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Binocular Deficits Associated With Early Alternating Monocular Defocus. II. Neurophysiological Observations

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Zhang, Bin, Kazuki Matsuura, Takafumi Mori, Janice M. Wensveen, Ronald S. Harwerth, Earl L. Smith III, and Yuzo Chino. Binocular deficits associated with early alternating monocular defocus. II. Neurophysiological observations. *J Neurophysiol* 90: 3012–3023, 2003; 10.1152/jn.00975.2002. Experiencing binocularly conflicting signals early in life dramatically alters the binocular responses of cortical neurons. Because visual cortex is highly plastic during a critical period of development, cortical deficits resulting from early abnormal visual experience often mirror the nature of interocular decorrelation of neural signals from the two eyes. In the preceding paper, we demonstrated that monkeys that experienced early alternating monocular defocus (−1.5, −3.0, or −6.0 D) show deficits in stereopsis that generally reflected the magnitude of imposed monocular defocus. Because these results indicated that alternating monocular defocus affected the higher spatial frequency components of visual scenes more severely, we employed microelectrode recording methods to investigate whether V1 neurons in these lens-reared monkeys exhibited spatial-frequency-dependent alterations in their binocular response properties. We found that a neuron's sensitivity to interocular spatial phase disparity was reduced in the treated monkeys and that this reduction was generally more severe for units tuned to higher spatial frequencies. In the majority of the affected units, the disparity-sensitivity loss was associated with interocular differences in monocular receptive field properties. The present results suggest that the behavioral deficits in stereopsis produced by abnormal visual experience reflect at least in part the constraints imposed by alterations at the earliest stages of binocular cortical processing and support the hypothesis that the local disparity processing mechanisms in primates are spatially tuned and can be independently compromised by early abnormal visual experience.

INTRODUCTION

The neural connections in V1 that support binocular vision in primates are known to be established and functional at or shortly after birth (Chino et al. 1997; Endo et al. 2000; Hatta et al. 1998; Horton and Hocking 1996; LeVay et al. 1980). However, the maintenance and refinement of these neural connections critically depend on normal binocular visual experience during early development. Normal binocular vision requires the appropriate interocular matching of similar monocular inputs (Hubel and Wiesel 1962; Poggio et al. 1988), and discordant binocular signals as a result of strabismus or interocular differences in refractive errors can readily disrupt the postnatal development of the visual cortical connections that support binocular vision (Kiorpes et al. 1987, 1998; Kumagami et al. 2000; Movshon and Kiorpes 1990; Smith et al. 1997a; Wiesel 1982).

The preceding paper reported that monkeys reared with alternating monocular defocus showed spatial-frequency-dependent losses of local stereopsis but relatively normal monocular spatial vision in both eyes (Wensveen et al. 2003). In this study, we investigated the neural factors that may have constrained the binocular visual capacities of these monkeys that experienced early monocular defocus. Specifically, because the presence of normal arrays of disparity-sensitive units in the early stages of cortical processing is a fundamental requirement for fusion and local stereopsis (Marr and Poggio 1979), we asked whether alternating monocular defocus early in life reduces the ability of individual V1 neurons to detect interocular spatial phase disparities of dichoptically presented sine wave gratings. Alternating monocular defocus reduces interocular matching of monocular signals primarily for high spatial-frequency components of visual scene. Therefore our specific goal was to determine whether or not V1 units that are tuned to higher spatial frequencies are more severely affected by early monocular defocus and, if so, whether the observed binocular deficits are associated with interocular differences in the monocular receptive field properties of these units.

METHODS

All experimental and animal care procedures were in compliance with the *Guiding Principles for Research Involving Animals and Human Beings* and were approved by the Institutional Animal Care and Use Committee of the University of Houston.

Subjects

Between 3 wk and 9 mo of age, each of the six experimental monkeys wore a negative-powered, continuous-wear contact lens on alternate eyes on successive days (Wensveen et al. 2003). Although this treatment allowed each eye normal monocular visual experience every other day, the monkeys never experienced clear binocular vision during the rearing period. We recorded from three monkeys that wore −1.5 diopter (D) lenses, one monkey that wore −3.0 D lenses, and two monkeys that wore −6.0 D lenses. Because the primary goal of our neurophysiological experiments was to reveal the cortical alterations that are associated with the observed behavioral deficits, we

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selected these six monkeys based on the severity of their behavioral deficits in local stereopsis rather than the power of defocusing lenses that they wore during the rearing periods (Fig. 1, *A* and *B*). The three monkeys reared with −1.5 D lenses showed mild losses in disparity sensitivity primarily at high spatial frequencies (Mild group). These monkeys did not show any signs of monocular contrast sensitivity loss (see Fig. 2 of Wensveen et al. 2003). Three of the experimental monkeys (2 reared with −6.0 D lenses and 1 with −3.0 D lenses) showed relatively severe losses in disparity sensitivity at all spatial frequencies (severe group). However, all of these six treated monkeys exhibited relative disparity-sensitivity deficits that were greater for high spatial frequencies, even the monkeys in the severe group. Comparison data, much of which has been published in a separate paper (Mori et al. 2002), were obtained from five normal adult monkeys.

Neurophysiology

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 · kg^{-1} · h^{-1}) and artificially ventilated with a mixture of 59% N_2O-39% O_2, and 2% CO_2. Anesthesia was maintained by the continuous infusion of pentobarbital sodium (2–4 mg · kg^{-1} · h^{-1}). Core body temperature was kept at 37.6°C. Cycloplegia was produced by the topical instillation of 1% atropine, 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 and the traditional seven-category classification scheme (Hubel and Wiesel 1962). To quantitatively analyze a neuron's monocular response properties and its binocular signal interactions, each of the cell's monocular receptive fields was projected onto the center of two matched cathode ray tube (CRT) screens (P-31 phosphores; Fig. 2*A*). The CRTs had a space-average luminance of 56 cd/m^2. The visual stimuli were drifting sine-wave gratings. Neuronal responses were sampled at a rate of 100 Hz (10-ms bin widths) by a lab computer and compiled into peristimulus time histograms that were equal in duration to, and synchronized with, the temporal cycle of the sine-wave grating. The amplitudes and phases of the temporal response components in the peristimulus time histograms were determined by Fourier analysis.

DATA ANALYSIS. *Monocular response properties.* 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). For simple cells, the amplitude of the first harmonic component (F1) was used as the response measure, and, for complex cells, the amplitude of the DC component (i.e., the average discharge rate) was used for all analyses. Responses to drifting sinusoidal gratings (TF = 3.12 Hz, contrast = 30%) were measured to determine the orientation (Fig. 2*B*) and spatial-frequency tuning functions for both monocular receptive fields of each neuron (Fig. 2*C*). The optimal orientation and orientation bandwidth for each receptive field were determined by fitting the orientation tuning functions with wrapped Gaussian functions (Swindale 1998)

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

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

To determine each cell's optimal spatial frequency, the spatial

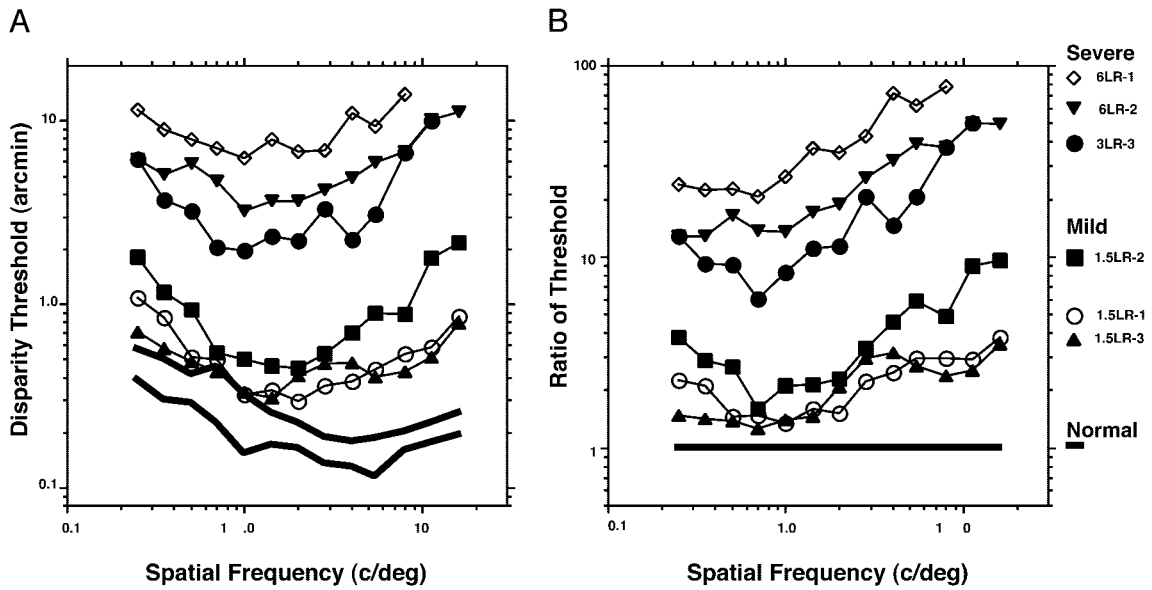

FIG. 1. *A*: disparity threshold as a function of stimulus spatial frequency for 6 monkeys used in this study that were reared with alternating monocular defocus. The identification labels for individual monkeys match those in the preceding paper (Wensveen et al. 2003). Thick lines represent data from 2 normally reared monkeys. *B*: relative reductions in disparity sensitivity as a function of spatial frequency for the treated monkeys. At each spatial frequency, disparity thresholds for the treated monkeys were divided by the average threshold of the 2 normal monkeys.

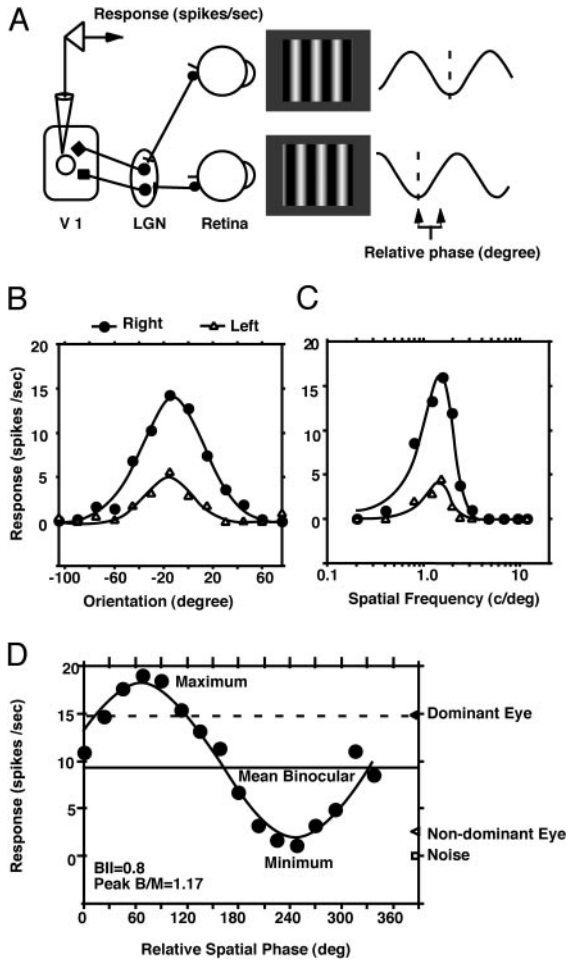

FIG. 2. *A*: stimulation and recording methods. Drifting sine wave gratings (temporal frequency: 3.12 Hz; contrast: 30%) were used as stimuli. *B*: typical orientation response functions of a simple cell in V1 of a normal adult monkey. *C*: spatial frequency response functions of the same cell shown in Fig. 1B. *D*: an example of an interocular spatial phase-tuning function for the same cell in Fig. 1, *B* and *C*. The cell's maintained firing rate is indicated by noise.

frequency response data were fitted with Gaussian functions (DeAngelis et al. 1993)

$$G(m_0) = m_1 \times \exp\{-(m_0 - m_2)^2/(2 \times m_3^2)\}$$

where m_0 = spatial frequency, m_1 = amplitude, m_2 = optimal spatial frequency, and m_3 = SD of the Gaussian function.

Binocular response properties. The ocular dominance of individual units was quantitatively determined by comparing the peak monocular responses for the optimal stimuli presented to each eye (Chino et al. 1997; Smith et al. 1997b). Specifically, the ocular dominance index (ODI) of a neuron was determined with the following formula: ODI = (Ri – noise)/(Rc – noise) + (Ri – noise), where Ri is the peak response amplitude for ipsilateral eye stimulation, Rc is the peak response amplitude for contralateral eye stimulation, and noise is the spontaneous activity. ODI values ranged from 0.0 (contralateral response alone) to 1.0 (ipsilateral response alone) with 0.5 indicating perfect binocular balance.

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 (Ohzawa and Freeman 1986a,b; Smith et al. 1997b) (Fig. 2*D*). For comparison purposes, monocular stimuli for each eye and one zero-contrast control were included in each phase-tuning parameter file. For descriptive and analytical purposes, a single cycle of a sine wave was fit to each neuron's binocular phase tuning function. The amplitude of the fitted sine wave was used to calculate the degree of binocular interaction exhibited by a given neuron and its sensitivity to relative interocular spatial phase disparities [binocular interaction index (BII) = amplitude of the fitted sine wave/the average binocular response amplitude]. To characterize whether binocular signal interactions were excitatory or inhibitory in nature, the peak binocular response amplitude/dominant monocular response amplitude ratios were calculated for each unit. The data from individual units were grouped into the two experimental and normal control groups that were described in the preceding text (i.e., normal, mild, and severe).

RESULTS

We quantitatively analyzed the monocular and binocular response properties of 162 simple cells and 269 complex cells in the six treated and five normal control monkeys. In each monkey, the electrode traversed all cortical layers of the operculum at similar angles to the surface, and we attempted to study every isolated unit in each penetration. The receptive fields of all units were located between 1.0 and 4.0° from the center of the fovea.

Binocular response properties

OCULAR DOMINANCE. Ocular dominance, the relative ability of monocular stimuli presented to the contralateral and ipsilateral eyes to excite a V1 neuron, was quantified by calculating an ODI for each cell (Fig. 3). The overall ODI distributions for the two treated groups were not different from that for normal controls (Fig. 3*A*). However, in the severely affected monkeys, there was a reduction in the proportion of units with either strong (ODI $\leq$0.20 or $\geq$0.80) or mild binocular imbalances (ODI = 0.20 $\sim$ 0.39 or 0.61 $\sim$ 0.80) that were tuned to higher spatial frequencies. Consequently, their mean optimal spatial frequency and spatial resolution were significantly lower than those in mildly affected or normal monkeys (1-way ANOVA, $P < 0.001$). Interestingly, the binocularly balanced units (ODI = 0.40 $\sim$ 0.60) in the monkeys with severe stereodeficits showed a normal range of spatial frequency preferences.

Another way of looking at ocular dominance is to compare the average peak firing rate of all units within each ocular dominance group and determine whether there was a systematic reduction in the responsiveness of cells in our experimental monkeys that was associated with ocular dominance. Figure 3*C* shows that the average peak monocular firing rate for binocularly balanced cells was generally lower than that for ocularly imbalanced units in all subject groups (1-way ANOVA, $P < 0.001$). However, it is important to note that if each ocular dominance group was examined, there were no significant differences in the peak firing rate between either of the treated-monkey groups and normal controls (1-way ANOVA, $P > 0.1$).

SENSITIVITY TO RELATIVE INTEROCULAR SPATIAL PHASE. Contrary to the ocular dominance results, early alternating defocus clearly altered how V1 neurons combine signals from the two eyes and reduced the sensitivity of V1 neurons to relative interocular spatial phase disparities. This loss in disparity sensitivity was generally largest for those units tuned to higher spatial frequencies. Figure 4 illustrates the binocular spatial

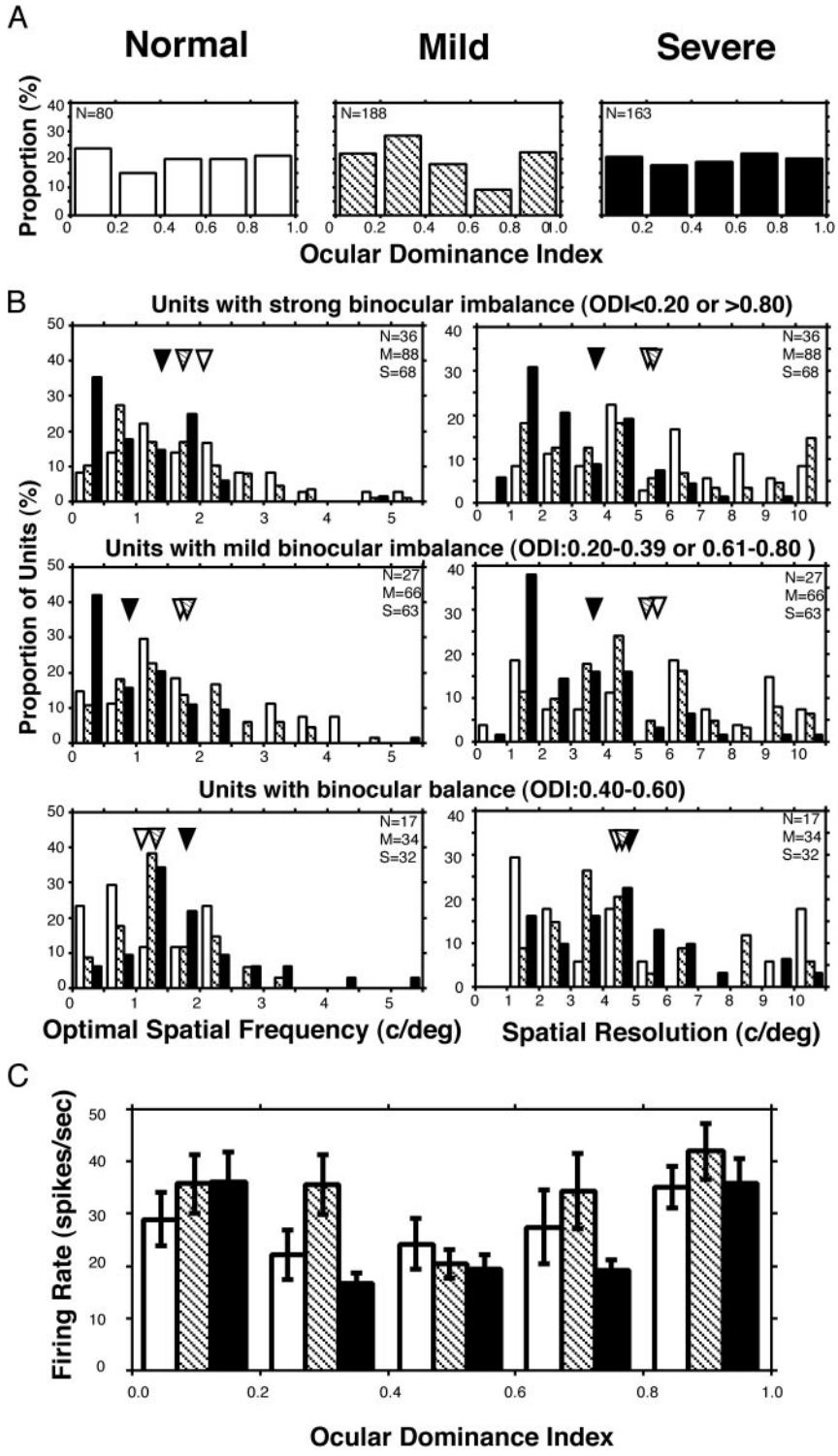

FIG. 3. *A*: frequency histograms of ocular dominance index (ODI) for normal (*left*), mildly affected (*middle*), and severely affected (*right*) monkeys. *B*: histograms showing the optimal spatial frequency (*left*) and spatial resolution (*right*) of V1 units with strong binocular imbalance or monocular cells (*top*), units with mild binocular imbalance (*middle*), and binocularly balanced cells (*bottom*). □, the proportion of units for normal; ▧, mildly affected; and ■, severely affected monkeys. ▼, ▽, and ⩛, mean values for each animal group. *C*: the mean ± SE monocular peak firing rates of V1 units as a function of their relative binocularity (ODI).

phase tuning functions for representative units that had different optimal spatial frequencies (<0.4, 0.4 ~ 1.0, 1.0 ~ 3.0, and ≥3.0 cycles/°) and that best characterized the observed binocular response deficits. These spatial frequency values were chosen based on the behaviorally determined disparity threshold versus spatial-frequency functions (Fig. 1*B*). Specifically, relative thresholds were slightly elevated <0.4 cycles/° in all but one experimental monkeys and were lowest between 0.4 and 1.0 cycles/° in all treated monkeys. The behavioral thresholds were progressively elevated beyond 1.0 cycle/° in all experimental monkeys.

Regardless of their optimal spatial frequency, all four of the units from the normal monkeys showed robust tuning to interocular spatial phase disparities (*top*). For example, the binocular response amplitude of the unit with the optimal spatial frequency ≥3.0 cycles/° peaked at a spatial phase disparity ~120° and decreased systematically until it approached the noise level for the phase value 180° away from the optimum

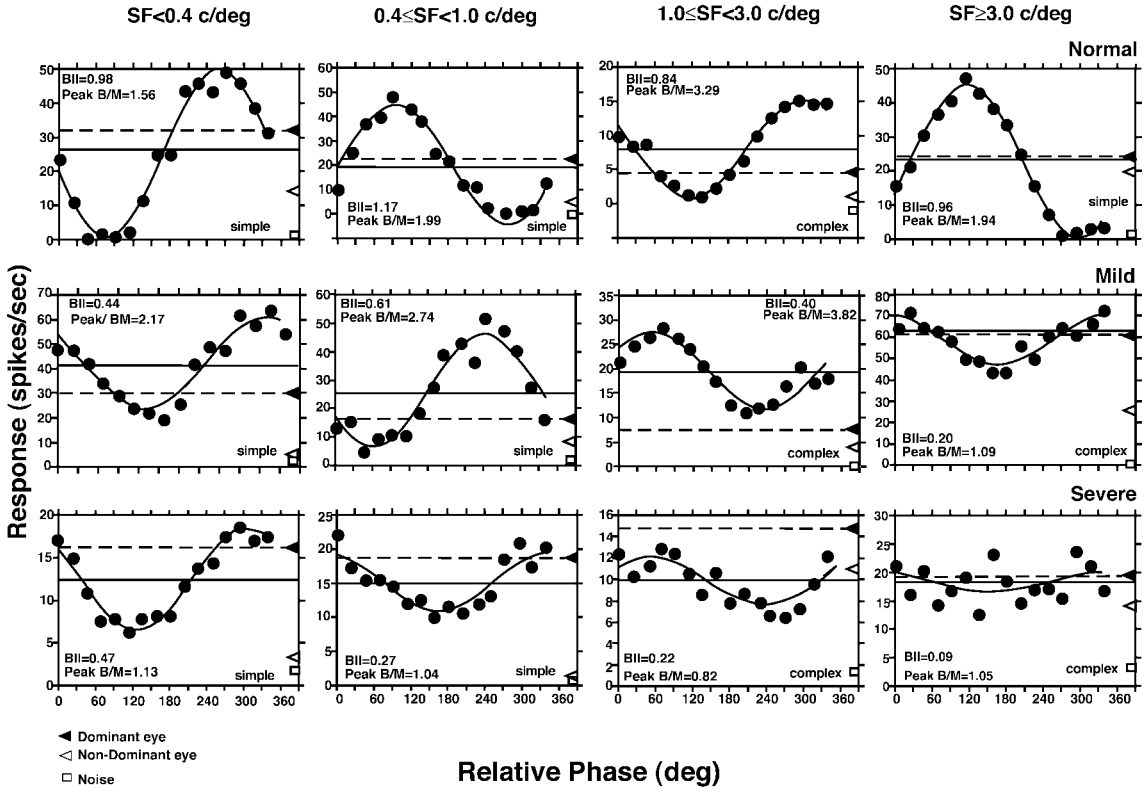

FIG. 4. Spatial phase tuning functions of representative units for the optimal spatial frequencies <0.4 cycles/° (*left*), between 0.4 and 1.0 cycles/° (*middle left*), between 1.0 and 3.0 cycles/° (*middle right*), and >3.0 cycles/° (right). *Top*: normal monkeys. *Middle*: mildly affected monkeys. *Bottom*: severely affected monkeys. Conventions are same as those in Fig. 2*D*.

(i.e., ~300°). The binocular response amplitudes were greater than the dominant monocular response amplitude for the spatial phase disparities between ~30 and 210° (binocular facilitation), while binocular amplitudes were less than the dominant monocular amplitude for the remaining phase disparities (binocular suppression). Similar tuning characteristics were observed for the other three representative units from the normal monkeys.

Units from the treated monkeys showed reductions in their sensitivity to interocular spatial phase disparities that depended on the unit's optimal spatial frequency and the severity of the animal's behavioral deficits. For example, for the monkeys with severe behavioral losses of disparity sensitivity (*bottom*), all the units except for the unit with the lowest optimal spatial frequency exhibited reduced BII values, and these reductions were more dramatic for cells with the higher optimal spatial frequencies (e.g., units at *right*). Also note that the binocular amplitudes were generally lower than the dominant monocular amplitude reflecting a lack of strong binocular facilitatory interactions.

In the mildly affected monkeys, the units having optimal spatial frequencies between 0.4 and 3.0 cycles/° (Fig. 4, *middle left* and *right*) were largely unaffected by early alternating defocus (i.e., these cells were clearly phase tuned and showed clear binocular facilitation). However, consistent with the behavioral deficits (Fig. 2), there was a mild reduction in disparity sensitivity for cells with the lowest optimal spatial frequencies (*left*) and an obvious disparity sensitivity loss for cells with relatively high optimal spatial frequencies (*right*).

Figure 5 illustrates the BII values for all units plotted as a function of their optimal spatial frequency. The representative units shown in Fig. 4 are outlined with squares in this figure. Compared with the data for normal control monkeys, major alterations were found in the treated monkeys. First, in both the mildly and severely affected monkey groups, we found a clear reduction in the proportion of units that had very high BII values and a substantial increase in units with very low sensitivity to phase disparity (e.g., BII < 0.3). For example, only 2/188 units in mildly affected monkeys and 1/163 units in severely affected monkeys, compared with 12/80 units in normal controls, showed BII values that were equal to or >1.0. Consequently, the mean and median BII values of both experimental groups were substantially lower than those for normal controls (*t*-test, mild vs. normal, $t = 4.92$, $P < 0.0005$; severe vs. normal, $t = 6.05$, $P < 0.0005$).

The second significant result was that units from the treated monkeys showed a spatial-frequency-dependent loss of disparity sensitivity. Specifically, for cells with higher optimal spatial frequencies, there was an increase in the proportion of units with low BII values and a corresponding decrease in units with high BII values. These V1 deficits appeared to parallel the behavioral loss of disparity sensitivity in the treated monkeys (i.e., the behaviorally measured disparity thresholds were abnormally elevated beyond 1.0 cycle/° in all experimental monkeys; Fig. 2). For example, in normal controls, 27 of the 56 units (48%) that had optimal spatial frequencies >1.0 cycle/° also had BII values equal to or >0.3. In contrast, there was a clear decrease in the proportion of such units in the animals with mild (34/125, 27%) and severe behavioral deficits (11/84, 13%; χ^2 tests; mild vs. normal, $P < 0.005$; severe vs. normal,

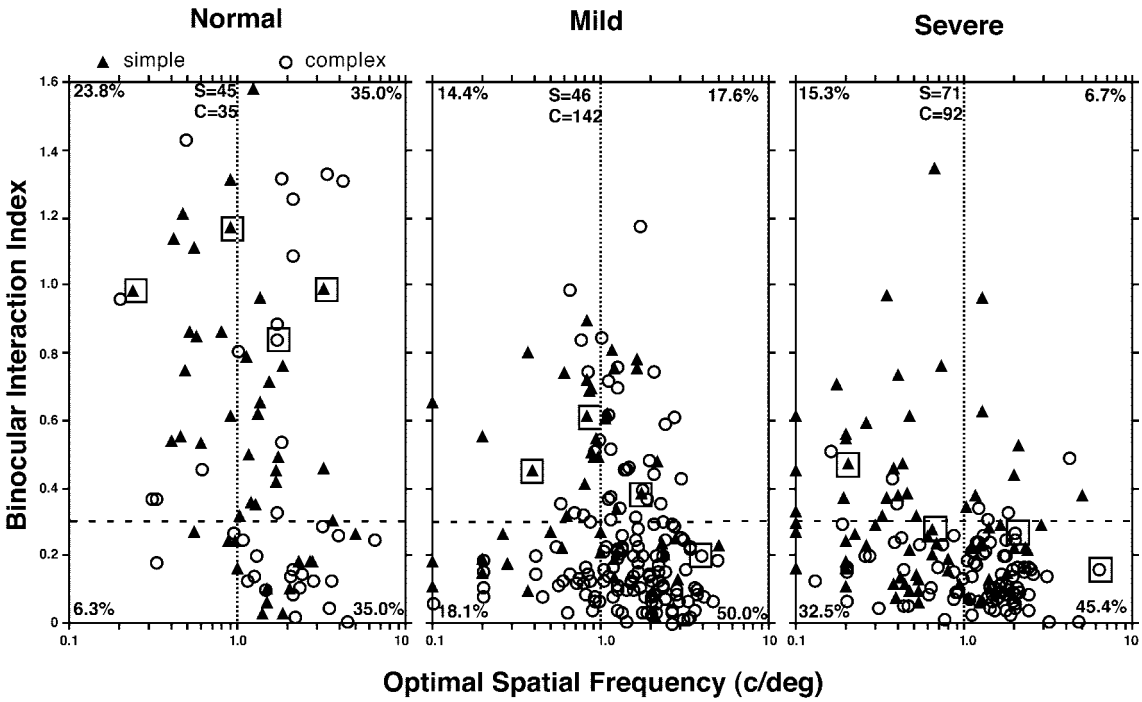

FIG. 5. Binocular interaction index (BII) values as a function of the optimal spatial frequency of individual simple (▲) and complex cells (○) for normal (*left*), mildly affected (*middle*), and severely affected monkeys (*right*). □, the representative units whose tuning functions were illustrated in Fig. 4. Units were divided into high vs. low spatial frequency tuned based on behavioral data illustrated in Fig. 1 (vertical dotted lines), and disparity tuned vs. nondisparity tuned (horizontal dotted lines) based on traditional criteria (Ohzawa and Freeman 1986; Smith et al. 1997b). The proportions of units in each sector are indicated (%).

$P < 0.0005$; mild vs. severe, $P < 0.01$). The mean BII values for units with optimal spatial frequencies >1.0 cycle/° were 0.18 ± 0.02 for the severe group and 0.25 ± 0.02 for the mild group compared with 0.44 ± 0.05 for normal controls. These differences in the mean BII values were also statistically significant (*t*-test: mild vs. normal, $t = 3.45$, $P < 0.0005$; severe vs. normal, $t = 4.63$, $P < 0.0005$; mild vs. severe, $t = 2.56$, $P < 0.01$).

Figure 5 also shows that for the units with optimal spatial frequencies <1.0 cycle/°, the binocular disparity tuning of V1 units paralleled the behavioral data (Fig. 2). Behaviorally measured disparity thresholds were elevated in both treated groups for spatial frequencies <1.0 cycle/° and the average disparity sensitivity of V1 units were significantly reduced in both the mild (mean BII = 0.27 ± 0.04) and severe (0.29 ± 0.02) subject groups compared with that in normal controls (0.73 ± 0.09; *t*-test: mild vs. normal, $t = 4.37$, $P < 0.0005$; severe vs. normal, $t = 5.37$, $P < 0.0005$). The proportion of phase-selective units (i.e., BII values ≥0.3) that had optimal spatial frequencies <1.0 cycle/° in the mild and severe subject groups was 41% (26/63) and 32% (25/79), respectively, compared with 75% (18/24) in normal monkeys. These differences in the proportion between the treated monkeys and normal controls were also significant (χ^2 tests: mild vs. normal $P < 0.005$; severe vs. normal, $P < 0.0001$; mild vs. severe, $P > 0.20$). However, for cells with optimal spatial frequencies <1.0 cycle/°, there were no differences in the mean BII values or in the proportion of phase-selective units between the mild and severe subject groups (*t*-test, mild vs. severe $t = 1.63$, $P > 0.10$).

The third major finding was that in both the mild and severe groups, the reduction in disparity sensitivity was more pronounced for complex cells compared with simple cells, and this difference in the magnitude of the deficit between simple and complex cells was generally greater for the units preferring higher spatial frequencies. Specifically, the mean BII values for simple cells were 0.32 ± 0.02 for the severe group, 0.42 ± 0.04 for the mild group, and 0.52 ± 0.04 for normal monkeys, whereas the corresponding BII values for complex cells were 0.16 ± 0.01, 0.24 ± 0.02, and 0.46 ± 0.06, respectively. The differences between severe and normal groups were significant for both simple and complex cells, although the relative reduction was greater for complex cells ($t = 3.85$, $P < 0.005$ for simple and $t = 5.30$, $P < 0.0005$ for complex cells). The differences between mildly affected and normal animals were significant only for complex cells (*t*-test, $t = 1.76$, $P > 0.05$ for simple and $t = 3.78$, $P = 0.0005$ for complex cells). Finally, the differences between mildly and severely affected monkeys were also significant for both simple and complex cells ($t = 2.20$, $P < 0.05$ for simple and $t = 3.74$, $P < 0.001$ for complex cells).

Monocular response properties

OPTIMAL SPATIAL FREQUENCY AND SPATIAL RESOLUTION. The behavioral experiments described in the preceding paper showed that the spatial contrast sensitivity of our severely affected monkeys was significantly reduced in both eyes at relatively high spatial frequencies (see Fig. 2 of Wensveen et al. 2003 for the spatial contrast sensitivity functions of the severely affected monkeys in this study; *3LR-3*, *6LR-1*, and *6LR-2*). Consistent with this behavioral observation, we found that the average spatial resolution for both simple and complex cells in the severely affected monkeys was substantially lower

than that in the mildly affected (*t*-test: simple, $t = 2.92$. $P < 0.005$; complex, $t = 4.16$, $P < 0.0005$) or normal control monkeys (*t*-test: simple, $t = 4.65$. $P < 0.001$; complex, $t = 3.82$, $P < 0.001$; Fig. 3*B*). However, we did not find any significant interocular differences in mean spatial resolution in either of the treated groups (1-way ANOVA, $P > 1.0$).

INTEROCULAR COMPARISONS OF ORIENTATION AND SPATIAL FREQUENCY TUNING. Because the spatial-frequency-dependent reductions in the BII values in our treated monkeys could be due to interocular differences in the spatial response properties of the monocular receptive fields (Movshon et al. 1987; Smith et al. 1997a,b), we compared the orientation and spatial frequency tuning functions of individual units for the two eyes. The sample sizes for the data analyses in Figs. 6 and 7 were generally smaller than those for the binocular response properties because for many cells in the treated animals the responses for the nondominant eye were either absent, weak, or difficult to quantify. The analyses of these units are addressed separately (see Figs. 8 and 9).

Figure 6*A* compares the preferred orientations for the left and right eyes of individual units. In normal monkeys, most units (89%) exhibited very similar preferred orientations in the two eyes (i.e., preferred orientations within ±20°). Only four units in the normal animals had interocular differences in preferred orientation that exceeded 20° (indicated by the dotted diagonal lines). In contrast, a substantial proportion of units in the mild (31%) and severe subject groups (36%) showed significant interocular differences in preferred orientation that were >20° (χ^2 tests: mild vs. normal $P < 0.02$; severe vs. normal, $P < 0.01$; mild vs. severe, $P > 0.5$).

The interocular differences in the degree of orientation tuning were also substantial in many units from the treated monkeys (Fig. 6*B*). In normal monkeys, only 4 of 41 units (<10%) showed interocular differences in orientation bandwidth that were >30° (- - -). In comparison, substantially larger proportions of units in the mild (28%) and severe subject groups (29%) had bandwidth differences >30°. These differences between the treated monkeys and normal control monkeys were significant (χ^2 tests: mild vs. normal $P < 0.05$; severe vs. normal, $P < 0.05$; mild vs. severe, $P > 0.9$).

Figure 7 shows the interocular differences in octaves in optimal spatial frequency between the dominant and nondominant eyes for each unit as a function of the optimal spatial frequency for the dominant eye. In the treated monkeys, the magnitudes of interocular differences were greater for those units tuned to higher spatial frequencies. Thus there were moderate but significant correlations between the interocular differences in optimal spatial frequency and the dominant eye's optimal spatial frequency in both the mild and severe subject groups (linear regression, correlation coefficient $r = 0.54$ for the mild group, $P < 0.001$, and $r = 0.41$ for the severe group, $P < 0.0005$, compared with $r = 0.08$, $P > 0.25$ for normal monkeys). Interestingly, we found no interocular differences in spatial frequency bandwidth in any of our subjects.

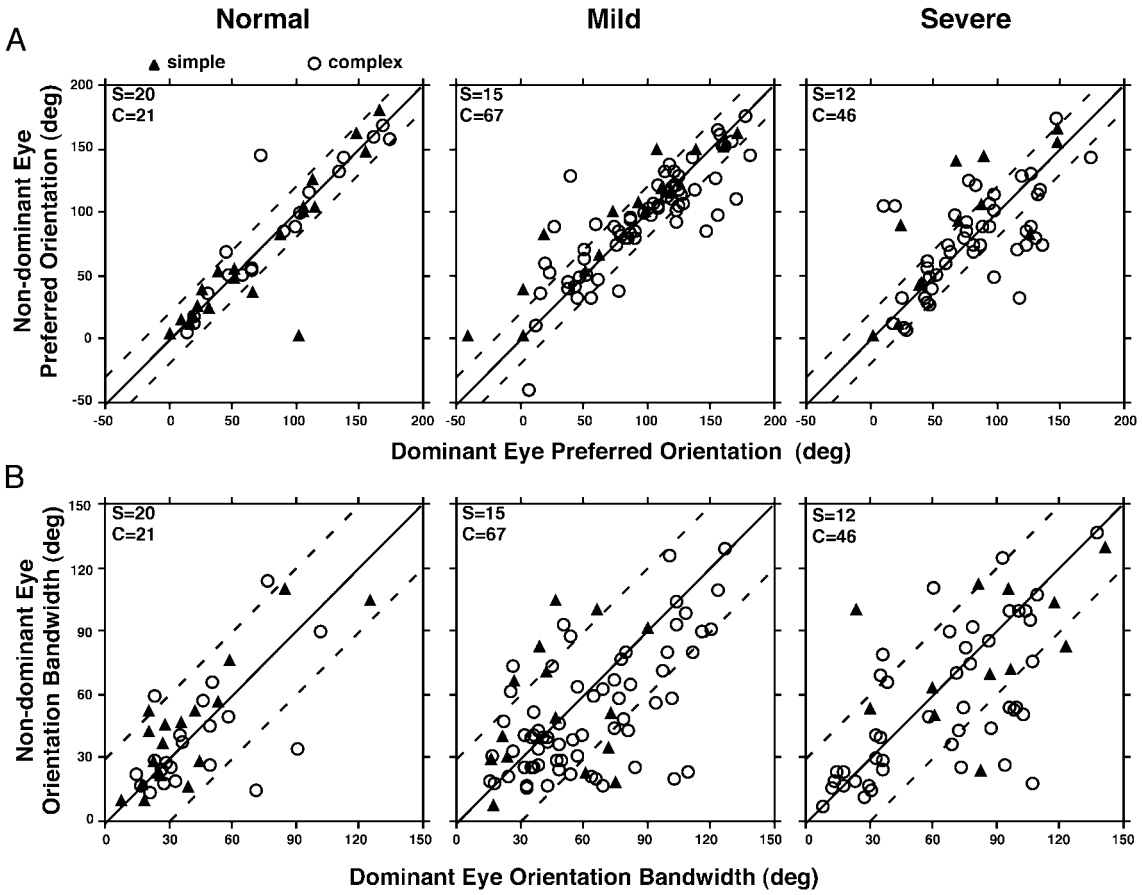

FIG. 6. Interocular comparisons of the preferred orientation (*A*) and the orientation bandwidths (*B*) of simple (▲) and complex cells (○) for normal (*left*), mildly affected (*middle*), and severely affected monkeys (*right*). - - - , the interocular differences of ±20° (*A*) and ±30° (*B*) from the perfect match (—).

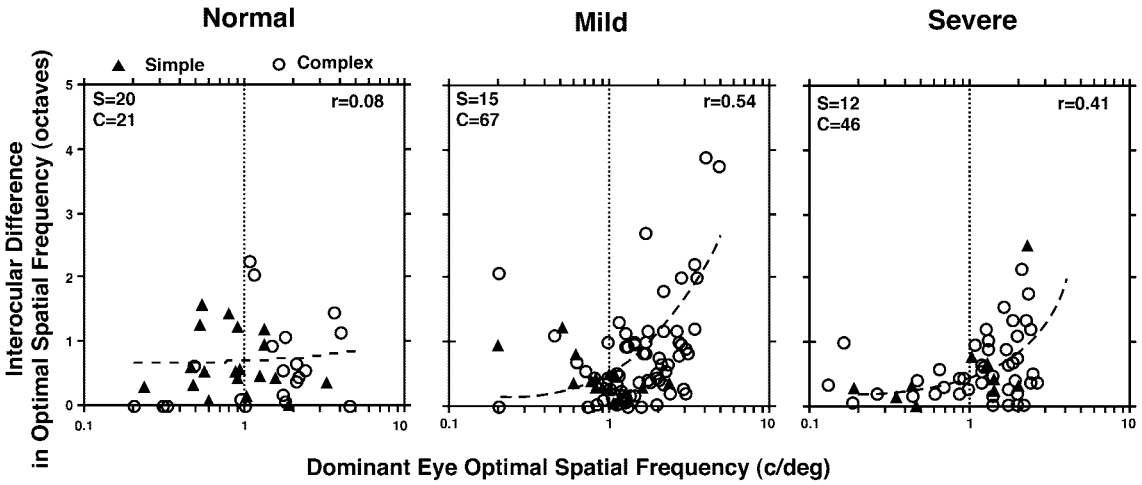

FIG. 7. Plots illustrating the interocular difference in the optimal spatial frequency of the dominant and nondominant eyes for each unit as a function of its dominant eye optimal spatial frequency for simple (▲) and complex cells (○) for normal (*left*), mildly affected (*middle*), and severely affected monkeys (*right*). – – –, linear regression.

MONOCULAR TUNING DIFFERENCES VERSUS DISPARITY SENSITIVITY. We investigated the relationship between the disparity sensitivity of individual units and the interocular differences in their monocular tuning properties. Initially, all units were operationally separated into four types according to the nature of the interocular differences in their monocular response properties (Fig. 8). It is important to keep in mind that these "cell types" were defined according to specific criteria strictly for the pur-

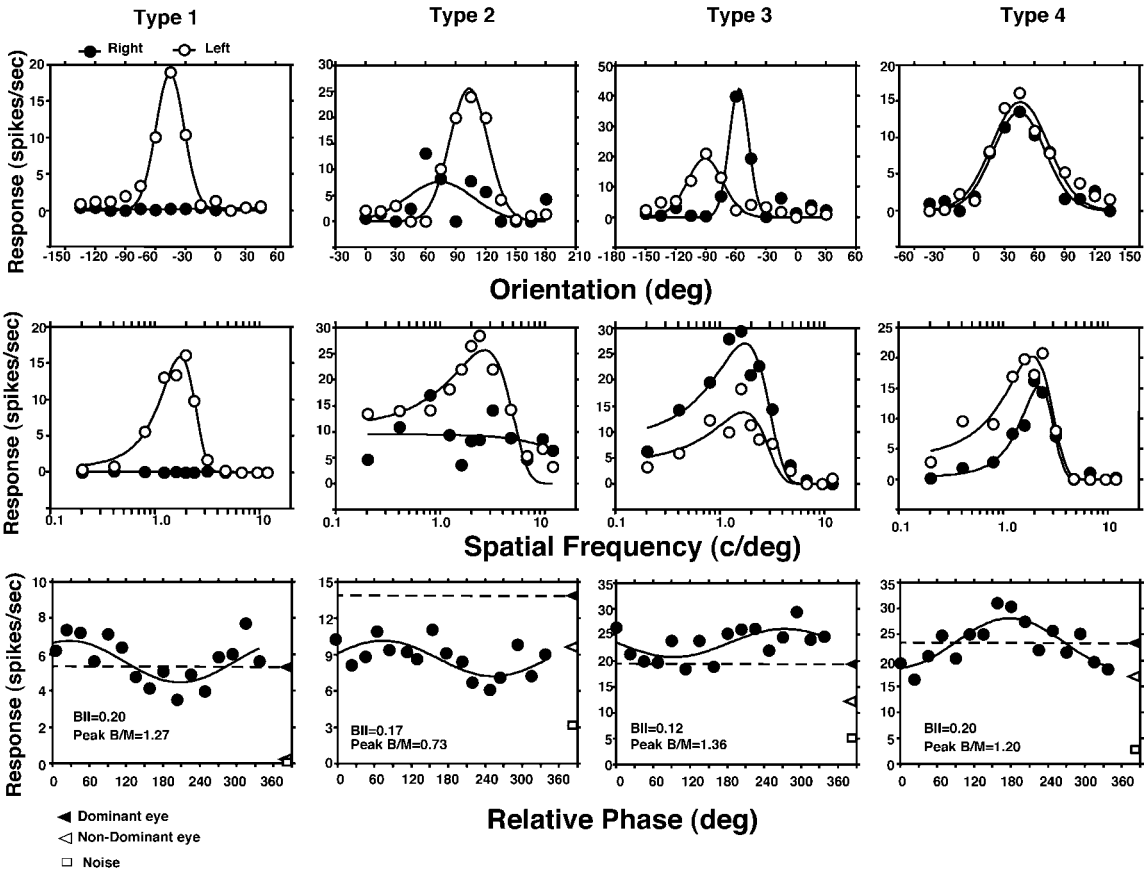

FIG. 8. The orientation tuning functions (*top*), spatial frequency tuning functions (*middle*), and binocular phase tuning functions (*bottom*) of 4 different types of V1 units from the treated monkeys that are separated according to their tuning characteristics. Type 1 cell (*left*) had no quantifiable responses from one eye, i.e., "monocular" cell by ocular dominance test. Type 2 cell (*middle left*) showed very irregular orientation and/or spatial frequency tuning characteristics in the nondominant eye. Type 3 cell (*middle right*) had orderly monocular tuning for stimulus orientation and spatial frequency in both eyes, but their tuning characteristics did not match between the two eyes. Type 4 cell (*right*) showed very regular normal tuning functions and very little or no interocular differences in either orientation or spatial frequency tuning characteristics.

pose of the data analyses described in the following text and do not imply the existence of discrete cell types in monkey V1. Specifically, one cell type had no quantifiable responses from one eye, i.e., a "monocular" cell by classic ocular dominance tests (type 1). Under dichoptic stimulation, type 1 cells also showed little or no binocular interactions (*bottom*). The second type of cell (type 2) showed very irregular orientation and/or spatial frequency tuning in the nondominant eye (e.g., *r* values for the fitted functions that were <0.85). Type 2 units showed no binocular phase tuning but exhibited substantial interocular suppression. The third type of cell (type 3) showed orderly monocular tuning functions for orientation and spatial frequency in both eyes (e.g., *r* values >0.85), but the tuning characteristics were not well matched in the two eyes (e.g., interocular differences in preferred orientations were $>20°$). Type 3 units exhibited a low degree of nonphase specific binocular facilitation. The last cell type (type 4) showed very regular monocular tuning functions and little or no interocular differences in either their orientation or spatial frequency tuning characteristics (e.g., *r* values were >0.85 and preferred orientation differences were $<20°$ and optimal spatial frequency differences were <1.0 octave). However, type 4 cell showed minimal phase tuning and the binocular response amplitudes were very similar to the dominant monocular response amplitude.

In the treated monkeys, the great majority of type 2 and 3 cells showed reduced disparity sensitivity (Fig. 9). For example, in the mildly affected monkeys, 74% of type 2 and 3 cells having their optimal spatial frequencies >1.0 cycle/° were not sensitive to interocular spatial phase disparity (i.e., BII values <0.3), whereas 80% of type 4 cells showed BII values ≥ 0.3. In the severely affected monkeys, the phase tuning deficits in type 2 and 3 cells were more pronounced particularly in complex cells. The units that retained relatively high BII values in the severely affected group (e.g., BII >0.3) were almost always simple cells (10 of 11 type 2 units). Because we infrequently encountered type 2 or 3 cells in normal monkeys, it is difficult to make definitive comparisons between the treated and normal monkeys. However, about one half of type 2 or 3 cells in normal monkeys were phase tuned.

One of the most intriguing results was that in the severely affected monkeys, an abnormally large proportion of cells with interocularly matched response properties (type 4) were not sensitive to interocular spatial phase disparities (84 compared

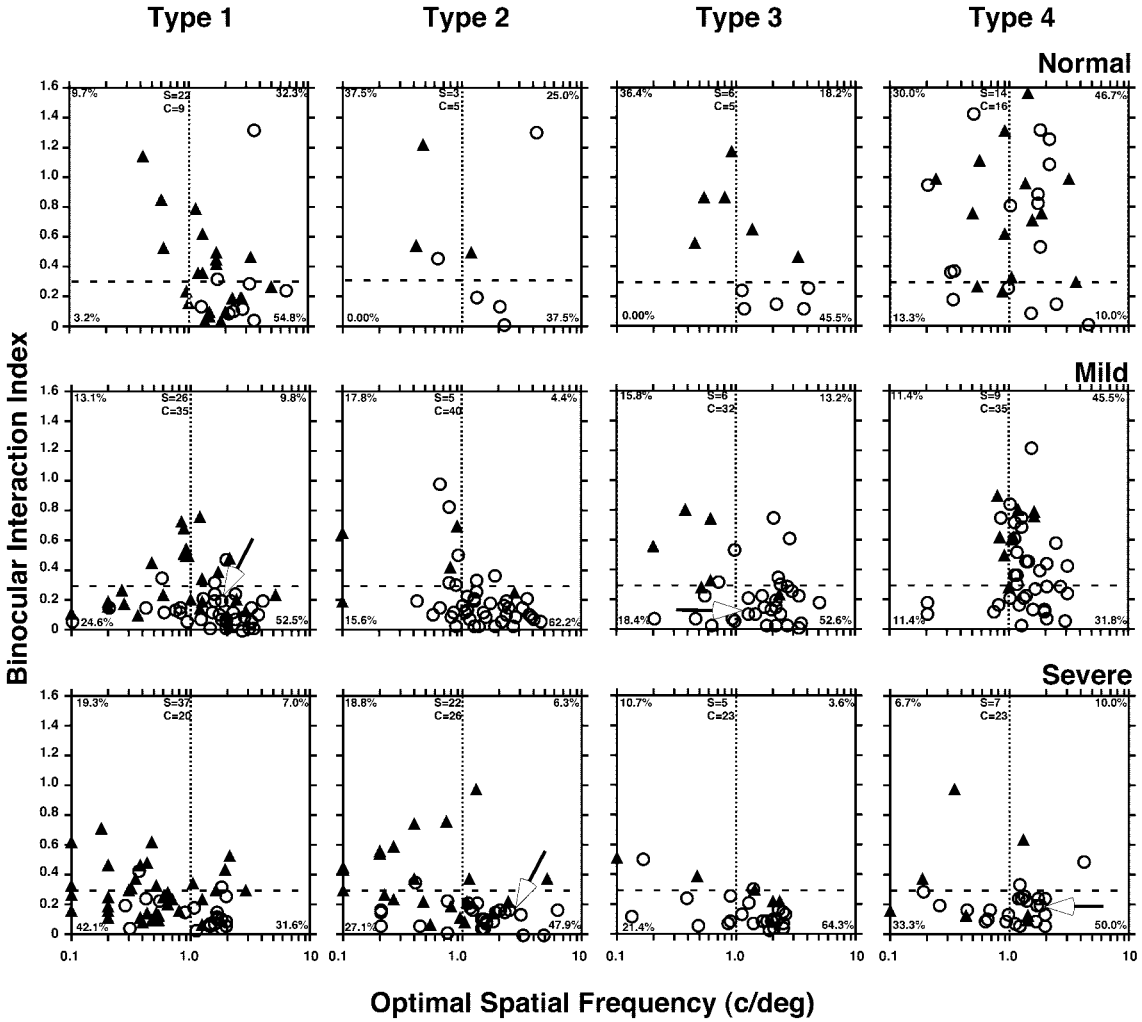

FIG. 9. Plots illustrating the BII as a function of the optimal spatial frequency of type 1 cells (*left*), type 2 cells (*middle left*), type 3 cells (*middle right*), and type 4 cells (*right*) for normal (*top*), mildly affected (*middle*), and severely affected monkeys (*bottom*). ▲, simple cells; ○, indicate complex cells. The units with ↓ correspond to the representative units in Fig. 8 whose tuning functions are illustrated.

with 26% in normal monkeys). However, in the mildly affected monkeys, the disparity sensitivity of cells with interocularly matched monocular response properties was less affected by early alternating defocus than in the severely affected monkeys (e.g., 43% were not disparity tuned; χ^2 tests: mild vs. normal $P > 0.05$; severe vs. normal, $P < 0.005$; mild vs. severe, $P < 0.005$).

DISCUSSION

The main findings of this study were that there was a spatial-frequency dependent reduction in the sensitivity of V1 neurons to interocular spatial phase disparity and that this reduction generally reflected the behavioral deficits manifested by the experimental monkeys (Wensveen et al. 2003).

Spatial-frequency-dependent loss of disparity sensitivity

In both normal cats (Ferster 1981; Maske et al. 1986; Ohzawa and Freeman 1986a,b) and monkeys (Read et al. 2002; Smith et al. 1997b), the disparity tuning functions of V1 neurons can be largely accounted for by a simple addition of signals from the two eyes. Thus it is reasonable to expect that binocular phase tuning functions of V1 units in monkeys would depend on their monocular receptive field properties (Smith et al. 1997a). Constant defocus in one eye (anisometropia) during early development disrupts the excitatory and inhibitory spatial organization of the monocular receptive fields dominated by the affected eye, and the normally precise spatial organization of monocular signals is scrambled (Smith et al. 1997a). Consequently, monocular signals from the eye that experienced chronic early defocus may be weak or distorted, and the resulting interocular imbalance in the monocular inputs typically interferes with the development of normal binocular connections in the visual cortex (Smith et al. 1997a).

In comparison to the constant unilateral defocus used in previous studies, our alternating defocus paradigm allowed our treated monkeys to have undisturbed vision in each eye every other day. Nevertheless, in the great majority of units excluding monocular units (type 1), the reduction in disparity sensitivity appeared to reflect a degradation of monocular response properties and/or an interocular mismatch in the receptive field properties of cells particularly those tuned to higher optimal spatial frequencies. Thus the neural basis of the observed loss in disparity sensitivity does not appear to be qualitatively different from that for the subjects reared with early unilateral defocus. Also it is important to point out that the observed receptive-field degradation may be closely associated with the behaviorally demonstrated reduction in contrast gain reported in the preceding paper (Wensveen et al. 2003).

In adult cats and ferrets, the preferred orientation and optimal spatial frequency of individual cortical units are virtually identical for the two eyes (see reviews by Chapman et al. 1999; Miller et al. 1999) as we found in our normal monkeys. Developmentally, the interocular matching of orientation preference of visual cortical neurons does not appear to require normal visual experience (Chapman et al. 1999; Crair et al. 1997; Godecke and Bonhoeffer 1996). Specifically, binocularly matched orientation maps are found by the end of the second postnatal week in normal kittens (Crair et al. 1997) and reverse-sutured kittens (i.e., animals in which the 2 eyes never had simultaneous normal visual experience) exhibit identical orientation maps in area 18 for the two eyes (Godecheck and Bonhoeffer 1996).

We found that early alternating monocular defocus resulted in an increased prevalence of interocular differences in a neuron's preferred stimulus orientation and, to a smaller degree, optimal spatial frequency. These mismatches occurred with (type 2 cells) or without (type 3 cells) a degradation of the tuning properties in one eye, but unlike in animals reared with constant unilateral defocus, this degradation in monocular tuning properties, if present, could be found for receptive fields in either eye. Our results suggest that stimulating cortical neurons with binocularly robust but interocularly discordant signals reduces the cell's ability to maintain a precise match between monocular receptive-field properties in the two eyes. The previous studies in cats and ferrets basically showed us that the initial development of orientation columns does not require visual experience. The findings in this study support the hypothesis that the maintenance of orientation preferences and orientation preference maps may require normal visual experience (Chapman and Stryker 1993; Crair et al. 1998).

A substantial number of V1 units in our treated monkeys exhibited both interocularly matched monocular response functions (type 4 cells) but low sensitivity to interocular spatial phase disparities (Fig. 9). This cell type was found mostly among complex cells that had relatively high optimal spatial frequencies in the severe subject group. In response to early alternating defocus, how can a complex unit preferring higher spatial frequencies lose it's sensitivity to spatial phase disparity while retaining reasonably good and matched monocular response properties for the receptive fields in each eye? This result may be a consequence of how complex cells, compared with simple cells, combine signals from the two eyes to detect the interocular spatial phase disparity of dichoptic sine wave gratings (Ohzawa and Freeman 1986a,b; Smith et al. 1997a,b).

Specifically, the sensitivity of a complex cell in mature subjects to binocular disparity requires the precise binocular matching of the spatial organization of the functional subunits that exhibit simple-cell like response properties and a preference for the same binocular disparity (i.e., complex cells performing an "interocular cross-correlation of images") (Anzai et al. 1999a,b; Fleet et al. 1996; Ohzawa and Freeman 1986b; Ohzawa et al. 1990, 1997). Consequently, complex cells, while maintaining similar orientation and/or spatial-frequency tuning properties in the two eyes, are particularly vulnerable to experiencing interocularly discordant signals early in life (Smith et al. 1997a). Complex cells tuned to higher spatial frequencies are more readily affected because the apparent mismatch of binocular images due to alternating monocular defocus is likely to occur primarily for the high spatial-frequency components of a visual scene.

We previously reported that interocularly discordant input signals due to early strabismus reduces the neuron's sensitivity to interocular spatial phase disparity (Mori et al. 2002; Smith et al. 1997a; Kumagami et al. 2000). However, contrary to the results in this study, the reduction in strabismic monkeys was generally more severe and was relatively uniform across the spatial frequency domain. These contrasting findings suggest that although an overall high susceptibility of those neurons preferring high spatial frequencies to interocularly discordant signals may not be entirely ruled out as a limiting factor, the

deficits in our lens-reared monkeys are, at least in part, due to retinal blur.

Conclusions

The present findings are consistent with the behavioral data in the preceding paper that demonstrated a spatial-frequency-dependent loss of disparity sensitivity (Wensveen et al. 2003). Both the behavioral and neurophysiological data support the hypothesis that binocular disparities are processed by independent channels that are tuned to different spatial frequencies (Blakemore and Hague 1972; DeAngelis et al. 1995; Felton et al. 1972; Julesz and Miller 1975; Schor et al. 1984; Smallman and McLeod 1994; Yang and Blake 1991) and that the disparity mechanisms that are required for local stereopsis can be altered by early abnormal visual experience in a spatial-frequency-dependent manner.

An increasing number of studies suggest that V1 neurons alone are not sufficient to support stereoscopic vision (Bakin et al. 2000; Cummings and Parker 1997, 1999, 2000; Cumming et al. 1998; DeAngelis et al. 1995) and that the extrastriate visual areas are critically important in generating a three-dimensional percept of the world. However, a fundamental requirement for stereoscopic vision is the presence of normal arrays of disparity-sensitive neurons in the visual cortex (Marr and Poggio 1979). The results in this paper support the importance of a normal proportion of disparity-sensitive neurons in V1 for fusion and local stereopsis because the sensory reductions in disparity sensitivity that were reported in the preceding paper appear in many respects to reflect constraints imposed by anomalies at the earliest stages of cortical processing for binocular signals. Our data are also consistent with the hypothesis that many of the neural factors that limit binocular vision development reside in V1 (Smith et al. 1997a).

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DISCLOSURES

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