior temporal cortex of the macaque. *J Neurophysiol* 86: 290–303, 2001.

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

Karni A, Bertini G. Learning perceptual skills: behavioral probes into adult cortical plasticity. *Curr Opin Neurobiol* 7: 530–535, 1997.

Karni A, Sagi D. Where practice makes perfectin texture discrimination: evidence for primary visual cortex plasticity. *Proc Natl Acad Sci USA* 88: 4966–4970, 1991.

Kiorpes L, Bassin SA. Development of contour integration in macaque monkeys. *Visual Neurosci* 20: 567–575, 2003.

Kiorpes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visualcortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci* 18: 6411–6424, 1998.

Kiorpes L, Movshon JA. Neural limitations on visual development in primates. In: *The Visual Neurosciences*, edited by Chalupa LM, Werner JS. Cambridge, MA: MIT Press, 2003, p. 159–173.

Kiorpes L, Walton PJ, O'Keefe LP, Movshon JA, Lisberger SG. Effects of early-onset artifical strabismus on pursuit eye movements and on neuronal responses in area MT of macaque monkeys. *J Neurosci* 16: 6537–6553, 1996.

Komatsu H. The neural mechanisms of perceptual filling-in. *Nat Rev Neurosci* 7: 220–231, 2006.

Kumagami T, Zhang B, Smith EL, 3, Chino YM. Effect of onset age of strabismus on the binocular responses of neurons in the monkey visual cortex. *Invest Ophthalmol Vis Sci* 41: 948–954, 2000.

Levi DM. Perceptual learning in adults with amblyopia : a reevaluation of critical periods in human vision. *Dev Psychobiol* 46: 222–232, 2005.

Levi DM. Visual processing in amblyopia: human studies. *Strabismus* 14: 11–19, 2006.

Levi DM, Polat U, Hu YS. Improvement in Vernier acuity in adults with amblyopia. Practice makes better. *Invest Ophthalmol Vis Sci* 38: 1493–1510, 1997.

Li RW, Levi DM, Klein SA. Perceptual learning improves efficiency by re-tuning the decision "template" for position discrimination. *Nat Neurosci* 7: 178–183, 2004.

Logothetis NK, Pauls J. Psychophysical and physiological evidence for viewer- centered object representations in the primate. *Cereb Cortex* 5: 270–288, 1995.

Mallot HA, Arndt PA, Bulthoff HH. A psychophysical and computational analysis of intensity-based stereo. *Biol Cybem* 75: 187–198, 1996.

Mori T, Matsuura K, Zhang B, Smith EL 3rd, Chino YM. Effects of the duration of early strabismus on the binocular responses of neurons in the monkey visual cortex (V1). *Invest Ophthalmol Vis Sci* 43: 1262–1269, 2002.

Morgan MJ, Caster E. The aperture problem in stereopsis. *Vision Res* 37: 2737–2744, 1997.

Movshon JA, Kiorpes L. Biological limits on visual development in primates. In: *Early Visual Development, Normal and Abnormal*, edited by Simons K. New York: Oxford, 1993, p. 296–305.

Neri P, Bridges H, Heeger DJ. Stereoscopic processing of absolute and relative disparity in human visual cortex. *J Neurophysiol* 92: 1880–1891, 2004.

Nover H, Anderson CH, DeAngeli GC. A logarithmic, scale-invariant representation of speed in macaque middle temporal area accounts for speed discrimination performance. *J Neurosci* 25: 1049–1060, 2005.

Ohzawa I, DeAngelis G, Freeman RD. Stereoscopic depth discrimination in the visual cortex: neurons ideally suited as disparity detectors. *Science* 249: 1037–1041, 1990.

Ohzawa I, Freeman RD. The binocular organization of simple cells in the cat's visual cortex. *J Neurophysiol* 56: 221–242, 1986.

O'Toole AJ, Kersten DJ. Learning to see random-dot stereograms. *Perception* 21: 227–243, 1992.

Patel SS, Bedell HE, Sampat P. Pooling signals from vertically and non-vertically orientation-tuned disparity mechanisms in human stereopsis. *Vision Res* 46: 1–13, 2006.

Patel SS, Ukwada MT, Stevenson SB, Sampath, Ogmen H. Seterescopic depth perception from oblique phase disparities. *Vision Res* 43: 2479–2492, 2003.

Poggio GF, Gonzalez F, Krause F. Stereoscopic mechanisms in monkey visual cortex: binocular correlation and disparity selectivity. *J Neurosci* 8: 4531–4550, 1988.

Popple AV, Smallman HS, Findlay JM. The area of spatial integration for initial horizontal disparity vergence. *Vision Res* 38: 319–326, 1998.

Prince SJD, Pointon AD, Cumming BG, Parker AJ. Qunatitative analysis of the responses of V1 neurons to horizontal disparity in dynamic random-dot stereograms. *J Neurophysiol* 87: 191–208, 2002.

Ramachandran VS, Braddick O. Orientation specific learning in stereopsis. *Perception* 2: 371–376, 1973.

Read JCA, Cumming BG. Undewrstanding the cortical specialization for horizontal disparity. *Neural Comput* 16: 1983–2020, 2004.

Sagi D, Tanne D. Perceptual learning: learning to see. *Curr Opin Neurobiol* 4: 195–199, 1994.

Sakai K, Miyashita Y. Neuronal tuning to learned complex forms in vision. *Neuroreport* 5: 829–832, 1994.

Schoups A, Vogels R, Qian N, Orban G. Practising orientation identification improves orientation coding in V1 neurons. *Nature* 412: 549–553, 2001.

Sigala N, Logothetis NK. Visual categorization shapes feature selectivity in the primate temporal cortex. *Nature* 415: 318–320, 2002.

Skottun BC, De Valois RL, Grosof DH, Movshon JA, Albrecht DG, Bonds AB. Classifying simple and complex cells on the basis of response modulation. *Vision Res* 31: 1079–1086, 1991.

Smirnakis SM, Brewer AA, Schmid Mc, Tolias AS, Schuz A, Augath M, Inhoffen W, Wandell BA, Logothetis NK. Lack of long-term cortical reorganization after macaque retinal lesions. *Nature* 435: 300–307, 2005.

Smith EL 3rd, Chino YM, Ni J, Cheng H, Crawford ML, Harwerth RS. Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *J Neurophysiol* 78: 1353–1362, 1997a.

Smith EL 3rd, Chino YM, Ni J, Ridder WH 3rd, Crawford ML. Binocular spatial phase tuning characteristics of neurons in the macaque striate cortex. *J Neurophysiol* 78: 351–365, 1997b.

Smith EL 3rd, Harwerth RS, Crawford ML. Spatial contrast sensitivity deficits in monkeys produced by optically induced anisometropia. *Invest Ophthalmol Vis Sci* 26: 330–342, 1985.

Swindale NV. Orientation tuning curves: empirical description and estimation of parameters. *Biol Cybern* 78: 45–56, 1998.

Tanabe S, Doi T, Umeda K, Fujita I. Dispariy-tuning characteristics of neuronal responseto dynamic random-dot stereograms in macaque visual area 4. *J Neurophysiol* 94: 2683–2699, 2005.

Thomas OM, Cumming BG, Parker AJ. A specialization for relative disparity in V2. *Nat Neurosci* 5: 472–478, 2002.

Tovee MJ, Rolls ET, Ramachandran VS. Rapid visual learning in neurones of the primate temporal visual cortex. *Neuroreport* 7: 2757–2760, 1996.

Tychsen L, Scott C. Maldevelopment of convergence eye movements in macaque monkeys with small- and large-angle infantile esotropia. *Invest Ophthalmol Vis Sci* 44: 3358–3368, 2003.

Tychsen L, Wong AM, Foeller P, Bradley D. Early versus delayed repair of infantile strabismus in macaque monkeys. II. Effects on motion visually evoked responses. *Invest Ophthalmol Vis Sci* 45: 821–827, 2004.

Uka T, DeAngelis GC. Linking neural representation to function in stereoscopic depth perception: roles of the middle temporal area in coarse versus fine disparity discrimination. *J Neurosci* 26: 6791–6802, 2006.

von Noorden GK, Crawford ML. Morphological and physiological changes in the monkey visual system after short-term lid suture. *Invest Ophthalmol Vis Sci* 17: 762–768, 1978.

von Noorden GK, Crawford ML. Failure to preserve cortical binocularity in strabismic monkeys raised in a unidirectional visual environment. *Invest Ophthalmol Vis Sci* 20: 665–670, 1981.

Watanabe I, Hua Bi, Bin Zhang, Eiichi Sakai, Takafumi Mori, Ronald S, Harwerth, Smith EL, 3, Chino YM. Directional bias of neurons in V1 and V2 of strabismic monkeys: temporal–to-nasal asymmetry? *Invest Ophthalmol Vis Sci* 46: 3899–3905, 2005.

Wong AM, Foeller P, Bradley D, Burkhalter A, Tychsen L. Early versus delayed repair of infantile strabismus in macaque monkeys. I. Ocular motor effects. *J AAPOS* 7: 200–209, 2003.

Yang T, Maunsell JHR. The effects of perceptual learning on neuronal responses in monkey visual area V4. *J Neurosci* 24: 1617–1626, 2004.

Yang T, Maunsell JHR. The effect of perceptual learning on neural responses in monkey visual area V4. *J Neurosci* 24: 7964–7977, 2004.

Zhang B, Bi H, Sakai E, Maruko I, Zheng J, Smith EL 3rd, Chino YM. Rapid plasticity of binocular connections in developing monkey visual cortex (V1). *Proc Natl Acad Sci USA* 102: 9026–9031, 2005a.

Zhang B, Zheng J, Watanabe I, Maruko I, Bi H, Smith EL 3rd, Chino Y. Delayed maturation of receptive field center/surround mechanisms in V2. *Proc Natl Acad Sci USA* 102: 5862–5867, 2005b.