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CHAPTER 1

Visual activity and cortical rewiring: activity-dependent plasticity of cortical networks

Sam H. Horng and Mriganka Sur*

Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Abstract: The mammalian cortex is organized anatomically into discrete areas, which receive, process, and transmit neural signals along functional pathways. These pathways form a system of complex networks that wire up through development and refine their connections into adulthood. Understanding the processes of cortical-pathway formation, maintenance, and experience-dependent plasticity has been among the major goals of contemporary neurobiology. In this chapter, we will discuss an experimental model used to investigate the role of activity in the patterning of cortical networks during development. This model involves the ''rewiring'' of visual inputs into the auditory thalamus and subsequent remodeling of the auditory cortex to process visual information. We review the molecular, cellular, and physiological mechanisms of visual ''rewiring'' and activity-dependent shaping of cortical networks.

Keywords: vision; auditory cortex; development; plasticity; connections; sensory processing

Introduction

Two critical features of brain development include: (1) the formation of specific pathways that connect brain regions, and (2) the assembly of appropriate processing networks in each brain region. Each of these features relies on a combination of intrinsic and environmental influences. In general, pathways form early in brain development whereas processing networks are not shaped until late, with changes continuing often into adulthood. Experience-induced change, or plasticity, represents an adaptive response of networks to patterns of stimuli. In the cortex, for example, such plasticity then serves to match processing in a cortical area to its specific inputs.

The specification of a cortical area, including the architecture of its neural networks, relies on a developmental program that involves patterns of gene expression together with both spontaneous and environmentally derived patterns of neural activity (Fig. 1(A); O'Leary, 1989; Rakic, 1988; Job and Tan, 2003; Sur and Rubenstein, 2005). During embryonic development of the anterior neural tube, signaling centers induce regional and graded expression patterns of transcription factors (Figdor and Stern, 1993; Rubenstein et al., 1994, 1998; Ragsdale and Grove, 2001; Nakagawa and O'Leary, 2002; Grove and Fukuchi-Shimogori, 2003; Shimogori et al., 2004). In the early cortex, localized sources of fibroblast growth factor 8 (FGF8), sonic hedgehog (Shh), and bone morphogenetic protein 4 (Bmp4) contribute to regional gradients of Emx2, Foxg1, COUPTF1, Pax6, and other transcription factors (Chalepakis et al., 1993; Toresson et al., 2000; Bishop et al., 2000, Crossley et al., 2001; Monuki and Walsh, 2001; Muzio and Mallamaci, 2003). These patterns confer positional information leading to the formation of discrete

*Corresponding author. Tel.: +1 (617) 253-8784; Fax: +1 (617) 253-9829; E-mail: msur@mit.edu

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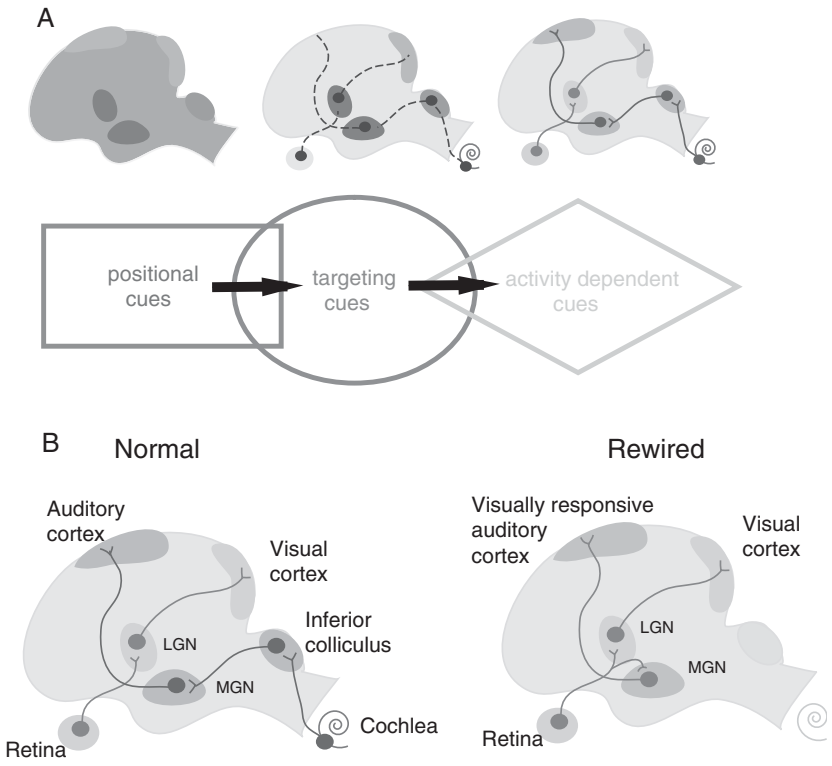

Fig. 1. Development of brain areas and connectivity. The role of novel activity on areal specification. (A) Early signaling centers secrete diffusible molecules, or patterning cues, which dictate positional information and establish regional patterns of transcription factor expression. Targeting cues along the pathways and at the targets of outgrowing axons instruct the connectivity between areas. Finally, activity-dependent cues further refine the networks. During normal development, areal specificity is dictated by a combination of patterning, targeting, and activity-dependent cues. In rewired animals, normal targeting of retinal afferents to the thalamus is disrupted, while thalamic patterning remains intact. Furthermore, activity-dependent patterning of auditory cortex is altered despite normal cortical patterning and targeting by thalamocortical inputs. (B) The visual pathway in normal ferrets and mice consists of retinal afferents innervating the lateral geniculate nucleus (LGN) and superior colliculus (SC), with LGN projecting to the primary visual cortex (V1). The auditory pathway in normal ferrets and mice begins with inputs from the cochlear nucleus (not shown) to the inferior colliculus (IC), continuing to the medial geniculate nucleus (MGN) and the amygdala, and then on to the primary auditory cortex (A1). Ablating the IC in neonatal animals induces retinal afferents to innervate the MGN and repattern the auditory cortex to process visual information. (A) Adapted from Sur and Rubenstein (2005); (B) adapted from Sur and Leamey (2001). See Plate 1.1 in Colour Plate Section.

cortical regions. Altering the expression levels or location of certain signaling molecules, such as FGF8, or transcription factors, such as Emx2, it has been shown that the cortical map will shift in size or location in response to atypical expression of critical patterning molecules (Mallamaci et al., 2000; Fukuchi-Shimogori and Grove, 2001, 2003; Hamasaki et al., 2004). "Proto-areas" of the cortical map acquire structurally distinctive features and begin to send and receive connections. Molecular cues enable migrating axons to locate their targets (Bolz et al., 2004). For thalamocortical axons, a number of sources, including subcortical regions of the basal ganglia, or prethalamus, the subplate, the cortex, as well as corticothalamic axons, have been implicated in the provision of necessary targeting cues (Garel et al., 2002; Hevner et al., 2002; Uziel et al., 2002; Garel and Rubenstein, 2004; Shimogori and Grove, 2005). Finally, activity provided by input pathways can refine and even alter connections within cortical areas (Cline, 2003; Sur and Rubenstein, 2005).

This chapter will focus on the potential of novel patterns of neural activity to alter the functional specificity and anatomical connectivity of cortical areas. We will review a model in which rerouting of retinal afferents to the auditory thalamus, or medial geniculate nucleus (MGN), after auditory deafferentation (Fig. 1(B)) directs visual information to the primary auditory cortex (A1), where neurons acquire novel retinotopic and feature-selective response properties (Sur and Leamey, 2001). Characterizing visually ''rewired'' A1 has allowed us to measure the extent to which cortical networks are modified to process information with novel spatial and temporal properties. While other models, such as the ability of eye-specific pathways in the primary visual cortex (V1) to change their spatial territory in response to imbalances of input, a paradigm referred to as ''ocular dominance plasticity,'' (Wiesel and Hubel, 1965; Shatz and Stryker, 1978; Antonini and Stryker, 1993; Katz and Shatz, 1996) are used to investigate the role of a relative reduction in the *amount* of activity, together with inter-pathway competition, in weakening and strengthening synaptic connections, the rewiring model probes the role of novel *patterns* of activity in shaping synaptic connections and function in existing cortical structures.

Developmental plasticity of sensory pathways: rewiring retinal inputs into the auditory thalamus

During development, sensory axons target unique regions, or nuclei, of the thalamus, which in turn send projections to specific areas of the cortex. Typically, these pathways process and transmit information of primarily one sensory modality (Wallace et al., 2004), while convergence at later stages represents the bulk of multisensory processing. In the visual pathway, retinal ganglion cells project to the dorsal and ventral subdivisions (LGd; LGv) of the lateral geniculate nucleus (LGN) in the thalamus and to the superior colliculus (SC) in the brainstem (Fig. 2(A)). From the LGd, thalamocortical axons project to V1. In the auditory pathway, cochlear afferents synapse first in the inferior colliculus (IC), which sends fibers along the brachium of the IC (BIC) to the MGN, which then projects to A1 (Fig. 2(A)). Using hamsters, Schneider discovered that retinal afferents could be induced to innervate the ventral MGN (MGv) when both the IC and SC were ablated after birth (Fig. 2(A); Schneider, 1973; Kalil and Schneider, 1975; see also Frost, 1982; Frost and Metin, 1985). IC loss deprives the MGN of auditory afferents and ipsilateral fibers of the BIC, while SC loss deprives both the MGN of contralateral fibers of the BIC and retinal axons of a normal target (Angelucci et al., 1998). ''Rewiring'' retinal afferents to MGN has subsequently been demonstrated and studied in the ferret and mouse models (Sur et al., 1988; Roe et al., 1990, 1992; Lyckman et al., 2001; Newton et al., 2004; Ellsworth et al., 2005).

''Rewiring'' alters anatomic and physiologic features of MGN to more closely resemble those of the normal LGN. In the ferret, rewired MGN neurons exhibit center-surround visual receptive fields during extracellular recording (Roe et al., 1993), as well as eye-specific segregation (Angelucci et al., 1997). Retinal axons in the MGN are topographically ordered with the central and peripheral fields located from medial to lateral and the ventral and dorsal fields represented from dorsal to ventral (Roe et al., 1991). Nonetheless, certain morphological aspects of rewired MGN are retained from normal MGN. Retinal axon terminations are elongated along the typical isofrequency axis, or lamellae, of the MGN as opposed to more focal, isotropic distributions in the LGN (Pallas et al., 1994). Furthermore, the eye-specific clusters of retinal inputs are smaller and cruder than the eye-specific layers of LGN (Angelucci et al., 1997).

Novel inputs alter functional specificity in the cortex: anatomical, physiological and behavioral consequences of rewiring

Similar degrees of functional and limited structural remodeling occur in rewired A1. Like their inputs, rewired A1 cells respond to visual-field stimulation and comprise a functional retinotopic map of visual space (Roe et al., 1990). However, the thalamocortical axons transmitting this information

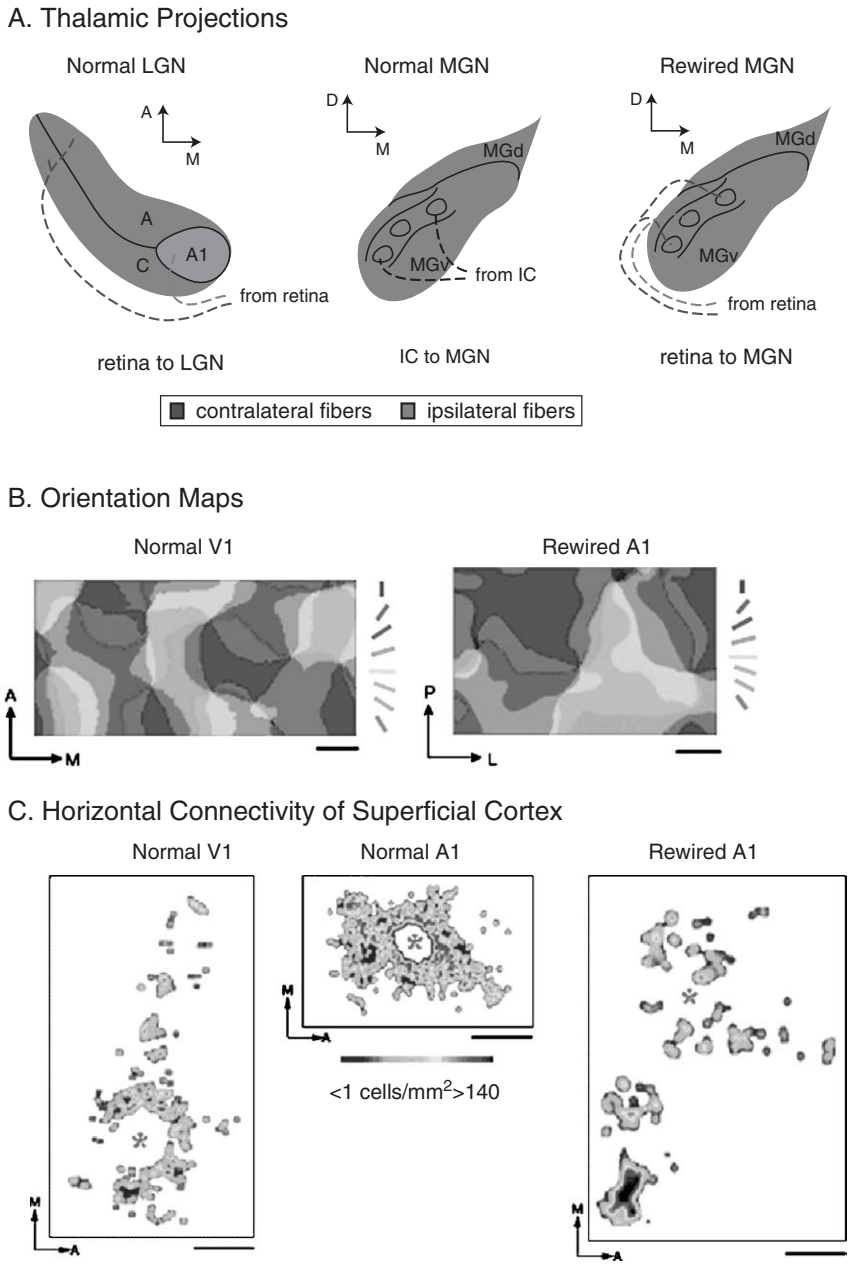

Fig. 2. Anatomical and physiological consequences of rewiring. (A) In normal ferrets, retinogeniculate axons terminate in eye-specific regions of the LGN (horizontal plane). Auditory afferents from the IC project to the ventral subdivision (MGv) of the MGN (coronal plane) and terminate along lamellae running parallel to the lateral-medial axis. Rewired auditory afferents innervate the MGv along adjacent, nonoverlapping eye-specific terminals within the MGv lamellae. (B) Orientation maps are observed in normal V1 and rewired A1 of ferrets using optical imaging of intrinsic signals. Hemodynamic changes in reflectance due to oxygen consumption are recorded from the cortex while gratings of different orientations are presented to the animal. A composite map of orientation preference is calculated by computing a vector average of the response signal at each pixel. Color bar: color coding representing different orientations. Scale bar: 0.5 mm.(C) Retrograde label reveals the distribution of horizontal connections in the superficial layers of the cortex in normal V1, normal A1 and rewired A1 of ferrets. The pattern of horizontal connectivity in rewired A1 more closely resembles that of normal V1 than normal A1, and potentially subserves the refinement of orientation mapping within rewired A1. Scale bars: 500 μm. (A) Adapted from Sur and Leamey (2001); (B) adapted from Sharma et al. (2000). See Plate 1.2 in Colour Plate Section.

retain their pattern of elongated projections along the anteroposterior axis of A1, which typically correspond to isofrequency bands (Pallas et al., 1990). In order to create a functional map of focal retinotopic representations, there must be either a refinement of the inputs from these elongated projections by an intracortical inhibitory network or a difference in drive along the projection itself (Sur et al., 1990). Thus, despite persistent structural features of A1 and thalamocortical input, functional representation is shaped by the novel patterns of activity transmitted to the cortex.

Rewired A1 also acquires computational response features, such as orientation and direction selectivity, that develop in normal V1 cells (Sharma et al., 2000). In ferrets, maps of orientation selectivity can be visualized by using optical imaging of cortical hemodynamic signals (Rao et al., 1997). In both normal V1 and rewired A1, but not in normal A1, orientation domains are present and converge at pinwheel centers representing the transition point between multiple domains (Fig. 2(B); Sharma et al., 2000). In rewired A1, orientation maps are smaller and less organized, though intracortical injections of retrograde tracer reveal that inhibitory horizontal connections bridge distantly located domains of the same orientation preference, as in V1 (Fig. 2(B); Sharma et al., 2000). In normal A1, horizontal connections are limited to isofrequency domains of the tonotopic map and stretch along these bands. Furthermore, calbindin-immunoreactive GABAergic neurons of rewired A1 display markedly more elongated axonal arbors in contrast to those in normal A1 (Gao et al., 2000).

Orientation and direction selectivity arise from the summed inputs of thalamocortical projections representing aligned receptive fields (Somers et al., 1995). Feed-forward inputs onto the cortical cells create levels of activity in preferential response to contrast edges of different orientations. Intracortical inhibitory inputs further refine the selectivity of these responses. Changes in the inhibitory microcircuitry of rewired A1 suggest that similar mechanisms organize the response preferences of V1 and rewired A1 cells.

The rewired auditory pathway also mediates functional changes in behavior. Experiments using ferrets with a unilaterally rewired left hemisphere demonstrate that after training to distinguish a left visual-hemifield stimulus from an auditory stimulus, the animals accurately perceive a right visual-hemifield stimulus as visual even after left LGN ablation (von Melchner et al., 2000). After left LGN ablation, the ferrets exhibit diminished yet intact spatial acuity in the right hemifield. Subsequent ablation of rewired A1 abolishes the animals' ability to distinguish a right-hemifield stimulus presented as visual. These experiments demonstrate that rewired A1 is sufficient and necessary in the absence of the ipsilateral visual pathway to detect a visual percept in trained ferrets. In mice, direct subcortical projections from the MGN to the amygdala have been implicated in mediating the rapid acquisition of a fear-conditioned response to an auditory cue (Rogan and LeDoux, 1995; Doran and LeDoux, 1999; Newton et al., 2004). Because of an indirect pathway from LGN through V1 and the perirhinal cortex to the amygdala, a fear-conditioned response to a visual cue requires many more training sessions (Heldt et al., 2000). In rewired mice, the acquisition time of a fear-conditioned response to a visual cue is accelerated and resembles that of a normal mouse in response to an auditory cue (Newton et al., 2004).

In sum, a number of functional properties of the rewired auditory pathway have been characterized: (1) structural reorganization of horizontal connections within the auditory cortex, (2) functional acquisition of visual receptive-field properties in rewired MGN and A1, (3) novel organization of retinotopic and orientation selective maps in rewired A1, (4) use of the rewired auditory pathway to mediate visual percepts, and (5) use of rewired subcortical connections to the MGN to rapidly entrain fear-conditioned behaviors in response to a visual cue.

Gene expression and the molecular mechanisms of rewiring

Although the response properties of the rewired auditory pathway have been characterized, the mechanisms by which retinal afferents target the MGN remain unclear. Experiments in ephrin A2/

A5 double knock-out mice reveal that surgically induced rewiring is enhanced in the absence of these repulsive ligands for which retinal axons bear receptors (Lyckman et al., 2001). Ipsilateral projections are increased, as they originate from the temporal retina and express the highest levels of ephrinA receptor (Ellsworth et al., 2005). Although the loss of ephrin A2 and A5 ligands is not sufficient to induce rewiring without surgery, the ability to enhance rewiring in their absence suggests that molecular cues play a role in the targeting of sensory axons to their respective thalamic compartments.

We hypothesize that surgical ablation of the IC induces changes in gene expression within the thalamus that mediate the aberrant ingrowth of retinal axons to the MGN. In order to discover molecular substrates for the targeting of retinal axons to the MGN, one strategy is to use gene microarrays to analyze gene expression in normal LGN and MGN and compare patterns of gene expression to rewired MGN. Differential patterns of gene expression between regions of neonatal (P0) mouse thalamus have been identified previously (Nakagawa and O'Leary, 2001; Jones and Rubenstein, 2004). We expect that molecules in the MGN that play a role in aberrant retinal targeting will either alter their levels of expression to resemble those of normal LGN or acquire novel levels of expression. In other words, targeting cues responsible for rewiring potentially correspond to those responsible for normal retinal ingrowth in the LGN or consist of novel factors uniquely expressed in the rewired MGN. Similar experiments could be applied to compare gene expression in normal A1, normal V1, and rewired A1 in order to discover changes in gene expression with a potential role in the structural and functional repatterning of A1 in response to novel input.

A number of developmental questions pertinent to the rewiring paradigm remain to be addressed. Presumably, the surgical ablation of IC (and SC) must be performed during a period in which retinal and BIC fibers target the LGN and MGN. In the mouse, both retinal and BIC fibers innervate the thalamus from E15 through birth (Tuttle et al., 1998; Gurung and Fritzsch, 2004). However, the precise developmental time window for effective rewiring has not been well-characterized. In the hamster, evidence for exuberant projections from the retina to the MGN early in normal development suggests that the rewiring surgery might simply stabilize these projections (Frost, 1982). In contrast, in the ferret, normal fibers from the retina do not reach the MGN and thus, rewiring must induce these fibers to innervate its novel target (Sur et al., 1988). In the mouse, retinal axons have not been observed to target MGN in normal development (Ellsworth and Sur, unpublished observations).

Implications of the rewiring model for human disability and comparative neurology

Processes of visual "rewiring" in the hamster, ferret, and mouse models could inform our understanding of functional compensation after early sensory loss in humans. Functional magnetic-resonance imaging has demonstrated that cortical areas can acquire novel processing properties in the absence of typical sensory input (Weeks et al., 2000). In congenitally blind individuals, auditory and somatosensory activation of the visual cortex can be seen (Cohen et al., 1997), while the auditory cortex may be activated by visual stimuli in congenitally deaf individuals (Bavelier and Neville, 2002). The phenomenon of "phantom limb" sensation suggests that somatosensory networks previously devoted to processing absent areas of the body, acquire new somatotopic receptive fields while still retaining residual percepts (Jones and Pons, 1998). Despite these examples of cross-modal plasticity in humans, the novel patterns of activation do not necessarily reflect actual changes in sensory input, in contrast to activation of existing intracortical, multisensory networks. Single-unit recording in the mouse demonstrate the presence of multimodal cells in primary sensory regions (Wallace et al., 2004). Activity in these areas can be modulated by stimuli of other modalities (Komura et al., 2005), and activation of primary sensory areas in the cortex can be elicited by stimuli of other modalities in humans (Schroeder and Foxe, 2005). Nonetheless, understanding the potential of primary sensory cortical areas for processing novel

stimuli could lead to important clinical strategies of optimizing sensory compensation.

Finally, rewiring of the auditory pathway may contribute to understanding general principles of brain evolution. Two strains of congenitally deaf mice (NKCC1, PMCA KO) exhibit visual rewiring in the absence of surgical IC ablation (Hunt et al., 2005). Furthermore, animal models of cross-modal plasticity are not limited to visual rewiring to the auditory cortex. Mice with congenital retinal defects, such as the ZRDCT/An mutant, exhibit auditory innervation of the LGN (Piche et al., 2004). Other strains, such as the oj/oj mutant, and mice enucleated at birth acquire somatosensory innervation of the LGN (Asanuma and Stanfield, 1990). Surgical ablation of IC and SC can also lead to retinal ingrowth to the ventrobasal nucleus (VB), or somatosensory thalamus (Frost and Metin, 1985). The general principle of sensory inputs compensating the target of a deprived modality suggests that divergence in the structure and function of brain networks could have developed after genetic mutations altering the strength or wholesale presence of certain sensory inputs. It has been hypothesized that the blind mole rat acquired expanded areas of the cortex devoted to somatosensory processing and audition after the loss of vision (Heil et al., 1991; Bronchti et al., 1991, 2002; Hunt et al., 2005). Thus, developmental plasticity in the targeting of sensory afferents to the thalamus may represent a general mechanism of evolving novel functional specificities for brain areas and networks.

Conclusions

"Rewiring" retinal afferents to the auditory pathway has enabled us to investigate the role of novel patterns of activity in shaping the response properties of cortical and thalamic areas. Areas within the cortex and thalamus appear to have a structural blueprint determined by gene-expression programs of the developing brain. This framework can nonetheless be instructed to process novel information and reorganize its microcircuitry to some degree in order to mediate functional behaviors appropriate to the stimulus. Mechanisms of rewiring are now being investigated to better understand the extent to which patterning, targeting, and activity-dependent programs of development can be dissociated and altered in order for a cortical area to acquire new functional response properties appropriate to novel stimuli.

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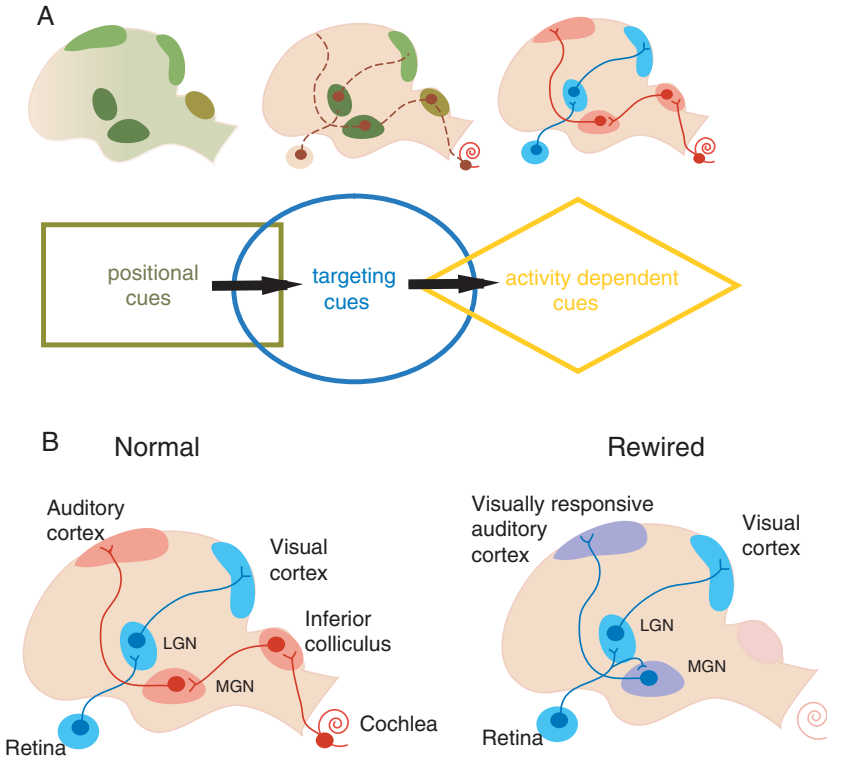

Plate 1.1. Development of brain areas and connectivity. The role of novel activity on areal specification. (A) Early signaling centers secrete diffusible molecules, or patterning cues, which dictate positional information and establish regional patterns of transcription factor expression. Targeting cues along the pathways and at the targets of outgrowing axons instruct the connectivity between areas. Finally, activity-dependent cues further refine the networks. During normal development, areal specificity is dictated by a combination of patterning, targeting, and activity-dependent cues. In rewired animals, normal targeting of retinal afferents to the thalamus is disrupted, while thalamic patterning remains intact. Furthermore, activity-dependent patterning of auditory cortex is altered despite normal cortical patterning and targeting by thalamocortical inputs. (B) The visual pathway in normal ferrets and mice consists of retinal afferents innervating the lateral geniculate nucleus (LGN) and superior colliculus (SC), with LGN projecting to the primary visual cortex (V1). The auditory pathway in normal ferrets and mice begins with inputs from the cochlear nucleus (not shown) to the inferior colliculus (IC), continuing to the medial geniculate nucleus (MGN) and the amygdala, and then on to the primary auditory cortex (A1). Ablating the IC in neonatal animals induces retinal afferents to innervate the MGN and repattern the auditory cortex to process visual information. (A) Adapted from Sur and Rubenstein (2005); (B) adapted from Sur and Leamey (2001).

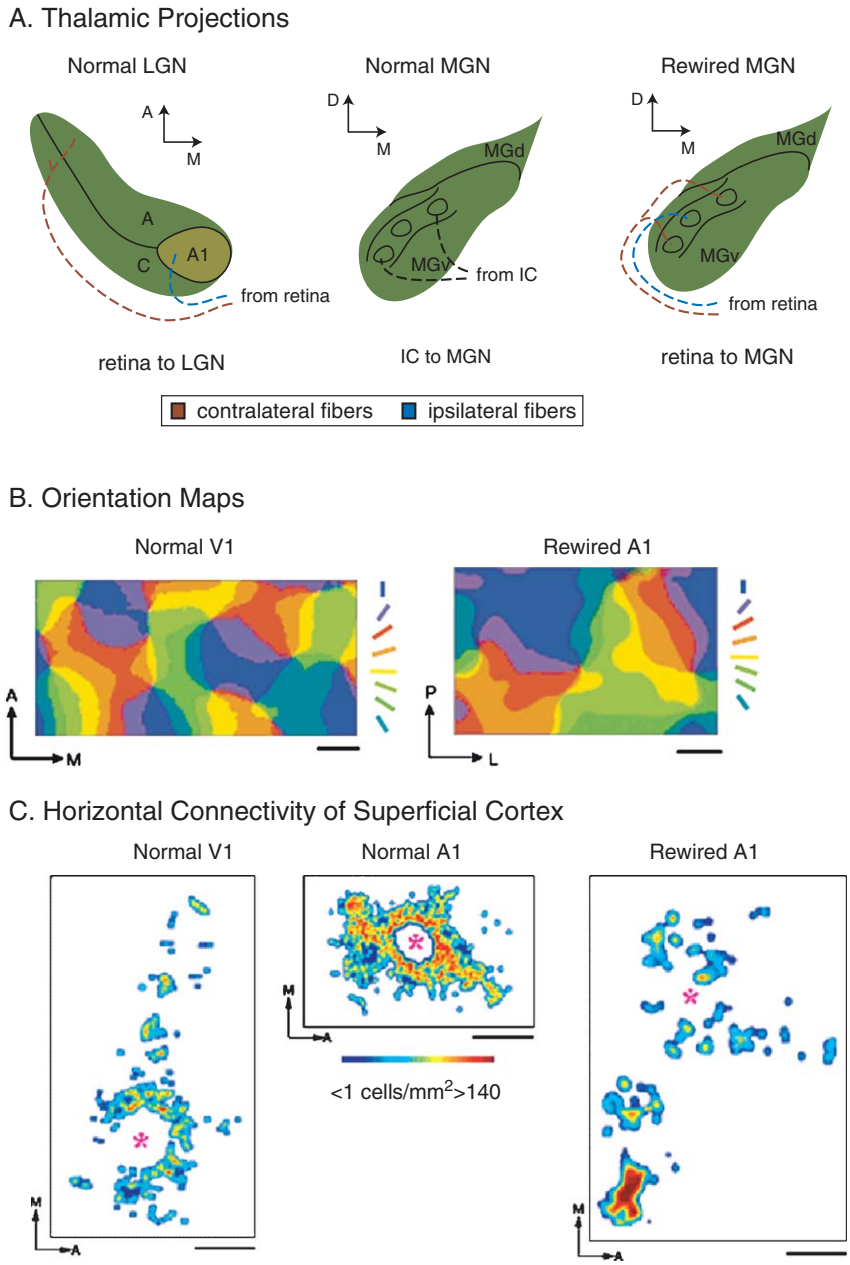

Plate 1.2. Anatomical and physiological consequences of rewiring. (A) In normal ferrets, retinogeniculate axons terminate in eye-specific regions of the LGN (horizontal plane). Auditory afferents from the IC project to the ventral subdivision (MGv) of the MGN (coronal plane) and terminate along lamellae running parallel to the lateral-medial axis. Rewired auditory afferents innervate the MGv along adjacent, nonoverlapping eye-specific terminals within the MGv lamellae. (B) Orientation maps are observed in normal V1 and rewired A1 of ferrets using optical imaging of intrinsic signals. Hemodynamic changes in reflectance due to oxygen consumption are recorded from the cortex while gratings of different orientations are presented to the animal. A composite map of orientation preference is calculated by computing a vector average of the response signal at each pixel. Color bar: color coding representing different orientations. Scale bar: 0.5 mm.(C) Retrograde label reveals the distribution of horizontal connections in the superficial layers of the cortex in normal V1, normal A1 and rewired A1 of ferrets. The pattern of horizontal connectivity in rewired A1 more closely resembles that of normal V1 than normal A1, and potentially subserves the refinement of orientation mapping within rewired A1. Scale bars: 500 μm. (A) Adapted from Sur and Leamey (2001); (B) adapted from Sharma et al. (2000).