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A precritical period for plasticity in visual cortex

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One of the seminal discoveries in developmental neuroscience is that altering visual experience through monocular deprivation can alter both the physiological and the anatomical representation of the two eyes, called ocular dominance columns, in primary visual cortex. This rearrangement is restricted to a critical period that starts a few days or weeks after vision is established and ends before adulthood. In contrast to the original hypothesis proposed by Hubel and Wiesel, ocular dominance columns are already substantially formed before the onset of the critical period. Indeed, before the critical period there is a period of ocular dominance column formation during which there is robust spontaneous activity and visual experience. Recent findings raise important questions about whether activity guides ocular dominance column formation in this 'precritical period'. One developmental event that marks the passage from the precritical period to the critical period is the activation of a GABAergic circuit. How these events trigger the transition from the precritical to critical period is not known.

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Introduction

A central dogma of neural development has been that formation of precise visual circuits is guided by experience. This theory was based on the pioneering work of Hubel and Wiesel, who demonstrated that altered sensory experience can influence the development of ocular dominance columns (ODCs), the eye-specific zones of thalamic innervation in Layer 4 and their corresponding cortical columns that characterize primary visual cortex [1–3]. Their work described a 'critical period' that is defined as the time during which transient closure of one eye can alter the structure of columns [2–5]. These classic studies suggested that the critical period also corresponds to the time during which ODCs were sculpted out of an initially unpatterned thalamocortical projection.

It is now clear that ODCs form much earlier than previously thought, soon after thalamic axons have entered the visual cortex and long before the onset of the critical period for monocular deprivation. We define the 'precritical period' as starting with the entrance of thalamic axons into layer 4 of the cortex (before eye-opening) up to the onset of the critical period (days to weeks after eye-opening, depending on the species — see Table 1). Here, we review recent observations that address whether or not the formation of ODCs during the precritical period is dependent on spontaneous activity and visual experience. We also discuss possible mechanisms underlying the transition between the precritical and the critical periods. We restrict this discussion to work conducted in species in which most of the precritical period is after birth, such as cats, ferrets and mice.

Ocular dominance columns are formed before the critical period

A predominant manipulation for inducing cortical plasticity is monocular deprivation, during which a single eye is sutured closed while the other eye remains open. After a period of monocular deprivation lasting a few days, there is an increase in the number of individual neurons in primary visual cortex that respond preferentially to the open eye compared with the number that respond to the deprived eye. These physiological changes are followed by anatomical rearrangements: initially, the thalamocortical arbors from the closed eye shrink their arborizations and then the axonal arbors driven by the open eye expand. In addition to thalamocortical axonal rearrangements, there are changes in horizontal connections between neurons in layer 2/3 [6,7].

These cortical rearrangements in response to monocular deprivation occur during a relatively short window in development called the critical period. The activity-dependent rearrangements that occur during the critical period have been used as a model for Hebbian-based plasticity. Until recently, a Hebbian-based model of activity-dependent competition between the two eyes has also been used to explain the establishment of ODCs (see [8] for a review). This model is based on two assumptions: first, that initial projections are overlapping until the start of the critical period, and second, that the strength of the connections from the two eyes is equally balanced.

Several findings in the past few years have called into question this model of development of ODCs. Using the

Table 1

Summary of various stages of development of the visual systems described in this manuscript.

Cats	Ferrets	Mice	Developmental period	Anatomy	Physiology
	P0	P0	Precritical	Retinal ganglion cells in dLGN	Retinal waves
E50	P9	P8	Precritical	Eye specific layers in dLGN, thalamic axons reach L4	Retinal waves
	P15			ODCs observed [10]	
	P20	P10	Precritical		Light responses [19] and retinal waves
P8	P32	P14	Precritical		Eye opening; vision (in all) and waves (in mouse [20] but not in ferret [63])
P14				ODC observed [9]	ODC observed [11]
P21	P38 [12]	P21	Start of critical period for monocular deprivation		Vision
P30	P48	P40	Peak of critical period		Vision
P40	P60		End of critical period		Vision

The table provides a list of the developmental periods, descriptions of retinogeniculate and thalamocortical projections and the origins of retinal activity for the various ages and species described in this review.

trans-synaptic marker 3H-proline, ODCs could not be clearly discerned until the onset of the critical period [3]. However, using anatomical techniques that better define projections from the eye-specific regions of the lateral geniculate nucleus (dLGN), ODCs can be detected as early as the onset of visual experience, at least 7 days before the critical period in cats [9] and 30 days before in ferret [10]. In addition, physiological studies in cats [9,11], ferrets [12], and mice [13] indicate that there is functional ocular dominance segregation in response to visual stimulation for several days to weeks before the onset of the critical period. These studies also revealed that during this precritical period there is a strong contralateral bias — namely that visual cortical cells are better driven by inputs from the contralateral eye than those from the ipsilateral eye. Hence, the connections from the two eyes are not equally balanced. The extent of this contralateral bias varies somewhat across species.

Is there a role for activity in ocular dominance map formation during the precritical period?

The early formation of ODCs does not imply that they are established independently of activity. There are two modes of activity in the visual system during the precritical period — spontaneous and visually driven.

At the beginning of the precritical period, when thalamic axons are growing into visual cortex, the immature retina spontaneously generates highly correlated activity patterns termed retinal waves [14]. Individual retinal ganglion cells fire short bursts of action potentials that are strongly correlated across neighboring cells and are separated by long periods of silence. This firing pattern makes it unlikely that retinal ganglion cells from the two eyes fire simultaneously, and therefore provides a signal for activity-dependent sorting of right and left-eye inputs. Indeed, spontaneous retinal activity drives the segregation of retinal ganglion cell projections into eye-specific layers within the dLGN (for recent review, see [15•]).

There is a significant portion of the precritical period during which response to light and retinal waves co-exist. In ferrets, light responses have been detected in the dLGN [16] and visual cortex [17] two weeks before eye opening. The developmental impact of this early visual activity is supported by the fact that dark rearing even before eye opening can alter the refinement of circuits within the retina [18] and dLGN [19]. Whether or not dark rearing during this period affects the development of cortical circuits is yet to be determined. In addition, in mice, it has been demonstrated that retinal waves persist for a few days after eye opening [20]. Hence, manipulations during this precritical period must take into account that both visually evoked and patterned spontaneous activity might be affected.

To date, experiments have only tested indirectly whether precritical spontaneous and visually evoked activity are involved in the establishment of ODCs. A transient population of subplate neurons resides below the developing cortex and is required for the normal ingrowth of thalamic axons into the appropriate regions of sensory cortex [21]. Elimination of these subplate neurons prevents thalamic axons from making strong synapses with layer 4 of visual cortex [22••]. This manipulation effectively decouples the spontaneous and visually evoked signaling from thalamus to cortex. Under these conditions, both spontaneous activity-driven and visually driven inputs are much weaker and ocular dominance maps fail to form. Although these data clearly suggest that electrical activity is important for ODC formation during the precritical period they do not address whether activity is instructive, namely that the pattern or balance of activity is critical for driving ODC formation, or is playing a 'permissive role', namely that some baseline level of firing is important for normal cell function [23,24].

Is there a specific role for retinal waves in the formation of ODCs during the precritical period? To date, no manipulations have been conducted that address this question

directly. Mice lacking the β2 subunit of the nicotinic acetylcholine receptor have no retinal waves but have maintained firing of individual retinal ganglion cells for the first postnatal week and normal retinal waves during the second postnatal week ([25,26], reviewed in [27]). In these mice retinogeniculate axons failed to segregate into the normal monocular layers in the dLGN, segregating instead into small disorganized regions [28,29]. Although mice have no ODCs as such, they have a binocular cortical region where the relative strength of the inputs from each eye can be shifted during the critical period with monocular deprivation protocols, similar to the situation in animals with ODCs. Visually evoked potential recordings in primary visual cortex of $\beta 2^{-/-}$ mice revealed a significant expansion of the binocular subfield of visual cortex [25]. These findings indicate that retinal waves might be crucial either directly by driving ocular dominance segregation in cortex or indirectly by establishing eye-specific segregation within the dLGN, which is in turn crucial for the formation of ODCs.

Is there a specific role for visual experience in the formation of ODCs during the precritical period? To address this question, manipulations of visual experience should be restricted to the precritical period. Crair and coworkers [11] found that in kittens, binocular deprivation from the onset of eye opening did not prevent the strengthening of ipsilateral inputs as assayed with electrophysiology and optical imaging (although the resulting ipsilateral projection was weaker than in normal kittens). These studies suggest that the activity involved in the formation of ODCs is not visually evoked or that the developmental increase in the strength of the ipsilateral representation is activity-independent during the precritical period. Interestingly, recent experiments using visual deprivation have concluded that visual experience during the precritical period might influence the development of visual cortical circuits by adjusting the strength of synaptic inputs [30] and influencing spine formation [31], although not spine motility [32,33]. Whether or not these results have implications for ODC formation is yet to be determined.

The most convincing evidence that neither visually evoked nor spontaneous retinal activity is required for ODC formation comes from enucleation studies. Crowley and Katz showed in ferret that neither monocular [10] nor binocular enucleation [34] at any time between P0 (before the formation of eye-specific layers) and P15 (after eye-specific layer formation and while dLGN axons are making synapses in cortex) affected the clustering of thalamic axons into ODCs. On the basis of these findings, Crowley and Katz hypothesized that activity was not required for thalamocortical axons to cluster into eye-specific domains. However, these manipulations do not rule out a role for activity downstream from the retina, for example in the dLGN [35] or visual cortex itself [36], in ODC formation during the precritical period. Indeed, after enucleation, spontaneous activity patterns in the dLGN persist that have similar spatial and temporal patterns to those induced by retinal waves, and could therefore instruct sorting of thalamocortical axons [35].

Are there activity-independent instructions for precritical ocular dominance map formation?

How might ocular dominance maps form if not by activity? There is intriguing evidence that molecular signatures could be used for sorting right-eye and left-eye inputs. Such molecular signatures have been found in retinogeniculate projections. Contralateral projecting retinal ganglion cells emerge from nasal retina and ipsilateral projections from temporal retina, and hence eye-specific layers in the dLGN also correspond to nasal or temporal layers. The zinc finger transcription factor Zic2, for example, is expressed at higher levels in retinal ganglion cells that do not cross the optic chiasm than in those that project contralaterally [37]. In addition, expression of Eph receptors follows a nasal–temporal gradient across the retina [38]. Molecular markers for contralateral or ipsilateral axons could be conveyed to thalamic neurons. Although no such markers have been discovered yet, it is interesting to notice that eye-specific layers in the dLGN, and hence eye-specific identity of relay neurons, are well defined before the arrival of thalamic axons in the visual cortex. Hence, these presynaptic markers might contribute the eye-specific fasciculation of thalamic axons thereby giving rise to ODCs in the cortex. A final possibility is that cortical molecular markers sort thalamic axons into ODCs according to a predetermined pattern.

The existence of molecular markers might be crucial for establishing eye-specific layers, perhaps by appropriate targeting of axons, but it cannot be the entire story. As described above, patterned activity is likely to be required for establishing eye-specific segregation of retinal projections to the dLGN. Whether activity functions to over-ride molecular cues or perhaps alter the expression of them is not yet established. Similarly, even if ODC formation develops with some activity-independent instruction, there is likely to be significant remodeling by activity. Thus, the completely genetically predetermined versus the completely activity instructive models might represent an artificial dichotomy.

Inhibition triggers the transition between precritical and critical period

What triggers the start of the critical period? To address this question, several studies have been conducted on mice lacking the γ-amino-butyric acid (GABA) synthetic enzyme GAD65. In contrast to the diffuse and predominant GABA synthesizing enzyme GAD 67, the GAD 65 isoform is localized at synaptic terminals of GABAergic axons and it is believed to contribute to GABA production during short (few hundreds of milliseconds) episodes of

high frequency activity [39]. In GAD65 knockout (KO) mice, brief monocular deprivation during the critical period does not lead to ocular dominance shift. If however, the affinity of $GABA_A$ receptors for GABA is enhanced through the administration of an allosteric modulator such as benzodiazepine (as a way to compensate for the reduced GABA synthesis), monocular deprivation produces the normal ocular dominance shift. These data suggest that in the GAD65KO mice the critical period does not begin unless GABAergic function is enhanced by benzodiazepines [40]. Interestingly, this benzodiazepine-dependent rescue of the critical period can occur at any stage of life in GAD65KO mice, indicating that the onset of the critical period is not tied to the age of the animal.

One should note that the presence of benzodiazepines is not necessary during the actual monocular deprivation protocol for the ocular dominance shift to take place in GAD65KO. In fact, brief monocular deprivation in GAD65KO mice up to two weeks after the administration of a bolus of benzodiazepines (i.e. long after benzodiazepines have disappeared from the organism) still leads to ocular dominance shift [41]. Hence, benzodiazepines trigger a series of events that outlast their presence in the system. In other words, benzodiazepines promote the transition to the critical period but are not necessary for its expression.

The induction of the critical period by benzodiazepines does not only occur in GAD65KO mice. In wild type mice, benzodiazepine treatment before the natural start of the critical period at P21 can trigger its precocious onset. As early as P16, application of benzodiazepines is sufficient to induce the occurrence of plasticity in response to monocular deprivation [40]. Importantly, the series of events triggered by benzodiazepine follows a time course very similar to the naturally occurring critical period, in that benzodiazepines applied during the precritical period in wild type mice not only accelerate the opening but also the closure of the critical period [41]. These observations suggest that activation of $GABA_A$ receptors is a crucial step in mediating the transition from the precritical to the critical period.

A series of different approaches are also consistent with a link between the maturation or efficacy of the GABAergic system and the time-course of the critical period. First, in transgenic mice that overexpress brain-derived neurotrophic factor (BDNF), the development of GABAergic neurons is accelerated as well as the transition to and closing of the critical period [42,43]. Second, in dark-reared animals, in which the maturation of inhibitory circuits is impaired, ocular dominance shifts can be triggered throughout life [44–47]. Third, transient benzodiazepine treatment appears to increase the strength of cortical inhibition in GAD65KO mice persistently [41].

By what mechanism does the allosteric modulation of cortical $GABA_A$ receptors promote the transition between precritical and critical period? Is the action of benzodiazepines at the beginning of the critical period conveyed by $GABA_A$ receptors with a specific subunit composition? Mammalian $GABA_A$ receptors are structurally heterogeneous, in that they are differentially assembled from at least 19 subunits (6α, 4β, 3γ, 1δ, 1ε, 1π, 3ρ; [48]). Benzodiazepines bind at the interface between any $\alpha 1,2,3,5$ and the $\gamma 2$ subunit, and a point mutation in the α subunit is sufficient to eliminate the sensitivity of $GABA_A$ receptors to benzodiazepines. Fagiolini *et al.* [49••] took advantage of a series of transgenic mice lines each expressing a point mutation on a specific α subunit, thus rendering the $GABA_A$ receptor expressing that subunit insensitive to benzodiazepines. These mice were originally generated to distinguish between the sedative and the anxiolitic effects of benzodiazepines [50,51]. Fagiolini *et al.* [49••] noticed that solely in those mice whose the $\alpha 1$ subunit had been mutated, the precocious transition to the critical period by benzodiazepines was no longer elicited. Hence, out of the many different $GABA_A$ receptor subtypes expressed in the cortex, the $\alpha 1$ expressing receptors appear to be uniquely responsible for the precocious trigger of the critical period through benzodiazepines.

This result might enable us to start unraveling the cellular mechanisms responsible for the transition between the precritical and the critical period: where are $\alpha 1$ containing $GABA_A$ receptors located and what is the source of GABA that activates them? The $\alpha 1$ subunit is the predominant α subunit in the cortex [52,53]. At the light-microscopic level, the $\alpha 1$ subunit appears to be expressed highly among all cortical layers, and is present on both pyramidal cells and GABAergic interneurons. A closer, electron-microscopic look at the somatic distribution of $\alpha 1$ subunits on pyramidal cells reveals that they are preferentially enriched at synapses formed by one of the two main types of basket cells, namely those expressing parvalbumin (PV) rather than cholecystokinin (CCK; [54,55] basket cells are a class of GABAergic interneurons that have axons that impinge on the soma and perisomatic regions of pyramidal cells [56•]). Interestingly, the $\alpha 1$ subunit is also expressed highly on the membranes of PV-expressing basket cells [55,57]. These data suggest that PV-positive basket cells might be involved in the opening of the critical period, either as the source of GABA for the activation of $\alpha 1$ expressing $GABA_A$ receptors, located, for example, on pyramidal cells, or as the recipients of inhibitory transmission by way of $\alpha 1$ containing $GABA_A$ receptors expressed on their somata.

Future work will elucidate whether or not additional classes of inhibitory neurons that might also release GABA on receptors preferentially containing the $\alpha 1$ subunit are involved in the opening of the critical period.

It is fascinating that a transient and selective activation of $GABA_A$ receptors with a pharmacological agent triggers a chain of events that ultimately enables visual experience to modify cortical circuits. This chain of events might involve the maturation and strengthening of the GABAergic system itself, as suggested by Iwai *et al.* [41].

One could imagine different scenarios of how increased inhibition through α1-containing $GABA_A$ receptors might trigger the opening of the critical period. One possibility is that a transient powerful inhibition, as produced by benzodiazepine or by the maturation of synaptic inhibition during normal development [58], results in a compensatory 'homeostatic' increase of excitation onto pyramidal neurons. A stronger synaptic excitation onto cortical neurons might then serve as the essential substrate for Hebbian competition between the two eyes to take place. A second possibility raised by Fagiolini *et al.* [49••] relies on the fact that synaptic inhibition plays an important part in maintaining the temporal structure of sensory inputs across synapses [59,60]. Accordingly, stronger inhibition might promote discrimination among independent inputs on the basis of temporal differences in their activity, providing the basis for Hebbian competition.

Conclusions

By the onset of the critical period ocular dominance maps exist. To understand the mechanisms by which these maps are formed future experiments need to address the role of spontaneous and visually evoked activity. As a first step, it is essential to ascertain the impact that manipulations have on activity. For example, visual deprivation experiments do not necessarily lead to fewer action potentials because there is a high level of intrinsic firing within the cortex [61•] that can be altered by visual deprivation [62••]. We also need to determine the role of molecular markers during the precritical period of map formation, bearing in mind that there might be reciprocal interactions between the level of activity and the expression of molecular markers. Finally, elucidating the role of specific elements of the cortical circuitry that mediate the transition between precritical and critical periods will provide key insights into the cellular basis of these two distinct developmental periods.

Why have both a precritical and a critical period? One possibility is that the precritical period enables gross map formation, which precedes and is distinct from map refinement. The critical period, with its exquisite sensitivity to visually evoked activity, will enable the refinement of the pre-formed maps according to the unique properties of individual sensory organs and the visual experience of the individual animals.

Update

A recent study by Frenkel and Bear [64] addresses how monocular TTX and monocular deprivation during the precritical period differentially affects cortical firing patterns and resulting cortical plasticity. Recently, a screen revealed factors that differentiated several functional regions within visual thalamus [65]. As part of this heroic study, tissue from each eye-specific layer of P16 ferret dLGN was microdissected and used to generate cDNA libraries. Factors specific for dLGN cells localized to the contra versus ipsi-recipient layer were not identified. However, the screen would not be sensitive to molecules expressed as gradients or ones that are transiently expressed during eye-specific segregation.

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