Ocular dominance development revisited

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New approaches to the study of ocular dominance development, a model system for the development of neural architecture, indicate that eye-specific columns in primary visual cortex emerge substantially before the onset of the critical period, during which neural connections can be altered by visual experience. The timing, speed and specificity of column emergence implicate molecular patterning mechanisms, along with patterns of neural activity, in the generation of this columnar architecture.

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Abbreviations
LGN lateral geniculate nucleus
P postnatal day
V1 primary visual cortex

Introduction

Ocular dominance column formation and plasticity in primary visual cortex (V1) have long been thought to rely on activity-dependent competition between thalamic afferents representing the two eyes. This hypothesis was largely based on data from anatomical studies, employing transneuronally transported tracers [1–5]. However, improvements in anatomical and physiological techniques over the past decade suggest that the development of ocular dominance columns involves two phases: an initial establishment phase that may utilize innate signals and a later, plastic phase, corresponding to the critical period, that relies on patterned neural activity. Although most experimental approaches have focused on activity-related events during the critical period, new experiments will be required to determine the nature of the signals involved in the initial establishment of cortical structures. This review summarises the evidence that the establishment and plasticity of ocular dominance columns may be temporally and mechanistically distinct developmental events.

A brief history of ocular dominance column development

Hubel and Wiesel initially described ocular dominance columns — the organization of binocular responses familiar to most neurobiologists — in the early 1960s, on the basis of electrophysiological recordings in cat V1 [6]. They noted that neurons differed in the extent to which they were activated by each of the two eyes — the physiological property of ocular dominance — and that cells with similar eye preference were grouped together into columns. The ocularity of these columns was dictated by the pattern of eye-specific lateral geniculate nucleus (LGN) afferents innervating layer 4 of V1 [7,8]. Subsequently, it became possible to visualize ocular dominance columns, with the use of transneuronal transport of tritiated amino acids, such as proline (and later, sugars), injected into one of the eyes [1–5].

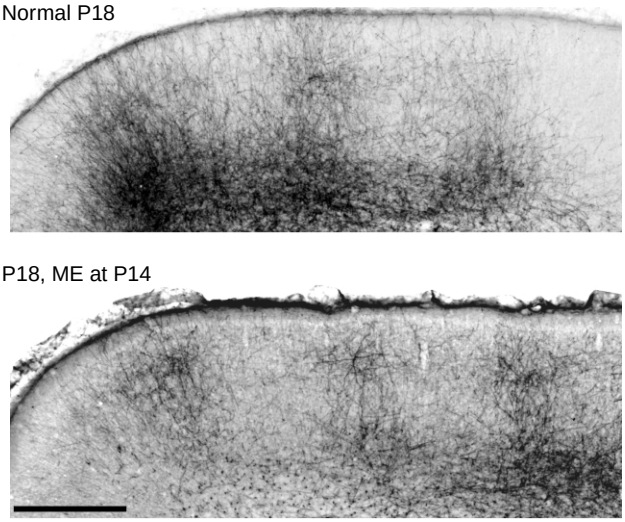
The organization of V1 into eye-specific columns was soon found to respond to alterations in visual experience. Monocular eye closure during the first months of life — the 'critical period' — led to a marked decline in the numbers of cells even partially activated by the closed eye, and dramatic increases in the number of neurons responding exclusively to stimulation through the open eye [9–11]. Transneuronal transport experiments revealed that these physiological changes were accompanied by corresponding anatomical changes, in which the size of the deprived eye columns was reduced and the size of the non-deprived eye columns expanded [4,5,12]. Thus, the termination patterns of axons arising from the eye-specific layers of the LGN correlated well with the physiological properties of cortical neurons following both normal and experimental rearing conditions. Recent data suggest that this relationship between anatomy and physiology in animals with experimentally manipulated visual experience may be initiated in layers 2 and 3 of V1 [13••,14]. But how do ocular dominance columns initially form? What mechanisms organize this cortical structure?

Separating establishment and plasticity: timing

There is now an emerging consensus that the initial establishment of ocular dominance columns takes place considerably before the critical period. In macaque monkeys, the basic anatomical structure of segregated LGN afferents in V1 is laid out well before birth [15,16]. Moreover, both anatomical ocular dominance segregation and physiological segregation are fully mature by birth [17,18]. Because the critical period for ocular dominance plasticity does not, by definition, begin until the onset of visual experience, critical period plasticity, strictly defined, cannot account for the initial instantiation of ocular dominance columns.

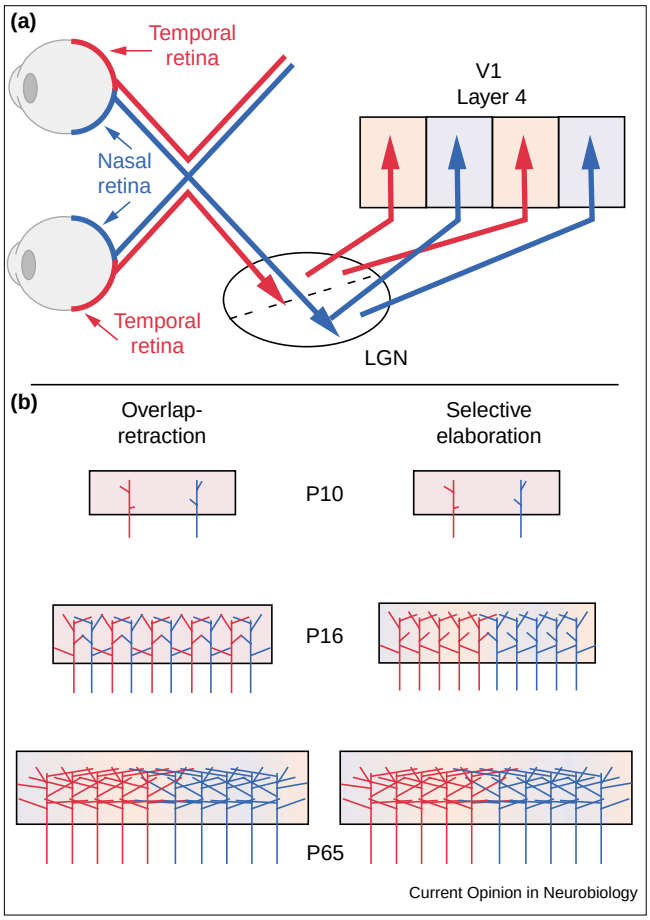
Recent data from the ferret indicate an even clearer distinction between the establishment of ocular dominance columns and the critical period. Following direct LGN injections of anterograde tracers — rather than transneuronal transport of label from eye injections — ocular dominance segregation is observed in the ferret within a week following the arrival of LGN axons in layer 4 (at postnatal day [P] 16; Figure 1) [19••]. This is at least three weeks before transneuronal tracing reveals columns (P36-37) [20,21], and well before the onset of the critical period in the ferret, which begins at about P33 [22]. *In vivo* multielectrode

Figure 1



Early appearance of ocular dominance columns and their resistance to monocular enucleation. Ocular dominance columns in ferret V1 appear prior to the onset of the critical period and are resistant to imbalances of retinal influence during this time. Both panels represent coronal sections and show three patches of labeled (dark) geniculocortical axons in layer 4 of the visual cortex, corresponding to ocular dominance columns. The top panel is from a normal P18 ferret. The bottom panel is a P18 ferret that was monocularly enucleated (ME) at P14. The size, spacing and general appearance of the columns from the two animals is similar. Scale bar, 500 μm, applies to both panels. Modified with permission from [19••].

Figure 2



Models for the development of the geniculocortical projection. **(a)** Eye-specific segregation of the retinogeniculate projection arises as axons from the nasal retina of the contralateral eye and the temporal retina of the ipsilateral eye terminate in eye-specific layers of the LGN. These eye-specific channels are conserved in the geniculocortical projection as LGN axons terminate into ocular dominance patches in layer 4 of visual cortex. **(b)** Two models for the development of the geniculocortical projection in the ferret. Both models begin with sparse geniculocortical innervation at P10 and end with segregated geniculocortical projections at P65 (end of the critical period). Red and blue axons correspond to different eye-specific populations of LGN axons. The model on the left is consistent with data from transneuronal transport. At P16, the projection consists of overlapping populations of axons. In this model, axon collaterals in this projection must retract and sprout in new locations in order to generate the adult pattern. The model on the right is consistent with data from direct LGN injections. It shows a segregated projection by P16 that is reinforced by selective elaboration in the appropriate regions.

recordings from the cortex of awake, behaving P22-28 ferrets have revealed patches of correlated activity that may correspond to ocular dominance columns or clustered horizontal connections [23••], suggesting that these early formed columns have a physiological correlate.

In developing cat cortex, it is also now evident that columns develop before the critical period. Using improved transneuronal tracing techniques and 2-deoxyglucose labeling, columns have been observed as early as P14 [24,25,26•], about a week before the onset of the critical period [27]. Because these findings relied on transneuronal transport, there is the possibility that in cats, as in ferrets, columns might emerge substantially earlier. Early studies of ocular dominance development recognized the difficulty associated with transneuronal transport labeling in the very young animals: the label tends to 'spill over' into inappropriate LGN layers. This problem may account for differences observed between transneuronal transport and direct LGN injection experiments.

In contrast to the original idea that column formation was a protracted process, it now appears that, in both cats and ferrets, columns emerge rapidly. In ferrets, LGN axons in V1 begin to enter the cortical plate at P10. At this age, these axons are sparse and simple (JC Crowley, LC Katz, unpublished data). In less than a week, clearly differentiated, eye-specific patches are apparent (Figure 2). This greatly attenuates the window for exuberant growth of axon arbors followed by retraction, and seems more consistent with selective elaboration of arbors into appropriate columns, similar to that observed in the development of eye-specific layers in the LGN [28]. Thus, development is relatively rapid and precise; it occurs before the retina (or the cortex) responds to visual stimulation, before layer 2/3 circuitry is in place and, as in the monkey, before the onset of the critical period [22].

Table 1

V1 features related to the structure of the geniculocortical projection.

Feature map	Relationship to LGN axons
Retinotopy	Spatial structure of environment is mirrored in retina, LGN and V1
Ocular dominance	Eye-specific LGN layers project to eye-specific patches in layer 4 of V1
Orientation	V1 layer 4 neurons receive axons with an oriented spatial bias
Spatial frequency	May result from variation in the population (magnocellular versus parvocellular) of LGN axons at a V1 site
Cytochrome oxidase blobs	Correlated with LGN K cell innervation in V1 layers 2 and 3

K cells: a neurochemically distinct population of LGN neurons that form a physiologically discrete channel in the geniculocortical projection.

Separating establishment and plasticity: mechanisms

In the most straightforward models of activity-based competition, afferents representing the two eyes compete with one another, on the basis of their ability to activate layer 4 cells. The starting point for this competition is assumed to be an equal representation of the two eyes and their roughly equivalent ability to activate postsynaptic neurons [29]. However, recent findings suggest that, before the critical period, the inputs from the two eyes may not be equivalent. Optical imaging of intrinsic signals in kittens revealed a strong bias towards the contralateral eye's inputs in the visual cortex, before the onset of the critical period. On the basis of conventional hypotheses of ocular dominance segregation resulting from Hebbian competition, this dominant contralateral innervation should prevent subsequent insertion of an ipsilateral columnar system, but this is not the case. In addition, short term monocular enucleation prior to the onset of the critical period [22], but after LGN axons have arrived in V1 layer 4, does not cause a corresponding change in the sizes of ocular dominance columns [19••]. This suggests that early-formed columns are refractory to imbalances in activity that later, during the critical period, will produce profound morphological changes. Thus, non-Hebbian mechanisms may be involved in the initial generation of ocular dominance columns [24], as some factor must permit ipsilateral eye inputs to overcome their initial disadvantage. These data imply, albeit indirectly, that the establishment of ocular dominance segregation relies on different mechanisms than the subsequent critical period. The speed and specificity of the initial establishment of ocular dominance columns, along with their resistance to manipulations of retinal input, may implicate molecular cues, intrinsic to the developing thalamocortical system, in the establishment of columns.

In addition to visually driven retinal activity, endogenous patterns of activity are also present in the prenatal mammalian retina. Retinal waves, the endogenous patterned activity occurring in the normal developing retina before the onset of vision [30–33], meet many of the theoretical requirements for the establishment of circuitry in the visual system [34]. Retinal waves generate local correlations of activity in the retina of one eye that are not correlated with activity in the other eye, and thus could segregate afferents by eye, according to Hebbian competition. However, even when retinal influence is removed before LGN axons reach layer 4 (at P0), LGN axons can still segregate in layer 4 [35]. These experiments indicate that retinal waves are not required for generating segregated patterns of thalamic afferents. Nevertheless, they cannot rule out a role for activity that persists in the developing geniculocortical circuit [36], including Hebbian competition. Recordings from the developing ferret LGN indicate that bilateral enucleation increases the correlation between activity patterns in the eye-specific layers of the LGN [36], but does not eliminate them. Moreover, enucleation can result in substantial changes in the organization of the LGN [37], and these segregated patterns could represent something other than differences in ocularity.

Visual stimulation clearly affects the structure of ocular dominance columns during the critical period, and this period of plasticity corresponds to the time that ocular dominance columns first become visible using transneuronal transport labeling [4]. Because activity driven by retinal stimulation can pattern LGN axons and ocular dominance columns, and the critical period coincided with the time that transneuronally transported tracers demonstrated segregation, it was reasonable to hypothesize that the mechanisms underlying both developmental events were the same [4,5,12]. Thus, a single, parsimonious hypothesis was able to explain both the well-described phenomenon of ocular dominance plasticity and the initial organization of eye-specific afferents into discrete columns.

However, ocular dominance columns do not develop in a vacuum, but are constrained by several other features of cortical organization. Ocular dominance columns are related to a variety of columnar systems, as well as to the map of visual space. Some of the most striking features of V1 organization, such as retinotopy, ocularity, orientation, direction, spatial frequency, and cytochrome oxidase rich blobs, are spatially organized. Like ocular dominance columns, many of these maps arise, in part, from the pattern of LGN axons in V1 (Table 1), and are related to the pattern of ocular dominance columns. For example, there are clear relationships between the map of visual space (i.e. retinotopy) and ocular dominance columns [38]. Retinotopy in many visual system structures is likely to arise from chemical gradients in afferents and target structures [39,40]. Thus, at some level, columnar patterns must also be constrained by such cues. In contrast to retinotopy, ocular dominance development has been viewed largely as an outcome of activity-dependent competition [4,29,34,41,42]. Yet, if maps generated by molecular mechanisms are aligned with ocular dominance columns, some mechanism(s) must be in place

to bring these maps in register; LGN axons must obey a number of rules simultaneously. It has been suggested that the tangential pattern of ocular dominance columns optimizes cortical processing of binocular responses [43]; this would imply that a pattern present prior to birth [15,16,18] anticipates visual experience, rather than being patterned by it. Such anticipatory development seems more consistent with an innate set of map relationships.

Conclusions and future directions

Until recently, there has been little experimental foundation for the idea that the establishment and plasticity of ocular dominance columns may rely on different mechanisms [44]. Consequently, few experiments have been designed to directly search for evidence of other patterning signals. If molecular patterning is involved in forming ocular dominance columns, new types of investigations, in addition to manipulations of activity, will be required. For example, an examination of the structure of V1 maps in identical twin animals could yield important structural correlations between the maps of animals with identical genetic backgrounds (although the value of such experiments has been questioned [45]). Through the comparison of human monozygotic and dizygotic twins and unrelated subjects, a recent report has demonstrated strong genetic influences on the structure and formation of neocortical gray matter [46]. The similarities and/or differences between such maps could lead to a better understanding of the types of cues involved in generating cortical maps, such as ocular dominance columns. To date, no evidence has shown that V1 maps in the two hemispheres of individual animals are mirror images of each other, but similarities in map structure do exist between the hemispheres of individuals [47–50] and common genetically based patterning forces should yield commonalities in map structure. Such potential relationships in V1 map structure have been examined using 'wavelet analysis' to extract multiple spatial features of cyclic cortical maps for comparison and analysis [49,50,51•]. This represents a substantial improvement over previous studies that have relied on more rudimentary analyses of column size and spacing.

Another important area of future research concerns the relationships between different V1 maps. As mentioned above, the geniculocortical projection is closely associated with several V1 maps (Table 1). Many different structural relationships have been observed between a variety of map combinations, including ocular dominance and retinotopy (see above), ocular dominance and orientation [3,52–56], and cytochrome oxidase staining and ocular dominance [57–60]. It has been argued that such relationships are optimized for the coverage of stimulus features [3,61•,62]. Because feature maps constrain each other, a closer examination of the nature of map relationships and their development may yield insights into the mechanisms that generate ocular dominance columns and other maps.

In addition, an explicit search for patterning molecules in the visual system seems warranted. The Eph family of receptor protein tyrosine kinases has been directly implicated in topographic mapping in the mammalian central nervous system, and has been shown to affect the sizes of modular structures in the somatosensory system [63]. Additional signaling systems, as yet unknown, are also likely to be present. As microarray and differential display technologies improve, patterning molecules that could play a role in the generation of ocular dominance segregation may be identified. Left and right eye columns actually arise from different layers of the same LGN; these layers can be thought of as specific for either nasal or temporal retina, rather than for the left or right eye (Figure 2) [64]. Cues involved in constructing this dichotomy in the retina may be reflected in more central structures, such as the visual cortex.

The suggestion that molecular mechanisms may play a significant role in the establishment of ocular dominance columns does not exclude a pivotal developmental role for neural activity. Patterns of activity could participate in the instruction of V1 organization, or activity patterns could provide essential cues for normal patterns of gene expression [34,44,65•]. Finally, previous observations on the role of the subplate in the development of ocular dominance columns [66] have taken on renewed importance, as the establishment of ocular dominance columns has been found to occur just after the time that LGN axons reside in the subplate.

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