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Ocular Dominance Columns: Enigmas and Challenges

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Abstract

In some mammalian species, geniculocortical afferents serving each eye are segregated in layer 4C of striate cortex into stripes called ocular dominance columns. Having described the complete pattern of ocular dominance columns in the human brain, the authors enumerate here the principal enigmas that confront future investigators. Probably the overarching challenge is to explain the function, if any, of ocular dominance columns and why they are present in some species and not others. A satisfactory solution must account for the enormous natural variation, even within the same species, among individuals in column expression, pattern, periodicity, and alignment with other components of the functional architecture. Another major priority is to explain the development of ocular dominance columns. It has been established clearly that they form without visual experience, but the innate signals that guide their segregation and maturation are unknown. Experiments addressing the role of spontaneous retinal activity have yielded contradictory data. These studies must be reconciled, to pave the way for new insights into how columnar structure is generated in the cerebral cortex.

Keywords

V1, visual cortex; striate cortex; retinotopic; amblyopia; visual deprivation; functional architecture; cytochrome oxidase; patches; stereopsis; color vision; form

The first hint of ocular dominance columns was found by Hubel and Wiesel (1962) during recordings from cells in anesthetized cats. They observed that cells with different ocular preference did not appear to be “scattered at random through the cortex.” However, not until they made recordings in cats raised with strabismus did they recognize the existence of ocular dominance columns (Hubel and Wiesel 1965). In kittens raised with ocular misalignment, monocular cells are more prevalent in the striate cortex. Hubel and Wiesel noted that the ocular preference of single cells switched consistently from one eye to the other, on a scale of hundreds of microns, as their recording electrode advanced parallel to the cortical layers. This segregation was reminiscent of the columns discovered by Mountcastle in somatosensory cortex, where cells are arranged according to their preference for cutaneous versus joint stimulation (Mountcastle and others 1955).

Ocular dominance columns were first visualized anatomically by making lesions in single layers of the macaque lateral geniculate nucleus (LGN). The distribution of degenerating terminals was plotted in cortical layer 4C, which receives the bulk of input from LGN axons (Hubel and Wiesel 1969, 1972). This cumbersome approach was soon replaced by autoradiography, which allows one to label the ocular dominance columns simply by making an injection of [^3H]proline into one eye (Wiesel and others 1974). The cortex was sectioned in a plane parallel to the pial surface, and fragments of layer 4C were montaged to view the columns (Hubel and others 1977; LeVay and others 1980). Eventually, the complete pattern of ocular dominance columns was reconstructed by using a computer to compile autoradiographs prepared from serial sections cut through the occipital lobe in a single plane of section (LeVay and others 1985).

Wong-Riley (1979) employed a novel alternative to autoradiography for labeling ocular dominance columns, by examining the distribution of cytochrome oxidase (CO) in the cortex. The levels of this mitochondrial enzyme are tied closely to the physiological activity of neurons. Removal of an eye in adulthood causes a reduction in CO activity in cells formerly driven by the missing eye, revealing the ocular dominance columns. The pattern produced by changes in CO following monocular enucleation in adulthood is identical to that produced by labeling the ocular dominance columns with [^3H]proline eye injection (Sincich and Horton 2002a) (Fig. 1). This finding indicates that CO can be used as a reliable substitute for [^3H]proline autoradiography.

Ocular Dominance Columns across Species

After ocular dominance columns were identified in cats and macaques, many other species were examined to determine whether ocular dominance columns are a universal phenomenon. They were found in the owl monkey, marmoset, green vervet, red monkey, baboon, spider monkey, talapoin monkey, capuchin monkey, white-faced saki, chimpanzee, galago, ferret, and mink. However, they were absent in the rat, mouse, tree shrew, squirrel, possum, rabbit, sheep, and goat (for review, see Horton and Hocking 1996b). Why ocular dominance columns are present in some species and not others remains an enigma. This enigma is only the first of many concerning the organization and function of ocular dominance columns.

The occurrence of ocular dominance columns among mammalian species does not appear to follow any general principle, except that all animals with columns are predators, endowed with frontally placed eyes and largely overlapping visual fields. This fact has led to the assumption that columns are required for stereopsis. This appealing idea has been accepted widely, but it is probably incorrect. As we shall see, members of some primate species, for example, squirrel monkeys, that presumably have intact stereopsis, can lack ocular dominance columns.

Human Ocular Dominance Columns

After ocular dominance columns were discovered in animals, it was naturally of interest to learn whether they also occur in humans. The Gies silver stain revealed a pattern of parallel

stripes in normal autopsy specimens, suggesting that they are indeed present in human striate cortex (Hitchcock and Hickey 1980). Once the CO technique became available, it was applied in humans who had become blind in one eye prior to death (Horton and Hedley-Whyte 1984; Horton and others 1990; Duffy and others 2007). Ocular dominance columns were found, but only fragments of their pattern were recovered, because the human cortex is so convoluted. Eventually, techniques were developed to unfold and flatten the cortex, allowing column patterns to be reconstructed over wide areas (Olavarria and Van Sluyters 1985; Tootell and Silverman 1985; Sincich and others 2003). Figure 2 shows the process of flattening the entire medial face of the human occipital lobe to prepare the cortical sheet before sectioning (Adams and others 2007). This individual lost sight in his left eye a year prior to death. The complete layout of columns was reconstructed in each hemisphere by reacting individual serial sections for CO. The sections were then digitized, aligned using blood vessels, and montaged to reveal the distribution of CO in layer 4C β (Fig. 3). The columns appear as alternating dark (normal eye) and pale (blind eye) bands of enzyme activity. The typical width of human ocular dominance columns is about 1 mm, twice the width of macaque columns. Although wider, they form a similar pattern, consisting of roughly parallel stripes oriented perpendicular to the V1/V2 border, with frequent bifurcations and blind endings. A second enigma is why the columns form this general pattern, which is fairly consistent among primate species (LeVay and others 1985).

The representations of the blind spot and the monocular temporal crescent are clearly visible, because these regions receive input from only one eye. The blind spot representation in the striate cortex is supplied only by the temporal retina of the ipsilateral eye. Consequently, it appears as a solid mass of dark CO activity in the cortex ipsilateral to the eye with intact vision. In contrast, the monocular crescent representation is pale, because it receives input from only the contralateral eye.

The V1/V2 border, which corresponds to the representation of the vertical meridian, is revealed clearly by CO because of an abrupt drop in enzyme activity. The characteristic pattern of ocular dominance columns in V1 gives way to a novel staining pattern in V2. In macaque V2, this pattern consists of repeating parallel stripes of pale-thin-pale-thick CO activity (Tootell and others 1983). The stripes receive input from different CO compartments in V1 and may have different physiological functions (Livingstone and Hubel 1984; Ts'o and others 2001; Sincich and Horton 2002b). In this vein, it is worth noting that in the human it has been impossible to differentiate between thin stripes and thick stripes (Adams and others 2007). There is only a single class of dark stripes, alternating with pale stripes (Fig. 3).

In addition to a map of ocular dominance, the striate cortex contains a map of the contralateral hemifield of vision (Inouye 1909; Horton and Hoyt 1991; Sereno and others 1995; DeYoe and others 1996; Engel and others 1997). These two maps are shown together in Figure 4. Note that anatomical landmarks defined by CO, such as the representations of the fovea, vertical meridian, blind spot, and monocular crescent, are situated at appropriate locations within the retinotopic map. Knowledge of the retinotopic map allows one to translate between the visual field and striate cortex. In Figure 4, the ocular dominance column pattern has been transformed onto a fronto-parallel representation of the visual

hemifield. The representation of the blind spot is centered at its expected location in the visual field ($\sim 15^\circ$), and the border of the monocular crescent (the transition between the columns and the solid monocular area) forms a contour that matches the extent of the binocular field plotted by perimetry. This exercise allows one to appreciate pictorially the vastly greater cortical magnification of the macula, compared with the peripheral retina. The same emphasis on macular vision occurs in macaque striate cortex. In the human, the mean surface area of striate cortex (2643 mm^2) is at least twice that found in the macaque (1343 mm^2) (Sincich and others 2003; Adams and others 2007), although there is little difference in visual acuity between the two species (De Valois and others 1974). This brings us to the third enigma: What is the advantage of this extra brain tissue in the human?

fMRI of Ocular Dominance Columns

Many attempts have been made to map noninvasively ocular dominance columns in humans using functional magnetic resonance imaging (fMRI). The columns offer a tempting target to showcase the capacity of this powerful noninvasive technique to resolve the functional architecture of the human cortex. To have a chance at capturing the ocular dominance columns, images must be obtained that are composed of sub-millimeter elements. The first study of ocular dominance using fMRI showed a smattering of voxels responsive principally to either left eye or right eye stimulation, but no evidence of columns (Menon and others 1997). Improvements in fMRI scanners and techniques for data analysis have allowed regions of tissue to be imaged at higher resolution (Menon and Goodyear 1999; Cheng and others 2001; Goodyear and Menon 2001).

The spatial resolution of the BOLD signal itself is the most difficult limitation to overcome. The BOLD signal can be divided into two components; the first is a small, short latency reduction in signal (the “initial dip”). This is followed by a larger and longer lasting signal (the delayed positive BOLD signal) that reflects enhanced cerebral blood flow associated with the region of increased neuronal activity. The initial dip is potentially more useful for detection of localized changes in neuronal activity, because it is restricted spatially to the site of changed activity. However, its low amplitude results in a poor signal-to-noise ratio, limiting spatial resolution. The delayed positive BOLD signal has a relatively large signal-to-noise ratio, but its location can be shifted physically with respect to the site of increased neural activity (Disbrow and others 2000; Logothetis 2008). If the spatially nonspecific signal arising from the vasculature is minimized, sufficient resolution to map human ocular dominance columns is possible (Kim and Fukuda 2008; Yacoub and others 2007). The best fMRI signal is obtained when the plane of imaging is tangential to the cortical sheet (Fig. 5). This approach maximizes the likelihood that a high proportion of each voxel will contain tissue devoted to a single eye, improving the contrast of the signal obtained by alternating stimulation of each eye. Because the cerebral cortex is so folded, only fragments of the human ocular dominance column pattern have been mapped with fMRI.

Another factor that limits the ability to image the ocular dominance columns is the mode of stimulus presentation. To obtain a complete map of the ocular dominance columns using a functional technique, one must stimulate the entire binocular visual field. Practical considerations make this difficult in the scanner; most studies have been limited to the

central 15° for both ocular dominance and retinotopy. The blind spot representation has been located (Tong and Engel 2001), but not the monocular crescent representation. No imaging study has yet demonstrated the anatomical shrinkage of an amblyopic eye's columns, which occurs from form deprivation during the critical period (Adams and others 2007).

When the opportunity arises, it would be worthwhile to confirm fMRI studies in humans with CO histochemistry at autopsy. This would increase confidence in the technique's capacity to map columnar structures in less familiar regions of the brain. Although fMRI has many virtues as an experimental technique, it has difficulty resolving columnar structure in the human brain. As one can see by comparing Figures 3 and 5, neurohistological methods still have a role to play in mapping the functional architecture of the human cerebral cortex.

Variability of Ocular Dominance Columns

There is huge variability in the surface area of striate cortex among individual members of various primate species. For example, the V1 surface area in macaques has been measured between 690 and 1950 mm² in normal animals (Van Essen and others 1984; Sincich and others 2003). There is also remarkable variability in the periodicity of ocular dominance columns (Horton and Hocking 1996c). Figure 6 shows three examples of striate cortex, with the same surface area, from three different macaques. There is at least a twofold range among these animals in the width of the ocular dominance columns, and hence, in the number of sets of columns. A fourth enigma is why this variation in column width occurs, and how it affects intracortical wiring and receptive field properties. Curiously, in macaques there is no correlation between the area of striate cortex and the periodicity of ocular dominance columns (Tootell and others 1988). However, across primates, there is a trend for larger columns in species with a larger V1 (e.g., human > chimpanzee > macaque).

Ocular dominance columns can vary not only in periodicity but also in morphology. Figure 7 shows another human case, chosen because the columns show a close resemblance to the pattern in the macaque. The columns appear quite different from those shown in Figure 3; in fact, one would not guess that they were from the same species. A fifth enigma is whether such variations in column pattern across normal individuals have any significance for visual function.

The squirrel monkey provides the ultimate example of a species exhibiting variability in ocular dominance columns (Adams and Horton 2003a) (Fig. 8). The columns in some members of this species are highly segregated. In this respect, they are similar to the columns in humans and macaques, although their layout and appearance differ. In other squirrel monkeys, ocular dominance columns appear to be essentially absent. It has been proposed that the segregation of geniculocortical afferents in layer 4C gives rise to monocular cells in striate cortex (Hubel and Wiesel 1977). If correct, one would predict few monocular cells in layer 4C of squirrel monkeys without columns. In fact, monocular cells are plentiful in such animals (Adams and Horton 2006a). This finding implies that intermingled geniculocortical afferents, driven by either the left eye or the right eye, can target selectively cells in layer 4C of striate cortex to produce populations of monocular cells intermixed like salt and pepper. Clearly then, ocular dominance columns are not needed for

the existence of monocular cells. A sixth enigma is why ocular dominance columns occur in some squirrel monkeys, but not in others.

To compound the mystery: Ocular dominance columns are present within only a portion of striate cortex in some squirrel monkeys. Figure 9 shows an example of an animal whose columns dissolve within a portion of the central visual field representation, yet are obvious elsewhere. If ocular dominance columns serve a function, then this function must be absent in this particular monkey from 1° to 5° in the visual field. It is difficult to conceive of any important visual function that might be idiosyncratically ablated within just a portion of the visual field in an otherwise normal monkey. This finding poses a seventh enigma: Why do columns occur in only part of the striate cortex in some animals?

Ocular dominance columns are present in all macaques and humans. The radical variability of column expression among squirrel monkeys has not been documented in any other primate species. Should one avoid generalizing from this species, because it is just an oddity? Some adult marmosets have been found to lack columns, resulting in the hypothesis that columns are lost with age in this species (Spatz 1989). An alternative explanation is that column expression in the marmoset is also variable. Capricious expression of columns may also account for conflicting reports about whether the owl monkey has ocular dominance columns (Kaas and others 1976; but see Rowe and others 1978; Diamond and others 1985). We predict that for many primate species, individual members will be found to show variable expression of ocular dominance columns.

Patches, Blobs, Puffs, and Columns

The CO stain reveals punctuate, regularly spaced zones of increased metabolic activity in striate cortex, described originally as “patches” or “puffs” (Horton and Hubel 1981; Livingstone and Hubel 1982; Carroll and Wong-Riley 1984). Later, they were termed “blobs” (Livingstone and Hubel 1982). Whether described as patches, puffs, or blobs, their structure is columnar, spanning the entire cortex from pia to white matter, although they are most obvious in layers 2/3. Only in layers 4A and 4C are they absent. Patches are present in every primate species, even those that lack ocular dominance columns, and perhaps even in some nonprimate species (Murphy and others 1995).

CO patches form rows in the human and macaque, which are centered within the core of each ocular dominance column in layer 4. Each patch is dominated by one eye or the other, evinced by the fact that alternate rows of CO patches turn pale after monocular enucleation. Following [³H]proline eye injection, alternating rows of patches are labeled transneuronally. The labeled rows of patches align perfectly with the labeled ocular dominance columns in layer 4 (Horton and Hocking 1996a). After injection of patches in layer 2/3 with a retrograde tracer, many labeled cells are found in the koniocellular divisions of the LGN (Hendry and Yoshioka 1994; Ding and Casagrande 1997). This has led to the classification of the koniocellular pathway, the only direct source of LGN input to patches, as the third geniculocortical division. The other two LGN divisions terminate primarily in layer 4, with parvocellular input going to 4C β and magnocellular input going to 4C α .

Livingstone and Hubel (1984, 1988) reported that cells within patches have unique receptive field properties, for example, they are unoriented, center-surround, and color opponent. They proposed that patches represent a specialization for color vision in the primate. However, Leventhal and others (1995) found no correlation between orientation tuning, color opponency, and CO patches. Moreover, striate cortex contains many color-tuned cells that appear to have well-oriented receptive fields (Johnson and others 2001; Friedman and others 2003). Other studies have found no difference in orientation tuning between cells in patches versus interpatches, although they did not focus per se on the issue of color selectivity (Edwards and others 1995; O'Keefe and others 1998). Thus, the role of patches in color perception remains unclear, the eighth enigma.

The relationship between CO patches and the map of orientation columns in the striate cortex constitutes the ninth enigma. Optical imaging reveals singularities or pinwheels where orientation domains converge (Blasdel and Salama 1986; Bonhoeffer and Grinvald 1991). Blasdel (1992) suggested that CO patches may correspond to orientation singularities, which would place these orientation interstices in the middle of ocular dominance columns. Subsequent studies have both denied and affirmed this relationship (Landisman and Ts'o 2002; Lu and Roe 2008). The spatial uncertainty in optical imaging and the vexing problem of alignment with postmortem CO histology make it difficult to come to a definitive conclusion one way or the other (Polimeni and others 2005).

Why does the orientation and color selectivity of cells in CO patches matter? Livingstone and Hubel (1988) proposed a tripartite scheme, based on data showing three distinct anatomical pathways from V1 to V2. A specific functional property was associated with each of these pathways: color vision (layer 2/3 patches → thin stripes), form vision (layer 2/3 interpatches → pale stripes), and stereopsis (layer 4B → thick stripes). The validity of this theory depends on evidence that color-coded cells in the striate cortex are unoriented and confined to CO patches (Livingstone and Hubel 1984). For this reason, it is important to settle the nagging controversy over the receptive field properties of cells in CO patches.

Doubt regarding the Livingstone and Hubel model of three segregated functional streams from V1 to V2 has come from the discovery that the anatomical connections are bipartite, not tripartite. There is agreement that cells in patches project to thin stripes (Livingstone and Hubel 1984; Sincich and Horton 2005; Sincich and others 2007). Previously, it was reported that cells in 4B project to thick stripes and cells in 2/3 interpatches project to pale stripes (Livingstone and Hubel 1984, 1987). More recent data show that cells located in interpatches (layer 4B and 2/3) project to both thick CO stripes and pale CO stripes. The challenge now is to learn what information is carried by these two separate pathways: patches → thin stripes, interpatches → thick and pale stripes. This dichotomy poses the tenth enigma.

Figure 10 shows the one-to-one relationship between rows of CO patches and ocular dominance columns in the macaque. Surprisingly, this robust relationship is not found in all primates. As mentioned earlier, ocular dominance columns are present in some squirrel monkeys but not others. In those squirrel monkeys with columns, the columns exhibit no spatial correlation with CO patches (Horton and Hocking 1996b; Adams and Horton 2006b)

(Fig. 11). Even more surprising, every CO patch is labeled in the squirrel monkey after [^3H]proline eye injection, whether or not the animal has columns. In contrast, in the macaque, transneuronal label is confined to alternating rows of patches after tracer injection into one eye. There seems to be no common principle governing the organization of the basic functional module of striate cortex among primates, at least in terms of the spatial relationship between patches and ocular dominance columns. In the human and macaque, the ocular dominance columns and patches form a crystalline array, and each patch belongs to an ocular dominance column. In species such as the squirrel monkey, owl monkey, and galago, the ocular dominance columns and patches are divorced (Xu and others 2005; Kaskan and others 2007). This difference constitutes the eleventh enigma.

Can ocular dominance columns exist without segregation of geniculocortical afferents in layer 4C? Kaskan and colleagues (2007) have shown ocular dominance columns by optical imaging in the owl monkey. They termed these “cryptic,” based on their prior study that ocular dominance columns are absent after [^3H]proline eye injection in the owl monkey (Kaas and others 1976). Although some owl monkeys seem to lack ocular dominance columns, others possess them, just as in the squirrel monkey (Rowe and others 1978). It would be optimal to examine the segregation of geniculocortical afferents in the actual owl monkeys used for optical imaging. Unless this step is taken, it may be premature to conclude that functional columns can exist in the absence of obvious differences in the distributions of activating inputs.

Development of Ocular Dominance Columns

Initially, geniculocortical afferents are intermingled completely in layer 4 of the striate cortex. Eye injection with [^3H]proline in utero at E110 (term = E165) in the macaque produces a continuous band of label in layer 4 of the striate cortex. Injection made three weeks before birth shows a hint of segregation of ocular inputs (Rakic 1976). At birth, the ocular dominance columns are well formed and organized into the pattern found in adult animals (Horton and Hocking 1996a). Thus, in macaques the formation of ocular dominance columns begins late in gestation and does not rely on visual experience.

Although visual experience is not required for column segregation, neuronal activity appears to be essential. In the cat, Stryker and Harris (1986) blocked retinal ganglion cell firing by injecting tetrodotoxin into each eye. This intervention prevented the formation of ocular dominance columns. It has been proposed that synchronous firing of geniculocortical afferents driven by the same eye could lead to a “like-with-like” clustering that ultimately results in ocular dominance columns (von der Malsburg and Willshaw 1976; Swindale 1980; Miller and others 1989; Jones and others 1991). This theory offers an obvious explanation for how tetrodotoxin interferes with column generation.

A potential source of correlated geniculocortical activity is the retina. In the fetal cat, spontaneous waves of spikes roll across each retina, giving rise to firing patterns in ganglion cells that are spatially correlated within, but not between, each eye (Meister and others 1991; Wong and others 1993). The waves are present at E52, a time that coincides with the segregation of retinal ganglion cell axons in the LGN. However, the ocular dominance

columns do not begin to form until P15, about three to four weeks later. This would be too late for retinal waves to play a direct role in their genesis.

It is also worth noting that at P15 in the cat, the eyes are open and fuse on common visual targets. This presumably results in a high correlation between the activity of geniculocortical afferents serving the right eye and the left eye. At precisely this point in development, the geniculocortical afferents begin to segregate into ocular dominance columns. Thus, contrary to the “fire together, wire together” theory, afferents that fire together at P15 appear to wire apart.

The ultimate synchronization of ocular activity occurs in strobe-reared animals. In kittens raised under strobe illumination (10 μ sec pulses, 8 Hz), the ocular dominance columns segregate normally. Under these conditions, the left eye afferents and the right eye afferents fire together, but nonetheless, they wire apart (Schmidt and others 2008). This experiment also seems to argue that asynchronous ocular firing is not the recipe for column segregation.

A theory that can be reconciled with the data in one species may be contradicted in another, often because the timing of events in the maturation of the visual system varies across species. The ferret is born before geniculate afferents reach the striate cortex. Column formation occurs even if binocular enucleation is performed at birth, implying that retinal activity is not a prerequisite (Crowley and Katz 1999). This result poses a twelfth enigma: It seems to contradict data gathered in the cat that retinal activity is required for the formation of ocular dominance columns. Perhaps retinal blockade in the cat, which was conducted at a relatively later phase of cortical development than in the ferret, masked columns that had already begun to form. This could occur by triggering nonspecific outgrowth of terminals (Antonini and Stryker 1993). Whatever the case, in the ferret the initial formation of ocular dominance columns appears to follow programmed instructions, presumably relying on molecular cues present on thalamic axons, cortical cells, or both (Sengpiel and Kind 2002).

Another explanation is that there is a difference in the response to binocular enucleation (ferret data) and pharmacological blockade (cat data). An instructive experiment would be to block retinal waves in newborn ferrets. This was done recently using epibatadine, a nicotinic agonist, from P1 to P10 (Huberman and others 2006). Ocular dominance columns were present in the visual cortex, just as in the binocular enucleation experiment, although they showed some abnormal features. These results deal a blow to the retinal wave theory of ocular dominance column formation.

In some animals, ocular dominance columns do not form throughout striate cortex, despite the presence of binocular input (Fig. 9). The location where columns are missing is always mirror-symmetric between the two hemispheres. If retinal waves generate ocular dominance columns, they must not occur during development in a local patch of retina in each eye, corresponding retinotopically to the cortical regions where columns are missing. This is not impossible, but descriptions of retinal waves have emphasized that they are spontaneous and random (Stellwagen and Shatz 2002).

Amblyopia and Ocular Dominance Columns

Wiesel and Hubel's (1963) seminal experiments in kittens showed that during a critical period early in life, the ocular preference of single cells can be shifted by visual deprivation. To mimic monocular congenital cataract, they sutured closed the lids of one eye. Recordings later showed that most cells in striate cortex responded only to stimulation of the normal, open eye.

This physiological perturbation is accompanied by a change in the morphology of the ocular dominance columns. Columns belonging to the normal eye expand, at the expense of those receiving input from the deprived eye (Hubel and others 1977; Shatz and Stryker 1978). No more vivid example exists in neuroscience of an alteration in brain anatomy induced by abnormal sensory stimulation. It occurs in humans with dense amblyopia from early form deprivation (Adams and others 2007). However, it does not occur with strabismic amblyopia and anisometropic amblyopia, which generally develop at a later age (Horton and Stryker 1993; Horton and Hocking 1996d; Horton and others 1997). The anatomical changes underlying these milder types of amblyopia remain unknown.

A postnatal exchange of cortical territory can also occur in normal animals due to a peculiarity of the mammalian eye. The blood vessels that supply the inner retina run in front of the photoreceptor layer. Because blood cells are pigmented, they cast a shadow on rods and cones. As a result of this local form deprivation, geniculate afferents retract, abandoning cortical territory corresponding to the location of retinal vessels. If one eye is removed during adulthood, CO staining reveals the pattern of retinal blood vessels in striate cortex (Fig. 12) (Adams and Horton 2002). Even partial shadowing of a handful of photoreceptors is sufficient to generate rewiring of geniculocortical afferents (Adams and Horton 2003b).

The remodeling of geniculocortical afferents, which causes a change in the morphology of ocular dominance columns, reflects the competition to make permanent synapses upon cells in layer 4C. This phase in the maturation of the geniculocortical projection is driven by visual experience. When it is upset, either by wholesale deprivation of an eye or by local deprivation from retinal vessels, the deprived columns shrink. This phenomenon should not be viewed as an adaptive change designed to confer an advantage upon the open eye. In fact, the visual function of the open eye does not become "supernormal" by virtue of having extra cortical territory at its disposal. The shrinkage of the deprived eye's ocular dominance columns is simply an inevitable side effect of a normal developmental process gone awry.

Mechanism of Ocular Dominance Column Shrinkage

In normal animals, the ocular dominance columns serving each eye are nearly equal in width in the representation of the central visual field. From the blind spot to the monocular crescent, the ipsilateral eye's columns become progressively narrower, reflecting the increasing influence of the contralateral eye in the peripheral visual field (Fig. 1). In a monkey raised with monocular eyelid suture from age eight days, the ocular dominance columns serving the deprived eye shrink everywhere (Fig. 13). The most devastating effect is seen between the blind spot and the monocular crescent, because the columns were already

narrow in this region prior to the onset of visual deprivation. In the corresponding area of the opposite hemisphere, the deprived eye's columns appear relatively robust, because they started out wider than the normal eye's columns.

In the monkey, geniculocortical afferents have segregated nearly completely by age eight days. The best explanation for the data in Figure 13 is that an exchange of territory occurs along the borders of the ocular dominance columns, where the two eyes compete for synaptic connections. The geniculocortical afferents of the deprived eye retract, whereas those of the normal eye sprout. A shift in column borders, about 100 to 200 μm , takes place throughout the striate cortex. What limits this process from going to completion, and obliterating the deprived columns, remains unknown. The columns show a progressive decline in their susceptibility to shrinkage over the first few months of life (LeVay and others 1980; Horton and Hocking 1997). However, column shrinkage takes place in a matter of days, implying that mechanisms must exist to limit the process.

In the cat, the cellular events that underlie column shrinkage are more difficult to explain. At age eight days, kittens are just beginning to open their eyes, and their cortex is far more immature than in the macaque. Yet, surprisingly, monocular suture at age eight days produces a similar result (Fig. 14A). The geniculocortical afferents of the deprived eye appear as shrunken islands, immersed in a sea of cortex belonging to the open eye (Schmidt and others 2002). This result is extraordinary, when one considers that the geniculocortical afferents serving the two eyes were intermingled completely when visual deprivation was initiated. In the cat, ocular dominance columns do not begin to segregate until age 15 days (Crair and others 2001). Despite visual deprivation, the sutured eye's afferents coalesce and develop into ocular dominance columns, albeit shrunken ones. Within these deprived columns, the open eye's afferents are largely excluded (Fig. 14B). These data pose the thirteenth enigma: When visual deprivation is initiated before the segregation of geniculocortical afferents, why do ocular dominance columns form at all? One would predict that the open eye's geniculocortical afferents should win the binocular competition for synapses everywhere in the striate cortex, wiping out any territory that might belong to the deprived eye. However, the deprived eye's afferents not only form columns, but they drive the open eye's afferents from these columns. Hebbian-based rules of column formation would predict the opposite result. These data suggest that column formation proceeds according to programmed instructions and is not choreographed by spontaneous imbalances in neuronal activity. Column formation can be modified by deprivation, because the cortex depends on sensory stimulation for the normal refinement and maturation of its circuitry, but the basic column pattern is inherent.

Conclusion

The spectacular patterns formed by ocular dominance columns in many species have attracted the attention of anatomists, physiologists, developmental biologists, and theoreticians. A concerted effort has been mounted to explain the development and function of ocular dominance columns. Although progress has been made over decades of labor, the riddles posed by ocular dominance columns continue to elude solution. To focus attention on clues that may provide answers, we have raised 13 enigmas in this review. Their solution

may get us past the Sphinx and provide the breakthrough needed to propel this field of neuroscience ahead.

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Figure 1.

Ocular dominance columns in a normal macaque monkey. *A*, Montage of layer 4C, prepared from a V1 flatmount after enucleation of the right eye and processing of the tissue for cytochrome oxidase (CO) activity, revealing the pattern of ocular dominance columns. *B*, Digital representation of the data in (*A*), showing the left (black) and the right (white) ocular dominance columns, along with approximate retinotopic coordinates. Columns are present everywhere, except in the representation of the monocular crescent (MC) and the blind spot (*). Between these two landmarks, the ipsilateral columns become progressively more diminutive. Gray regions denote two sulci where the column pattern was obscured. *C*, Autoradiograph prepared from alternate sections after injection of [³H]proline into the remaining left eye. The perfect match between *A* and *C* proves that CO can be used as a substitute for autoradiography to label the ocular dominance columns (Sincich and Horton 2002a).

Figure 2.

Preparation of flatmounts from the human occipital lobe. *A*, Intact right occipital lobe after removal of the leptomeninges, showing the medial face. The dashed line indicates the V1/V2 border, where it is present on the surface of the brain. Arrow = parieto-occipital sulcus; CC = corpus callosum; CS = calcarine sulcus. *B*, Midway through the dissection, showing the opened calcarine sulcus. The numbers denote corresponding locations in each image. *C*, Final flattened tissue block, ready to be frozen and cut with a microtome. The location of V1, determined later from cytochrome oxidase–stained sections, is shown by the dashed line. The surface area of the flatmount is 9413 mm². Reprinted from Adams and others (2007) with permission from the Society for Neuroscience.

Figure 3.

Ocular dominance columns in the human brain. Computer montages of layer 4C processed for cytochrome oxidase (CO) activity in a patient who became blind in the left eye about a year before death show the complete pattern of ocular dominance columns in striate cortex. The digital versions of the columns shown below were prepared by high-pass Fourier filtering of CO data followed by application of a threshold. The dotted line denotes the V2/V3 border. In area V2, alternating dark and light CO stripes are visible, but dark stripes cannot be classified as thick and thin. The process of flattening this right striate cortex is shown in Figure 2. Reprinted from Adams and others (2007) with permission from the Society for Neuroscience.

Figure 4.

The retinotopic map and ocular dominance column pattern in the human striate cortex. The medial face of the right hemisphere is depicted, with the calcarine sulcus opened to expose the striate cortex. Visual eccentricity is color-coded: The representation of the fovea is red and the far periphery is violet. CC = corpus callosum; POS = parieto-occipital sulcus. The visual field map is shown on a flattened specimen, with the retinotopic coordinates derived from Horton and Hoyt (1991). In this case, the ocular dominance columns were labeled by cytochrome oxidase staining, as shown in Figure 3. Projection of the striate cortex back onto the visual hemifield demonstrates the enormous magnification of central vision in the cortex. The central 16° are shown at higher magnification at the lower right. Because ocular

dominance columns are relatively constant in size, their projection onto the visual field is greatly distorted by cortical magnification.

Figure 5.

Human ocular dominance columns obtained using Hahn spin echo BOLD fMRI at 7 tesla. The image depicts a 3 mm thick slice through a flat portion of the cortex on the lower bank of the calcarine sulcus. Differential increases in activity following left eye stimulation (blue) and right eye stimulation (red) with a flickering checkerboard were imaged on two consecutive days and the maps registered. Arrows indicate the locations of left (cyan) and right (yellow) ocular dominance columns. Reprinted from Yacoub and others (2007) with permission from Elsevier.

Figure 6.

Ocular dominance columns in the right striate cortex of three different macaques. The columns were visualized by cytochrome oxidase staining after enucleation of the right eye in adulthood. Note the twofold variation in column periodicity among normal individuals from the same species. Reprinted from Horton and Hocking (1996c) with permission from the Society for Neuroscience.

Figure 7.

Comparison of human and macaque. Ocular dominance columns in the human after loss of the right eye, prepared by montaging cytochrome oxidase sections from layer 4C in the right V1. A thresholded version of the columns is shown below. For comparison, a typical column pattern from the macaque is shown (Horton and Hocking 1996c, their Fig. 3; reprinted with permission from the Society for Neuroscience.). The macaque pattern has been enlarged to equal the size of the human V1 illustrated above. These examples were chosen because the human and macaque patterns are quite similar; in general, columns in humans exhibit greater heterogeneity in periodicity and appearance. Reprinted from Adams and others (2007) with permission from the Society for Neuroscience.

Figure 8.

Capricious expression of ocular dominance columns in squirrel monkeys. For comparison, cytochrome oxidase (CO) montages of layer 4C from the left striate cortex of two squirrel monkeys are shown, after enucleation of the left eye. The case on the left shows large, crisply segregated columns, in stark contrast to the near absence of columns in the case on the right. The presence of the blind spot and angioscotoma representations on the right proves that the CO staining worked properly, that is, where monocular regions exist, they are visible. Reprinted from Adams and Horton (2003a) with permission from Nature Publishing Group.

Figure 9.

Mirror symmetry of column patterns. Left and right hemispheres from a squirrel monkey after removal of the left eye; the columns are well segregated in the peripheral cortex but dissipate in the central visual field (0° – 5°), except in the foveal representation (asterisk). Note the symmetry between the left and right hemispheres in the column patterns, although they are not identical. MC = monocular crescent. Reprinted from Adams and Horton (2003a) with permission from Nature Publishing Group.

Figure 10.

Macaque: Alignment of ocular dominance columns and patches. *A*, Autoradiograph of layer 4C, showing brightly labeled ocular dominance columns after monocular [^3H]proline eye injection. *B*, Cytochrome oxidase patches from the same region in layer 2/3. Arrows indicate blood vessels used to align the two images. *C*, The center of each patch is represented by a red dot and superimposed on a thresholded version of the column pattern. There is an obvious tendency for patches to align with column centers. Scale bar 5 mm.

Figure 11.

Squirrel monkey: Misalignment of ocular dominance columns and patches. *A*, Cytochrome oxidase patches from the upper layers of the squirrel monkey striate cortex. *B*, Autoradiograph of an adjacent section following [^3H]proline injection into the right eye. In contrast to the macaque, in which only alternate rows of patches are labeled, here every patch contains [^3H]proline. *C*, Layer 4C from the same region of striate cortex, showing the ocular dominance columns. Arrows denote blood vessels used to align the patches and columns. *D*, Patch centers are shown as red dots, overlying the thresholded ocular dominance column pattern. Unlike the situation in the macaque (Fig. 10), there is no relationship between patches and columns. Scale bar 5 mm.

Figure 12.

Shadows cast by retinal blood vessels are represented in the striate cortex. *A*, Retina of a normal squirrel monkey. *B*, Cytochrome oxidase (CO) staining after enucleation of the right eye reveals fine ocular dominance columns and blood vessel representations. Most angioscotomas are dark, because they represent vessels of the right eye's nasal retina, but a few are pale, representing the left eye's temporal retina. *C*, Drawing of the right fundus. Star = right fovea. The dotted lines denote the left eye's blind spot and major inferior fundus vessels (see left eye retinal, inset). Their temporal segments account for the two pale angioscotoma representations visible in the lower left cortex. *D*, Drawing of CO pattern, color-matching retinal and cortical features. MC = monocular crescent; BS = blind spot. Reprinted from Adams and Horton (2002) with permission from the American Association for the Advancement of Science.

Figure 13.

Macaque column shrinkage. Autoradiographic montages of layer 4C β in an adult macaque raised from age eight days with right eyelid suture. The right eye was injected with [^3H]proline to label the deprived columns (bright regions). They appear eroded, as if the open eye has worn away their surface by the same amount everywhere. Note the contrasting appearance of the deprived columns between the optic disc and monocular crescent in the two hemispheres. Their shrinkage seems greater in the right cortex, only because ipsilateral columns are small and fragmented in this region in normal monkeys (see Fig. 1). Surprisingly, the left eye's blind spot representation (inset) appears moth-eaten, although the deprived right eye's afferents should be at no competitive disadvantage in this region.

Figure 14.

Cat column shrinkage. *A*, Autoradiographic montage of layer 4, left V1 in a cat raised from age eight days with left eyelid suture, after left eye proline injection. The deprived columns are modestly shrunken. The remarkable finding is that the deprived eye's afferents formed into columns at all, considering that none were present when deprivation was initiated. *B*, Montage from another cat deprived at age eight days, prepared this time after injection of proline into the open, right eye. Arrow shows regions where the open eye has ceded territory to the deprived eye, despite its competitive advantage. Reprinted from Schmidt and others (2002) with permission from Oxford University Press.