Postnatal Development of Disparity Sensitivity in Visual Area 2 (V2) of Macaque Monkeys

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monkeys do not reliably discriminate binocular depth cues until about
8 wk of age. The neural factors that limit the development of fine
depth perception in primates are not known. In adults, binocular depth
perception critically depends on detection of relative binocular dis-
parities and the earliest site in the primate visual brain where a
substantial proportion of neurons are capable of discriminating rela-
tive disparity is visual area 2 (V2). We examined the disparity
sensitivity of V2 neurons during the first 8 wk of life in infant
monkeys and compared the responses of V2 neurons to those of V1
neurons. We found that the magnitude of response modulation in V2
and V1 neurons as a function of interocular spatial phase disparity was
adult-like as early as 2 wk of age. However, the optimal spatial
frequency and binocular response rate of these disparity sensitive
neurons were more than an octave lower in 2- and 4-wk-old infants
than in adults. Consequently, despite the lower variability of neuronal
firing in V2 and V1 neurons of infant monkeys, the ability of these
neurons to discriminate fine disparity differences was significantly
reduced compared with adults. This reduction in disparity sensitivity
of V2 and V1 neurons is likely to limit binocular depth perception
during the first several weeks of a monkey's life.

INTRODUCTION

In macaque monkeys, stereopsis is absent during the first
2–3 postnatal wk and binocular disparities are not reliably
detected until ~6–8 wk of age (O'Dell and Boothe 1997).
Similarly human infants do not show stereopsis until ~4–6 mo
of age (Birch 1993; Birch et al. 1983; Brown et al. 2007). The
neural factors that constrain the early development of binocular
depth perception have not been extensively studied. The ability
of the primary visual cortex (V1) neurons to process local
disparity information is thought to be a fundamental require-
ment for stereopsis and is likely to put some limits on perfor-
mance (Cumming and DeAngelis 2001; Nienborg et al. 2004;
Prince et al. 2000). Previously, we found that an adult-like
proportion of V1 neurons is sensitive to interocular spatial
phase disparity only 6 days after birth (Chino et al. 1997),
indicating that the basic binocular connections in V1 required
for stereoscopic vision are present near birth.

It is becoming increasingly clear, however, that in adult
monkeys, V1 neurons alone could not directly support binoc-
ular depth perception (Cumming and Parker 1999; Read et al.
2002). Instead, extrastriate neurons that are sensitive to relative
binocular disparity are thought to more directly underlie fine

depth perception (Parker 2007; Roe et al. 2007 for reviews).
Thus an emerging view on binocular vision development is that
immaturities in cortical neurons beyond V1, yet to be discov-
ered, are likely to be involved in limiting stereopsis in neonates
(Chino et al. 2004; Kiorpes and Movshon 2004; O'Dell and
Boothe 1997). Consistent with this view, several lines of
evidence suggest that the overall functional maturation of
extrastriate visual areas appears to proceed at a slower pace
relative to V1 (Batardiere et al. 2002; Distler et al. 1996;
Kiorpes and Movshon 2004; Zhang et al. 2005; Zheng et al.
2007).

In adults, V2 is the earliest site beyond V1 where a substan-
tial proportion of neurons are capable of detecting relative
binocular disparity (Thomas et al. 2002). Also, a link between
the disparity sensitivity of cortical neurons in individual mon-
keys and their ability to discriminate depth cues can be estab-
lished by quantifying their choice-related activity in these
neurons while the monkeys perform a discrimination task.
Disparity sensitive V2 neurons, but not V1 neurons, have been
shown to exhibit "choice-related" activity (Nienborg and Cum-
ming 2006). However, it is not known whether V2 neurons of
infant monkeys are sensitive to relative binocular disparity or
whether disparity selective V2 neurons in infants show choice-
related activity. This is simply because, at these early ages, it
is not feasible to conduct microelectrode recording experi-
ments in awake behaving monkeys. In this study therefore we
estimated the ability of V2 and V1 neurons to discriminate fine
disparity differences by analyzing their sensitivity to binocular
phase disparities, their optimal spatial frequencies, and their
response amplitudes and variabilities during the first several
postnatal weeks (Nienborg et al. 2004). We found that, although
the abilities of V2 neurons to combine binocular signals and to
detect interocular spatial phase disparities were qualitatively
adult like as early as 14 days after birth, the median disparity
threshold of V2 neurons was >4 times higher in 2- and
4-wk-old infants than in adults. We also found that relative
changes in the median disparity threshold for V2 and V1
neurons between 2 and 8 wk of age paralleled behavioral
improvement in stereoacuity (O'Dell and Boothe 1997).

METHODS

Microelectrode recording experiments were conducted in anesthe-
tized and paralyzed monkeys (*Macaca mulatta*). 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.

Subjects

Five 2-wk-old, four 4-wk-old, and three 8-wk-old infant monkeys and four adult monkeys served as subjects. The weights of the infant monkeys varied between 480 and 600 g at 2 wk, between 500 and 525 g at 4 wk, and between 550 and 750 g at 8 wk of age. Some results on monocular response properties of cortical neurons from these monkeys have been previously reported (Zhang et al. 2007; Zheng et al. 2007).

Preparation

The surgical preparation and recording procedures have been described in detail elsewhere (Chino et al. 1997; Zhang et al. 2005; Zheng et al. 2007). 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). After all surgical procedures were completed, the animals were paralyzed by an intravenous injection of vercuronium bromide (Norcuron; 0.1 mg/kg/h) 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 a mixture of propofol (4 mg/kg/h) and sufentanyl citrate (0.05 μg/kg/h). Core body temperature was kept at 37.6°C. Cycloplegia was produced by 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. Additional spectacle lenses were also used if necessary.

Recording and visual stimulation

Tungsten-in-glass microelectrodes (FHC, Bowdoinham. ME) were used to record and isolate the activity from individual cortical neurons. A typical penetration in V1 began several millimeters posterior to the lunate sulcus and ~1.5 cm from the midline and ended when the electrode tip entered the white matter. The tangential penetrations in V2 (the angle of deviations from perpendicular was ~20°) were typically started right behind the blood vessels running along the lunate sulcus and also ~1.5 cm from the midline. The penetration ended when the electrode tip exited V2. All receptive fields were located within 5.0° of the center of the projected fovea.

For each isolated neuron, the receptive field for each eye was mapped, and its ocular dominance was initially determined using hand heldstimuli (Hubel and Wiesel 1962). Responses to drifting sine wave gratings (3.1 Hz, 80% contrast) were measured for a broad range of stimulus orientation and spatial frequency from which the preferred orientations, direction of stimulus drift, and spatial frequencies were

determined for each unit. The visual stimuli for these experiments were generated on a monochrome monitor (VRG) with ultra-short persistence (frame rate = 140 Hz; 800 × 600 pixels, screen size = 20 × 15° at 114 cm and mean luminance = 50 cd/m²). Recorded action potentials were digitized at 25 kHz and sampled at a rate of 140 Hz (7.14-ms bin widths) and compiled into peristimulus time histograms (PSTHs) that were equal in duration to, and synchronized with, the temporal cycle of the grating (TDT data acquisition system; TD). 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).

Measurements of orientation, spatial frequency, and disparity tuning functions

ORIENTATION TUNING. The preferred orientation and orientation bandwidth for each receptive field were determined by fitting the orientation tuning functions with wrapped Gaussian functions (Fig. 1A) (Swindale 1998)

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

where θ = orientation, m_1 = the response rate, m_2 = the preferred orientation, and m_3 = the 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 (Fig. 1B) (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 = the response rate, m_2 = the optimal spatial frequency, and m_3 = the SD of the Gaussian function. The spatial resolution for each unit was determined by locating the highest spatial frequency that evoked responses which were significantly higher than the cell's average spontaneous firing rate (i.e., more than ±2 SD).

BINOCULAR INTERACTIONS INDEX. 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 (Fig. 1C). The sensitivity to relative interocular spatial phase disparities was quantified using a binocular interaction index (BII) that was calculated from the sine function fit to
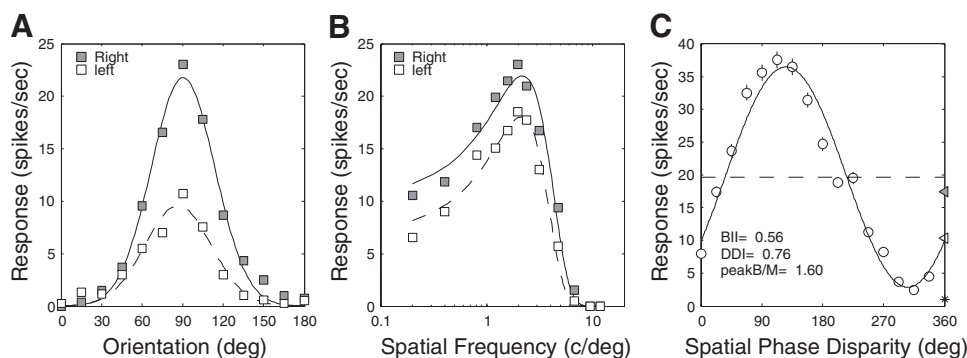

FIG. 1. Methods used to measure the disparity sensitivity of a visual area 2 (V2) neuron. A: determination of the preferred orientation from its orientation tuning function fitted with a wrapped Gaussian function. B: determination of optimal spatial frequency and spatial resolution of the unit after fitting its spatial frequency response function with a Gaussian function. C: disparity tuning function of the V2 neuron. Binocular response amplitude was plotted as a function of interocular spatial phase disparity. BII, binocular interaction index; DDI, disparity discrimination index; peak B/M, peak binocular response amplitude/monocular response amplitude. Note that the calculation of these values was performed after taking the square root of firing rates. Dotted line indicates the mean binocular response amplitude. Filled triangle, dominant monocular amplitude; open triangle, nondominant monocular amplitude; asterisk, spontaneous activity.

the binocular phase tuning data (Ohzawa and Freeman 1986a,b; Prince et al. 2002b; Smith et al. 1997). BII here is defined as

$$BII = (R_{max} - R_{min})/(R_{max} + R_{min})$$

where R_{max} is the largest response on the tuning function, and R_{min} is the smallest response. These values were obtained from fit functions.

DISPARITY DISCRIMINATION INDEX.   To take effects of variability in neuronal firing and firing rates of individual cells into account, we also calculated the disparity discrimination index (DDI) (Prince et al. 2002b; Uka and DeAngelis 2003)

$$DDI = (R_{max} - R_{min})/[(R_{max} - R_{min}) + 2 \times RMS_{error}]$$

where R_{max} is the largest response on the tuning function, and R_{min} is the smallest response. RMS_{error} is the square root of the residual variance around the mean across the entire tuning function.

To characterize whether binocular signal interactions were facilitatory or suppressive in nature, the peak binocular response/dominant monocular response 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. For the calculation of BII and DDI, the Peak B/M ratio was performed on the square root of firing rate (Prince et al. 2002b; Uka and DeAngelis 2003).

HISTOLOGY.   At the end of each penetration, small electrolytic lesions (5 μA, 5 s, electrode negative) were made at three points along the track for later reconstruction. Experiments were terminated by administering an overdose of pentobarbital sodium (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. The laminar distribution of individual units was estimated from the recording depths and the histologically identified electrode tracks. Our sampling frequency was generally uniform and similar in all subject groups.

RESULTS

We recorded responses from a total of 788 neurons (158 simple and 361 complex in V2 and 78 simple and 191 complex in V1) and quantitatively analyzed the binocular and monocular response properties of 104 V2 and 78 V1 neurons in 2-wk-old infants, 84 V2 and 48 V1 neurons in 4-wk-old infants, 138 V2 and 63 V1 neurons in 8-wk-old infants, and 193 V2 and 80 V1 neurons in adult monkeys. Because we did not find major differences between simple and complex cells or laminar differences in any of the response measures that we studied, we combined data in these cell types from all cortical layers for the subsequent analyses. Statistical significance was tested for group differences with Kruskal-Wallis test for median values, unless specified otherwise.

Binocular signal combination in V2 is adult-like at 2 wk of age

One of the most efficient and highly sensitive ways to assess the strength and characteristics of binocular signal combination in a visual cortical neuron is to measure its BII (Chino et al. 1997; Ohzawa and Freeman 1986a,b; Prince et al. 2002b; Smith et al. 1997). As we have previously reported for V1 neurons (Chino et al. 1997) and as can be seen in Fig. 2, the response modulation of the representative V2 neuron from a 2-wk-old infant as a function of interocular spatial phase disparity was as robust as those in older infants and adults; and the calculated BII values were also comparable at all ages. However, it is important to note that the mean binocular response rates (dotted lines) for these representative units from infants were substantially lower than those from adults.

The population analysis of disparity tuning functions showed that, in V2, the median BII values were 0.18, 0.16, and 0.19 in 2-, 4- and 8-wk-old infants, respectively, and were not statistically different from the median BII value in adults (0.18) ($P > 0.01$; Fig. 3, *left column*). The median BII values in V1 also did not change over age ($P > 0.01$; Fig. 3, *right column*). Moreover, the proportion of disparity-sensitive units, defined as neurons that exhibited a statistically significant response modulation as a function of phase disparity (Prince et al. 2002b), was similar for all the infant groups and adults ($P > 0.01$, χ^2 test; Fig. 3, filled bars). Note that the frequency distribution of the BII in V1 of our adult monkeys was similar to that previously reported for awake behaving adult monkeys (Prince et al. 2002b).

The BII of a give neuron does not take the variability of firing into account and tends to be negatively correlated with
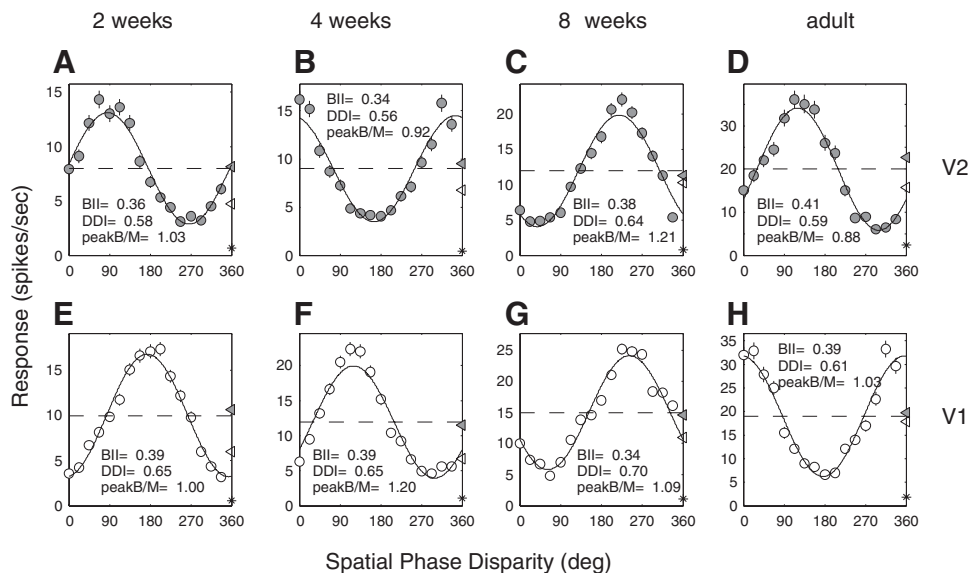

FIG. 2.   Examples of binocular spatial phase tuning functions of V2 (*A–D*) and V1 neurons (*E* and *F*) of 2-, 4-, 8-wk-old infants and adults. Plotting conventions are same as in Fig. 1*C*. Note that the disparity tuning function of the V2 neuron at 2 wk of age was very similar to that for the adult unit except its low mean binocular response rate.
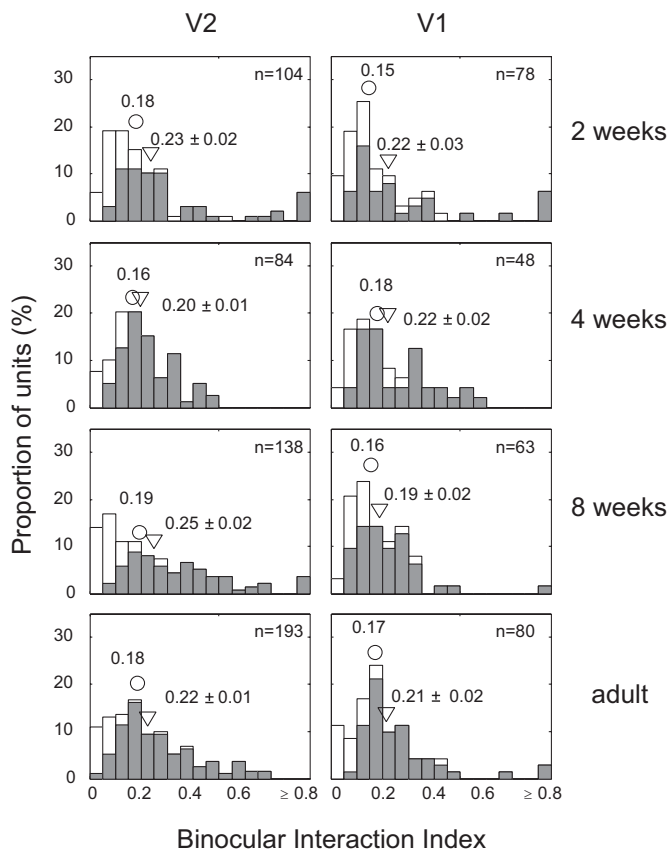
FIG. 3. Population data for disparity tuning functions in infants and adults. Open histograms, the distribution of BII values for all V2 and V1 neurons in infants and adults; filled histograms, the distribution of V2 and V1 neurons that had statistically significant disparity tuning, i.e., disparity sensitive units (1-way ANOVA, $P < 0.05$, Prince et al. 2002a). Mean ($\pm$SE) and median values are indicated by triangles and circles, respectively. Note that the calculation of the BII values was performed after taking the square root of firing rates.

the mean firing rate (Prince et al. 2002b). Because V2 and V1 neurons in our infant macaques showed much lower firing rates than in adults (Chino et al. 1997; see also Fig. 6), BII values of 2- and 4-wk-old infants might have been artificially elevated and might have not reflected the credible estimate of neuron's sensitivity to binocular disparity at these early ages. To examine this possibility, we calculated the DDI (Prince et al. 2002b; Uka and DeAngelis 2003). The frequency distribution of DDI values in our adult V1 (Fig. 4) was very similar to that in awake adult monkeys (Prince et al. 2002b). More importantly, the distribution and the median DDI values in V2 and V1 neurons of all infant groups were not significantly different from those in adults ($P > 0.01$; Fig. 4).

The nature of binocular signal interactions (i.e., excitatory vs. inhibitory) in V2 and V1 neurons were examined by taking the ratio of the peak binocular response over the dominant monocular response, and the resulting values were expressed in terms of relative strengths (db), i.e., 10 log Peak B/M. Although the median B/M value (0.45 db) at 2 wk of age was considerably lower than that in adults (0.76 db), the difference did not reach statistical significance ($P > 0.01$; Fig. 5). A similar difference was found for V1 neurons at 2 wk of age (0.33 db in infants vs. 0.56 db in adults; $P > 0.01$). The median ratios for 4- and 8-wk-old-infants (0.83 and 0.52 db in V2, 0.69

and 0.39db in V1) were not different from the corresponding ratios in adults ($P > 0.01$). The overall distribution of Peak B/M ratios for V1 neurons in our anesthetized and paralyzed adults were similar to the distribution of binocular/monocular response ratios of V1 neurons found in awake behaving adult monkeys (Prince et al. 2002a).

Firing rates, response variability, and optimal spatial frequency are low in infants

The ability of individual V1 neurons to discriminate fine disparity differences depends on a cell's optimal spatial frequency, discharge rate, and response variability (Nakatsuka et al. 2007; Nienborg et al. 2004; Prince et al. 2002b; also see Nover et al. 2005; Yang and Maunsell 2004 for a similar analysis). Thus we examined the maturation of these response properties. In V2, although the binocular/monocular ratios were adult like at 2 and 4 wk of age, the median binocular response rate at 2 wk of age (8.61 spikes/s) was less than one half of the adult value (19.93 spikes/s) and was significantly lower at 4 (8.33 spikes/s) and 8 wk of age (13.41 spikes/s) than in adults ($P < 0.01$; Fig. 6A). Similarly the mean binocular response rate of V1 neurons in all infant groups was significantly lower than the response rate in adults ($P < 0.01$).

As anticipated from these low firing rates in infants, however, the response variances of V1 and V2 neurons were also
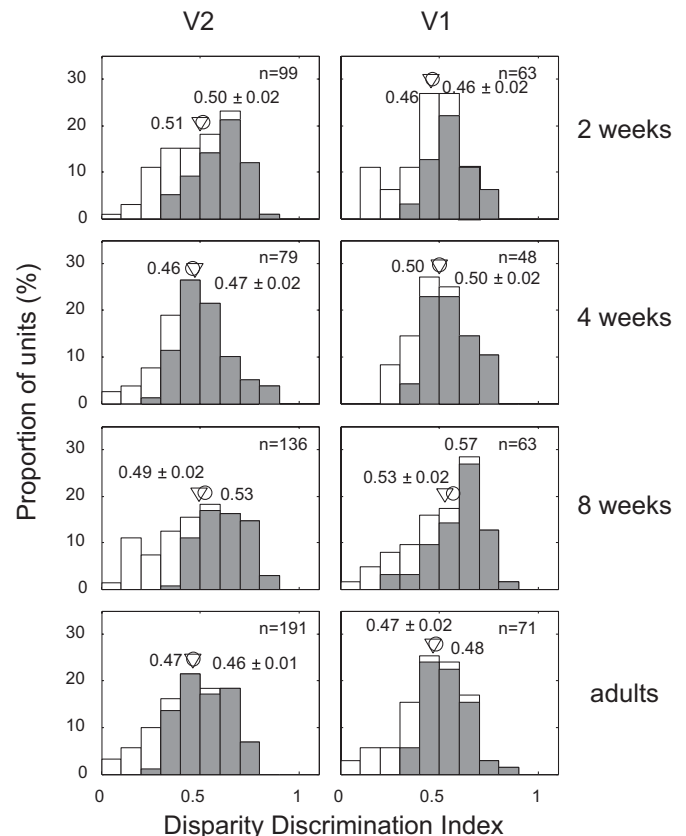

FIG. 4. Developmental changes in disparity tuning functions. Open histograms, the distribution of DDI values for V2 and V1 neurons in infants and adults; filled histograms, the distribution of DDI values for V2 and V1 neurons that had statistically significant disparity tuning (1-way ANOVA, $P < 0.05$, Prince et al. 2002a). Mean ($\pm$SE) and median values are indicated by triangles and circles, respectively. Note that the calculation of the DDI values was performed after taking the square root of firing rates.
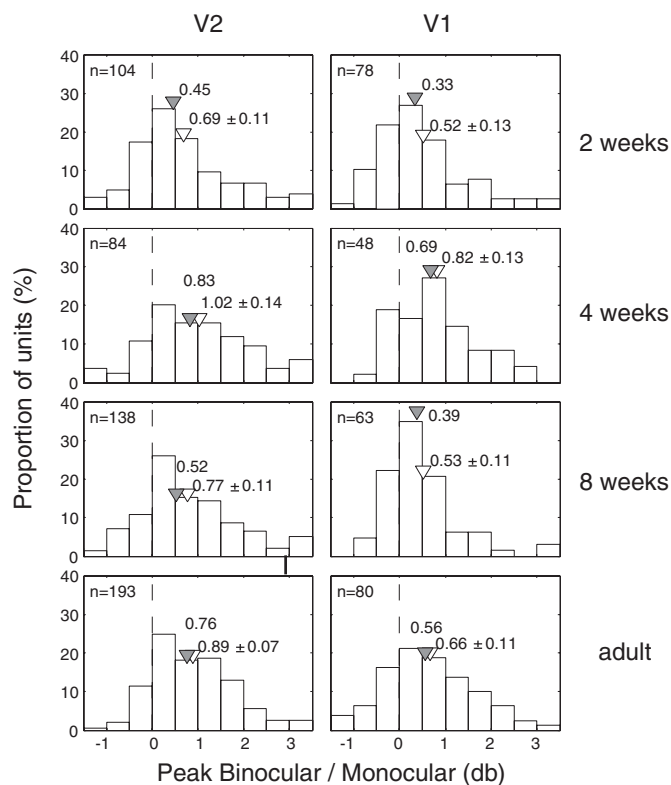
FIG. 5. Frequency histograms showing the distribution of peak binocular response over monocular response ratios of V2 and V1 neurons in infants and adults. Mean (±SE) and median values are indicated by triangles. The dotted lines indicate the border between excitatory (>0.0 db) and inhibitory (<0.0 db) binocular interactions. Note that the calculation of the peak binocular/monocular ratios was performed after taking the square root of firing rates.

much lower in infants than in adults. The median variance-to-mean ratio of V2 neurons at 2 wk of age (α^2/μ, calculated for the duration of 322 ms for 20 epochs at each phase disparity) was only one half (1.10) of the adult value (2.20; $P < 0.01$; Fig. 6B). Similarly, the median variance-to-mean ratios of V2 neurons at 4 (1.27) and 8 wk of age (1.13) were also significantly lower than that in adults ($P < 0.01$). The median ratio for V1 neurons was 1.04 at 2 wk, 1.06 at 4 wk, and 0.94 at 8 wk of age, all of which were significantly lower than that in adults (1.59; $P < 0.01$). Thus the firing pattern of V1 and V2 neurons in our infants was less noisy than in adults. It is important to note that the differences in variance-to-mean ratios between V2 and V1 were statistically significant at 8 wk of age ($P < 0.01$) and for adults ($P < 0.01$), whereas there were no significant differences at 2 and 4 wk of age ($P > 0.01$).

One of the most important variables affecting the disparity sensitivity of individual cortical neurons is its spatial frequency tuning characteristics. The optimal spatial frequency was determined for each neuron from its fitted spatial frequency tuning function (Fig. 1B). In V2, the median optimal spatial frequency at 2 (0.70 c/deg) and 4 (0.91 c/deg) and 8 wk of age (1.37 c/deg) were significantly lower than that in adults (2.04 c/deg, $P < 0.01$; Fig. 7A). Similar differences were found between infants and adults (2.04 c/deg) for V1 in 2- (1.0 c/deg, $P < 0.01$) and 4-wk-old infants (1.02 c/deg, $P < 0.01$) but not in 8-week-old infants (1.60 c/deg, $P > 0.01$).

The median spatial resolution of V2 neurons at 2 wk of age (3.49 c/deg), determined by locating the highest spatial fre-

quency that evoked responses significantly higher than the average spontaneous firing of the unit (more than ±2 SD), was less than one half the adult median value (8.19 c/deg; $P < 0.01$; Fig. 7B). The median spatial resolutions at 4 and 8 wk of age (3.65 and 5.1 c/ded, respectively) were also significantly lower compared with adults ($P < 0.01$). In contrast, 2- (4.00 c/deg) and 4-wk-old infants (4.41 c/deg), but not 8-wk-old infants (5.50 c/deg), had lower median spatial resolutions for V1 neurons compared with adults (7.50 c/deg; $P < 0.01$). Our data on the developmental changes in the average spatial resolution of V1 neurons are similar to those previously reported (Kiorpes and Movshon et al. 2004). Although we did not directly measure the contrast threshold of V2 or V1 neurons for high spatial frequency gratings, the lower spatial resolutions found for infants using gratings of 80% contrast suggest that the contrast sensitivity of these neurons for higher spatial frequency is likely to be substantially lower than that in adults.

Normalized optimal disparity sensitivity is low at 2 and 4 wk of age

Based on the response modulation as a function of spatial phase disparity, optimal spatial frequency, and response variance of each neuron, we estimated its ability to discriminate small disparity differences, defined here as the neuronal dis-
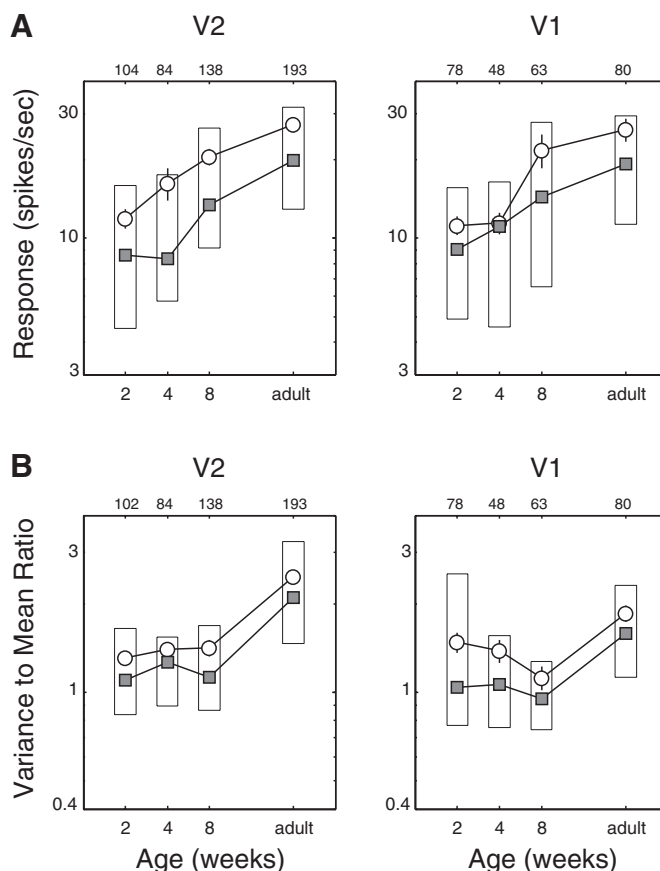

FIG. 6. Developmental changes in neuronal firing patterns of V2 and V1 neurons. A: the average (±SE) (○) and median (■) mean binocular response rate of V2 and V1 neurons in infants and adults. Rectangular boxes indicate the range of quartile values. B: the distribution of response variance-to-mean ratios of V2 and V1 neurons in infants and adults. Plotting conventions are same as in A. Note the lower firing rates and variance-to-mean ratios of infant's units.
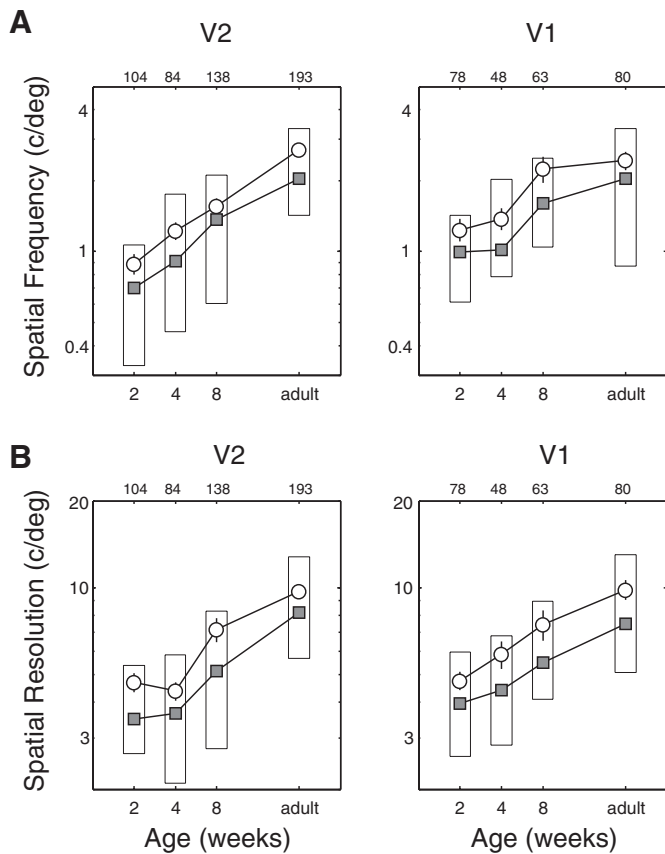
A

V2 — 104 84 138 193

V1 — 78 48 63 80

Spatial Frequency (c/deg)

B

V2 — 104 84 138 193

V1 — 78 48 63 80

Spatial Resolution (c/deg)

Age (weeks)

FIG. 7. Developmental changes in spatial frequency tuning. The average (±SE) (○) and median (■) optimal spatial frequency of V2 and V1 neurons in infants and adults. Rectangular boxes indicate the range of quartile values. *B*: the distribution of spatial resolution of V2 and V1 neurons in infants and adults. Plotting conventions are same as in *A*. Note the lower optimal spatial frequency and resolution of infant's units.

parity threshold (Fig. 8). The effects of the optimal spatial frequency (2.0 c/deg) on disparity sensitivity for a representative disparity-tuned V2 neuron are shown in Fig. 8*A*. The changes in the cell's absolute firing rate per unit of angular disparity (right ordinate, spikes/s/arc min) were calculated for the phase disparity tuning function. Note that the highest sensitivity is found at the steepest slope of the disparity tuning function (indicated by an arrow and the thick line at spatial phase disparities around 180°). The optimal disparity sensitivity for this unit therefore was 2.99 spikes/s/arc min.

In adults, the ability to detect small disparity differences is also influenced by the variability of neuronal firing (Nakatsuka

et al. 2007; Nover et al. 2005; Yang and Maunsell 2004). To take response variability into account, the relationship between the mean firing rate and response variance was initially determined by plotting a cell's mean response rate as a function of its response variance. Figure 8*B* shows data for a representative V2 neuron. From the best linear fit for the data points, the response variance of this unit was estimated for the response rate that corresponded to the steepest portion of its phase disparity function (the dotted line). The optimal disparity sensitivity for this unit (2.99 spikes/s/arc min) was normalized with the square root of response variance. The disparity threshold for this V2 neuron was calculated by taking the inverse of the ratio of cell's firing rate per unit of angular disparity/$\sqrt{}$response variance (2.13 arc min).

The population analysis for the optimal disparity sensitivities shows the effects of the low optimal spatial frequencies and the low firing rates of V2 and V1 neurons in infants (Fig. 9). Specifically, the median optimal disparity sensitivity of V2 neurons at 2 wk of age (0.14 spikes/s/arc min) was nearly 10 times lower than that in adults (1.21 spikes/s/arc min; $P < 0.01$). At 4 and 8 wk of age, the median disparity sensitivity was still far lower than in adults ($P < 0.01$). In V1, the optimal disparity sensitivity at 2 and 4 wk of age was significantly lower than in adults ($P < 0.01$), but at 8 wk of age, the median optimal disparity sensitivity was indistinguishable from adults ($P > 0.01$), primarily because optimal spatial frequencies of V1 neurons had become adult-like (Fig. 7*A*).

The median disparity threshold of V2 neurons in 2-wk-old infants was >4 times higher than that in adults. In addition, for all of the other infant groups, the median disparity threshold of V2 neurons was significantly higher than that in adults ($P < 0.01$; Fig. 10). The median threshold values for V1 units were also significantly higher than in adults but only for 2- and 4-wk-old infants ($P < 0.001$). Interestingly, the median threshold of V2 neurons in 2-wk-old infants was significantly higher than that in V1 neurons ($P < 0.01$). It is worthwhile to note that the adult median disparity threshold values (4.51 arc min in V2 and 5.26 arc min in V1) were very similar to the median neurometric disparity threshold value of V1 neurons in awake behaving monkeys (estimated from Fig. 13 of Prince et al. 2000), which was on average ≥4 times higher than their psychometric disparity thresholds.

To obtain a clearer picture of which limiting factor may have relatively larger impact on the neuronal disparity threshold, we compared the relative developmental change in neuronal disparity acuity (1/disparity threshold) with improvement in the BII/DDI, variance-to-mean ratio, spatial frequency (optimal

A

Optimal SF=2 c/deg
Optimal Disparity Sensitivity = 2.99

Response (spikes/sec) / Disparity Sensitivity (spikes/sec/arc min)

Spatial Phase Disparity (deg)

B

Neuronal Threshold = 2.13 arc min

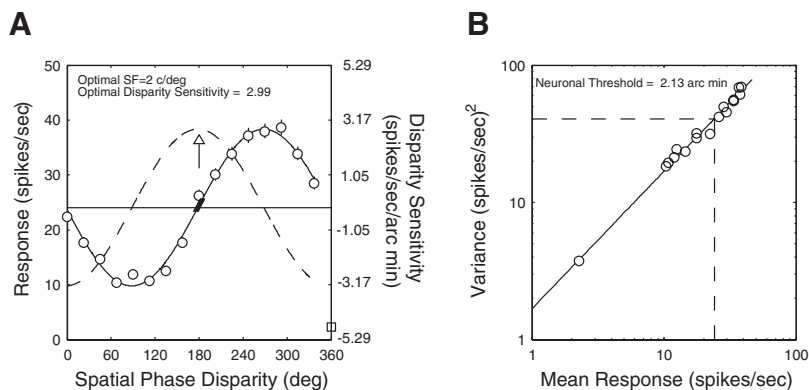Variance (spikes/sec)²

Mean Response (spikes/sec)

FIG. 8. Procedures for estimating the disparity threshold for a representative V2 neuron. *A*: disparity tuning function (solid curve) of a V2 neuron from an adult monkey from which the optimal disparity sensitivity of the cell (dotted curve) was determined by taking its optimal spatial frequency (2.0 c/d) into account. The optimal disparity sensitivity at the steepest portion of the tuning function (2.99 spikes/s/arc min at the thick line) is indicated with a large arrow. *B*: mean binocular responses (data points) were plotted on log-log coordinate as a function of response variances for the same unit as in *A*. Each data point indicates 1 spatial phase disparity including spontaneous firing (the lowest data point). The solid line is the best linear fit. The response variance was estimated from the fit function for the steepest portion of the phase tuning function (dotted lines). The optimal disparity sensitivity was normalized with its variance of responses to obtain its disparity threshold.
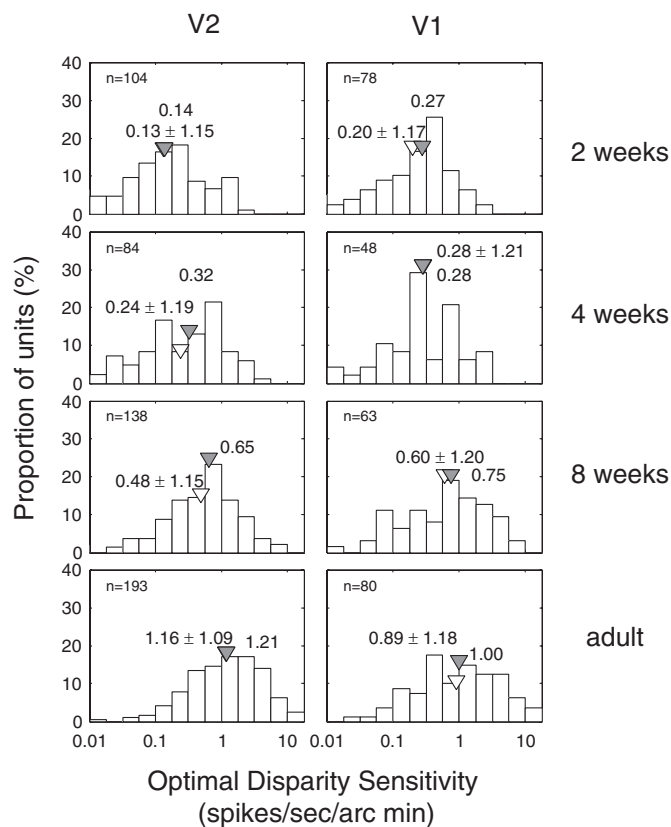
FIG. 9. The distribution of optimal disparity sensitivity (spikes/s/arc min) of V2 and V1 neurons in infants and adults. Mean (±SE) and median values are indicated by triangles.

and resolution), and the response rate of V1 and V2 neurons (Fig. 11). The median values for these response measures at 2, 4, and 8 wk of age were normalized to their respective values in adults. The BII or DDI values did not significantly change over age in V2 or V1. For V1 neurons, the improvement in disparity acuity was closely associated with their age-dependent changes in optimal spatial frequency, resolution, and response rate. In V2, however, the disparity acuity of neurons at 2 wk of age was far more immature than any of these responses. Together, in V2, but not in V1, additional limiting factor(s) might have contributed to the lower disparity acuity at 2 wk of age.

DISCUSSION

The primary findings of this study are that the binocular responses of V2 neurons of 2- and 4-wk-old infant monkeys modulate at near adult levels as a function of binocular spatial phase disparity but that their relatively low binocular response amplitudes and their coarser spatial frequency tuning impose severe limits on their ability to discriminate fine disparity differences.

According to the only psychophysical study in the literature on the normal maturation of steropsis in monkeys, stereoscopic vision could not be detected during the first 3 postnatal wk even for random-dot stimuli having disparities as large as 30 arc min (O'Dell and Boothe 1997). By 4 wk of age, however, nearly 80% of monkeys showed "evidence of stereopsis," and all 11 monkeys exhibited stereopsis by 8 wk. The average

stereo-acuity rapidly dropped from 21.7 arc min at 3 wk ($n = 6$) down to ~3.3 arc min by 8 wk of age ($n = 11$), although the stereoacuity at 8 wk of age was several times worse than in adults (O'Dell and Boothe 1997; Prince et al. 2000). Assuming that these represent an estimate of the infant's optimal visual performance, what prevents the emergence of stereopsis during the first 2–3 wk of life and what limits stereoacuity development during the first 8–10 wk of life? The critical immaturities that have been previously proposed to explain reduced binocular performance in infant primates are *1)* abnormal binocular alignment and vergence eye movements (O'Dell and Boothe 1997), *2)* the slow maturation of cortical binocular mechanisms (Birch 1993; Held 1993; Kiorpes and Movshon 2004), and *3)* the poor visibility of binocular stimuli (Brown et al. 2007; Schor et al. 1984) because of coarse spatial frequency tuning and/or low contrast sensitivity (Chino et al. 1997; Zheng et al. 2007).

Alignment and vergence

Normal binocular vision requires high degrees of coordination between motor and sensory systems. In particular, stereopsis has been shown to depend on precise interocular alignment (Harwerth et al. 1995). A critical variable to be considered for behavioral assessments of stereopsis in primate infants would be potential immaturities in alignment and vergence eye movements that compromise or prevent fusion of binocular images. For this experiment, this was not an issue because we used anesthetized and paralyzed preparations, and the binocular disparities for our experiments were optically controlled with a high degree of precision. However, according to the
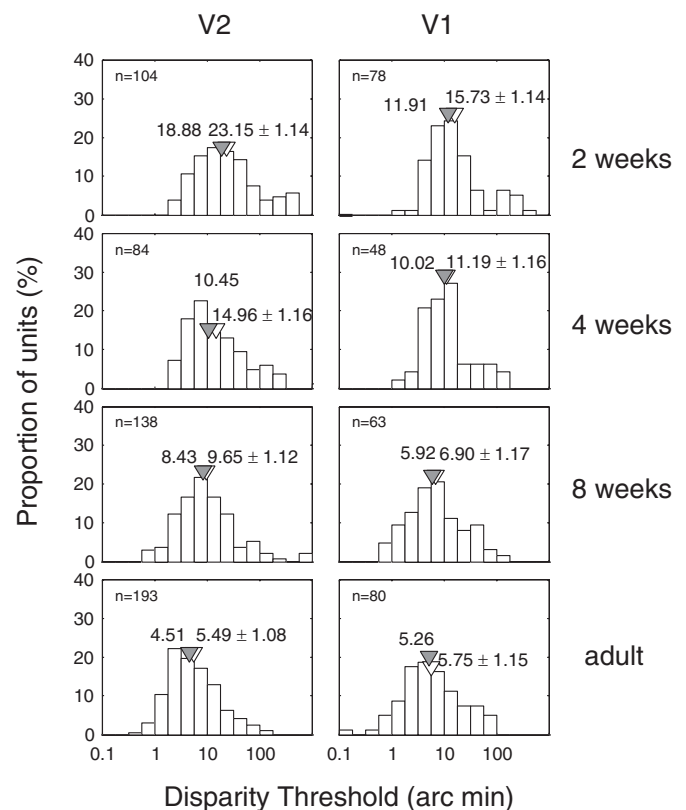

FIG. 10. Developmental changes in disparity threshold of V2 and V1 neurons. Mean (±SE) and median values are indicated by triangles.
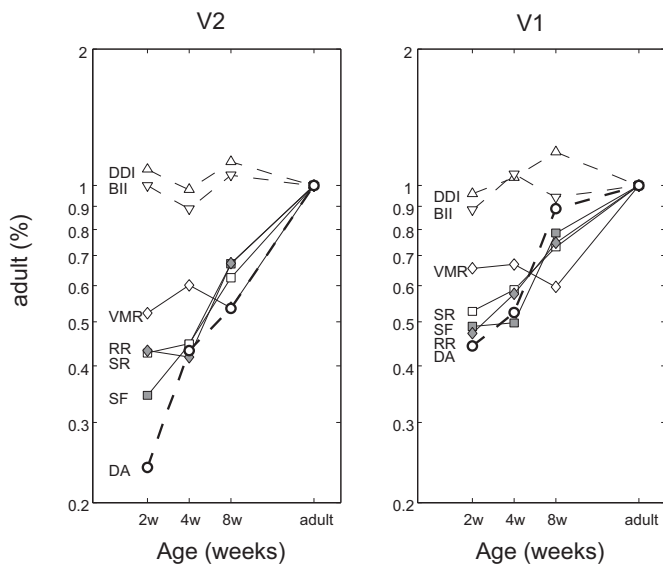
FIG. 11. Comparisons of relative developmental changes in neuronal 'disparity-acuity' (1/disparity threshold) with improvement in BII/DDI, variance-to-mean ratio, spatial frequency (optimal and resolution), and response rate. The median values for these response measures at 2, 4, and 8 wk of age were normalized to their respective adult values. BII, binocular interaction index; DDI, disparity discrimination index; VMR, variance-to-mean ratio; SR, spatial resolution; SF, optimal spatial frequency; RR, response rate; DA, disparity acuity.

only data available in the literature on alignment and vergence in awake behaving infant monkeys (published only as an abstract), neonates and young infant monkeys were reported to exhibit unsteady fixation and interocular alignment (Boothe and Gong 1992). Thus O'Dell and Boothe (1997) concluded that immaturities in oculomotor mechanisms were the primary reason why they could not reliably detect stereopsis during the first several postnatal weeks.

Several lines of evidence suggest, however, that the role of errors in interocular alignment in limiting binocular vision development in monkeys may not be as substantial as these investigators suggested. For example, in human infants of equivalent ages, binocular alignment and/or vergence eye movements do not seem to significantly limit stereoscopic vision (Birch et al. 1983; Braddick 1996; Brown et al. 2007; Hainline and Riddell 1995). Consistent with this view, we found in our infant monkeys that the fundamental sensory requirements for binocular fusion and alignment (e.g., relatively well-developed binocular mechanisms and adult-like sensitivity to binocular disparity) are present in V1 and V2 as early as 6–14 days after birth, if not at birth (also see Chino et al. 1997). A recent study showed that many infants between 7 and 24 wk of age show "adult-like" latencies for accommodation and vergence responses during binocular viewing (Tondel and Candy 2008). Equally important are the previous findings that fixating eye movements (saccades) of human infants are relatively mature near birth (Aslin 1977), and as early as 2–3 mo of age (roughly equivalent to 2–3 wk in monkeys), adult-like amplitude and velocities are attained in reactive saccades (Garbutt et al. 2006; Hainline et al. 1984; Matsuzawa and Shimojo 1997; Richards and Holley 1999). These results suggest that subcortical mechanisms supporting motor components of fixation and alignment and the extraocular muscula-

ture are relatively well developed near birth provided that stimuli for fixation are visible to infants.

Maturation of binocular mechanisms

These results rule out a lack of disparity detectors in V2 (or V1) as the primary source of stereo-deficiencies in infants. We found that the binocular response modulation of neurons in these areas as a function of interocular spatial phase disparity (BII and DDI) was as robust as in adults. Moreover, the distributions of binocular/monocular response ratios of V2 and V1 neurons in our infant monkeys were very similar to those for adults and to the distribution of binocular/monocular response ratios found in V1 of awake, behaving adult monkeys (Prince et al. 2002a). Interestingly, these investigators also found that those units in which the peak binocular responses were substantially greater than the maximum monocular responses were classified as tuned excitatory (TE) or far cells (FA), whereas those with binocular to monocular ratios ~1.0 or slightly <1.0 were classified as either near or tuned inhibitory cells, respectively. In this respect, it is tempting to speculate that cortical circuitry underlying conventional disparity cell types (i.e., near, far, tuned-excitatory, and tuned-inhibitory) may be largely adult-like in V2 and V1 at 2 wk of age.

Although qualitatively adult-like binocular mechanisms exist in the visual cortices of neonates, it is not known whether disparity sensitive V2 neurons in our infants are sensitive to relative disparity. As mentioned earlier, this is because microelectrode recording experiments in awake, behaving monkeys are not currently plausible at these ages. However, there is indirect evidence from our separate studies (Zhang et al. 2005)

$$Y = (R_{max} - R_{min}) * e^{(-x/T_c)} + R_{min}$$

Perception: Tc= 2.92 (week)
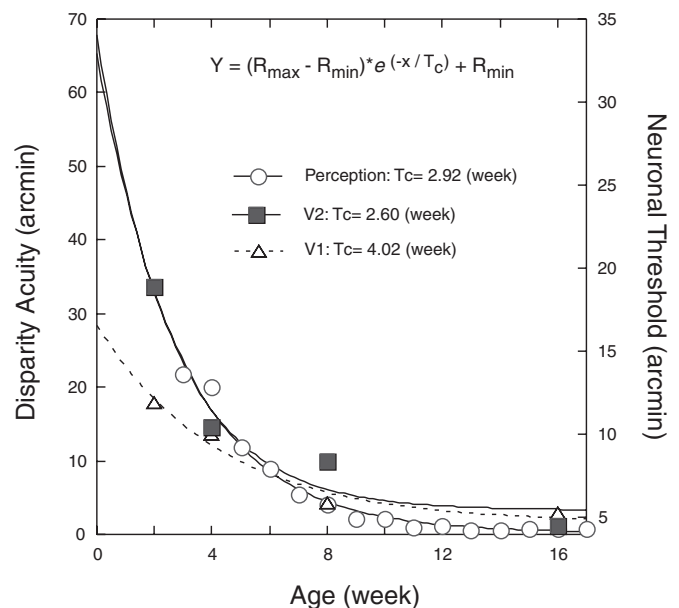V2: Tc= 2.60 (week)
V1: Tc= 4.02 (week)

FIG. 12. Comparisons of developmental changes between behaviorally measured stereoacuity of infant monkeys O'Dell and Boothe 1997 and the disparity threshold (neuronal disparity acuity) of V2 (solid line) and V1 (dotted line) neurons for our infant monkeys. Note that the relative time course of improvement in the disparity threshold of V2 and V1 neurons parallels improvement in behaviorally measured stereoacuity. Data points were fitted with an exponential function, $y = (R_{max} - R_{min}) \times \exp(-x/Tc) + R_{min}$; R_{max}, maximum value at birth; R_{min}, minimum value in adults; x, time in weeks; Tc, time constant.

that relative disparity sensitivity might be very weak or absent all together in V2 near birth. To have robust sensitivity to relative binocular disparity, extrastriate neurons must be able to compare and integrate signals over relatively large areas, e.g., units with receptive field (RF) centers and surrounds that are tuned to different disparities (Nienborg and Cumming 2006; Parker 2007; Roe et al. 2007; Umeda et al. 2007). In this respect, we previously found that the RF center/surround organization of V2 neurons is exceedingly immature at 2 wk of age; for example, there are little or no measurable RF surrounds. There is considerable improvement by 4 wk of age, and the RF centers and surrounds become largely adult-like by 8 wk of age (Zhang et al. 2005), the age at which infant monkeys typically exhibit good stereoacuities (O'Dell and Boothe 1997). Thus immaturities in the relative disparity detectors of V2 could be a major factor limiting stereopsis development.

Effects of spatial frequency tuning, firing rate, and contrast sensitivity

Even if disparity tuned V2 neurons in our infant monkeys were sensitive to relative disparity, their performance in stereotasks could still be limited by the reduced ability of these neurons to detect fine disparity differences. We found that the median disparity threshold of V2 neurons was ~4–5 times worse in 2-wk-old infants than in adults (Fig. 10). The primary reason for the poor discrimination performance of V2 neurons was their low optimal spatial frequencies (Fig. 5A) and their low response rates at these ages (Fig. 6A).

How might the normalized optimal disparity sensitivity of V2 neurons in our infant monkeys affect their binocular depth perception? Figure 12 compares the relative time courses for the improvement in behavioral stereoacuity (adopted from O'Dell and Boothe 1997) with the disparity thresholds of V2 and V1 neurons obtained in this study (Fig. 10). The best neuronal threshold value (~5 arc min in our adults, see Fig. 10) on the right scale was aligned with the optimal value in the left scale for behaviorally measured stereoacuity in adults (<0.5 arc min; Harwerth et al. 1995; O'Dell and Boothe 1997) to facilitate the comparison. The different data sets were fitted with exponential functions that characterized the relative changes in disparity sensitivity between the maximum value at birth and the minimum value for adults. Relative changes in the median disparity threshold for V2 neurons (and somewhat less in V1 neurons) closely paralleled the behavioral improvement in stereoacuity between 2 and 8 wk of age. Comparing time constants (Tc) is a simple and efficient way to determine whether the relative changes in perception and cortical physiology are different. The Tc for perceptual changes was 2.92 wk, which was similar to the Tc for V2 disparity sensitivity (2.60 wk). The Tc for changes in disparity sensitivity of V1 neurons was slightly longer (4.02 wk) because at 2 wk of age disparity sensitivity of V1 neurons was far better than in V2 (Fig. 10), i.e., the V1 changes were more moderate than that in V2, not because the functional maturation of disparity mechanisms was delayed in V1. Considered together, the spatial frequency tuning, firing rate, and response variability of V2 and V1 neurons in the developing visual brain are likely to play a critical role in limiting binocular vision development because the basic cortical mechanisms in V2 and V1 for binocular combination are adult like as early as 2 wk of age.

Similar conclusions were reached in previous psychophysical studies in human infants. For example, the development of stereopsis was shown to largely depend on the maturation of spatial frequency tuning and contrast sensitivity (Schor 1985). A more recent study with human infants showed that the most critical factor limiting stereopsis in infants was their poor visual performance caused by insensitivities to stimulus contrast (Brown et al. 2007). Common to both studies is that binocular vision development is severely constrained by the visibility of stimuli. Our recent studies also found that, in comparison to adults, the contrast sensitivity of infant V2 neurons is substantially lower until 8 wk of age (Zhang et al. 2005; Zheng et al. 2007).

Conclusions

During early postnatal development, the sensitivity of binocular disparity mechanisms in early cortical processing (V1/V2) is constrained by the relatively coarse spatial frequency tuning, the lower response rate, the low contrast sensitivities, and/or the immaturities in the RF center-surround organization of cortical neurons. One or more of these immaturities in turn are likely to limit the development of binocular depth perception. Alternatively, immature cortical mechanisms beyond V2, yet to be discovered, could be another limiting factor. However, this study unambiguously showed that, regardless of the maturational state of extrastriate visual areas beyond V2, immaturities in the response properties of V2 and V1 neurons described in this study are likely to impose substantial constraints on binocular performance of infant primates.

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