Oblique effect in visual area 2 of macaque monkeys

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The neural basis of an oblique effect, a reduced visual sensitivity for obliquely oriented stimuli, has been a matter of considerable debate. We have analyzed the orientation tuning of a relatively large number of neurons in the primary visual cortex (V1) and visual area 2 (V2) of anesthetized and paralyzed macaque monkeys. Neurons in V2 but not V1 of macaque monkeys showed clear oblique effects. This orientation anisotropy in V2 was more robust for those neurons that preferred higher spatial frequencies. We also determined whether V1 and V2 neurons exhibit a similar orientation anisotropy soon after birth. The oblique effect was absent in V1 of 4- and 8-week-old infant monkeys, but their V2 neurons showed a significant oblique effect. This orientation anisotropy in infant V2 was milder than that in adults. The results suggest that the oblique effect emerges in V2 based on the pattern of the connections that are established before birth and enhanced by the prolonged experience-dependent modifications of the neural circuitry in V2.

Introduction

Our visual system shows higher sensitivity to horizontally or vertically oriented stimuli than to obliquely oriented stimuli, the "oblique effect" (Appelle, 1972; see Li, Peterson, & Freeman, 2003 for a comprehensive review). The oblique effect is commonly thought to reflect an imbalance in the proportion of striate cortical neurons preferring the cardinal orientations to the oblique orientations. For example, Li and his colleagues unambiguously demonstrated that significantly more neurons in cat striate cortex preferred cardinal orientations, especially the horizontal orientation, and that those neurons had significantly sharper orientation tuning. Also this orientation anisotropy in cat area 17 was more clear-cut among simple cells that were tuned to higher spatial frequencies.

Macaque monkeys exhibit an oblique effect (J. A. Bauer, Owens, Thomas, & Held, 1979; Harwerth, Smith, & Okundaye, 1983). However, electrophysiological studies of the primary visual cortex (V1) in nonhuman primates reported mixed results (De Valois, Yund, & Hepler, 1982; Li et al., 2003). Moreover, the orientation anisotropy favoring the cardinal orientations has not been extensively studied in primate extrastriate visual areas, and the existing data do not offer a clear picture as to whether there is an oblique effect in cortical areas beyond V1. For example, no significant oblique effect was found in V2 of macaque monkeys (Levitt, Kiper, & Movshon, 1994) although neurons in the macaque inferior temporal cortex showed preferences for the cardinal orientations over the oblique orientations (Orban & Vogels, 1998). A recent imaging study reported a robust oblique effect in

the MT of owl monkeys, yet their V1 showed little or no consistent orientation anisotropy (Xu, Collins, Khaytin, Kaas, & Casagrande, 2006). Importantly, some of the key psychophysical studies in humans suggest that the neural basis of the oblique effect is likely to exist beyond V1 (e.g., Gros, Blake, & Hiris, 1998; Westheimer, 2003). In the first part of this study, we analyzed neuronal responses to high-contrast gratings in a relatively large number of macaque V1 ($n = 1369$) and V2 ($n = 633$) neurons in order to determine to what extent these cortical areas show significant preference for the vertical and/or horizontal orientations over the oblique orientations.

Another important issue concerning the oblique effect is how this orientation anisotropy emerges in the visual cortex. One idea is that because our visual scenes are dominated by "rich" contours of the cardinal orientations and the cortical wiring is quite plastic for a considerable period of time after birth, the oblique effect in our visual brain may gradually develop after birth based on experience-dependent modifications of cortical circuitry (e.g., Coppola, White, Fitzpatrick, & Purves, 1998; Keil & Cristobal, 2000; Sengpiel, Stawinski, & Bonhoeffer, 1999; White, Coppola, & Fitzpatrick, 2001). Alternatively, the cortical oblique effect depends on a mechanism that does not require visual experience (e.g., Coppola & White, 2004; Jaffer, Vorobyov, & Sengpiel, 2012; Leventhal, 1983; Leventhal, Schall, & Wallace, 1984). Obviously, these ideas are not mutually exclusive (see Li et al., 2003, for a comprehensive review). Nearly all the previous studies dealing with the influence of visual experience on the development of orientation tuning have been conducted in subprimate species. To explore the issue of the innate versus developmental factors underlying the oblique effect in nonhuman primates, we measured the preferred orientation of a relatively large number of V1 and V2 neurons in infant macaque monkeys ranging in age between 4 and 8 postnatal weeks.

Methods

Subjects

For the study in adult monkeys, the orientation-tuning data were collected during our previous investigations of other cortical response properties. In particular, the distribution of the preferred orientations and the nature of orientation tuning of V1 or V2 neurons have not been previously reported. For the developmental study, the subjects were 17 4-week-old, 14 8-week-old, and 44 adult monkeys (*Macaca mulatta*). All experimental and animal care procedures were in compliance with NIH Guiding Principles for

Research Involving Animals and were approved by the Institutional Animal Care and Use Committee of the University of Houston.

Surgical preparation

The surgical preparation methods have been described elsewhere (Maruko et al., 2008; Tao et al., 2012; Zhang et al., 2013). Briefly, the animals were initially anesthetized with an intramuscular injection of ketamine hydrochloride (20–30 mg/kg) and acepromazine maleate (0.15–0.2 mg/kg). A venous cannula was placed to allow subsequent continuous infusion of propofol (4 mg/kg/hr) and sufentanil citrate (0.05–0.10 μg/kg/hr). Sodium pentobarbital (2–4 mg/kg/hr) was used for maintenance in earlier studies that produced about 20% of the data for this study. The preferred orientation and orientation tuning was not affected by the use of different anesthetics. A tracheotomy was performed to facilitate artificial ventilation with a mixture of 59% N_2O, 39% O_2, and 2% CO_2. In order to insert the electrode, a craniotomy and a small durotomy were performed over the lunate sulcus though which a guide tube was positioned close to the surface. The exposed area was protected with a plastic well that was filled with warm agar and then closed with melted wax. The animals were paralyzed with an intravenous injection of vecuronium bromide (Norcuron, 0.1 mg/kg/hr) after all surgical procedures were completed. Core body temperature was monitored and kept at 37.6°C by a temperature controller (Harvard, USA). Cycloplegia was produced with atropine (1%), 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

We recorded exclusively from V1 in 26 adult and six infant monkeys. A typical penetration in V1 began several millimeters posterior to the lunate sulcus and about 12–15 mm from the midline and ended when the electrode entered the white matter. We recorded exclusively from V2 in nine adult and 15 infant monkeys. The tangential penetrations in V2 were confined to a parasagittal plane, and the angle of the penetration was typically 15°–20° from vertical. The penetrations were started right behind the blood vessels running along the lunate sulcus and 12–15 mm lateral to the midline. The penetrations ended when the electrode exited V2. In nine adult and 10 infant monkeys, we recorded from both V1 and V2. For these experiments, we began our recording in V1 as described

above, but when the electrode entered the white matter, we continued to advance the electrode until it reached V2. After recording in all layers of V2 and the electrode exited V2, the penetration ended. For each penetration, unit activity was isolated at intervals of 50–100 μm, and we made records of the cortical depth for each isolated unit. This approach allowed us to sample units consistently from similar regions of V1 and V2 for both infants and adults. Most receptive fields both in infants and adults were located within 5°–6° of the centers of the projected fovea (Figures 4 and 8).

A monitor (Vision Research Graphics) with ultra-short persistence (frame rate = 140 Hz, 800 × 600 pixels) was used to present visual stimuli. The viewing distance was set to 114 cm, and the display subtended a visual angle of 20° (horizontal) × 15° (vertical). In early studies, a pair of CRT monitors (P-31 phosphors) was used for stimulus display (frame rate = 100 Hz, average luminance of 56 cd/m²). Multiunit or single-unit activities were extracellularly recorded with tungsten-in-glass microelectrodes (Fredric-Haer, ME). Action potentials from individual cortical neurons were amplified, isolated, and stored using the data acquisition components in our workstation (Tucker-Davis Technology, FL). For each isolated neuron, handheld stimuli were initially used to map the receptive fields in each eye and to qualitatively determine the neuron's ocular dominance and preferred stimulus orientation. Quantitative measurements using drifting gratings followed these procedures and are described below.

A neuron's responses to drifting gratings were sampled at a rate of 140 Hz (7.14 msec bin widths) or 100 Hz (10 msec bin widths in earlier studies) and compiled into peristimulus time histograms (PSTHs) that were equal in duration to and synchronized with the temporal cycle of the grating. The amplitude and phase of the temporal response components in the PSTHs were determined by Fourier analysis. The stimuli were presented to the right or left eyes in a randomly ordered sequence for relatively short periods (e.g., 3.22 s). Rerandomized stimulus sequences were repeated three to six times during a given experiment. Blank stimuli (i.e., zero contrast control) were included in each repeat to provide a measure of a neuron's maintained firing rate. For each neuron, the orientation, spatial frequency, and size-tuning functions were first obtained using sine wave gratings (80% contrast and temporal frequency = 3.1 Hz; 45% contrast and 3.1 Hz in earlier studies).

The preferred orientation and orientation bandwidth for each receptive field were determined by fitting the orientation-tuning functions with wrapped Gaussian functions (Swindale, 1998):

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

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

Orientation bias was calculated by using a vector summation method (Bi et al., 2011; Levick & Thibos, 1982; Smith, Chino, Ridder, Kitagawa, & Langston, 1990). A neuron's response to a given orientation is expressed by a complex number

$$R = r \exp(j2\theta).$$

The response amplitude for a grating of orientation θ is described by a vector with a length of r at an angle coordinate of 2θ, where j = square root of -1. The orientation bias is expressed as the mean response vector for a series of equally spaced stimulus orientations: $R_{mean} = \Sigma R/N$, where N = number of orientations. The mean response vector was then normalized with respect to the average amplitude of the vectors for all orientations, i.e., $\Sigma r/N$. A normalized phasor for all stimulus orientations was computed by the following formula:

$$B = b\exp(j2\theta_p) = \Sigma R/\Sigma r,$$

where ΣR is the vector sum for all 12 orientations, and Σr is the scalar sum of the amplitudes of all of the response vectors. The normalized phasor b represents orientation bias, which varied between 0 (no orientation bias) and 1.0 (responsive to only one orientation). The term $2\theta_p$ signifies the angular coordinates of the resultant vector, and the angle θ_p is the preferred stimulus orientation of the unit. The above normalization procedure minimizes the sensitivity of the measure to the responsiveness of the neuron (Thibos & Levick, 1985).

Each cell's optimal spatial frequency was determined by fitting the spatial frequency response data with Gaussian functions (DeAngelis, Ohzawa, & Freeman, 1993a, b):

$$G(f) = m_1 \exp\left[-(f - f_0)/2s^2\right]$$

where f = spatial frequency, m_1 = response amplitude, f_0 = preferred spatial frequency, and s = standard deviation of the Gaussian function.

To determine the position and extent of a neuron's receptive field center and surround and the strength of surround suppression, we measured *area-summation functions* with drifting high-contrast (80%) sinusoidal gratings of the optimal orientation, spatial frequency, and temporal frequency (Zhang et al., 2005). Specifically, neuronal responses were measured as a function of the diameter of the grating patch. The measured area-response functions were fitted by the formula:

$$R(x) = K_c L_c(x)/[1 + K_s L_s(x)],$$

where $L_c(x) = [w_c \times \mathrm{erf}(x/w_c)]^2$, $L_s(x) = [w_s \times \mathrm{erf}(x/w_s)]^2$, x is the stimulus diameter, K_c and K_s are the

gains of the center and surround, L_c and L_s are the summed squared activities of the center and surround mechanisms, w_c and w_s represent the spatial extents of the center and surround components, and w_c is always constrained to be less than w_s during the curve-fitting procedures.

The receptive field center size was determined by searching for the smallest center stimulus diameter at which neuronal discharges reached 95% of the peak firing rate. The border of the surround was the point at which further increases in stimulus diameter did not alter the response amplitude. The surround suppression strength was quantified for each neuron by calculating a suppression index (SI): SI = (peak response − suppressed responses)/peak response for the unit's area summation function.

It should be noted that much of the data for this study come from our previous studies but that the results on the distributions of preferred orientation or the degree of orientation tuning of V1 or V2 neurons have not been previously published.

Anatomical methods

To identify recording sites both in V1 and V2, small electrolytic lesions were produced at three locations along the electrode track (at the end of each penetration, at the midpoint of the penetration, and near the cortical surface) by passing current through the electrode ($5\mu A$ for <5 s, electrode tip negative). At the end of the recording experiments, an overdose of sodium pentobarbital (100 mg/kg) was administered intravenously to induce a deep level of anesthesia, and the animals were euthanized. The animals were perfused through the heart with an aldehyde fixative (2% paraformaldehyde and 0.5% glutaraldehyde in 0.1 M phosphate buffer, pH = 7.4). The brains were removed immediately and kept overnight in fixative with 20% sucrose. The tissues were cut in 40 μm sections on a freezing microtome in parasagittal planes.

Results

We measured the orientation tuning of V1 and V2 neurons in adult macaque monkeys using high-contrast sine wave gratings (50%–80%) that were drifted at 3.1 Hz. The great majority of the receptive fields of both V1 and V2 units were located within 5° of the projected fovea (see Figures 4 and 8 for details). In all experiments, we classified each unit according to its optimal orientation into one of the four primary orientation categories, i.e., horizontal, vertical, 45 oblique, and 135 oblique (±22.5°).

Oblique effect in adult V1

The orientation tuning of 1,369 V1 neurons in 35 macaque monkeys was quantitatively analyzed with respect to a neuron's preferred orientation, peak firing rate, and the sharpness of orientation tuning. It should be noted that in nine out of 44 monkeys, we recorded from both V1 and V2 (exclusively from V1 of 26 monkeys).

Preferred orientation

There was little evidence for oblique effects in adult V1 (Figure 1Aa) (z test, $p > 0.7$). Also all units were similarly distributed for the four primary orientations, i.e., horizontal, vertical, oblique 45 and oblique 135 orientations (Figure 1Ab) (chi-square test, $p > 0.9$). The results suggest that, contrary to the clear oblique effect in area 17 of cats (Li et al., 2003) and ferrets (Chapman & Bonhoeffer, 1998; Coppola et al., 1998; Grabska-Barwinska, Distler, Hoffmann, & Jancke, 2009), there was no sign of an oblique effect in the V1 of macaque monkeys with respect to the distribution of preferred orientations. When we separated simple cells from complex cells, there was no significant difference in the proportion of units preferring the cardinal orientations for either cell group (not shown).

Responsiveness

Although the preferred orientation of units is similarly distributed, stronger responses of units preferring the cardinal orientations could explain a perceptually demonstrated oblique effect. Therefore, we compared the average firing rate after sorting V1 units into the cardinal versus oblique orientations (Figure 1Ba) and the four primary orientations (Figure 1Bb). The firing rate of V1 units preferring the cardinal orientations were slightly *lower* than that for units preferring the oblique orientations, but this difference was not significant (Rank-sum test, $p > 0.08$).

Orientation tuning

Another aspect of the orientation anisotropy is that adult humans can discriminate stimuli better if they are oriented either horizontally or vertically rather than obliquely (e.g., Coletta, Segu, & Tiana, 1993; Orban et al., 1984; Vogels & Orban, 1998). A neural basis for this effect is thought to be related to differences in the sharpness of orientation tuning of V1 neurons and, specifically, that those neurons preferring the cardinal orientations have sharper orientation tuning than those preferring oblique orientations. However, we found that neither the orientation bandwidth (Figure 1Ca)
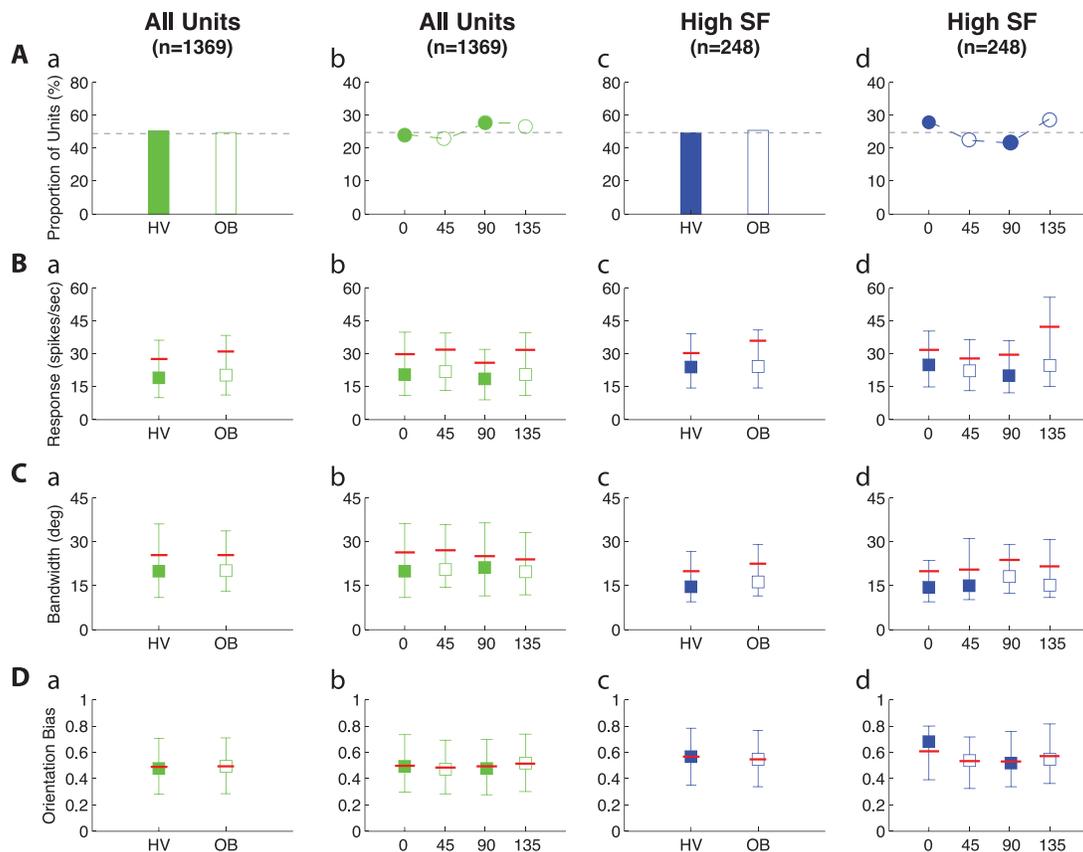
Figure 1. Absence of oblique effects in adult V1. (A) The proportion of units preferring the cardinal orientations (HV) versus the oblique orientations (OB) (a) and four primary orientations, horizontal (0), vertical (90), oblique 45 (45), and oblique 135 (135) (b). The proportion of units tuned to high spatial frequency (>2.5 c/d) preferring the cardinal orientations and the oblique orientations (c) and the four primary orientations (d). (B) Comparisons on the firing rate. Symbols signify the median values, and thin horizontal bars indicate quartile values. Thick horizontal bars signify the mean values. (C) Comparisons of orientation bandwidths. (D) Comparisons of orientation biases.

nor the orientation bias (Figure 1Da) of V1 neurons in our adult monkeys was different between those units preferring the cardinal orientations and those tuned to the oblique orientations (Rank-sum tests, $p > 0.4$). Also, the orientation selectivity did not differ for the four primary orientations (Figure 1Cb and Db) (Rank-sum test, $p > 0.2$).

Effects of spatial frequency

In a previous study, the oblique effect in cat area 17 was more pronounced for those neurons tuned to higher spatial frequencies (Li et al., 2003). Therefore, we divided V1 neurons into those preferring "higher" spatial frequencies (optimal SF ≥ 2.5 c/d, the average optimal spatial frequency of all V1 units) and "lower" spatial frequencies (SF < 2.5 c/d). With respect to the relative proportion of units, there was no spatial frequency–dependent difference between those V1 neurons preferring the cardinal orientations and units preferring the oblique orientations (Figure 1Ac and

Ad; chi-square tests for independence, $p = 0.66$), firing rates (Figure 1Bc and Bd; two-way ANOVA, $p > 0.5$ and $p > 0.05$), orientation bandwidth (Figure 1Cc and Cd; two-way ANOVA, $p > 0.26$ and $p > 0.57$), or orientation bias (Figure 1Dc and Dd; two-way ANOVA, $p > 0.42$ and $p > 0.23$).

Although there was no spatial frequency–dependent orientation anisotropy in V1, the optimal spatial frequencies of individual V1 neurons significantly affected the firing rate and orientation tuning of these neurons; the response rate was significantly higher and the orientation tuning was sharper for those units with higher optimal spatial frequencies *regardless of their preferred orientations* (Figure 1B through D, two-way ANOVA, $p < 0.05$ for firing rate, $p < 0.001$ for orientation bandwidth and orientation bias).

Together, having quantitatively examined the orientation tuning of 1,369 V1 neurons, we did not find any significant evidence for an oblique effect in adult macaque monkeys.
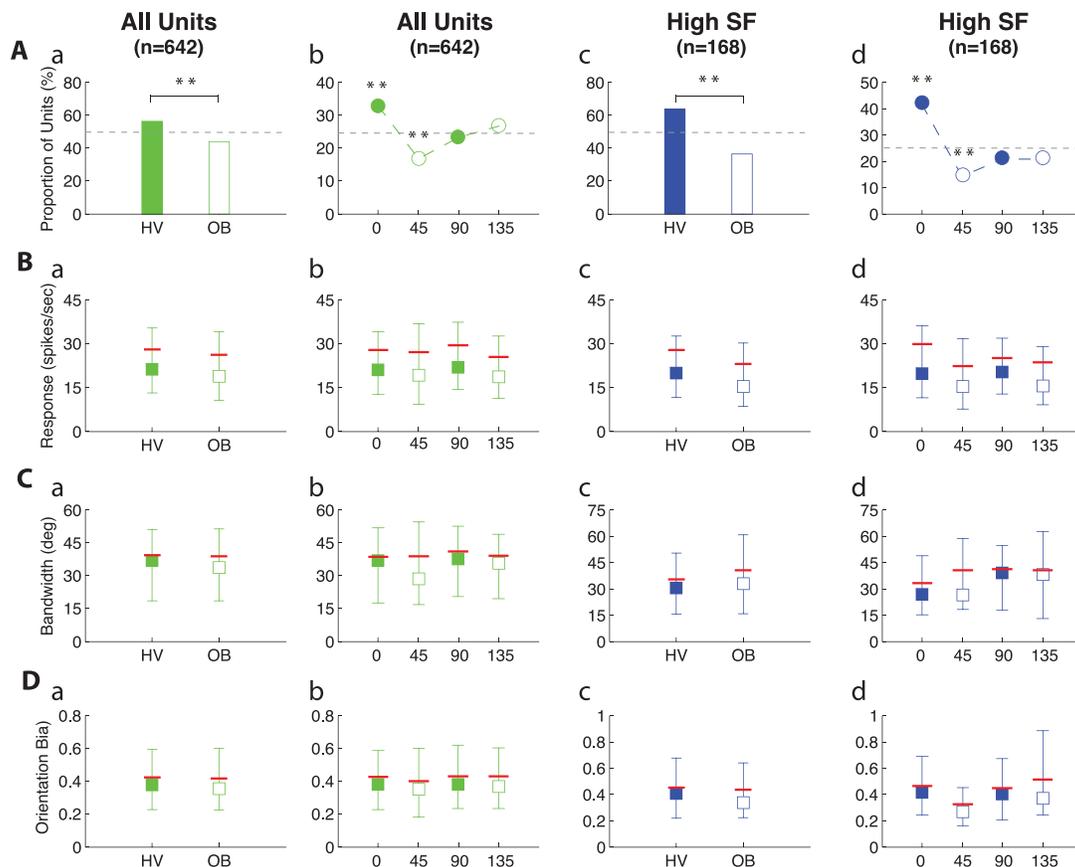
Figure 2. Oblique effects in adult V2. (A) The proportion of units preferring the cardinal orientations (HV) versus the oblique orientations (OB) (a) and the four primary orientations, horizontal (0), vertical (90), oblique 45 (45), and oblique 135 (135) (b). The proportion of units tuned to high spatial frequency (>2.5 c/d) preferring the cardinal orientation and the oblique orientations (c) and four primary orientations (d). (B) Comparisons on the firing rate. Symbols signify the median values, and thin horizontal bars indicate quartile values. Thick horizontal bars signify the mean values. (C) Comparisons of orientation bandwidths. (D) Comparisons of orientation bias. ** indicates a statistical significance at the level of $p < 0.01$.

Oblique effect in adult V2

To determine whether or not V2 of adult macaque monkeys exhibits an orientation anisotropy preferring the cardinal orientations, we quantitatively examined the preferred orientations, the firing rates, and the orientation selectivity of 642 V2 neurons in 18 macaque monkeys. As mentioned above, in nine out of 44 monkeys, we recorded from both V2 and V1 (exclusively from V2 in nine monkeys).

Preferred orientation

Fifty-six percent of V2 neurons preferred the cardinal orientations compared to 44% for the oblique orientations (Figure 2Aa). This difference was statistically significant (z test, $p = 0.0016$). Figure 2Ab illustrates that the proportion of units preferring the horizontal was highest and that the oblique 45 was lowest. These differences were statistically significant (z test, $p < 0.0001$ for both horizontal and oblique 45).

Next, because we did not find any orientation anisotropy in V1 with respect to the proportion of units (Figure 1Aa and Ac), we tested for "areal interactions." Not surprisingly, there was a strong areal effect (chi-square test for independence, $p < 0.004$).

Responsiveness

The median firing rate of units preferring the cardinal orientations was greater than that for units tuned to the oblique orientations (Figure 2Ba). However, this difference did not reach a statistical significance (rank-sum test, $p = 0.067$).

Orientation selectivity

As in V1, we did not find an oblique effect with respect to orientation bandwidth (Figure 2Ca and Cb) or orientation bias (Figure 2Da and Db) of V2 neurons (rank-sum tests, $p > 0.3$).
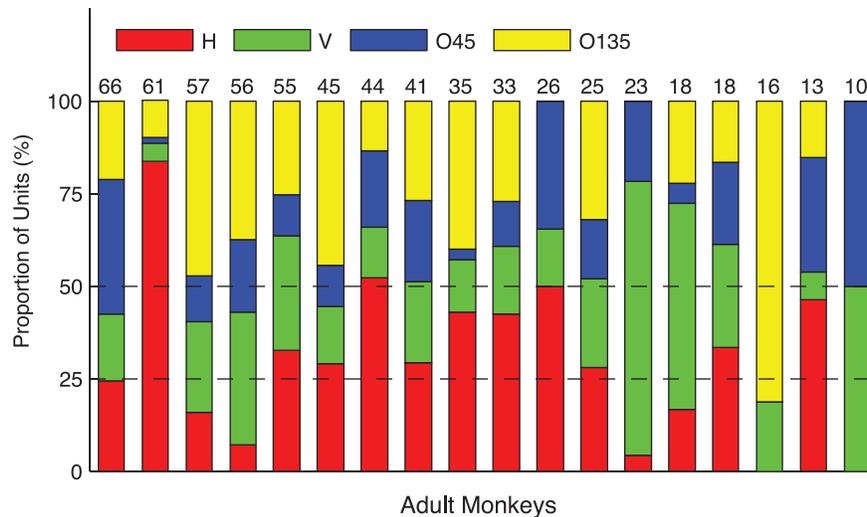
Figure 3. The proportion of V2 units in adult monkeys tuned to horizontal (red), vertical (green), oblique 45 (blue), and oblique 135 (yellow) orientation in individual monkeys. The number on top indicates sample size for each monkey.

Effects of spatial frequency

Unlike in V1, we observed a robust effect of stimulus spatial frequencies on the distribution of V2 neurons according to their preferred orientations (Figure 2Ac). Over 63% of V2 neurons tuned to high spatial frequencies preferred the cardinal orientations to the oblique orientations, and 47% of V2 units having low preferred spatial frequency preferred the cardinal orientations (z test, $p < 0.001$). These spatial frequency–dependent differences were statistically significant (chi-square test for independence, $p = 0.023$). Also, there were far more units preferring the horizontal (43%) and far fewer units preferring oblique 45 than the two other primary orientations (20%) (Figure 2Ad), and these differences were statistically significant (z test, $p < 0.0001$ for horizontal and $p < 0.0025$ for oblique 45). A similar preference for horizontally oriented contours was found in cat area 17 (Li et al., 2003). The differences between V1 and V2 described above were found for neurons regardless of their spatial frequency–tuning characteristics (chi-square tests for independence, $p < 0.004$ for both high SF and low SF). Finally, we did not find a significant oblique effect with respect to *response rate*, *orientation bandwidth* (Figure 2Cc and Cd) (two-way ANOVA, $p > 0.1$ and $p > 0.4$), or *orientation bias* (Figure 2Dc and Dd) for V2 neurons having higher optimal spatial frequencies (two-way ANOVA, $p > 0.6$).

Analysis for individual monkeys

Although we recorded from a relatively large number of V2 neurons ($n = 642$), a potential sampling bias for each monkey can be problematic. Therefore, we analyzed the proportion of units preferring one of the four primary orientations for individual monkeys (Figure 3). For those monkeys from which we recorded both V1 and V2, the sample size was indeed smaller (<30). However, all four primary orientations are well represented in each animal with a few exceptions, indicating that our electrodes were in all primary orientation clusters of V2. Importantly, in 15 out of 18 monkeys, the percentage of units tuned to either horizontal or vertical orientation exceeded 25% of the total number of units in each animal (sign test, $p < 0.05$), and the same analysis for units tuned to oblique 45 or oblique 135 yielded an insignificant result (sign test, $p > 0.05$). These results rule out the possibility that the oblique effect illustrated in Figure 2 is a result of biased cell sampling.

Radial bias in adult V1 and V2

A different kind of orientation anisotropy, a radial bias, has been reported in human fMRI studies (Freeman, Brouwer, Heeger, & Merriam, 2011; Mannion, McDonald, & Clifford, 2010; Sasaki et al., 2006; Sun et al., 2013) and in electrophysiological studies of nonhuman primates and cats (R. Bauer & Dow, 1989; Durand, Celebrini, & Trotter, 2007; Leventhal, 1983; Leventhal et al., 1984; Schall, Vitek, & Leventhal, 1986). More specifically, V1 neurons near the horizontal or vertical meridian tend to have cardinal biases whereas those units away from the meridians tend to show oblique biases, reflecting similar biases in precortical structures. Therefore, if we sampled far more V2 neurons viewing near the horizontal or vertical meridians than in V1, such sampling bias can explain the difference between V1 (*absence*) (Figure 1) and V2 (*presence*) of oblique effects (Figure 2) in this study.
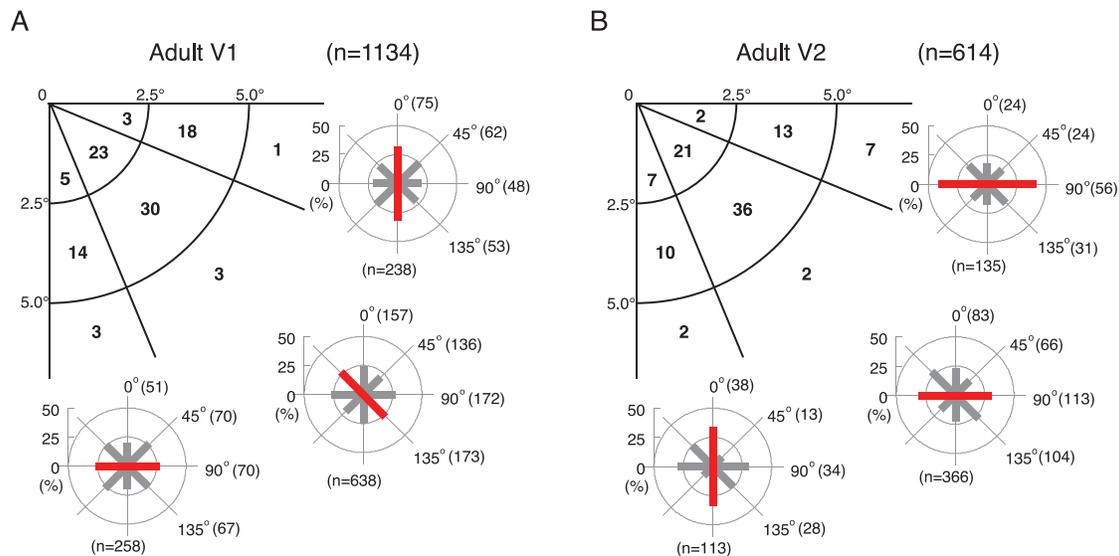
Figure 4. Radial biases in adult V1 (A) and V2 (B). The visual fields that contain information on the location of receptive fields were equally divided into nine sectors according to radial angles and eccentricities: near the horizontal meridian ($\theta = 22.5°$), near the vertical meridian ($\theta = 22.5°$), and between the two meridians ($\theta = 45°$). The map was further divided into the central 2.5°, 5.0°, and beyond 5.0°. The numbers in the maps show the *proportion of units* for each sector. The circular graphs show the *distribution of preferred orientations* (number of units and proportion) for the three radial regions: near the horizontal meridian, near the vertical meridian, and between the two meridians.

To determine whether our sample neurons exhibited a radial bias, we first determined the polar angle of the preferred orientation and the eccentricity for each unit. Next, we placed the unit into one of the nine sectors of the visual field that was defined by polar angles (near the horizontal meridian, near the vertical meridian, and between the two) and by the eccentricity (the central 2.5°, 5.0°, and beyond 5.0°) (Figures 4 and 8). The data from the right and left visual fields were combined to make the map simpler than otherwise. Then we calculated the *proportion of units* and the *distribution of preferred orientations (bias)* for each of the nine sectors. The total number of V1 and V2 neurons are slightly lower than that in the previous figures because the position of receptive fields was not accurately recorded in a small number of units.

The proportions of units (percentage) sampled in each sector were very similar in V1 (Figure 4A) and V2 (Figure 4B). With respect to eccentricity, the great majority of units had their receptive fields within the central 5° (93% in V1 and 89% in V2) and the proportions of units within the central 2.5° were identical in the two areas (30%). The receptive-field locations in relation to the meridians were also similar for the two cortical areas: 22% of both V1 and V2 neurons had their receptive fields near the horizontal meridian, and the receptive fields of 22% of V1 and 19% of V2 units were located near the vertical meridian. The remaining 56% of V1 units and 59% of V2 units had their receptive fields away from the two

meridians. Together, the observed differences in oblique effects between V1 and V2 cannot be explained by a sampling bias between the two cortical areas.

Having established a relatively homogeneous and similar sampling of units in all sectors (radial or eccentricity) for the two cortical areas, we analyzed the distribution of preferred orientations of units for the three radially oriented local regions; near the horizontal ($<22.5°$) or vertical ($<22.5°$) meridians and between the two regions. The preferred orientation of each unit was classified as a vertical (90°), oblique (45° or 135°), or horizontal (0°) preferring unit, and the relative proportions of these units were calculated for the three regions defined above. The maps in Figure 4 show that there was no sign of a radial effect in V1 although the sample size was much larger in V1 than in V2. The only significant bias was found along the horizontal meridian, but the preferred orientation of V1 units in this region was vertical (z test, $p < 0.02$).

Neurons in V2 exhibited a clear radial bias. Near the horizontal meridian, significantly more V2 units preferred horizontal orientation (z test, $p < 0.00001$), and near the vertical meridian, a significantly larger percentage of V2 neurons were tuned to vertical orientation (z test, $p < 0.04$). Interestingly, between the two radial regions, significantly more V2 neurons preferred horizontal orientation (z test, $p < 0.01$), and a smaller percentage of V2 neurons preferred oblique 45° orientation (z test, $p < 0.01$). Taken together, V2 of our

adult monkeys exhibited both oblique and radial effects although there was no sign of either oblique or radial effect in V1.

Oblique effects in V1 and V2 of infant monkeys

We next asked whether the oblique effect in adult V2 is a result of prenatally determined connections between V1 and V2 and/or the experience-dependent modifications of the feed-forward and intrinsic wiring in V2. We have analyzed the orientation tuning of V1 and V2 neurons for 4- and 8-week-old infant monkeys. We recorded exclusively from V1 units in six infants and from V2 in 15 infant monkeys. In another 10 infants, we recorded from both V1 and V2. These infant ages were chosen based on our previous studies on the normal development of V1 and V2; 4 weeks of age is the youngest age when we could reliably analyze the receptive field properties of V1 and V2 neurons, and 8 weeks of age is the critical point of the postnatal development of neuronal development when neuronal responses become very similar to those in adults (Chino, Smith, Hatta, & Cheng, 1997; Maruko et al., 2008; Zhang, Smith, & Chino, 2008; Zhang et al., 2013; Zhang et al., 2005; Zheng et al., 2007).

Preferred orientation

Consistent with the data from adult monkeys, there was no orientation anisotropy in V1 of 4- or 8-week-old monkeys (Figure 5A). Even if the data from the two infant age groups were combined to increase the sample size, there was no oblique effect in infant V1 (z test, $p > 0.4$) (Figure 5B).

In V2 of 4-week-old ($n = 432$) and 8-week-old infants ($n = 363$), there were more units preferring the cardinal orientations than those tuned to the oblique orientations (Figure 6A). However, these differences were not statistically significant (z test, $p = 0.07$ for 4 weeks and $p = 0.23$ for 8 weeks). However, if the data from the two infant age groups are combined (*infant*), there is a statistically significant oblique effect ($n = 795$; z test, $p = 0.03$) (Figure 6Ba). It is important to note that there was a distinct difference in the magnitude of the oblique effect between infants (combined) and adults, i.e., the orientation anisotropy was relatively larger for adults than for infants (compare Figure 6Ba and Ca). However, this difference between infants and adults was not significant (chi-square test for independence, $p > 0.3$, but see below for the effect of spatial frequency). Finally, we did not find any significant preference for one of the four primary orientations (horizontal, vertical, two oblique orientations) in infants (z test, $p > 0.6$) (Figure 6Bb).
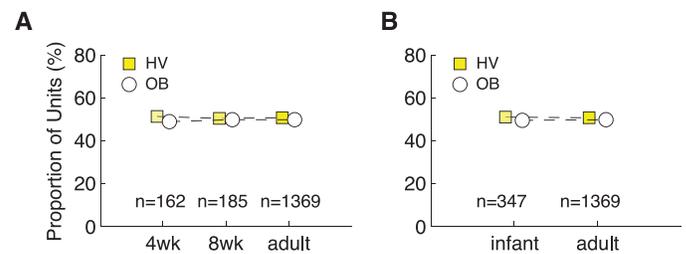

Figure 5. Absence of oblique effects in infant V1. (A) Proportion of V1 neurons preferring the cardinal orientations (HV) and the oblique orientations (OB) in 4-week-old (4wk) and 8 week-old (8wk) monkeys. (B) Proportion of V1 neurons preferring the cardinal orientations (HV) and the oblique orientations (OB) after combining the data from 4-week-old and 8-week-old infants (infant). Control data from adult monkeys are also shown (adult).

Effects of spatial frequency

For our infant monkeys, we did not find an effect of a neuron's optimal spatial frequency (Figure 6Bc and Bd). We classified a neuron as a "high-frequency unit" if its optimal spatial frequency was higher than 1.6 c/d. This value was higher than the average optimal spatial frequency of V2 neurons in 4-week-old (1.43 ± 0.04 c/d) and in 8-week-old infants (1.59 ± 0.06 c/d). In adults, as described above, the oblique effect was pronounced among those units tuned to higher spatial frequencies (Figure 6Cc). Consequently, the difference between infants and adults with respect to the proportion of the high frequency–tuned neurons preferring the cardinal orientations was statistically significant (chi-square test for independence, $p = 0.041$). The result suggests that the more robust oblique effect in adults compared to that in infants was largely attributed to the orientation anisotropy in V2 neurons that preferred higher spatial frequencies.

Analysis for individual infants

We analyzed the proportion of units preferring one of the four primary orientations for individual infant monkeys (Figure 6D). For those monkeys from which we recorded both V1 and V2, the sample size was also smaller. In one infant, we recorded from only two units; hence, the data from this monkey is not included in this analysis. Regardless, all four primary orientations are well represented in each infant monkey with a few exceptions, indicating that our electrodes were in all primary orientation clusters of infant V2. In 20 out of 24 monkeys, the percentage of units tuned to either horizontal or vertical orientation exceeded 25% of the total number of units for each animal (sign test, $p < 0.05$), and the same analysis for units tuned to oblique 45 or oblique 135 yielded an insignificant result (sign test, $p > 0.05$). As in adults, these results rule out the possibility
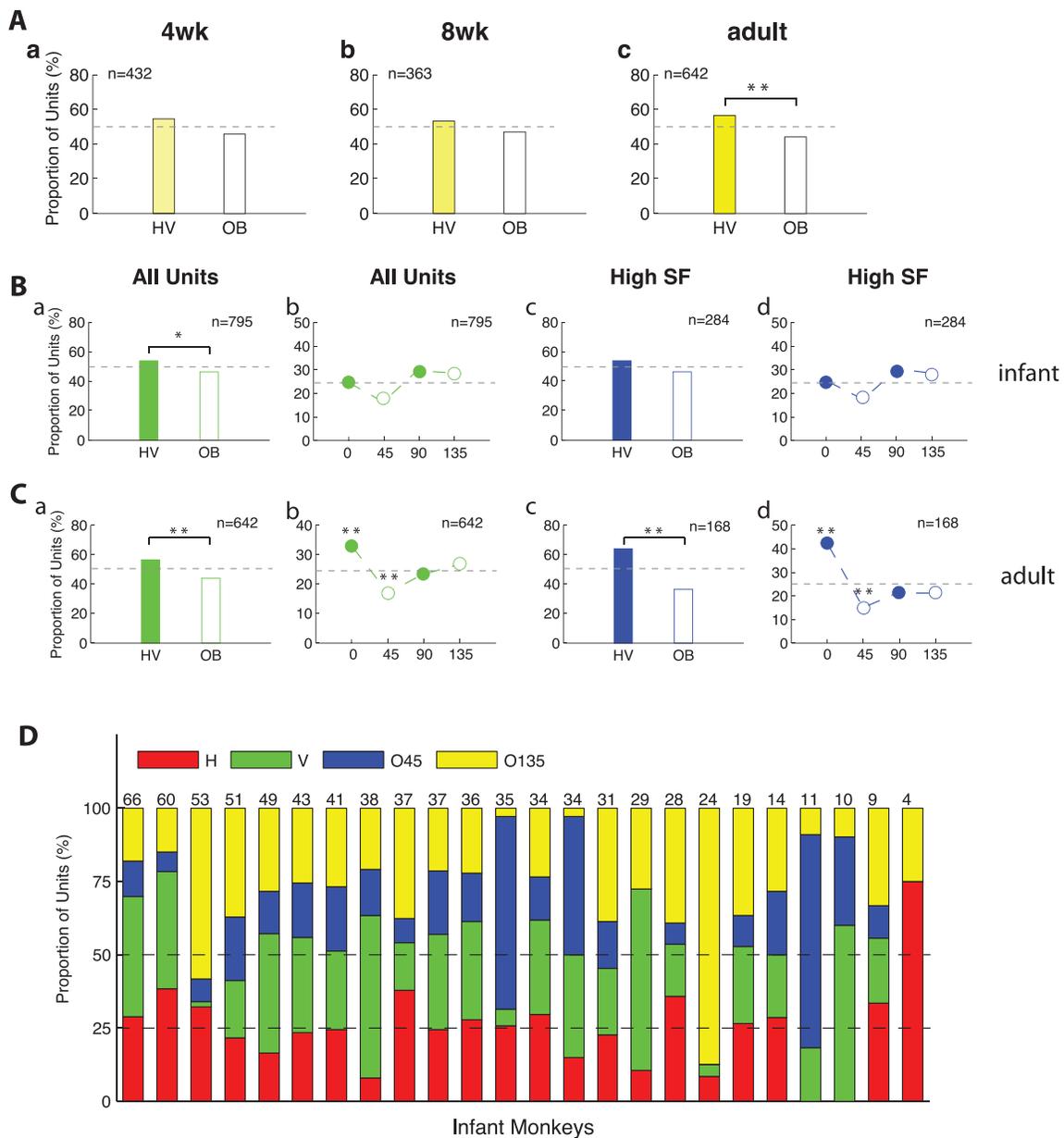
Figure 6. Oblique effects in infant V2. (A) Proportion of V2 neurons preferring the cardinal orientations (HV) and the oblique orientations (OB) in 4-week-old (4wk) (a) and 8-week-old (8wk) (b), and adult monkeys (c). (B) Proportion of V2 neurons preferring the cardinal orientations (HV) and the oblique orientations (OB) after combining the data from 4-week-old and 8-week-old infants (infant) (a) and the four primary orientations (b). The proportion of units tuned to high spatial frequency preferring the cardinal orientations and the oblique orientations (c) and the four primary orientations (d). (C) Comparable data from adult monkeys are also shown (adult). ** indicates a statistical significance at the level of $p < 0.01$. * signifies a statistical significance at the level of $p < 0.05$. (D) The proportion of V2 units in infant monkeys tuned to horizontal (red), vertical (green), oblique 45 (blue), and oblique 135 (yellow) orientation in individual monkeys. The number on top indicates sample size for each monkey.

that the oblique effect in infant V2 illustrated in Figure 6B is a result of biased cell sampling.

Firing rate

As in adults, the median or average response rate for V2 neurons tuned to the cardinal orientations were similar to those preferring the oblique orientations in 4- and 8-week-old infants (Figure 7). Interestingly, the median response rate was greater for neurons that were tuned to higher spatial frequencies and preferred the *oblique* orientations (rank-sum test, $p < 0.05$). This orientation anisotropy favoring the oblique orientations disappeared by 8 weeks of age.
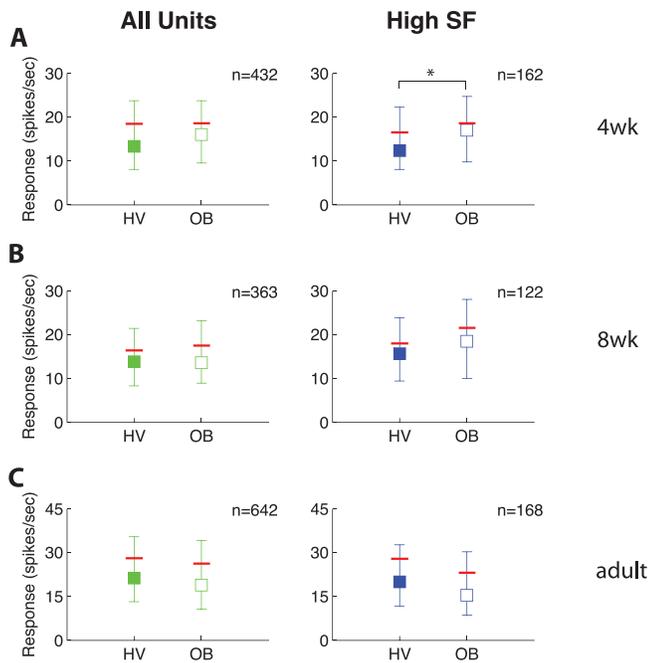
Figure 7. Oblique effects for firing rates in V2 of 4-week-old infants (A), 8-week-old infants (B), and adults (C). Left columns show the data for all units, and right columns show the data for units tuned to higher spatial frequencies. * signifies a statistical significance at the level of $p < 0.05$.

Orientation tuning

As in adults, there was no orientation anisotropy in 4- and 8-week-old infants when we analyzed the orientation bandwidth or orientation bias of V1 or V2 neurons (data not shown).

Radial bias in infant V1 and V2

Using the same approach as in adults, we determined whether V1 and V2 of infants show a radial bias by focusing on the proportion of units and the distribution of preferred orientations for each of the nine sectors of the visual field (Figure 8). Unlike in adult V1 (56%), 79% of our samples had their receptive fields away from the vertical or horizontal meridian (Figure 8A). Among those units, a significantly larger percentage of V1 units (56/175) showed preference for the oblique 135 orientation (z test, $p = 0.033$). However, because of the small sample size ($n = 221$) and the apparent sampling bias with respect to the unit's receptive-field location, it was not possible to determine whether a radial bias is present in our infant V1.

More importantly, infant V2 exhibited an unambiguous radial bias in preferred orientations despite a sampling bias that was similar to V1; 70% of 746 V2 units had their receptive fields away from the vertical or the horizontal meridian (Figure 8B). A significantly higher number of V2 units near the horizontal meridian
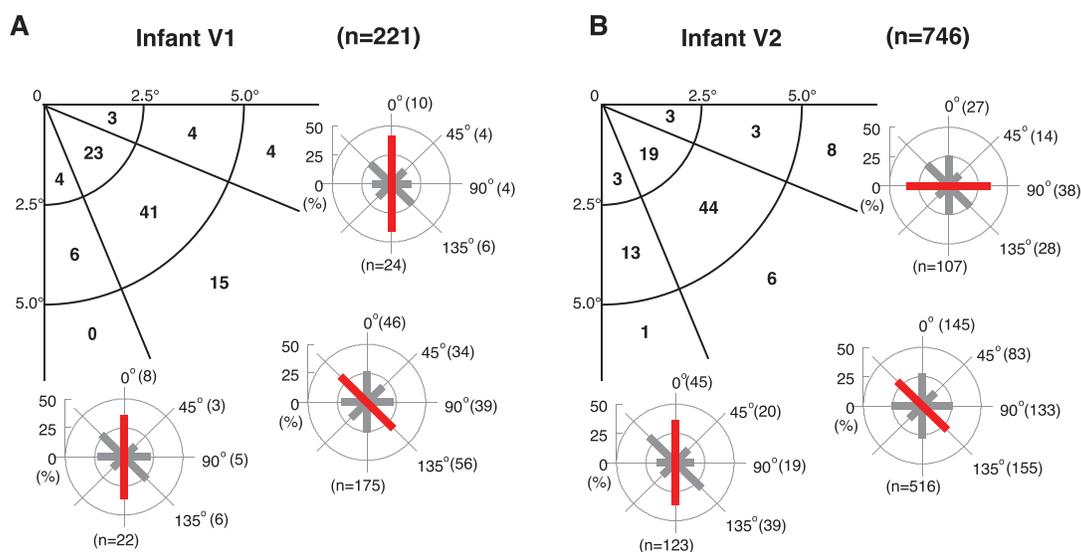

Figure 8. Radial biases in infant V1 (A) and V2 (B). The visual fields that contain information on the location of receptive fields were equally divided into nine sectors according to radial angles and eccentricities: near the horizontal meridian ($\theta = 22.5°$), near the vertical meridian ($\theta = 22.5°$), and between the two meridians ($\theta = 45°$). The map was further divided into the central 2.5°, 5.0°, and beyond 5.0°. The numbers in the maps show the *proportion of units* for each sector. The circular graphs show the *distribution of preferred orientations* (number of units and proportion) for the three radial regions: near the horizontal meridian, near the vertical meridian, and between the two meridians. The data from 4- and 8-week-old infants were combined.

(38/107) preferred horizontal orientation (z test, $p = 0.012$), and 37% of units (45/123) near the vertical meridian preferred vertical orientation (z test, $p = 0.003$). Also the highest number of units between the two meridians (155/516) exhibited a significant preference for oblique 135 orientation (z test, $p = 0.0082$). These data indicate that a radial bias is present as early as 4–8 weeks of age in macaque V2. Also it is important to note that although far more receptive fields were located away from the horizontal or vertical meridian, the oblique effect was found in infant V2 (Figure 6Ba). One of the reasons is that of those V2 neurons having their receptive fields located between the two meridians, 278 out of 516 units (54%) preferred either horizontal or vertical orientations.

Discussion

The important findings of this study were (a) V2 but not V1 neurons of macaque monkeys showed oblique effects; (b) this orientation anisotropy in V2 was more robust for those neurons that preferred higher spatial frequencies; (c) the oblique effect was also absent in V1 of infant monkeys, but their V2 neurons showed a milder oblique effect compared to that in adults; and (d) a radial bias was present in both infant and adult V2 whereas the bias was absent in infant and adult V1. Our study is, to the best of our knowledge, the first to demonstrate a radial bias in V2 of macaque monkeys with unit recordings. Also, this is the only study that demonstrated both oblique effects and a radial bias in V2 for the same subjects.

Absence of oblique effect and radial bias in V1

Although we examined the orientation tuning of 1,369 units, we did not find evidence for an oblique effect in V1 of macaque monkeys. A previous optical-imaging study in owl monkeys also found a "small and inconsistent" oblique effect in V1 (Xu et al., 2006). Earlier electrophysiological studies on oblique effects in primate V1 reported conflicting results largely due to sampling issues, i.e., small sample sizes, different cell types, and/or the issue of central versus periphery (see a review by Li et al., 2003). Nevertheless, the absence of an oblique effect in primate V1 is somewhat puzzling considering the overwhelming evidence for the oblique effect in cat area 17 (Li et al., 2003). Also, optical-imaging studies in ferrets reported clear-cut evidence for an orientation anisotropy in V1 (e.g., Chapman & Bonhoeffer, 1998; Coppola et al., 1998; Grabska-Barwinska et al., 2009). The results of this study suggest that there appear to be genuine species differences

between nonhuman primates and subprimate species. Besides the species difference, the most significant difference between our study and that of Li et al. (2003) or optical-imaging studies in ferrets was that these investigators analyzed the data obtained from neurons viewing the central 15° of the visual field, and we analyzed the orientation tuning of V1 units that had 93% of their receptive fields within the central 5° (Figure 4).

Consistent with our results, recent fMRI studies in humans reported that there is no evidence for an oblique effect in V1 although the same subjects perceptually exhibited preference for cardinal orientations (Freeman et al., 2011; Nasr & Tootell, 2012; Swisher et al., 2010). However, other human fMRI studies showed a substantial oblique effect (Furmanski & Engel, 2000; Sun et al., 2013). Methodological differences between these fMRI studies with respect to visual stimuli and sampling, the resolution of fMRI, the nature of responses analyzed (e.g., differences in amplitude vs. the number of voxels), and retinal locations stimulated (e.g., central vs. peripheral) may explain these inconsistent observations among MRI studies.

Several fMRI studies reported a radial orientation bias in V1, a higher sensitivity to radial orientations (Freeman et al., 2011; Mannion et al., 2010; Sasaki et al., 2006). Moreover, an elegant study by Sun et al. (2013), using a high-resolution fMRI and a "novel" visual stimulation method, reported that both an oblique effect and a radial bias are present in human V1. However, we did not find a radial bias or an oblique effect in V1 of our adult monkeys. Besides the obvious differences in methodology (central vs. periphery for sampling and imaging vs. unit recordings) and species (macaque monkeys vs. humans), it is difficult to explain the apparent differences between the studies. It is worth noting that Freeman et al. (2011) did not find a radial effect for the central 5° although these investigators found a robust radial effect beyond the central 5°, which is, in part, consistent with our results. In our study, the great majority of our sample neurons had their receptive fields within the central 5°.

The results shown in Figure 4A provide a critical control data for the analysis of oblique effects in adult V1; if we sampled a disproportionately large number of units having their receptive fields away from the two meridians and if there were a radial bias, such sampling bias could have explained the apparent lack of oblique effect in V1. Instead, we had a relatively balanced distribution (56% vs. 44%) and found little evidence for a radial effect (Figure 4A) or oblique effect (Figure 1). Also it is important to note that the preferred orientations of V1 units in this study were similarly distributed for the four primary orientations, i.e.,

horizontal, vertical, oblique 45, and oblique 135 orientations (Figure 1Ab). This suggests that we were sampling from nearly all orientation "columns" or "domains" in V1.

Oblique effect and radial bias in V2

More V2 neurons preferred either the horizontal or vertical orientations to the oblique orientations (Figure 2). Also adult V2 showed a clear radial bias (Figure 4B). These findings differ from the previous report in macaque V2 based on a relatively small sample size (Levitt et al., 1994) or in a human fMRI study (Furmanski & Engel, 2000). However, optical imaging studies in marmoset V2 (Liu & Pettigrew, 2003) and in MT of owl monkeys (Xu et al., 2006) reported observations that are consistent with our study; the oblique effect in V2 or MT was much more robust than in V1. The only previous unit recording study in extrastriate visual areas that reported a robust oblique effect was in the inferior temporal cortex (Vogels & Orban, 1994). The available data from this series of studies suggest that the orientation anisotropy is more pronounced downstream from the primary visual cortex in the cortical hierarchy, at least in nonhuman primates. Also the present results are consistent with the proposal in human perceptual studies that the neural mechanisms underlying the oblique effect in primates are likely to exist beyond V1 (Gros et al., 1998; Nasr & Tootell, 2012; Westheimer, 2003).

Innate mechanisms versus experience-dependent changes

Does the oblique effect in V2 depend on an innate mechanism or require visual experience? As early as 4 weeks of age, we found a "mild" oblique effect. There were more V2 but not V1 neurons that preferred the cardinal orientations to the oblique orientations although this difference was not statistically significant (Figure 6). Only when we combined the data from 8-week-old and 4-week-old monkeys to increase our sample size did the orientation anisotropy become significant. These results raise a few important questions. First, was the visual experience between birth and 4 weeks of age sufficient to forge the "mild" oblique effect in V2? Second, if we increase the sample size in 4-week-old-infants, would we find a significant oblique effect? Third, if the answer to the second question is positive, can we find a similar orientation anisotropy in V2 of one-week-old or younger monkeys? These issues are difficult to address because recording reliably from *many* neurons of one-week-old infants or younger is practically impossible, and imaging in V2 of macaque neonates will not generate reliable or interpretable data.

The key finding to this issue was that the magnitude of the oblique effects in V2 was significantly greater in adults than in infants, especially for those units tuned to higher spatial frequencies (Figure 6). Considered together, the oblique effect and the radial bias in adult V2 appear to depend largely on the prenatally determined cortical circuits, and the experience-dependent refinement of such circuitry enhances the orientation anisotropy during development.

How does V2 exhibit the oblique effect and a radial bias while V1 does not? There is no anatomical study in the literature that can give us an insight into how the connections between V1 and V2 and/or the intrinsic circuitry of V2 neurons in adult monkeys are specifically arranged to generate these orientation anisotropies in V2. The present results suggest that the feedforward connections between V1 and V2 and the intrinsic connections of V2 are organized to provide a basis for the orientation anisotropy in V2 that is strengthened by early visual experience. Consistent with this view, our previous anatomical study using a tracer (CTB) injection method showed that the feedforward projections from V1 to V2 and the intrinsic connections in V2 of macaque monkeys are present at birth but relatively immature (diffuse) at 2 weeks of age. With normal visual experience, these fine connections become more orderly at 4 weeks and near adult-like patterns of connections emerge between 8 and 16 weeks of age (Baldwin et al., 2012).

Conclusions

We propose that the observed orientation anisotropy in V2 emerges largely based on the patterns of connections that are established before birth, which is strengthened by the prolonged experience-dependent modification of the functional connections. Such modification of functional circuitry is minimal in V1 and is gradually amplified downstream from V1 both in the dorsal and ventral pathways of the primate visual brain.

Acknowledgments

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