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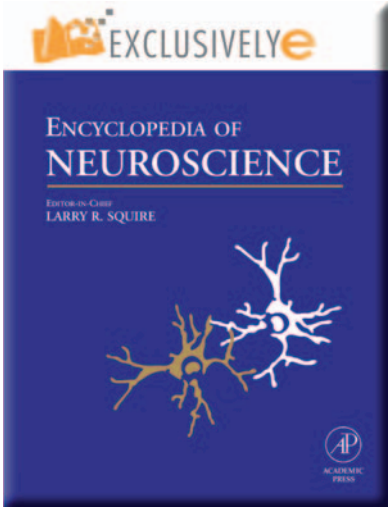

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Feller M B and Ruthazer E S (2009) Activity in Visual Development. In: Squire LR (ed.) Encyclopedia of Neuroscience, volume 1, pp. 47-51.
Oxford: Academic Press.

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Activity in Visual Development

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Introduction

The development of neuronal circuits involves initial coarse wiring under the guidance of molecular cues and the refinement of connections through mechanisms that are governed by patterned spontaneous activity and sensory experience. This fine-tuning of neuronal circuits is evident in the development of sensory maps in the brain. Sensory maps are organized layouts of neurons in which cells that prefer specific stimulus features are found in close physical proximity. The term map can apply either to the central representation of the sensory periphery, as in the case of retinotopic or other topographic maps, or to the orderly representation of higher order stimulus features such as orientation or interaural time difference.

Neural activity can be either permissive or instructive for circuit formation. When serving a permissive role, the presence of activity acts as a switch to regulate other downstream signaling events. In this case, neural activity essentially converts neurons from one state to another. An example of this is the ability to delay the onset of the critical period for plasticity by dark-rearing animals. Even brief visual experience can activate critical period plasticity in such animals. In contrast, an instructive role for activity is where the specific levels or patterns of neuronal firing carry information that allows different neurons to be distinguished from one another exclusively on the basis of these activity patterns. It is often difficult to prove unambiguously that activity plays an instructive role in a system because the simplest experiments involving blocking activity cannot distinguish between instructive and permissive roles. Nonetheless, there is compelling evidence from experiments in which activity patterns but not levels are altered, such as the ocular dominance shift in strabismic animals or the requirement for retinal waves of activity in the refinement of the retinocollicular map, that activity can also play an instructive role.

Activity in the developing visual system is not limited to that driven by visual experience. Throughout the visual system, in the thalamus, colliculus, and cortex, visual experience appears to be important in the maintenance of functional maps, but early development in these structures actually precedes vision. In this latter case, internally generated patterns of spontaneous activity play a key role in circuit refinement.

Sources of Activity in the Developing Visual System

In mammals, retinal ganglion cell (RGC) axons reach their targets before mammals' eyes open, and even before they have functional photoreceptors. In these early stages of development, in the absence of light responses, retinas are spontaneously active. These early activity patterns are called 'retinal waves' because they propagate across the ganglion cell layer, correlating the firing of tens to hundreds of RGCs. The synaptic circuits that mediate retinal waves are transient, with retinal waves disappearing as light responses are first developing. In contrast, in lower vertebrates, such as turtles, frogs, and chicks, there is an extended time during which waves and visual responses overlap. The synaptic mechanisms underlying retinal waves are described elsewhere in this encyclopedia.

An interesting feature of retinal waves is that they coincide with the period of development when visual responses are first detected in the retina. In mice, light-evoked responses have been detected as early as P10, which is 3 or 4 days before eye opening. In ferrets, which are born at approximately the same developmental stage as mice but have an elongated developmental period lasting 4 weeks until eye opening, light-driven responses are detectable in the dorsal lateral geniculate nucleus of the thalamus (dLGN) and visual cortex as much as 14 days before eye opening. Several experiments in mice, rats, and ferrets indicate that both spontaneous and light-evoked activity are detected in visual cortex before eye opening, indicating that both may influence developmental events. Visual deprivation by dark rearing, even when the eyelids are closed, alters the refinement of circuits within the retina and dLGN. Similarly, dark rearing and/or pharmacological manipulations of spontaneous activity have distinct influences on the development of RGCs in turtle retina, which have an extended period of light-evoked activity and retinal waves.

Once the eyes open, vision improves quickly, as determined by several measures. There is an immediate and steady increase in acuity and contrast sensitivity and a more gradual increase in spectral sensitivity. Neurons tuned to several features of the visual scene can be detected at eye opening, including ocular dominance and orientation.

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Another source of neural activity that may be critically important for development is the activity patterns that are intrinsic to local circuits. Even in the absence of sensory input, there is a tremendous amount of spontaneous activity, some of which can be highly patterned. For example, spindle waves, which are fast oscillations in the cortical field potential generated by thalamocortical circuits, persist when the eyes are removed.

Retinotopic Maps in Tectum/Superior Colliculus

The two primary targets of RGCs in the brain are the superior colliculus (SC) and the LGN of the thalamus. In these targets, RGCs establish an arrangement of connections in target fields, termed a retinotopic map, that reflects the spatial arrangement of the RGCs in the retina, and eye-specific maps with inputs from the two retinas layering in neighboring but nonoverlapping regions.

The precise retinotopic and eye-specific targeting of RGCs axons observed in the adult emerges from initially diffuse and overlapping projections, prior to visual experience. There is a clear role for both neural activity and molecular factors, such as the ephrins and their corresponding receptors, for the establishment of these maps, although the relative importance of the two throughout the process of axon targeting and refinement is the subject of ongoing research. This article reviews the evidence that activity plays a role in the establishment of retinotopic maps.

The degree of retinotopic mapping can be assayed by different techniques. Most studies have relied on small focal injections of anterograde tracers (e.g., DiI) into the retina to visualize the axonal arbors in the SC/tectum, which is referred to as the termination zone. In addition, retinotopic maps have also been assayed by the spatial distribution of RGCs that are labeled by focal injections of retrograde tracers into the SC. Third, physiological measures in *in vitro* slices containing the optic tract and SC can assay the number of functional retinal inputs onto individual SC neurons. Last, *in vivo* physiological measurements of receptive sizes of SC/tectum neurons reveal the physiological consequences of topographic refinement.

The first preparations used for establishing a role for activity in retinotopic map formation were frogs and fish. These species have two advantages. First, topographic refinement occurs throughout life. The retina is constantly adding new cells at its periphery, whereas the tectum grows from the caudal end. Consequently, the retinal projections must constantly shift in order to maintain a retinotopic map. Second, in these species, RGC axons regenerate after injury, and hence maps can be studied while reforming in this more adult stage. Blockade of activity during either development or regeneration does not affect the course topography of projections but does profoundly affect the development of fine topography – the projections that mediate the fine point-to-point connectivity between RGCs and tectal neurons. These classic experiments led to the generation of a major dogma in developmental neuroscience that molecular cues mediate the development of course maps, whereas activity is important for the establishment of fine topography.

There has been growing evidence for activity also playing a role in the refinement of maps in mammalian systems. One fundamental difference between refinement in mammals and in frogs and fish is the location of axon branches that undergo refinement. In frogs and fish, refinement is mediated by small-scale changes in higher order axon branching emerging from the tip of the RGC axon. In contrast, during the development of retinocollicular maps in mammals (and similar to retinotectal maps in chicks), RGC axons overshoot their targets in the A–P axis. Branching in the appropriate retinotopic location occurs along the RGC axonal shaft, at sites anterior to the growth cone. Then, in what appears to be a distinct process, the overshooting axon and, in some cases, entire axonal branches are eliminated.

Pharmacological blockade in mammals leads to small, although significant, effects on the final level of retinotopy. To demonstrate a role for correlated retinal activity, mice that lack β_2-containing nicotinic acetylcholine receptors (nAChRs), which exhibit a pattern of retinal activity in which RGCs spike in a seemingly random pattern with little correlation between the spike trains of neighboring RGCs, have been examined. β_2-nAChR$-/-$ mice exhibit less retinotopic refinement than wild-type mice. The absence of retinal waves in β_2-nAChR$-/-$ mice is correlated with the irregular refinement of retinotopic maps despite the presence of approximately normal levels of activity in individual RGCs. Similar results were obtained with intraocular injections of nAChR antagonists, indicating that disruption of retinal waves can prevent the retinotopic refinement of retinocollicular projections.

Eye-Specific Maps in the Lateral Geniculate Nucleus

RGC axons project to the dLGN of the thalamus terminating in regions that are organized topographically and are segregated into eye-specific layers (i.e.,

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projections from one eye end in regions spatially distinct from those of the other eye). When RGC projections from the eyes first grow into the dLGN, they are partially intermixed. The eye-specific layers then emerge gradually as the termination fields of the eyes segregate into regions containing either ipsilateral or contralateral retinal projections. This process is known to be activity dependent since intracranial infusion of TTX, a blocker of voltage-activated sodium channels, prevents segregation. Moreover, experiments have revealed that the activity driving this segregation comes from the retina since prolonged desynchronization of spontaneous retinal activity by parmacological disruption of nAChR activation in the eye also prevents layer formation. Blocking spontaneous activity in a single eye also significantly alters the distribution of RGC axons, indicating that competition from the two eyes is critical for the formation of eye-specific layers.

A wide array of transgenic mice and pharmacological manipulations have been used to gain insights into the mechanisms that mediate the formation of eye-specific layers. A few studies have taken advantage of the fact that the cellular basis of retinal waves switches from one mediated by nAChR to one mediated by ionotropic glutamate receptors to transiently block retinal waves. If nAChR-mediated retinal waves are eliminated during the initial period of refinement, either by pharmacological manipulation or by using β_2-nAChr−/− mice, eye-specific layers fail to form. However, even in the absence of the initial establishment of layers, RGC axons segregate into local eye-specific regions, with ipsilaterally regions segregated into small islands within the contralateral region. Thus, axons segregate without forming distinct eye-specific layers, indicating that eye-specific segregation and layer formation are separable processes that may occur through different mechanisms.

Retinal activity is essential not only for the establishment but also for the maintenance of eye-specific layers. In ferrets, intraocular injections of APB block glutamate-mediated waves after layers have been established and it has been shown to result in desegregation. In no-b-wave (*nob*) mice, RGCs fire in very frequent synchronous bursts that desegregate after layers have been established.

Whether retinal waves provide an instructive or permissive signal for driving eye-specific segregation is controversial. β_2-nAChR−/− mice do not form eye-specific layers, but pharmacological and genetic manipulations that significantly disrupt nearest neighbor correlations by increasing the uncorrelated firing of RGCs do not prevent layers from forming. The resolution of this controversy may rely on gaining insights into what aspect of the highly correlated activity is critical or driving refinement. Information required for activity-dependent segregation might be encoded in the slow periodic firing generated in individual neurons by waves. These periodic bursts of action potentials lead to substantial increases of intracellular calcium concentration in the participating neurons. There is growing evidence that periodic changes in intracellular calcium occurring on the order of minutes can profoundly influence a variety of intracellular processes. Thus, the periodicity of circuit activation may be tuned to the periodicity of intracellular signaling required to ensure the normal maturation of neurons in the retina or the segregation of retinal inputs in the dLGN.

Similarly, important information might be encoded in the spatial pattern of the activity. Synchronous activation of cells contains no distinct spatial information regarding the relative positions of cells involved in each event. However, the propagating activity seen in the retina synchronizes the activity of subsets of cells, thereby encoding their relative positions. A single retinal wave synchronizes firing of cells along a wavefront with a particular orientation on the retina, generating an activity pattern that might be used to establish orientation selectivity in visual cortical neurons. Activity patterns averaged over a large number of waves would lose orientation information but would maintain highly correlated firing among neighboring neurons, thus providing information that might be used to establish topographic projections.

The resolution of the question of whether the retinal waves are instructive or permissive for map refinement will rely on better targeted disruptions of spontaneous retinal activity based on a deeper understanding of the cellular mechanisms underlying plasticity.

Ocular Dominance Column Formation and Plasticity

The segregation of retinal inputs from each eye into eye-specific layers in the dLGN sets the stage for further segregation of eye-specific inputs in the thalamocortical projection to primary visual cortex. Transneuronal labeling studies in which radioactive amino acid or other anterograde neuronal traces that can jump synapses such as wheat germ agglutinin–horseradish peroxidase (WGA-HRP) are injected into one eye reveal a high degree of segregation of thalamocortical afferents into ocular dominance columns (ODCs) in layer 4 of the visual cortex of carnivores and certain primates, including humans.

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Note, however, that eye-specific segregation is not evident in the visual cortices of all mammalian species: mice, rats, and even highly visual animals such as squirrels lack ODCs. Regardless of whether a species has segregated ODCs in the binocular zone of its visual cortex, binocular responsiveness (along with orientation and direction selectivity) of neurons is an important emergent property of the cortex not found at earlier levels of the visual system in normal adult animals.

This binocularity has proven to be a remarkably useful tool for studying cortical developmental plasticity. The pioneering work of Hubel and Wiesel revealed that deprivation of visual information through one eye by eyelid suture or image defocusing, known as monocular deprivation (MD), results in a dramatic shift of the responsiveness of cortical neurons to favor the nondeprived eye. These changes in the response properties of individual neurons are accompanied in most cases by a corresponding loss of visual acuity through the deprived eye, or amblyopia. The ocular dominance (OD) shift in response to MD is particularly powerful during a limited critical period in development, although evidence suggests that some degree of shift is possible even in adults. During the critical period, MD for as little as 1 day leads initially to a reduction of responsiveness to the deprived eye followed by an enhancement of the response driven by the nondeprived eye.

These changes are stronger and more rapid in extragranular (outside layer 4) layers of visual cortex, suggesting that plasticity of local cortical circuitry may guide the process. Nonetheless, the MD shift does propagate to cells in layer 4 and ultimately back to the dLGN. With less than 1 week of MD in the cat, the axonal arbors of thalamocortical neurons representing the deprived eye shrink, whereas those representing the nondeprived eye expand. Bulk transneuronal labeling from the eyes, as well as physiological assays, also reveals a gross shrinkage of deprived eye ODCs and a corresponding expansion of nondeprived eye columns. This propagation of OD plasticity back to successively earlier stages of the visual processing stream suggests the existence of retrograde messengers. This is further supported by numerous experiments in which blockade of spiking activity or of synaptic transmission through *N*-methyl-D-aspartate (NMDA) receptors in cortical neurons results in a disruption of the OD plasticity of thalamic afferents.

In addition to MD, misalignment of the eyes, or strabismus, during the critical period can also lead to a shift in the distribution of OD responses of cortical neurons, including the selective loss of binocular responses accompanied by a sharpening of ODC borders. This observation, together with the fact that comparable periods of binocular deprivation do not result in significant loss of visual responsiveness, argues that the equilibrium of inputs representing the two eyes is the result of a developmental competitive process.

This raises the question of whether a competitive process such as ocular dominance plasticity could be responsible for the initial segregation of ODCs. This question remains unresolved. Computer simulations, as well as the finding that RGC axons spontaneously segregate in an activity-dependent manner into ODC-like stripes in the optic tectum of fish and amphibia, indicate that the information contained in the spontaneous firing of retinal ganglion cells should be sufficient in principle to drive segregation into ODCs without the need for a molecular scaffold. On the other hand, ODCs are evident soon after thalamocortical innervation prior to the onset of the critical period for MD effects, and they do not appear to be disrupted by monocular enucleation at this early time. The presence of spontaneous activity within the already segregated dLGN at this stage, however, does not permit activity-dependent segregation of thalamocortical inputs to be ruled out at this point.

Molecular Mechanisms of Plasticity

It has become increasingly clear that developmental plasticity in the visual system is not mediated by a single mechanism. For example, in the dLGN of the ferret, segregation of eye-specific layers does not appear to require NMDA receptor (NMDAR) activation, whereas the segregation of inputs from on-center and off-center RGCs into sublaminae in the dLGN is prevented by application of NMDAR antagonists. In the visual cortex, NMDARs appear to play a key role in ocular dominance plasticity because pharmacological blockade or genetic knock-down of cortical NMDARs prevents the shift of OD in response to MD. The fact that current through NMDARs in response to presynaptic glutamate release is blocked by Mg^{2+} ions except when relieved by concurrent depolarization of the postsynaptic neuron allows NMDARs to serve as molecular detectors of correlated pre- and postsynaptic firing. Consistent with the role of NMDARs in the induction of synaptic plasticity, mutant mice deficient in the alpha isoform of Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) or the serine/threonine phosphatase calcineurin, required for NMDAR-mediated long-term potentiation and long-term depression, respectively, lack normal OD plasticity.

Long-lasting neuronal plasticity generally requires protein synthesis. This is also true for OD plasticity

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because application of cyclohexamide to visual cortex (but not LGN) to inhibit protein synthesis prevents the OD shift. The identities of the gene products required for OD plasticity have not been revealed. However, at least two key regulators of gene transcription, the extracellular signal-related kinase (ERK) and cyclic adenosine monophosphate response element-binding (CREB) transcription factors, which have both been implicated in long-term synaptic plasticity, are required to produce an OD shift. These protein synthesis-dependent pathways may be important for long-lasting structural plasticity, such as axonal arbor and dendritic spine remodeling in visual cortex.

Structural plasticity involves both the assembly of new connections and the dismantling of existing connections. Existing connections may be stabilized by interactions with the extracellular matrix and through cell–cell adhesion and signaling. Consistent with this model, activity of the serine protease tissue plasminogen activator has been shown to facilitate the OD shift during the critical period, leading to dendritic spine remodeling. After the critical period, a large degree of plasticity can be restored under conditions that reduce signaling by outgrowth inhibitory molecules such as chondroitin sulfate proteoglycans or the myelin inhibitor receptor NogoR.

These myriad molecular signaling cascades all nonetheless share a requirement for discriminable differences between the patterned neural activity in the two eyes. The ability of cortical neurons to detect these differences appears to rely critically on the balance between excitation and inhibition in the circuit. Evidence points to the developmental maturation of inhibitory circuitry, GABAergic basket cells in particular, as a key event for initiating the critical period for OD plasticity. The critical period in mice is opened precociously by augmenting the immature endogenous inhibitory circuitry with administration of the GABA-A receptor partial agonist diazepam. The excitatory–inhibitory balance may be regulated in part by the activity-regulated expression of brain-derived neurotrophic factor (BDNF). Such activity-dependent control of the susceptibility to undergo plastic changes, known as 'meta-plasticity,' is a prediction of the influential Bienenstock–Cooper–Munro (BCM) model for neuronal plasticity. The BCM model posits that activity levels determine a sliding threshold of input strengths required for synaptic modification, above which synaptic strengthening occurs and below which synapses are weakened. Alternatively, an important role for inhibition may be to help sharpen the temporal precision of firing of postsynaptic neurons in response to sensory inputs. Spike timing-dependent plasticity, in which synaptic changes depend critically on whether a postsynaptic neuron fires before or after its presynaptic partner, may be facilitated by maintenance of an appropriate excitatory–inhibitory balance.

The increasing availability of useful transgenic mouse models for the study of activity-dependent developmental plasticity ensures that many more candidate genes will be found to participate in this process.

See also: Adult Cortical Plasticity; Spontaneous Patterned Activity in Developing Neural Circuits; Vision: Light and Dark Adaptation; Visual Associative Memory; Visual Deprivation; Visual Development.

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