Patterning and Plasticity of Maps in the Mammalian Visual Pathway

SAM HORG AND MRIGANKA SUR

ABSTRACT Maps at successive stages of the visual system, and in particular visual cortex, organize salient stimulus features into complex cortical networks. Retinotopic maps and ocular dominance domains arise during development using a molecular program that specifies the rough topographic order of projections. Genetic mutations in mice have identified guidance and patterning cues that mediate this organization of maps and may lead to the creation of new maps. Spontaneous activity produced in the retina refines the precision of the maps before eye opening, and patterned activity after eye opening drives further refinement and maintenance. For ocular dominance, the cortex has a critical period for synaptic plasticity during which it is especially sensitive to changes in input. During this time, changes in eye-specific drive lead to Hebbian and homeostatic changes in the cortical network. This potential for plasticity represents a functional reorganization in response to changing demands from the outside world and allows the organism to adapt to its environment.

A critical function of the brain is to provide an orderly and efficient neural representation of salient sensory stimuli from the outside world. In the mammalian visual pathway, representations of light reflectance in visual space are relayed from the retina as a topographic map to the thalamus and superior colliculus. Along this pathway, projections from the two eyes are kept in parallel. Retinotopic and eye-specific information from the thalamus is transferred to the primary visual cortex, where additional stimulus features are extracted. The mechanisms by which visual stimulus feature maps are established and modified in response to experience are an active area of research, as these mechanisms are central to specifying the organizational details of the visual pathway and the functional characteristics of vision.

In this chapter, we will review the processes of retinotopic mapping and cortical plasticity in the mammalian brain. Molecular mechanisms of these phenomena have been studied most extensively in the mouse, a model for which genetic manipulations are available. What we currently know of these mechanisms illustrates how circuits are shaped by genetic programs, electrical activity, and experience-dependent modulation of stimulus input.

During development, the formation of a retinotopic map requires that axons responsive to neighboring positions in visual space maintain their relative positions as they innervate their target. This process involves graded patterns of guidance receptors expressed across the population of axons and matched to a complementary gradient of ligands on the target cells. The genetic patterning of guidance cues confers a rough order and spatial efficiency to the retinotopic map. However, further retinotopic precision and ocular dominance segregation depend upon patterns of spontaneous activity in the retina and experience-driven input. Changes in the pattern or pattern of activity can alter the structure and function of the retinotopic map in early development and of ocular dominance regions in later development and adulthood. Ocular dominance plasticity occurs in response to changes in competitive input between the eyes, and a variety of molecular pathways, many of which reflect the maturational state of the circuit, have been implicated in this process. Thus the development of the visual pathway during early development

REGIONALIZATION OF VISUAL PATHWAY CENTERS

Functional pathways of the brain arise out of genetic programs of early development, which establish structural regions and wire them together (Rakic, 1988; O’Leary, 1989; Job & Tan, 2003; Sur & Rubenstein, 2005). During embryogenesis, sources of diffusible molecules, called signaling centers, induce regional and graded patterns of gene expression in the anterior neural tube. These patterns translate into structurally parcelled and functionally differentiated brain regions, including those devoted to processing incoming visual stimuli (Fildor & Stern, 1993; Rubenstein, Martinez, Shimamura, & Puelles, 1994; Rubenstein, Shimamura, Martinez, & Puelles, 1998;
expressing axons to the proper decussation site for optic chiasm formation (Erskine et al., 2000; Ringstedt et al., 2000; Plump et al., 2002), and ephrin-B2 expression at the optic chiasm steers EphB1-receptor-expressing ventromedial axons ipsilaterally (Williams et al., 2003; Lee, Petros, & Mason, 2008). Matrix metalloproteinases (MMP) have been implicated in optic chiasm crossing and tectal targeting (Hehr, Hocking, & McFarlane, 2005). Additionally, traditional morphogens influence retinal ganglion cell pathfinding (Charron & Tessier-Lavigne, 2005): FGF-2 repels RGC growth cones along the optic tract (Webber, Hyakutake, & McFarlane, 2003), BMP7 promotes axonal outgrowth at the optic disk (Carri, Bengtsson, Charettte, & Ebendal, 1998; Bovolenta, 2005), and Shh exhibits concentration-dependent attractive or repulsive effects in the retina and optic chiasm, respectively (Trouse, Marti, Gruss, Torres, & Bovolenta, 2001; Kolpak, Zhang, & Bao, 2005). Less is known about the specific cues mediating ganglion cell ingrowth to the LGN and geniculo-cortical targeting to area 17, or V1.

However, molecules that contribute to the topographic ordering of projections have been investigated in the LGN and V1, as well as the SC. The spatial position of visual stimuli is inverted through the lens and encoded on a sheet of retinal ganglion cells. This topographic map gets projected into the LGN and V1, as well as the SC. Because axon guidance cues must not only flag targets but also convey information about the relative topography of neighboring axons, positional cues are needed to maintain the retinotopic order of the projecting pathway. To avoid employing an infinitely large number of distinct positional cues, a gradient of one molecule along the sheet of axons may be matched to a complementary gradient of its binding partner in the target (Sperry, 1963). This “chemoaffinity” model has been confirmed with the discovery of a number of different receptor-ligand gradients expressed in projecting axons and target cells along the visual pathway.

The most comprehensively studied of these graded mapping molecules are the ephrin ligands and Eph family of tyrosine kinase receptors (figure 6.1B). The contribution of ephrin-A-EphA receptor interactions to topographic mapping was first described in the optic tectum, where low-to-high ephrin-A2/A5 expression along the anterior-posterior axis was found to interact with a complimentary high-to-low EphA3 receptor gradient in terminals of the temporal-nasal axis of retina (Nakamoto et al., 1996; Feldheim et al., 1998, 2000; Hansen, Dallal, & Flanagan, 2004; Botz et al., 2004). Interactions between ephrin-A and EphA receptors were initially thought to be repulsive, though subsequent studies revealed a concentration-dependent transition from attraction to repulsion: with low ephrin-A concentrations causing axonal attraction and high levels causing repulsion (Hansen et al., 2004). The ability of the ligand-receptor system to both attract and repel allows for

TARGETING AND RETINOTOPIC WIRING

The visual pathway is wired (figure 6.1A) when roughly one-third of the ganglion cell axons from the retina project to the dorsal and ventral subdivisions (LGNd, LGNv) of the LGN while the remaining two-thirds target the superior colliculus (SC) in the brain stem (Jones, 1985; Tuttle et al., 1998). Axonal pathfinding to fugal (i.e., thalamic) and collicular targets begins around E15–16 and peaks at E19 (Coleslo & Guillery, 1990; Figdor & Stern, 1993; Tuttle et al., 1998; Inoue et al., 2000; Gurung & Fritzsch, 2004; Guido, 2008). In the mouse, axons from the ventrotemporal retina project ipsilaterally while the rest of the axons project contralaterally, with contralateral innervation to the thalamus occurring earlier (E13–16) than ipsilateral targeting (P0–2) (Dräger & Olsen, 1980; Godefent, Salau, & Imbert, 1984). Connections between the LGN (in this review, LGN is used to denote LGNd) and V1, both in the feedforward geniculocortical direction and in the feedback corticogeniculate pathway, emerge around E14 (Zhou et al., 2003).

Elucidating the mechanisms of retinotopic targeting and mapping has become a comprehensive field of study (figure 6.1B). Molecular mechanisms of retinal ganglion cell (RGC) guidance have been extensively studied in Xenopus, zebrafish, chick, and mouse models. Much of this work has focused on guidance to the optic disk, descussation at the optic chiasm, and topographic map formation at the optic tectum, or SC (Inatani, 2005; Mann, Harris, & Holt, 2004). In the retina, laminin and netrin repulse DCC receptor-expressing RGC axons out of the optic head and into the optic nerve (Hopker, Shewan, Tessier-Lavigne, Poo, & Holt, 1999). Along the optic nerve, a repulsive semaphorin 5a sheath maintains the integrity of an interior axon pathway (Shewan, Dwivedy, Anderson, & Holt, 2002; Oster, Bodecker, He, & Sretavan, 2003). Slit1- and slit2-expressing cells guide repulsed robo-
Figure 6.1 (A) Representation of the rodent visual pathway. Retinal ganglion cells project to the LGN, which in turn projects to the primary visual cortex (V1). A central region of the visual field is represented by both eyes along the pathway (ipsilateral, red; contralateral, blue). Contralateral and ipsilateral retinal ganglion cell terminals representing this binocular region are segregated in the LGN (red, ipsilateral zone; blue, contralateral zone). Geniculocortical fibers representing this region converge onto a binocular zone located in the lateral half of V1 (red, binocular zone; blue, monocular zone). (B) Schematic representation illustrating retinotopic map organization at each stage of the visual pathway and known guidance cues contributing to patterning. The visual field can be divided into two Cartesian axes, azimuth and elevation. For clarity, the azimuthal map on the left is diagrammed onto the visual pathway of the right hemisphere. The elevation map on the right is diagrammed onto the pathway of the left hemisphere. In reality, both axes of visual space are represented concurrently in both hemispheres. The ganglion cell sheet of the retina is divided into a contralaterally projecting region and an ipsilaterally projecting region. The ipsilateral retina originates from the ventrotemporal quadrant and is characterized in late embryogenesis by Zic2 and EphB1 expression. Conversely, the contralateral retina is characterized by Isl2 expression. Retinal ganglion cells express DCC and are repulsed out of the optic head by laminin and netrin. Factors, such as semaphoring-5a, keep retinal axons on course in the optic tract, where ipsilateral axons are repulsed by ephrin-B2 while contralateral axons decussate. High temporal to low nasal gradients of EphA receptor and ten_m3 expression in retinal axons likely influence terminal zones onto gradients of ephrin-A in the LGN. Ipsilateral axons terminate in a dorsomedial core of the LGN, segregated from surrounding contralateral axons. Activity-dependent refinement is necessary for proper eye-specific segregation. While ephrin-A gradients shape retinotopic termination zones, ten_m3 specifically influences ipsilateral targeting. Geniculocortical axons innervate V1. Ipsilateral inputs and corresponding contralateral fibers converge in the lateral binocular zone, while contralateral inputs representing regions not detected by the ipsilateral eye terminate in the medial monocular zone. Loss of ephrin-As leads to the disorganization of cortical maps only on the azimuthal axis, suggesting that other, unidentified factors contribute to the mapping of elevation. (See color plate 2.)
the target to be filled more parsimoniously than with separate attractant and repulsant molecules.

High lateral-to-medial gradients of ephrin-A2/A5 are also present in the mouse and ferret LGN and direct topography of high levels of EphA5/A6 expression from the contralateral nasal projections and low levels in the ipsilateral temporal projections (Huberman, Murray, Warland, Feldheim, & Chapman, 2005). Loss and ectopic gain of ephrin-A2, 3 and 5 lead to disruptions of the topographic map in both the LGN and V1: loss produces a medial shift in V1, in addition to internal disorganization, while lateral expression leads to a compression of V1, suggesting that EphA-expressing geniculocortical axons respond to a high medial to low lateral gradient of ephrinA (Cang et al., 2005). High dorsal EphB receptor expression in retina responds to low ventral ephrin-B expression in the tectum, and EphB-ephrinB gradients are speculated to similarly organize distinct axes in the LGN and V1 (Hindges, McLaughlin, Genoud, Henkemeyer, & O'Leary, 2002; McLaughlin, Hindges, Yates, & O'Leary 2003). The role of potential cis and trans mediated interactions among ephrin and Eph receptors from countergradients expressed on axons of the same area have yet to be explored (Luo & Flanagan, 2007). Finally, additional graded positional cues have been identified in the retinotectal map. Repulsive guidance molecule (RGM), a novel membrane-associated glycoprotein expressed in the posterior tectum, repels temporal axons in vitro (Monnier et al., 2002), while engrailed-2 (En-2), a homeodomain transcription factor, is secreted by the posterior tectum, is endocytosed into axons, and attracts nasal axons while repelling temporal axons (Brunet et al., 2005). A high-to-low gradient of Wnt3 in the medial-lateral axis of the optic tectum mediates patterning via ventral-dorsal differences in Ryk receptor expression (Schmitt et al., 2006), and a Wnt signaling inhibitor, SFRP1, interacts with RGC receptor Fz2, to steer axons along the optic tract en route to the tectum (Rodriguez et al., 2005).

Experiments in which half of retinal ganglion cells are ablated or a disordered set of cells gain EphA expression reveal that retinotectal axons persistently fill their target (Brown et al., 2000; Feldheim et al., 2000). Thus it is the relative level of positional-information rather than absolute signaling that determines the topography of retinal axons. Some limiting factor, whether from the axon-axon interaction or target-derived cues, may ensure that target filling occurs (Luo & Flanagan, 2007). Loss of L1CAM leads to incomplete filling of the tectum, and this molecule may have such a role (Demyanenko & Maness, 2003).

Eye-Specific Domains A second fundamental organizational feature of the visual pathway is its segregation into eye-specific domains. Maintaining parallel channels for eye-specific input allows for stereoscopic vision, or depth perception. In mice, ipsilateral projections form a dorsal core in the LGN (LGNd) and are flanked laterally by contralateral terminals representing matched areas of visual space. These axons intermix when projecting to layer IV cells of the binocular zone, a V1 subregion bounded medially by a monococular zone of contralateral input (figure 6.1A,B). In mammals with more complex visual systems, such as the ferret, cat, primate, and human, eye-specific domains form a map of ocular dominance stripes in V1 (figure 6.3). Whether eye-specific domains are influenced by positional cues in addition to activity dependent processes of terminal segregation has only recently begun to be explored. Developmental time course studies in the mouse show that early (P0–P5) ipsilateral axons are diffusely targeted to the dorsal-medial portion of the LGN and progressively become more strictly confined to a central core by P28 (Jaubert-Miazza et al., 2005). Although activity-dependent processes to be discussed later contribute to the refinement of ocular domains in the LGN (Shatz, 1983; Shatz & Stryker, 1988; Pfieffenberger et al., 2005), the initial ingrowth of ipsilateral axons shows a bias toward the binocular region in the central part of the dorsal half of the LGN, and eye-specific guidance cues likely instruct this initial positioning (Godement et al., 1984). The presence of functional markers, Isl2 and Zic2, during late embryogenesis (E13–E17), for contralaterally and ipsilaterally projecting retinal ganglion cells, respectively, suggests that the two populations have distinct differentiation programs and potentially respond to unique cues in their target (Herrera et al., 2003; Pak, Hindges, Lim, Pfaff, & O'Leary, 2004). Loss of ten_m3, a homophilic binding protein expressed strongly on ipsilaterally projecting axons, leads to the selective ventral expansion of ipsilateral axons and no disruption in contralateral axons in the LGN (Leamey, Glendining, et al., 2007; Leamey, Merlin, et al., 2007). Therefore, ten_m3 and potentially other unknown cues may contribute to the formation of eye-specific domains. Mechanisms of how corresponding ipsilateral and contralateral axons are coordinated and aligned to form binocular maps are poorly understood.

Other Feature Maps and the Formation of New Maps In mice and other mammals, additional stimulus features are encoded in the visual pathway at the cortical level. Cells in V1 are selective for orientation, spatial frequency, and the direction of visual stimuli. In carnivores and primates, these cells are organized into selectivity maps of their own. For example, multiple stripes converging around a pinwheel center on the cortical surface represent graded regions of different orientation selectivity. Within these orientation-selective regions, directionally selective subregions are present. Using a layout that maximizes map continuity and cortical coverage (Swindale, Shoham, Grinvald, Bonhoeffer, & Hübener, 2000), multiple feature
maps are superimposed and organized in systematic fashion, with regions of high gradients from different maps spatially segregated from one another (Yu, Farley, Jin, & Sur, 2005). That is, while individual, adjacent neurons respond best to different values of the same feature, the way in which these features are mapped varies systematically. The critical parameter is the rate of change of each feature across the same set of neurons: at locations where one feature changes rapidly, other features change little.

Mechanisms of map formation for these additional stimulus features are not well understood, although the role of intrinsic genetic programs of patterning and activity-dependent input may differ depending on the specific feature map (White & Fitzpatrick, 2007). Whereas the retinotopic and eye-specific maps are patterned roughly before birth and eye opening, the orientation map is detectable only by the time of eye opening in the ferret (Chapman, Stryker, & Bonhoeffer, 1996; White, Coppola, & Fitzpatrick, 2001; Coppola & White, 2004), and the direction-selective map appears 1–2 weeks later (Li, Fitzpatrick, & White, 2006). Therefore, the formation of these maps likely depends critically on developmental processes coincident with patterned input into the cortex.

The formation of orientation maps coincides with a period during which axonal connections in V1, especially long-range horizontal inhibitory projections in layer 2/3, proliferate (Bosking et al., 2002). Orientation tuning has been hypothesized to arise from feedforward patterns of thalamocortical connectivity (Ferster & Miller, 2000) and to be shaped by intracortical connections (Somers, Nelson, & Sur, 1995) and balanced inhibition (Marino et al., 2005). The maturation of this supragranular inhibitory network may contribute to the appearance of orientation tuning and organization of tuned cells into selective domains. Mice deficient in Arc, an activity-dependent cytoskeletal-associated protein implicated in the synapse-specific modulation of AMPA receptor number, show weaknesses in orientation tuning in V1 (Wang et al., 2006). Dark-reared animals exhibit a delay in the formation of the orientation map, while binocularly lid-sutured animals have a near complete degradation of the map (White et al., 2001), suggesting that low levels of non-patterned activity have a greater disruptive effect than the absence of input. Therefore, unknown intrinsic properties of the cortex instruct the formation of the orientation map in the weeks after eye opening and induce the map even in the absence of vision. However, the orientation map is susceptible to disruption in response to disorganized activity.

In contrast to orientation maps, a 2-week period following eye opening is both necessary and sufficient for the formation of direction-selective maps (Li et al., 2006). Thus the direction-selective map is induced by changes in either the cortex or LGN that are driven by activity. Sharpening of retinotopic tuning and decreases in the response latency of LGN cells may play a role (Tavazoie & Reid, 2000). Different feature maps in V1 appear to be guided by independent mechanisms. Loss of the direction-selective map leaves the orientation map intact, and monocular enucleation to eliminate the ocular dominance map does not interfere with the formation of the remaining V1 feature maps (Farley, Yu, Jin, & Sur, 2007). However, the relative positioning of different maps in V1 is responsive to alterations in a given map, as monocular enucleation leads to the coordinated reorganization of the remaining map dimensions (Farley et al., 2007). Therefore, while the formation of stimulus-specific maps or networks likely relies on unique developmental mechanisms, whether they be genetically determined or instructed by activity, the detailed organization of each map and its structural and spatial coordination with other maps is a key feature of activity-dependent cortical organization.

Because of the independent origin of individual maps (and response features), the appearance of new maps in evolution may have depended on unique events and developmental processes for a given map. However, there may be general properties in neural circuits that allow for the introduction of a novel map. Novel maps may arise potentially through the duplication and subsequent functional divergence of an existing map, or the addition of a novel input into an existing region and subsequent reorganization of cortical circuitry into a new map. An example of the former is the induction of duplicate barrel cortices by ectopic posterior cortical FGF8 expression (Fukushi-Shimogori & Grove, 2001). An example of novel input leading to the introduction of a new map includes the implantation of a third eye leading to triple ocular dominance stripes in the tectum of the frog (Constantine-Paton & Law, 1978), rewired retinal input to the MGN driving retinotopic maps to form in primary auditory cortex (A1) (Sur, Garraghty, & Roe, 1988), and ten_m3 mutation in mouse leading to a medial expansion of ipsilateral input to V1 and the de novo formation of cortical ocular dominance stripes (C. Leamey, personal communication).

Rewiring vision into the auditory pathway

After neonatal surgical ablation of the inferior colliculus (IC), retinal ganglion cells are rerouted to target the auditory thalamus and subsequently induce the auditory pathway to process visual information (figure 6.2). This experimental paradigm allows us to investigate the role of novel input in producing retinotopic and feature maps, and to screen for unknown guidance cues involved in wiring together sensory pathways. The normal auditory pathway comprises cochlear afferents projecting to the inferior colliculus (IC), which sends fibers along the brachium of the IC (BIC) to the medial geniculate nucleus (MGN) in the thalamus, which then innervates the primary auditory cortex (A1; figure 6.2A). Using hamsters, Schneider discovered that retinal afferents form...
novel connections to the ventral MGN (MGv) when the IC is ablated after birth (figure 6.2B; Schneider, 1973; Kalil & Schneider, 1975; Frost, 1982; Frost & Metin, 1985). This "rewiring" paradigm has subsequently been demonstrated and studied in the ferret and mouse models (Sur et al., 1988; Roe, Pallas, Hahm, & Sur, 1990; Roe, Pallas, Kwon, & Sur, 1992; Lyckman et al., 2001; Newton, Ellsworth, Miyakawa, Tonegawa, & Sur, 2004; Ellsworth, Lyckman, Feldheim, Flanagan, & Sur, 2005).

On receiving retinal ganglion cell input, the MGN adopts some of the anatomic and physiologic features of the normal LGN (figure 6.2C). Rewired MGN neurons of the ferret exhibit center-surround visual receptive fields (Roe, Garraghy, Esquerra, & Sur, 1993), topographic ordering (Roe, Hahm, & Sur, 1991), and eye-specific segregation (Angelucci, Ciasca, Bricolo, Cramer, & Sur, 1997). The potential to form ordered retinotopic and ocular dominance regions in MGN indicates that common patterning cues exist between the LGN and MGN. Experiments in ephrin A2/A5 double knockout mice reveal that surgically induced rewiring is enhanced (Lyckman et al., 2001), with ipsilateral projections especially increased, as they originate from the temporal retina and express the highest levels of EphA receptor (Ellsworth et al., 2005). Loss of innervation to the MGN somehow makes this nucleus permissive to retinal axon ingrowth, and a gene-screening process between the normal and rewired MGN may facilitate the discovery of trophic or repulsive agents regulating retinal axon affinity for different sensory nuclei of the thalamus.

Nonetheless, certain morphological aspects of rewired MGN are resistant to change (figure 6.2C). In ferrets, retinal axon terminations are elongated along the typical iso-frequency axis, or lamellae, of the MGN as opposed to more focal, isotropic distributions in the LGN (Pallas, Hahm, & Sur, 1994). In addition, eye-specific clusters are smaller and cruder than the eye-specific layers of LGN (Angelucci et al., 1997).

In the cortex of rewired ferrets, cells in A1 respond to visual field stimulation and form a functional retinotopic map of visual space (Roe et al., 1990). However, the thalamocortical axons transmitting this information retain their pattern of elongated projections along the anteroposterior axis of A1, which typically correspond to isofrequency bands (Pallas, Roe, & Sur, 1990). In order to create the functional map of focal retinotopic representations, either a refinement of these elongated inputs by a reorganized intracortical inhibitory network or a difference in drive along the projection itself is required (Sur, Pallas, & Roe, 1990). Consistent with the first possibility, calbindin-immunoreactive GABAergic neurons of rewired A1 have more elongated axonal arborizations (Gao, Wormington, Newman, & Pallas, 2000). Thus, despite persistent structural features of A1 and thalamocortical input, functional retinotopy can be driven by novel patterns of activity.

In the ferret, rewired A1 acquires novel maps of orientation selectivity with pinwheels and orientation domains (figure 6.2D), similar in general to maps in normal V1 (Sharma et al., 2000; Rao, Toth, & Sur, 1997). In rewired A1, orientation maps are less organized, although intrinsic horizontal connections of superficial layer pyramidal neurons are clustered and bridge distantly located domains of the same orientation preference, as in V1 (figure 6.2E; Sharma et al., 2000). This pattern of intracortical connectivity is in contrast to horizontal connections in normal A1, where horizontal connections are limited to isofrequency domains of the tonotopic map and stretch along these bands. Such reorganization of horizontal connections driven by visual activity is likely related to changes in the inhibitory circuits of rewired A1, and it suggests that coordinated activity-dependent changes in inhibitory and excitatory networks of at least the superficial cortical layers are a prominent feature of cortical map organization and plasticity.

Finally, the rewired auditory pathway is sufficient to instruct visually mediated behavior. After training to
distinguish a left visual hemifield stimulus from an auditory stimulus, ferrets with a unilaterally rewired left hemisphere are able to accurately perceive a right visual hemifield stimulus as visual even after left LGN ablation (von Melchner, Pallas, & Sur, 2000). After left LGN ablation, the ferrets also possess diminished yet intact spatial acuity in the right hemifield. Subsequent ablation of the rewired A1 abolishes the animals’ ability to distinguish a right hemifield stimulus presented as visual. Thus rewired A1 is sufficient and necessary in the absence of ipsilateral visual pathway input to detect a visual percept in trained ferrets. In mice, direct subcortical projections from the MGN to the amygdala are involved in rapid fear conditioning to an auditory cue (Rogan & LeDoux, 1995; Doran & LeDoux, 1999; Newton et al., 2004). Because of an indirect pathway from the LGN through V1 and the perirhinal cortex to the amygdala, a fear conditioning to a visual cue requires many more training sessions (Heldt, Sufin, Wilott, & Falls, 2000). In rewired mice, the acquisition time of a fear conditioning to a visual cue is accelerated and resembles that of a normal mouse in response to an auditory cue (Newton et al., 2004).

Activity-dependent refinement of visual maps

Although topography of the retinotopic map and eye-specific domains are roughly established by programmed guidance and patterning cues, activity plays a critical role in the refinement and maturation of these maps. Single cells in the mouse LGN receive weak input from one to two dozen retinal ganglion cells, which occupy 30% of the cell surface, in the first postnatal week, and then begin to prune these connections down to one to three strong monocular inputs that occupy 1–5% of the cell surface (Chen & Regher, 2000; Jaubert-Miazza et al., 2005; Guido, 2008). Ipsilateral projections to the LGN are also diffuse and widespread during this first week, occupying nearly 60% of the nucleus area. By the time of eye opening (P12–P14), the ipsilateral zone occupies only 10% of the LGN (Jaubert-Miazza et al., 2005; Guido, 2008).

Both the retinotopic and eye-specific pruning of synapses is affected by altering spontaneous activity caused by cholinergic waves that sweep across the retina (Meister, Wong, Baylor, & Shatz, 1991; Wong, Meister, & Shatz, 1993). Blockade of retinal electrical activity with TTX (Harris, 1980) or loss of retinal waves by genetic loss of the β2 nAChR (Rossi et al., 2001; McLaughlin, Torborg, Feller, & O’Leary, 2003; Grubb, Rossi, Changeux, & Thompson, 2003; Chandrasekaran, Plas, Gonzalez, & Crair, 2005) causes terminals to remain desegregated and diffuse. Combined ephrin-A and β2 nAChR mutants lead to additive defects in retinotopic organization in the LGN and V1 along the elevation axis in visual space, demonstrating that activity-dependent refine-
removal plus contralateral deprivation, were not examined in this study.

In addition to Hebbian pruning and strengthening of feedforward inputs, changes due to activity that contribute to map refinement potentially involve additional developmental processes, including the remodeling of excitatory connections, the maturation of inhibitory circuits, and the timed expression of L-type Ca$^{2+}$ channels. Excitatory synapses in the LGN initially contain NMDA receptors but increase their proportion of AMPA receptors as synaptic elimination proceeds (Chen & Regehr, 2000; X. Liu & Chen, 2008). Networks of GABAergic interneurons in the LGN also appear at P5 and mature by P14 (Ziburkus, Lo, & Guido, 2003; Jaubert-Miazza et al., 2005). L-type Ca$^{2+}$ channels are expressed in excitatory LGN synapses before eye opening and are necessary for eye-specific segregation and CRE-mediated gene transcription (Cork, Namkung, Shin, & Mize, 2001; Pham, Rubenstein, Silva, Storm, & Stryker, 2001; Jaubert-Miazza et al., 2005).

In sum, mechanisms of map refinement in response to activity likely involve a number of different processes that contribute to the functional maturation of the circuit, including the selection and elimination of synapses, the modulation of synaptic strength, and the structural formation of inhibitory networks. Activity may also in turn influence the actions of guidance cues; activity blockade prevents ephrinA-mediated repulsion because of disruptions in cAMP signaling (Nicol et al., 2007).

**Ocular dominance plasticity**

Once a functional map is refined, ongoing patterns of activity contribute to the maintenance and alteration of this map in response to experience. The potential for plasticity is of particular interest for understanding how neural circuits adapt their structure and function to accommodate changing demands in the environment. Plasticity in the V1 ocular dominance map has become a paradigmatic model of activity-driven reorganization in network structure and function (figure 6.3d).

**Structural and functional changes in response to lid suture** Within the binocular zone of V1 in mammals, neurons particularly in the superficial and deep
layers of cortex are driven by both eyes, though neurons in layer 4 of carnivores and primates are primarily driven by one eye (Hubel & Wiesel, 1963; Stryker & Harris, 1986). When an imbalance of input occurs after lid suturing one eye for several days (monocular deprivation, or MD), a series of structural and functional changes leads to the weakening of the deprived eye input and the strengthening of nondeprived eye input (figure 6.3B). The mechanisms underlying these changes (figure 6.3C) shed light on core principles of plasticity in the developing brain in response to experience. Before functional shifts are apparent, spine motility increases (Majewska & Sur, 2003; Oray, Majewska, & Sur, 2004), followed by transient pruning of spines (Mataga, Mizuguchi, & Hensch, 2004; Oray et al.). Electrophysiological and optical imaging techniques reveal that deprived-eye connections are weakened first, while supragranular horizontal connections are remodeled (Trachtenberg, Trepel, & Stryker, 2000; Trachtenberg & Stryker, 2001; W. Lee et al., 2005). Strengthening of nondeprived eye connections follows (Frenkel & Bear, 2004), and finally, layer IV geniculocortical axons representing the nondeprived eye grow and expand their terminals at the expense of shrinking deprived-eye terminals (Antonioni & Stryker, 1996; Antonioni, Fagioli, & Stryker, 1999). The chronology of these events has been best characterized for the developmental “critical period” in mouse, though differences in structural and physiological response may exist for MD during adulthood or under different paradigms of development, such as dark rearing (Jiang, Treviño, & Kirkwood, 2007). The developmental context under which MD is applied can make a qualitative and quantitative difference in the ocular dominance plasticity observed and likely involves different cellular and network mechanisms.

**Critical Periods and the Developmental Context of Plasticity**

The ability to induce and reverse ocular dominance plasticity was initially thought to exist only during a “critical period” in development, a time approximately 10 days after eye opening during which short MD (a few days in the mouse) leads to a robust shift in ocular dominance toward the nondeprived eye (Hubel & Wiesel, 1970; Gordon & Stryker, 1996). This “critical period” is delayed by roughly three weeks in dark-reared animals (Cynader, Berman, & Hein, 1976; Fagioli, Pizzorusso, Berardi, Domenici, & Maffei, 1994; G. Mower, 1991), suggesting that the cortex must reach a maturational state that is facilitated by a period of patterned vision. This maturational state has been shown to involve the development of an inhibitory network that depends on BDNF produced in response to neural drive (Hensch, 2005). Overexpression of BDNF leads to a precocious start of the critical period and premature development of inhibitory cells in the cortex (Huang et al., 1999; Hanover, Huang, Tonegawa, & Stryker, 1999), while administration of BDNF to dark-reared animals leads to the induction of a critical period (Gianfranceschi et al., 2003). Mice lacking polysialic acid also experience premature maturation of inhibitory networks and a precocious critical period (Di Cristo et al., 2007). GAD65 knockout mice, which lack axonal GABA synthesis and subsequent inhibitory transmission, do not experience a critical period unless induced with benzodiazepine drug infusion at any age (Hensch et al., 1998; Fagioli & Hensch, 2000). Therefore, tonic GABA release is sufficient to mature an intracortical inhibitory network and induce critical period plasticity. The process by which the critical period closes and why critical period induction is a one-time event are not understood.

Although the critical period occurs once during development, longer periods of MD (7 to 10 days in the mouse) are able to trigger ocular dominance plasticity in adulthood (Sawtell et al., 2003; Hofer, Mrsic-Flogel, Bonhoeffer, & Hubener, 2006; Fischer, Aleem, Zhou, & Pham, 2007). This form of plasticity is thought to differ mechanistically from that experienced during the critical period, as nondeprived-eye connections are strengthened more rapidly and deprived-eye connections remain stable (Kaneko, Stellwagen, Malenka, & Stryker, 2008). Previous experiences with MD, either in the critical period or in adulthood, facilitate plasticity in response to short MD later in life (Hofer et al.; Frenkel & Bear, 2004), suggesting that a functionally suppressed anatomical trace has been laid. Ocular dominance plasticity may also be induced in adulthood after a 10-day period of visual deprivation, and this process mimics the time course of plasticity present during the critical period (He, Hodos, & Quinlan, 2006; Frenkel & Bear, 2004). Therefore, even the apparent closure of critical period plasticity may be reactivated by a brief loss of visual input.

**Hebbian and Homeostatic Mechanisms of Plasticity**

Spike-timing-dependent activity has been demonstrated to lead to strengthening or weakening of geniculocortical and intracortical synapses in V1 (Frégnac & Shulz, 1999; Meliza & Dan, 2006). Long-term depression (LTD) of deprived-eye inputs occurs in vivo after MD and has been proposed to precipitate the eventual reduction in deprived-eye synapses (Heynen et al., 2003; Frenkel & Bear, 2004). Decreases in the threshold for LTD after dark rearing (as a result of decreases in NR2A/NR2B ratio of subunit composition in NMDA receptors) are posited to mediate the reactivation of plasticity (He et al., 2006). In hippocampal neurons, AMPA receptors are added to synapses during long-term potentiation (LTP) and removed during LTD (Manilow & Malenka, 2002), a mechanism that may act as the substrate for altering synaptic strength in visual cortex due to altered visual experience. Group 1 metabotropic glutamate receptors have been identified as inducers of LTD, and loss of mGlur5 blocks ocular dominance plasticity.
Gene transcription and protein synthesis downstream of synaptic events is necessary for ocular dominance plasticity. Blocking cortical protein synthesis while preserving LTD effectively prevents ocular dominance shifts (Taha & Stryker, 2002). Loss of the cAMP responsive element, CREB, a protein that promotes CRE-mediated gene transcription, prevents ocular dominance shifts (A. Mower, Liao, Nestler, Neve, & Ramoa, 2002). Upstream Ca²⁺-sensitive signaling kinases, including ERK, PKA, and CamKIIα, are also necessary for OD plasticity, and these likely activate a number of functional cascades that lead to gene transcription and structural modifications to the synapse (Di Cristo et al., 2001; Taha & Stryker, 2002; Berardi, Pizzorusso, Ratto, & Maffeì, 2003; Suzuki, al-Noori, Butt, & Pham, 2004; Gomez, Alam, Smith, Horne, & Dell’Acqua, 2002; Chierzi, Ratto, Verma, & Favacett 2005; Taha & Stryker, 2005). The extent to which LTD and LTP are necessary for ocular dominance shifts is uncertain, however. In mice lacking the protein phosphatase, calcineurin, LTD is blocked, but ocular dominance plasticity remains intact (Yang et al., 2005).

Although Hebbian mechanisms are likely to contribute to ocular dominance plasticity in which poorly driven synapses from the deprived eye are pruned and synapses from the nondeprived eye are strengthened (Katz & Shatz, 1996), additional cellular and network mechanisms likely affect the response of the cortex to MD. Homeostatic processes that work to preserve a certain level of cortical drive are known to operate in neuronal development (Turrigiano & Nelson, 2004) and may contribute to the ability of binocular neurons to undergo ocular dominance plasticity after deprivation (Desai, Cudmore, Nelson, & Turrigiano, 2002; Mrsic-Flogel et al., 2007). Nondeprived inputs strengthen only after deprived inputs are weakened (Frenkel & Bear, 2004), and pathways of synaptic scaling, the global (or cell-wide) modulation of synapses, may be operating. TNFα, a glial secreted cytokine which acts as a positive scaling factor by increasing synaptic GluR1 and mEPSC amplitudes, is necessary for scaling up synaptic strength in vitro (Stellwagen, Beattie, Sco, & Malenka, 2005; Stellwagen & Malenka, 2006) and for the increase in amplitude of nondeprived inputs after MD (Kaneko et al., 2008). Arc, a negative scaling factor that increases AMPAR endocytosis (Chowdhury et al., 2006; Rial Verde, Lee-Osbourne, Worley, Malinow, & Cline, 2006), may also influence ocular dominance plasticity (McCorry, Tropea, Wang, & Sur, 2007).

Inhibitory networks may provide an additional circuit mechanism for modulating input strength during MD. Somatic inhibition on excitatory pyramidal cells would allow for instructive gating of precisely correlated inputs by preventing the backpropagation, as well as subsequent strengthening, of imprecisely timed inputs (Bi & Poo, 2001; Song, Miller, & Abbott, 2000; Pouille & Scanziani, 2001; Hensch, 2005). Gap junctions between parvalbumin-expressing inhibitory cells would also allow for tightly coupled inputs to drive networks of inhibitory cells more strongly and facilitate discriminative responsiveness of pyramidal cells (Galarreta & Hestrin, 2001; Hensch, 2005). Endocannabinoid signaling on presynaptic terminals of layer 2/3 are necessary for plasticity, and these synapses may modulate the drive from the supragranular inhibitory network (C. Liu, Heynen, Shuler, & Bear, 2008).

**Structural Plasticity and Permissive Changes in Extracellular Matrix** Increasing evidence supports the role of proteases and perineuronal nets (PPN) of extracellular matrix in regulating the ability of cortex to respond to MD. Degradation of chondroitin-sulfate proteoglycans (CSPGs) leads to the reactivation of ocular dominance plasticity in adult cortex (Pizzorusso et al., 2002, 2006). The protease tissue plasminogen activator (tPA), which cleaves extracellular matrix and other molecules, is expressed during juvenile MD and is necessary for functional plasticity in the adult (Mataga, Nagai, & Hensch, 2002; Muller & Greisinger, 1998). Application of tPA enhances spine motility, and loss of tPA prevents the loss of superficial spines after 4 days of MD (Oray et al., 2004; Mataga et al., 2004). Extracellular matrix could have a restrictive effect on ocular dominance plasticity by constraining spine motility and axonal growth or by imposing structurally mature functional elements onto intracortical inhibitory cells. Parvalbumin-expressing GABAergic cells become ensheathed in PPNs as the cortex matures (Härtig et al., 2001); degradation of PPNs may reduce the efficacy of inhibitory input by altering the ionic or chemical milieu and allow for plasticity. Mice lacking myelination factors Nogo-66 receptor and Nogo-A/B exhibit ocular dominance plasticity after brief MD in adulthood as well as a prolonged critical period (McGee, Yang, Fischer, Daw, & Strittmatter, 2005), suggesting that extracellular factors strongly constrain plasticity.

**Gene Screens for Novel Plasticity Factors** The use of gene microarrays to screen for differences in cortical gene expression under different conditions has facilitated the discovery of novel pathways and functional molecules involved in ocular dominance plasticity. A screen comparing the expression of normal and MD cortex at different ages revealed common and age-specific pathways modulated by MD (Madjan & Shatz, 2006). A comparison of V1 at different ages and with MD cortex showed an upregulation of actin-stabilizing genes, including the calcium sensor, cardiac troponin C, and myelinating factors, which were reversed with MD (Lyckman et al., 2008). Comparisons of dark-reared with normal V1 found a reduction in genes with a role in functional inhibition, reflecting a maturational delay.
while MD and normal V1 comparisons identified a number of growth factor and immunomodulatory factors that were upregulated in response to MD (Tropea et al., 2006).

**Summary and conclusion**

Retinotopic and feature selective maps constitute key organizational principles of the visual pathway. Intrinsically genetic programs and activity-dependent processes both play a role in setting up the structure and function of these maps. In addition, patterns of activity interact with programs of gene expression as they modulate signaling pathways within the cell. Understanding specific mechanisms of how visual stimulus feature maps are assembled and modified in response to experience is central to identifying fundamental processes of neural circuit development and plasticity.

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