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Intrinsic patterning and experience-dependent mechanisms that generate eye-specific projections and binocular circuits in the visual pathway

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A defining feature of the mammalian nervous system is its complex yet precise circuitry. The mechanisms which underlie the generation of neural connectivity are the topic of intense study in developmental neuroscience. The mammalian visual pathway demonstrates precise retinotopic organization in subcortical and cortical pathways, together with the alignment and matching of eye-specific projections, and sophisticated cortical circuitry that enables the extraction of features underlying vision. New approaches employing molecular-genetic analyses, transgenic mice, novel recombinant probes, and high-resolution imaging are contributing to rapid progress and a new synthesis in the field. These approaches are revealing the ways in which intrinsic patterning mechanisms act in concert with experience-dependent mechanisms to shape visual projections and circuits.

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Introduction

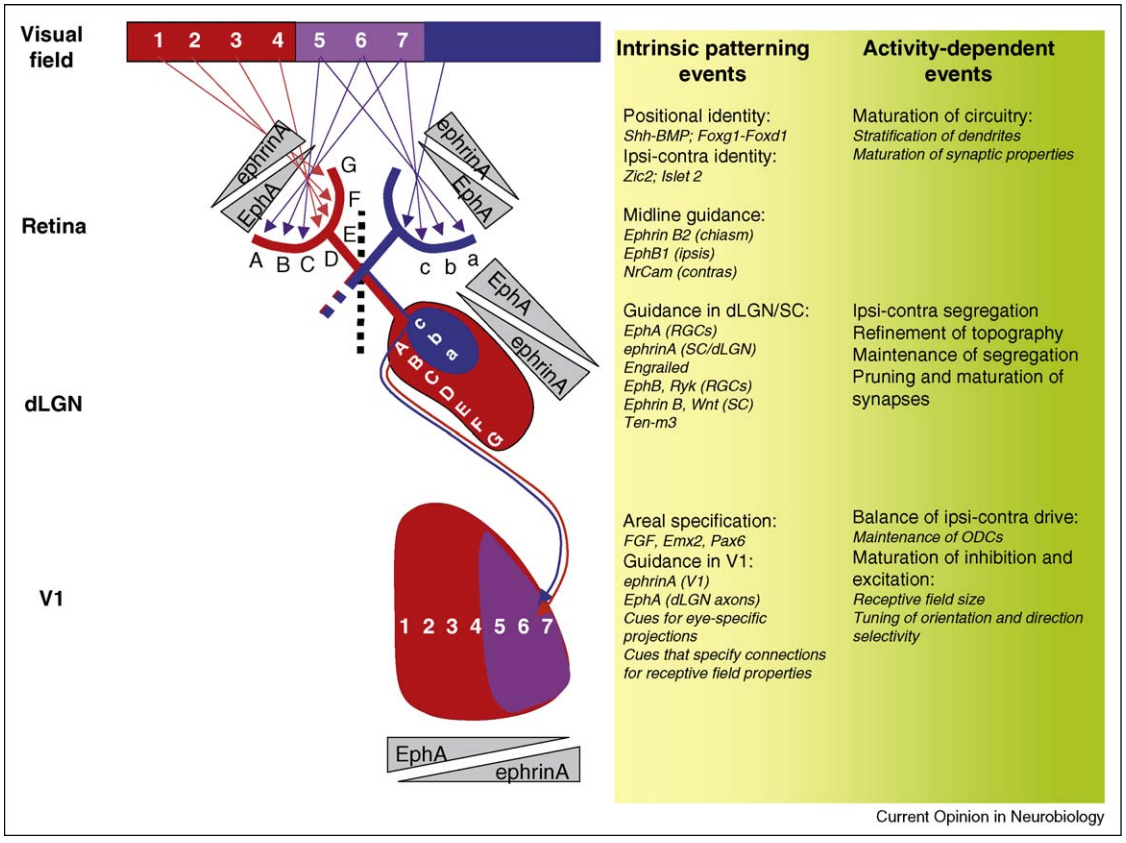
Specific neural connections underlie all our sensory, cognitive, emotional, and motor capacities. A fundamental organizing principle of many neural circuits is topography: the maintenance of relative spatial relationships between afferent and target fields. In the visual system this ensures that visual space is faithfully represented at successive levels of the neuraxis. The accessibility and highly stereotyped organization of the visual system is a useful and informative model for identifying the mechanisms which regulate neural connectivity. In particular, seminal studies performed almost 50 years ago by Roger Sperry showed that neurons have chemical identities which determine their overall projection patterns, while David Hubel and Torsten Wiesel showed that neural circuits can be modified by sensory experience. The mechanisms underlying the generation of visual, and particularly binocular, circuits has continued to 'blaze the way', serving as an important testing ground for the field. This review focuses on recent studies which provide insight as to how early patterning and experience-dependent mechanisms interact to generate neural connectivity.

The generation of visuotopy

Binocular vision improves visual ability, enhancing motion detection, acuity, and depth perception. In order to generate a single cohesive map of visual space, inputs from the two eyes which see the same part of visual space must converge in the brain. The alignment of the retinal ganglion cell (RGC) axons is a complex, multifaceted process, which requires the mapping of ipsilateral and contralateral inputs to be reversed across the azimuth (nasotemporal) axis (Figure 1). In primary targets such as the superior colliculus (SC) and dorsal lateral geniculate nucleus (dLGN) the inputs are visuotopically aligned but segregated into eye-specific domains. The inputs come together in the binocular region of the primary visual cortex (V1) where they ultimately converge onto single cells.

A critical step in the generation of binocular circuits is the pattern of decussation of the RGC axons. The ipsilateral projection originates from temporal retina and defines the binocular field (Figure 1). The size of the ipsilateral projection varies between species and is closely correlated with eye position (reviewed in [1]). In mice, contralateral projections arise from the entire retina and ipsilateral projections (3% of RGCs), are confined to the peripheral ventrotemporal crescent (VTC). In primates, the temporal half of the retina gives rise almost exclusively to the substantial (40% of RGCs) ipsilateral projection. The pattern of decussation is tied to the early specification of retinal identity. The zinc finger transcription factor Zic2 specifies ipsilateral identity by promoting the expression of the axon guidance molecule EphB1 [2•,3,4], which prevents axons from crossing the ephrinB2-rich optic chiasm midline. Foxd1, which is highly expressed in VT retina promotes ipsilateral identity [5] whereas Foxg1, which has the reciprocal expression pattern, represses ipsilateral fate

Figure 1



Intersection of intrinsic patterning and experience-dependent processes in the development of eye-specific projections. Left panel depicts the mapping of the contralateral visual field (1–7) in the geniculocortical pathway in the mouse. Only projections onto the right hemisphere of the brain are shown for simplicity. Visual field 1–7 projects onto the left (red) retina G–A. Visual field 5–7 is also seen by the right (blue) eye a–c in temporal retina (region of binocular overlap is shown is purple). Note that a given point in the binocular field (5–7) falls onto a different part of each retina (arrows). The entire left retina projects systematically onto the right dLGN (A–G). Repulsive interactions between reciprocal EphA and ephrinA gradients in the retina and dLGN help to mediate this mapping: high EphA expression in retina (point A) maps to region of lowest ligand expression in the dLGN. The ipsilateral projection also maps systematically onto the dLGN (a–c). The inputs are visuotopically aligned: red A is aligned with blue c; both these points view visual field 7. Note, however, that red A and blue c arise from different retinotopic positions. Visuotopic alignment requires a reversal of ipsilateral mapping across the azimuth; this is not accounted for by known EphA–ephrinA mapping mechanisms and suggests a role for eye-specific mapping cues. This specificity is critical for appropriate representation of the visual field in V1 where ipsilateral and contralateral inputs converge to generate a cohesive map of visual space. EphA–ephrinA interactions also help to mediate cortical mapping. Right panel lists intrinsic patterning events (with underlying molecular mechanisms in italics) and activity-dependent events (with specific features in italics) acting at different levels of the visual pathway that are critical for the generation of eye-specific projections and binocular circuitry. At some levels intrinsic patterning molecules provide a template which is further shaped by visual experience. At other levels there may be direct interactions between the two (see text for details).

[6]. Foxg1 may also regulate another major aspect of retinal identity, the topography of its projections [7].

Molecular gradients are present in the retina, SC, and dLGN and play important roles in the generation of topography (reviewed in [8]). Members of the EphA receptor family are expressed in a high temporal–low nasal retinal gradient in mice, whereas their ligands, the ephrinAs, are expressed in a high caudal–low rostral gradient across the SC. RGC axons from temporal retina, with high EphA expression, are repelled from regions of high ephrinA expression and map to rostral SC. Nasal axons, with low levels of EphA expression are not repelled, and may even be attracted by [9], high ephrinA expression and thus map to caudal SC. Engrailed may also attract nasal axons to caudal SC [10]. Deletion of ephrinAs or EphAs disrupts mapping, both anatomically [8] and functionally [11,12]. Similar relationships exist for the dLGN [13]. A critical step in the generation of retinotopy in rodents is the control of interstitial branching [8]. There is evidence that a high nasal–low temporal gradient of ephrinA across the retina interacts with a high rostral–low caudal EphA gradient across the SC to prevent nasal axons from branching in rostral SC [14]. Interestingly, recent work has demonstrated that the growth-promoting effects of BDNF and TrkB interact

with ephrinA to achieve region-specific branching [15•]. EphB–ephrinB interactions help to map the dorsoventral retinal axis onto the lateromedial axis of the SC [8]. Wnt–Ryk also plays a role in patterning the dorsoventral axis [16]. Topographic and eye-specific projections are fundamental aspects of retinofugal development, and the template for these identities is present from extremely early developmental stages. Antagonistic interactions between the sonic hedgehog (Shh) and bone morphogenic protein (BMP) signaling pathways pattern the dorsoventral axis of the neural retina (reviewed in [17]) and thus regulate topographic mapping, in part via EphB expression [18,19•]. Foxg1 can regulate the identity across both the nasotemporal and dorsoventral axes [7].

While important, intrinsic patterning mechanisms are not sufficient to generate mature patterns of connectivity. Neural activity is also required and recent evidence suggests that it may interact directly with axon guidance molecules. Deletion of the β2 subunit of the nicotinic acetylcholine receptor, which disrupts spontaneous waves of retinal activity before eye-opening without blocking all retinal activity, results in much larger, though appropriately placed terminal arbors [13,20]. Interestingly, disruption of retinal waves has a much greater impact on the mapping of the nasotemporal than the dorsoventral retinal axis [11,19•,20]. Mechanistically, this may relate to the observation that activity is required for RGC axons to respond to ephrinAs *in vitro* [21••] and/or interactions between ephrinA and BDNF–TrkB signaling [15•]. The reduced requirement for activity in patterning the dorsoventral retinal axis may also correlate with the presence of BMP-mediated order in the optic tract [19•].

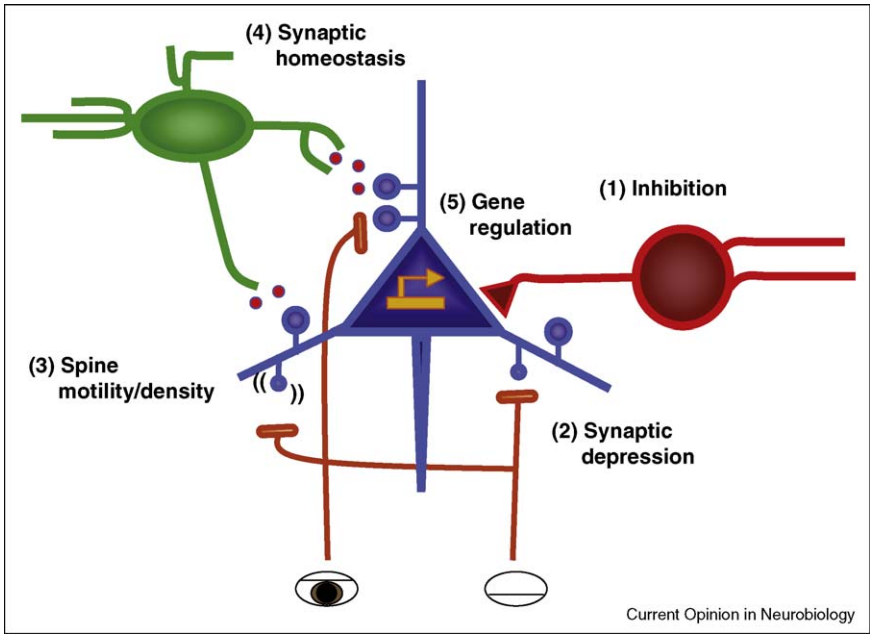
The mechanisms that regulate the mapping of ipsilateral axons are much less well understood than for contralateral axons. Ipsilateral and contralateral RGC terminals segregate to form distinct layers, which are highly stereotyped in terms of their placement within any given species. Segregation occurs before eye-opening and has been reported to rely on retinal activity via processes that involve activity-dependent calcium influx, CREB-mediated gene regulation, and synaptic pruning (reviewed in [22,23]). Interestingly, eye-specific segregation in the dLGN of the ferret has also been reported to rely on EphA–ephrinA interactions [24]. Disruption of ephrinA gradients in mice causes ipsilateral RGCs to project more caudally in the SC [12] or ventrolaterally in the dLGN [25••] — changes similar in direction to those observed for contralateral mapping. No change in the degree of eye-specific segregation was observed in the dLGN, however [25••]. Currently it is unclear how in the mouse, where contralateral axons arise from nearly the entire extent of the retina and eye-specific segregation and retinotopic order arise synchronously over the first eight postnatal days [22,26], EphA–ephrinA interactions could simultaneously and reliably mediate both processes. While there may be species differences, peripheral to central gradients of EphA expression reported in fetal human retina appear more consistent with a role in retinotopic mapping than eye-specific segregation [27].

The generation of visuotopy requires that ipsilateral mapping is reversed across the azimuth (Figure 1). Current knowledge of the mechanisms which regulate azimuthal mapping in mice, the species where these mechanisms have been most intensively studied, do not account for this. Recent work has demonstrated that the visuotopic alignment of ipsilateral and contralateral axons is critically dependent on the transmembrane glycoprotein, Ten-m3. In its absence ipsilateral, but not contralateral, RGC axons are profoundly mistargeted leading to an interocular misalignment in the dLGN which is transferred to the visual cortex [28••]. No change in eye-specific segregation was found, supporting the suggestion that topographic mapping and segregation are independent processes. Ten-m3 is critical for vision, as mice that lack it display profound visual deficits. The deficits almost certainly arise from the interocular mismatch as acute blockade of activity in one eye restores visual behavior [28••]. The mechanisms underlying the ipsilateral-specific mapping deficit remain to be determined. It is likely that Ten-m3 mediates its effects by interacting with or regulating the expression of other mapping molecules — these processes have important implications for the generation of visuotopy. The eye-specific mapping deficit provides a unique opportunity to probe the rules and mechanisms which generate binocular circuits in visual cortex (Figure 2).

Thalamocortical and intracortical connectivity: topographic and eye-specific mapping

Early in development, gradients of transcription factors specify cortical identity and determine initial placement of projections from the thalamic nuclei to primary visual cortex [29,30]. Even before the onset of vision, axons from eye-specific segments of dLGN have a patchy distribution, suggesting there may be chemical cues for eye-dominance in V1 [30–32]. In cats, ferrets, and monkey, these regions are alternating columns of ipsilateral and contralateral inputs, while mice have one discrete monocular and binocular zone. Across visual cortex, neurons with similar response properties are grouped together to form precisely overlying maps, including ocular dominance and retinotopy [33]. The molecular cues responsible for laying out these maps are only beginning to be identified; as for subcortical centres, EphA–ephrinA signaling helps to guide topography as well as the size and location of V1 [34••,35]. Cortical maps are further shaped by local and long-range connections.

Figure 2



Mechanisms that shape binocular circuitry in visual cortex. Growth-promoting and stabilizing mechanisms that influence connections from the two eyes to cortical cells have been teased apart experimentally using a monocular deprivation paradigm (see text for details). **(1)** Maturation of inhibition (GABAergic interneuron, red) determines the critical period for ocular dominance plasticity [50]. **(2, 3)** Reduced activity through the deprived eye (depicted by white oval at bottom right) leads to synaptic depression on the pyramidal cell (blue) and increased spine motility, followed by spine loss [65]. **(4)** Homeostatic feedback mechanisms, such as release of TNF-alpha (red circles) by glia (green), scale up synaptic strength globally to maintain activity levels [60,63••]. This scaling contributes to the increased strength of open-eye inputs (depicted by open-eye symbol at bottom left). **(5)** Calcium-activated signaling to the nucleus leads to the expression of activity-dependent genes [66].

Refinement of ocular dominance maps by visual experience

While the role of retinal activity in generating the anatomical foundation of ocular dominance (OD) maps is yet to be determined, there is clear evidence that visually driven activity during a critical period of postnatal development is critical for their maintenance and consolidation. OD columns do arise in animals reared in the dark from birth; however, properties of cortical neurons do not mature beyond what is normally observed at the time of eye-opening. For example, receptive field sizes are larger, and visual acuity, orientation, and direction tuning are reduced [36–38]. These changes may in part reflect the requirement for visual experience in the maturation of subcortical circuitry (reviewed in [22,39]). The absence of visual experience also alters the morphology and reduces the density of dendritic spines, the postsynaptic elements for the majority of glutamatergic connections in the brain [40].

A widely studied model for examining the role of visual activity in shaping and maintaining cortical circuits is ocular dominance plasticity (Figure 2). Following a brief period of early monocular deprivation, deprived eye responses get weaker, while open eye responses get stronger [41], broadening their representation in cortex at the expense of deprived-eye territory and synaptic space [42,43]. Changes in relative synaptic strength occur rapidly in superficial cortical layers, and are followed by changes in thalamocortical afferents. The classical view that OD plasticity arises strictly from competition-based, Hebbian learning rules has been challenged in recent years, by work demonstrating that a number of other activity-dependent factors are critical for plasticity and network stability [44].

Insight into such factors is gained from recent screens for genes modified by visual experience [45•,46,47]. These genes encode molecules important for an array of neuronal functions, including calcium regulation, GABAergic inhibition, actin-binding, G-protein signaling, and transcription. Interestingly, Lyckman *et al.* [45•] demonstrated that the onset of vision increases the expression of genes important for synaptogenesis, while expression changes during the critical period serve to stabilize existing connections. Altering the levels of visual drive by critical period MD reverses this genetic program, presumably to adjust the balance of factors that promote and restrict growth. Thus, visual activity is important for the progression of an innate genetic program, and unbalanced

activity can drive novel gene expression changes. These developmental changes likely specify the downstream effects of activity-dependent molecules that operate at all ages, such as MAPK [46]. It should also be noted that activity drives the expression of molecular factors subcortically as well, such as the homeoprotein Otx2, which is transferred to cortical interneurons to promote their maturation [48•].

Overview of molecular mechanisms underlying OD plasticity

One key factor for shaping cortical maps is the activity-dependent maturation of local inhibition within the circuit, particularly long-range basket cells, which innervate pyramidal cell somata (reviewed in [49]). Pharmacologically modifying the level of inhibition alters OD column width in cats and shifts or restricts the critical period for OD plasticity [50]. Interestingly, enzymatic degradation of perineuronal nets which surround specific subsets of GABAergic neurons, can reinstate OD plasticity in adults. A precise level of inhibitory drive likely guides plasticity by modulating spike timing and back-propagation of action potentials into dendrites.

Pyramidal cells detect changes in activity as calcium fluxes, primarily through activated postsynaptic NMDA receptors, which are important mediators of synaptic strength during OD plasticity [51]. This leads to the activation of number of signal transduction cascades, involving molecules critical for plasticity such as ERK, PKA, and CaMKIIalpha [52–54]. These kinases can directly phosphorylate synapse-associated molecules, such as subsets of glutamate receptors, to promote plasticity and may lead to structural rearrangements via remodeling of the actin cytoskeleton [55]. Indeed, within two days of activity manipulation via monocular deprivation (MD), spine motility is increased in binocular cortex [56], and spine pruning is observed by four days [57]. Further intracellular signaling can lead to CREB activation, which is necessary for OD plasticity [58], and may lead to CRE-driven regulation of genes that are critical for synaptic function.

The synapse-specific changes that result from coincidence detection of afferent activity are also balanced by homeostatic feedback mechanisms, which promote stability within the changing network (Figure 2). Such mechanisms involve the molecules beta3 integrin [59] and glial-derived TNF-alpha [60], as well as Arc [61,62], which respectively upregulate or downregulate global synaptic strength to maintain target firing rates. During MD, TNF-alpha-mediated synaptic scaling follows the reduction in deprived-eye drive, thereby contributing to the strengthening of open eye responses [63••]. This finding supports the idea that changes in deprived versus open eye drive may involve separable synapse-specific and global feedback processes, and provides the first direct evidence of a role for glia in shaping activity-dependent plasticity in cortex. Additional feedback processes such as scaling of intrinsic excitability and plasticity of inhibitory conductances have been demonstrated in monocular domains, but their role in shaping binocular interactions remains to be determined [64•].

Conclusion

The development of powerful new techniques such as two-photon imaging and informative animal models has greatly advanced our knowledge of how and when intrinsic patterning and experience-dependent processes intersect to shape neural connectivity in the visual pathway. Additional tools are being generated every day, and we foresee rapid progress in this exciting field.

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