Plasticity of Cerebral Cortex in Development

Jessica R. Newton and Mriganka Sur

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

Address correspondence to:
Mriganka Sur, PhD
MIT, E25-235
45 Carleton St.
Cambridge, MA 02139
Tel: (617) 253-8784
Fax: (617) 253-9829
Email: msur@ai.mit.edu

Keywords: plasticity, visual cortex, development, activity, function, connectivity, emergent properties

Plasticity of cerebral cortex in development

Jessica R. Newton & Mriganka Sur

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

The mammalian cerebral cortex is a convoluted sheet of neural tissue that forms the outer surface of the brain. It contains billions of neurons, and is responsible for our higher sensory, motor and cognitive abilities. A fundamental issue in cortical development is the degree to which "nature" (intrinsic factors such as genes or molecular gradients) or "nurture" (extrinsic factors such as sensory experience) shape the final structure and function of the cortex. Developmental plasticity - the ability of the brain (or neuron) to adapt to changes in its environment - provides vital insight into how the brain develops, functions and recovers from central nervous system damage. In essence, plasticity is the means by which environmental influences, which are relayed to the developing brain via changes in electrical activity, shape the connectivity and function of cortex. Experiments dating back at least four decades have explored this issue in the developing visual system, and considerable progress has been made in describing the phenomena and mechanisms of plasticity in the visual cortex.

1. Cortical Organization and Development

Cortical development is divided into two stages, an initial "establishment" phase where connections are formed, and a secondary "maintenance" phase where existing connections are

refined. Both intrinsic and extrinsic factors impact these two phases, and consequently the structure and function of the cortex. The cortex is subdivided into individual areas that process different types of information, and each region is characterized by a distinct set of inputs, outputs and internal connections.

The visual cortex consists of primary visual cortex and a number of other cortical areas that process different aspects of vision. The primary visual cortex contains systematic representations of different features of the visual environment. It contains a retinotopic map of visual space, with adjacent locations in the retina located next to one another in cortex. Overlaid on the retinotopic map is a functional architecture composed of maps of stimulus orientation, eye specific information (known as ocular dominance columns), and other features of visual stimuli. Orientation information is organized into domains of neurons that all represent a similarly oriented visual edge, clustered around singularities, called pinwheel centers. Ocular dominance columns are present in layer IV, or the input layer of visual cortex, and represent regions that receive input exclusively from one eye or the other via appropriate regions in the visual thalamus.

The function of primary visual cortex arises from the emergent responses of its neurons - that is, from properties that are created within the cortex and are not present in the inputs to the cortex. These properties crucially involve networks of neurons and a combination of thalamic and cortical connections. For example, orientation selectivity, which is critical for form perception, arises through the convergence of thalamic inputs to single cortical neurons together with intra-cortical excitatory and inhibitory connections. Sensitivity to visual depth and three-dimensional form is created by combining inputs from the two eyes within cortex, in layers adjacent to layer IV.

2. Developmental Plasticity

Understanding how genes, molecules, and visual experience contribute to the different phases of cortical development and how they influence the formation of cortical areas, maps and connections is critical to understanding developmental plasticity.

Cortical cells are born along the wall of the lateral ventricle and migrate to the cortical plate to form the six cortical layers. The formation of layers is regulated by the timing of cell birth, which in turn is largely regulated by factors intrinsic to the cell cycle of neuronal precursors in the ventricular zone. Cells that are born early form the deep cortical layers and cells that are born later give rise to the more superficial layers. The formation of cortical areas may also be influenced by genes expressed in the ventricular zone or by the differential expression of gene families and molecular gradients in the developing cortical plate, before axons from the thalamus arrive at the cortex. Genes that uniquely mark the visual (or any other) cortex have yet to be discovered, however. Molecular gradients within an area may also play a role in the establishment of cortical maps, such as the retinotopic map. Interestingly, some gradients are abruptly down-regulated at a time when maps are refined, suggesting a dynamic interaction between intrinsic and extrinsic factors during cortical map development.

Factors extrinsic to the cortex, such as the amount and pattern of electrical activity in input pathways, also contribute to cortical development. Electrical activity generated within the developing brain itself may be sufficient for the establishment of thalamo-cortical connections, as suggested by the existence of retinal waves of spontaneous activity and the presence of ocular dominance columns before eye opening. Visual experience, which influences the amount and pattern of electrical activity in pathways to the cortex, however appears to be critical for the

maintenance and refinement of cortical connections. Classic experiments by Hubel and Wiesel demonstrated that visual cortex displays remarkable plasticity during development, and that ocular dominance columns in visual cortex are profoundly influenced by sensory experience. In particular, depriving one eye of vision during a critical period of development, during which visual experience has a maximal effect on cortical structure, induces robust changes in the anatomy and physiology of visual cortex. Depriving both eyes, however, has less impact on the formation of ocular dominance columns, indicating that the balance of activity rather than the absolute level of activity is key for cortical connections to form during the critical period. Cortical plasticity is also impacted by limiting overall light exposure, such that rearing animals in the dark prolongs the critical period. After the critical period, visual experience has a minimal effect on cortical organization and function. These experiments demonstrate the importance of the relative amount of input activity in developmental plasticity as well as for the maintenance and refinement of cortical maps and connections during development.

Experiments that involve “rewiring” the brain demonstrate that the pattern of visual activity also has a fundamental role in the establishment of cortical maps and of emergent feature selective responses. In these experiments, retinal ganglion cell axons are induced to innervate the auditory thalamus by surgically removing its normal inputs at birth (see Fig. 1). This creates an alternative target for retinal axons: functional retinal connections form in the auditory thalamus, which conveys visual information through existing thalamo-cortical connections to the primary auditory cortex. Visual activity, which has a very different spatial and temporal pattern than auditory activity, leads to visual responses in “rewired” auditory cortex that resemble responses in primary visual cortex. Specifically, neurons in rewired auditory cortex develop response features such as orientation-, direction- and velocity-selectivity. Furthermore, orderly

maps of visual space and of orientation-selective neurons form in rewired auditory cortex (see Fig. 2). Underlying these functional responses, local and long-range connections in rewired auditory cortex are shaped by the visual input that the cortex receives, and resemble connections in primary visual cortex. The novel pathway from the retina to auditory cortex is capable of mediating visual behavior. Rewired ferrets (with the normal visual pathway removed) are able to detect visual stimuli and resolve gratings of varying spatial frequency when their auditory cortex is activated by vision. While the orientation modules in rewired auditory cortex are larger than in the visual cortex, as are receptive fields, collectively the rewiring studies provide powerful evidence that patterned visual activity plays an instructive role in the establishment (and not only the refinement and maintenance) of cortical connections.

3. Plasticity Mechanisms

"Hebbian" mechanisms of learning, which can be summed up by the adages "neurons that fire together, wire together" and "neurons that are out of sync, fail to link", are assumed to underlie activity-dependent synaptic plasticity. According to these learning rules, pre-synaptic inputs and post-synaptic cells that are simultaneously active are synaptically enhanced whereas ones that are not are reduced. Activity plays a key role in the formation and maturation of synapses at the post-synaptic neuron. For example, in many cortical areas, glutamatergic NMDA receptors are present before AMPA receptors, and NMDA receptor activation induces insertion and redistribution of AMPA receptors at active synapses. It has also been suggested that long-term potentiation and long-term depression of synapses, which is observed in the hippocampus and follows Hebbian learning rules, may underlie developmental plasticity in the visual system. Studies of long-term synaptic plasticity in the visual cortex and other cortex <u>in vitro</u> have shown

that synaptic potentiation and depression is accompanied by structural and molecular changes at the level of single synapses. In the hippocampus, NMDA-mediated activity induces rapid outgrowth of dendritic filopodia and new spine formation, and these changes may be correlated with the formation of new synapses. Activity dependent plasticity may also reflect competition for neurotrophic factors like brain derived neurotrophic factor, which is developmentally regulated by visual experience and influences neuronal growth. Blocking electrical activity in the eye results in a decrease in brain derived neurotrophic factor in visual cortex, and application of the factor to the developing visual cortex interferes with the effects of monocular deprivation and the formation of ocular dominance columns. Related molecules such as TrkB, which are required for the long-term maintenance of cortical connections during development, also appear to be necessary for the expression of long-term potentiation during the critical period of development, and are involved in the formation of ocular dominance columns in visual cortex.

Although the presence of visual activity alone supports the establishment of cortical connections and maps, patterned visual activity may also play a role in their establishment and certainly influences the refinement of these connections and cortical maps throughout development. The current body of work on developmental plasticity in the visual system suggests that intrinsic factors such as spatial and temporal patterns of gene expression and molecular gradients, and extrinsic factors such as the amount and pattern of electrical activity, dynamically interact to shape the final structure, organization and function of the cortex.

Further Readings

Sengpiel F, Kind PC (2002): The role of activity in development of the visual system. *Curr Biol* 12: 818-826

Sur M, Leamey CA (2001): Development and plasticity of cortical areas and networks. *Nat Rev Neurosci* 2: 251-262

Figure Legends

Figure 1. Normal and rewired projections demonstrate plasticity of the cerebral cortex in development. (top) A schematic of the visual (blue) and auditory (red) pathways in a normal brain. In normal animals, the retina projects heavily to the visual thalamus (specifically the lateral geniculate nucleus, LGN), which in turn projects to primary visual cortex. The auditory pathway consists of projections from the cochlea to the cochlear nucleus, which innervates the inferior colliculus. The inferior colliculus projects heavily to the auditory thalamus (the medial geniculate nucleus, MGN), which in turn projects to the primary auditory cortex. **(bottom)** Schematic of the rewired pathway after retinal axons are induced to innervate the medial geniculate nucleus in neonates. (Modified from Sur and Leamey, *Nat. Rev. Neurosci.,* 2001).

Figure 2. Orientation maps in normal visual cortex and rewired auditory cortex demonstrate the role of input activity in cortical development. (left) Lateral view of normal primary visual cortex (V1) in the ferret brain. The upper two panels show activity maps in normal V1 using optical imaging of intrinsic signals in response to vertical and horizontal grating stimuli, respectively. Dark regions denote areas of high activity. The bottom map is a composite map of all orientations tested. The color key to the right of the panel shows the orientations represented. **(right)** Lateral view of rewired primary auditory cortex (A1) in the ferret brain. The upper two panels represent the single orientation activity maps generated in rewired A1 under the same conditions as the left panels. The bottom map is a composite map of all orientations tested. The color key to the right of the panel shows the orientations represented. Scale bars, 0.5mm. (Modified from Sur and Leamey, *Nat. Rev. Neurosci.,* 2001, and from references therein).

Figure 1

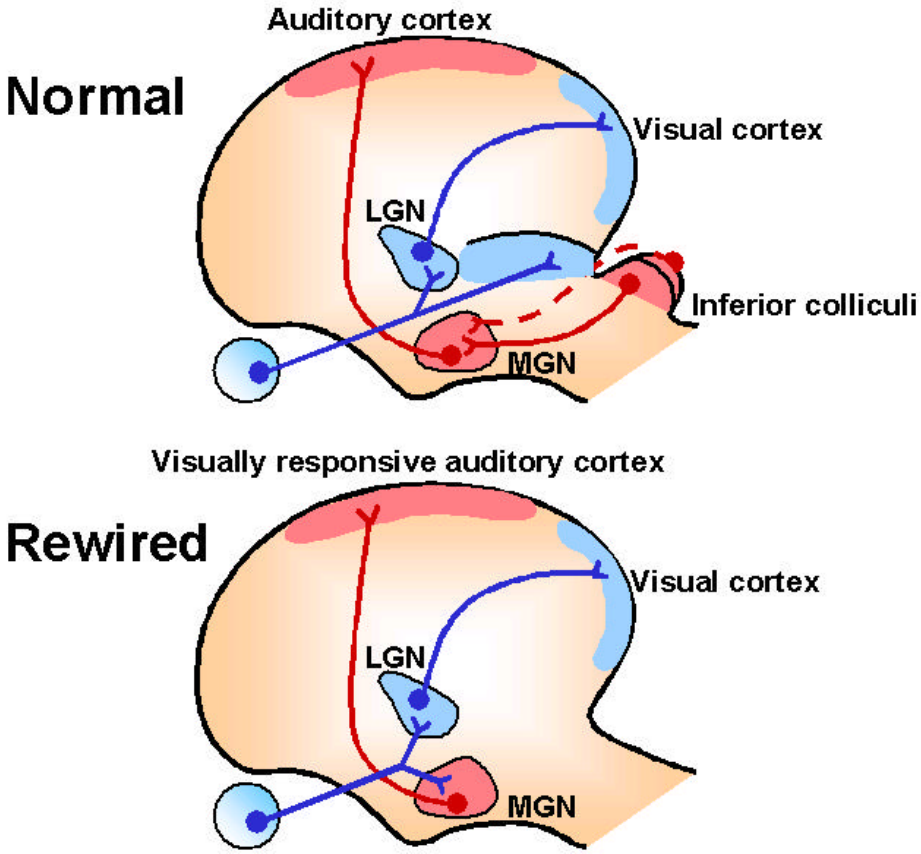
Auditory cortex
Normal
Visual cortex
LGN
Inferior colliculi
MGN
Visually responsive auditory cortex
Rewired
Visual cortex
LGN
MGN

Figure 2