Chapter 55. Formation and Elimination of Synapses
Course Outlines

1. Recognition of Synaptic Targets Is Specific
2. Principles of Synaptic Differentiation Are Revealed at the Neuromuscular Junction
3. Central Synapses Develop in Ways Similar to Neuromuscular Junctions
4. Some Synapses Are Eliminated After Birth
Three key processes drive synapse formation

• First, axons make choices among many potential postsynaptic partners, usually at specific sites (cell bodies, dendrites, axons...) on particular target cells.
• Second, after formation of cell-cell contacts, precise coordination of pre- and postsynaptic differentiation depends on interactions between the axon and its target (neuromuscular junction as an example).
• Finally, once formed, synapses continue to mature.
Molecular programs versus neural activity

• Interplay of molecular programs and neural activity shapes synaptic patterns.

• The initial steps in synaptic formation appear to be “hardwired” by molecular programs.

• However, as soon as synapses form, the nervous system begins to function, and the activity of neural circuits plays a critical role in subsequent development.
1.1 Recognition Molecules Promote Selective Synapse Formation

- Immunoglobulin-like adhesion molecules promote homophilic interactions (they bind to the same protein on other cell surfaces).
- The amacrine and bipolar cells that contact a particular ganglion cell type in a specific sublamina often express the same adhesion molecules as their target cell. Thus, a “like-binds-like” recognition system appears to contribute to synaptic specificity in retina.
- lamina-specific connection
Light-sensitive photoreceptor

Retina

Inner plexiform layer

Amacrine and bipolar interneuron

Retinal ganglion cell

Optic nerve

Optic tectum

Retinal input layers

Off layer

On layer

Spike rate

Light

A

B

Sdk1  Sdk2  Dscam  DscamL

Sdk1  Sdk2  Dscam  DscamL
Figure 55–2 Retinal ganglion neurons form layer-specific synapses. (Reproduced, with permission, from Sanes and Yamagata 2009.)

A. The dendrites of retinal ganglion neurons receive input from the processes of retinal interneurons (amacrine and bipolar cells) in the inner plexiform layer, which is subdivided into at least 10 sublaminae. Specific subsets of interneurons and ganglion cells often arborize and synapse in just one layer. These lamina-specific connections determine which aspects of visual stimuli (their onset or offset) activate each type of retinal ganglion cell. The responses of OFF and ON retinal ganglion cells are shown on the right.

B. Immunoglobulin superfamily adhesion molecules (Sdk1, Sdk2, Dscam, and DscamL) are expressed by different subsets of amacrine and retinal ganglion neurons in the developing chick embryo. Amacrine neurons that express one of these four proteins form synapses with retinal ganglion cells that express the same protein. Manipulating Sdk or Dscam expression alters these patterns of lamina-specific arborization.
1.2. Different Synaptic Inputs Are Directed to Discrete Domains of Postsynaptic Cell

In the cerebellum, the axons of different types of neurons terminate on distinct domains of the Purkinje neurons:

1. Granule cell axons contact distal dendritic spines.
2. Climbing fiber axons contact proximal dendritic shafts.
3. Basket cell axons contact the axon hillock and initial segment.
**Figure 55–4** The axons of inhibitory interneurons in the cerebellum terminate on a distinct region of the cerebellar Purkinje cell. Many neurons form synapses on cerebellar Purkinje neurons, each selecting a distinct domain on the Purkinje cell. The axons of inhibitory basket cells form most of their synapses on the axon hillock and initial segment. Basket cells select these domains by recognizing neurofascin, a cell surface immunoglobulin superfamily adhesion molecule that is anchored to the initial segment of the axon by ankyrin G. When the localization of neurofascin is perturbed, basket cell axons fail to restrict synapse formation to the initial segment. (Adapted, with permission, from Huang 2006.)
1.3. Neural Activity Sharpens Synaptic Specificity

• Activity-dependent processes refine the axonal arbors of retinal ganglion cells, thus sharpening the tectal map.

• One mechanism is that the level and pattern of neuronal activity regulates the expression of recognition molecules.

• Overall, molecular cues (like recognition molecules) control initial specificity. However, once the circuit begins to function, specificity is sharpened through neural activity.
Figure 55–5 Electrical activity refines the specificity of synaptic connections in the retina. Some retinal ganglion cells initially form dendritic arbors that are limited to specific sublaminae in the inner plexiform layer of the retina, whereas others initially form diffuse arbors that are later pruned to form large specific patterns. Similarly, the axonal arbors of retinal ganglion cells initially innervate a large region of their target fields in the lateral geniculate nucleus and optic tectum. This expansive axonal arbor is then refined so as to concentrate many branches in a small region. Abolishing electrical activity in retinal ganglion cells decreases the remodeling of dendritic and axonal arbors.
Neural activity can turn an inappropriate target into an appropriate one

- The contractile properties of the muscle can be partially transformed in a direction imposed by the **firing properties** of the motor nerve.
- Different patterns of neuronal activity are responsible for the switch in muscle properties.
- Indeed, direct electrical stimulation of a muscle with patterns normally evoked by slow or fast nerves leads to changes that are nearly as dramatic as cross-innervation.
2. Principles of Synaptic Differentiation Are Revealed at the Neuromuscular Junction

The neuromuscular junction comprises three types of cells: a motor neuron, a muscle fiber, and Schwann cells.
Figure 55–7  The neuromuscular junction develops in sequential stages.

A. A growth cone approaches a newly fused myotube (1) and forms a morphologically unspecialized but functional contact (2). The nerve terminal accumulates synaptic vesicles and a basal lamina forms in the synaptic cleft (3). As the muscle matures, multiple axons converge on a single site (4). Finally, all axons but one are eliminated and the surviving terminal matures (5). (Adapted, with permission, from Hall and Sanes 1993.)

B. At the mature neuromuscular junction, pre- and postsynaptic membranes are separated by a synaptic cleft that contains basal lamina and extracellular matrix proteins. Vesicles are clustered at presynaptic release sites, transmitter receptors are clustered in the postsynaptic membrane, and nerve terminals are coated by Schwann cell processes. (Image reproduced, with permission, courtesy of T. Gillingwater.)
Three general features of neuromuscular junction development

1. Nerve and muscle organize each other’s differentiation. Likewise, muscles signal retrogradely to motor nerve terminals.

2. Motor neurons and muscle cells can synthesize and arrange most synaptic components without each other’s help. The developmental signals that pass between nerve and muscle do NOT induce wholesale changes; rather they assure that these synaptic components are organized at the correct time: organizers rather than inducers.
Three general features of neuromuscular junction development

3. New synaptic components are added in several distinct steps. For example, the postsynaptic membrane acquires junctional folds only after the nerve terminal has matured. Also, several different axons innervate each myotube around the time of birth, but during early postnatal life all but one axon withdraws. This elaborate step probably involves multiple signals pass between the cells sequentially.
Figure 55–8  Nerve and muscle cells express synaptic components, but synaptic organization requires cell interactions. Acetylcholine receptors (AChR) are synthesized by muscle cells cultured without neurons. Many receptors are diffusely distributed, but some form high-density aggregates similar to those found in the postsynaptic membrane of the neuromuscular junction. When neurons first contact muscle they do not restrict themselves to the receptor-rich aggregates. Instead, new receptor aggregates form at sites of neurite-muscle contact, and many of the preexisting clusters disperse. Similarly, motor axons contain synaptic vesicles that cluster at sites of neurite contact with muscle cells. (Adapted, with permission, from Anderson and Cohen 1977; Lupa, Gordon, and Hall 1990.)
2.1. Differentiation of Motor Nerve Terminals Is Organized by Muscle Fibers

• Components of **basal lamina** organize presynaptic specialization.

• **Laminins** are one of the organizers.

• Laminins are major components of all basal laminae and promote axon outgrowth.

• Heterotrimeric of $\alpha$, $\beta$, and $\gamma$ chains.

• Lack of **laminin-211** ($\alpha_2$, $\beta_1$, and $\gamma_1$) leads to severe muscular dystrophy.
**Figure 55-9** Synaptic portions of basal lamina contain proteins that organize developing nerve terminals.

A. After nerve damage motor axons regenerate and form new neuromuscular junctions. Nearly all of the new synapses form at the original synaptic sites. (Micrograph reproduced, with permission, from Glicksman and Sanes 1983.)
B. A strong preference for innervation at original synaptic sites persists even after the muscle fibers have been removed, leaving behind basal lamina “ghosts.” Regenerated axons develop synaptic specialization on contact with the original synaptic sites on the basal lamina. (Micrograph reproduced, with permission, from Glicksman and Sanes 1983.)
C. Following denervation of a skeletal muscle fiber and elimination of mature muscle fibers, muscle satellite cells proliferate and differentiate to form new myofibers. The expression of ACh receptors on the regenerated myofiber surface is concentrated in the synaptic areas of basal lamina, even when reinnervation is prevented. (Micrograph reproduced, with permission, from Burden, Sargent, and McMahan 1979.)
Figure 55–10  Different laminin isoforms are localized at synaptic and extrasynaptic areas of the basal lamina.

A. Different laminin isoforms are found in synaptic (brown) and extrasynaptic (green) areas of basal lamina. Isoforms, containing the β2 chain, are concentrated in the synaptic areas.

B. Maturation of neuromuscular junctions is impaired in mice lacking β2 laminins. These mutants have few active zones, and the synaptic cleft is invaded by Schwann cell processes (blue). (Micrograph reproduced, with permission, from Noakes et al. 1995.)
2.2. Differentiation of the Postsynaptic Muscle Membrane Is Organized by the Motor Nerve

• Once synapse formation is complete, ACh receptors become concentrated at the synaptic sites (10000/\(\mu\text{m}^2\)) and depleted in the nonsynaptic membrane (10/\(\mu\text{m}^2\)).

• Agrin plays a central role in the organization of ACh receptor.

• Agrin is synthesized by motor neurons, released from nerve terminals, and incorporated into synaptic cleft.
Figure 55–11 Agrin induces aggregation of ACh receptors at synaptic sites.

A. Agrin is a large (~400 kDa) extracellular matrix proteoglycan. Alternative splicing includes a "z" exon that confers the ability to cluster ACh receptors. When released by a nerve terminal, agrin binds Lrp4 on the muscle membrane, activating the membrane-associated receptor tyrosine kinase MuSK and triggering an intracellular cascade that results in ACh receptor clustering. Clustering is mediated by rapsyn, a cytoplasmic ACh receptor-associated protein. (Adapted, with permission, from DeChiara et al. 1996.)

B. Few ACh receptor clusters form on myofibers grown in culture under control conditions, but addition of agrin induces ACh receptor clustering. (Adapted, with permission, from Misgeld et al. 2005.)
2.3. The Nerve Regulates Transcription of Acetylcholine Receptor Genes

- ACh receptor subunit genes are expressed at higher levels in synaptic nuclei.
- Electrically active muscle synthesizes fewer ACh receptors than inactive muscle.
- Current passing through ACh receptor $\rightarrow$ opening of voltage-dependent calcium channel $\rightarrow$ calcium influx $\rightarrow$ repression of ACh receptor gene transcription (and muscle contraction, too!)
- The same voltage changes that produce muscle contraction also suppress transcription of ACh receptor genes.
Figure 55–12 Clustering of ACh receptors at the neuromuscular junction results from transcriptional regulation and local protein trafficking.

A. Acetylcholine receptors (AChR) are distributed diffusely on the surface of embryonic myotubes.

B. After the muscle is innervated by a motor axon the number of receptors in extrasynaptic regions decreases, whereas receptor density at the synapse increases. This reflects the aggregation of preexisting receptors and enhanced expression of ACh receptor genes in nuclei that lie directly beneath the nerve terminal. In addition, the transcription of receptor genes is repressed in nuclei in extrasynaptic regions. Electrical activity in muscle represses ACh gene expression in nonsynaptic nuclei, leading to a lower density of ACh receptors in these regions. The nuclei at synaptic sites are immune to this repressive effect. Following denervation, ACh receptor gene expression is upregulated in extrasynaptic nuclei, although not to the high level attained by synaptic nuclei. Paralysis mimics the effect of denervation, whereas electrical stimulation of denervated muscle mimics the influence of the nerve and decreases the density of ACh receptors in the extrasynaptic membrane.
2.4. The Neuromuscular Junction Matures in a Series of Steps
Each of these changes occurs while the synapse is functional, implying that **ongoing neural activity** plays an important role in synaptic maturation.
Central Synapses Develop in Ways Similar to Neuromuscular Junctions

• Pre- and postsynaptic elements regulate each other’s differentiation by organizing pre-synthesized synaptic components rather than by inducing expression of specific genes, and synapses develop in a progressive series of steps.

• The cellular logic of synapse formation is indeed conserved between neuromuscular junctions and central synapses, although different organizers are involved.
Figure 55–14 Ultrastructure of a synapse in the mammalian central nervous system.

A. Initial contact between an axon and a filopodium on a developing dendrite leads to a stable dendritic spine and an axo-dendritic synapse. This entire process can take as little as 60 minutes.

A Development stages

$t = 0$

Axon

Filopodium

Dendrite

$t + 60$ min

Immature spine

$t + 600$ min

Active zone protein

Spine

NMDA and AMPA receptors
B. In a mature interneuron synapse in the cerebellum, synaptic vesicles in the nerve terminal are clustered at active zones (arrows) directly opposite receptor-rich patches of postsynaptic membrane. (Reproduced, with permission, from J.E. Heuser and T.S. Reese.)
3.1. Neurotransmitter Receptors Become Localized at Central Synapses

- In the brains, receptors for various neurotransmitters are concentrated in patches of membrane aligned with nerve terminals that contain the corresponding transmitter.
- Both glutamatergic and GABAergic nerve terminals appear to stimulate clustering of appropriate receptors in the postsynaptic membrane.
- Nerves can induce expression of genes encoding glutamate receptors in central neurons, much as occurs for ACh receptors in muscle.
Figure 55–15 Localization of neurotransmitter receptors in central neurons. Glutamate and GABA receptors are localized at excitatory and inhibitory synapses in culture. Glutamate receptors are clustered underneath synaptophysin-labeled excitatory nerve terminals, but not all clusters of glutamate receptors are associated with nerve terminals. GABA receptors are clustered under inhibitory terminal boutons that express GAD67. (GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase.) (Images reproduced, with permission, from A. M. Craig.)
Figure 55–16 Cytoplasmic proteins are responsible for clustering of neurotransmitter receptors at central synapses.

A. Glycine receptors are linked to microtubules by gephyrin, whereas NMDA-type glutamate receptors are linked to each other and to the cytoskeleton by PSD-95 related molecules. The PSD family of molecules contain PDZ domains that interact with a variety of synaptic proteins to assemble signaling complexes. Other PDZ-containing proteins interact with AMPA-type and metabotropic glutamate receptors (see Chapter 10).

PSD-95: postsynaptic density protein 95

SH3: Src homology domain 3
GK: guanylate kinase-like domain
PDZ: PSD95, disc large tumor suppressor (Dlg1), and zonula occludens-1 (zo-1)
B. In gephyrin mutant mice glycine receptors do not cluster at synaptic sites on spinal motor neurons and the animals show spasticity and hyperreflexia. In the same neurons glutamate receptor clusters are unaffected. (Adapted, with permission, from Feng et al. 1998.)
3.2. Synaptic Organizing Molecules
Pattern Central Nerve Terminals

• Unlike neuromuscular junctions, central neurons do not have prominent basal lamina.
• Adhesion molecules link the pre- and postsynaptic membranes.
• Neurexin (presynaptic membrane) versus neuroligin (postsynaptic membranes)
• Neurexin-neuroligin interactions facilitate precise apposition of pre- and postsynaptic specializations.
• The C-terminal tails of neurexin-neuroligin may bind to **PDZ domains** in proteins such as **PSD-95**. The **PDZ-containing proteins** serve as scaffolding molecules that link components on both synaptic sides.

• Additional candidate for synaptic organizers include adhesion molecules of the **cadherin** and **immunoglobulin superfamilies**, **ephrins and Eph kinases**, and soluble members of the **fibroblast growth factor** and **Wnt** families of morphogens.
Fibroblast is NOT a CNS cell type!
Figure 55–17  Macromolecular complexes link pre- and postsynaptic membranes at central synapses. Interactions between neurexins and neuroligins promote synaptic differentiation. When brain neurons are cultured with cells that express neuroligin, those segments of the axon that contact these cells form presynaptic specializations, marked by clustered neurexin, Ca\textsuperscript{2+} channels, and synaptic vesicles. Neurons grown with control cells lacking neuroligins lack such presynaptic specializations. (Adapted, with permission, from Scheiffele et al. 2000 and Graf et al. 2004.)
3.3. Glial Cells Promote Synapse Formation

• Schwann cells are the glia at neuromuscular junctions, and astrocytes are the glia at central synapses.

• Neurons form few synapses when cultured in isolation but many when glia are present (next slide).

• Glial cell surface and secreted molecules are both required for optimal synapse formation.

• Thrombospondin and cholesterol from glia have been shown to enhance synapse function.
Figure 55–18 Signals from glial cells promote synapse formation.

A. Astrocytes promote the maturation of both pre- and postsynaptic elements of the synapse.

B. Neurons cultured with astrocytes form more synapses, as assessed by expression of synaptic proteins (yellow dots). (Reproduced, with permission, from Ben A. Barres.)

C. Retinal neurons cultured with astrocytes form a greater number of synapses, as shown by increased transmitter release.

D. Synapse formation is enhanced in the presence of astrocytes by three measures.
Some Synapses Are Eliminated After Birth

• Synapse elimination appears to be a competitive process.

• **Neural activity** plays a role in this competition process. Paralysis of muscle reduces competition, whereas direct stimulation enhances it. **Differential activity** among axons may be a determinant of axon winners and losers.

• The purposes may include: 1. each muscle fiber is innervated; 2. it allows all axons to capture an appropriate set of target cells; 3. it provides a means by which activity can changes the strength of specific synaptic connections.
Figure 55–19 Some neuromuscular synapses are eliminated after birth. Early in the development of the neuromuscular junction each muscle fiber is innervated by several motor axons. After birth all motor axons but one withdraw from each fiber and the surviving axon becomes more elaborate. Synapse elimination occurs without any overall loss of axons—axons that “lose” at some muscle fibers “win” at others.
Chapter 56. Experience and the Refinement of Synaptic Connections
Course Outlines

1. Development of Human Mental Function is Influenced by Early Experience

2. Development of Binocular Circuits in the Visual Cortex Depends on Postnatal Activity

3. Reorganization of Visual Circuits During a Critical Period Involves Alterations in Synaptic Connections

4. Segregation of Retinal Inputs in the Lateral Geniculate Nucleus is Driven by Spontaneous Neural Activity In Utero
Course Outlines

5. Activity-Dependent Refinement of Connections Is a General Feature of Circuits in the Central Nervous System

6. Critical Periods Can Be Reopened in Adulthood
1.1. Early Experience Has Lifelong Effects on Social Behaviors

- A 6-month of social isolation during the first 18 months of life produced persistent and serious disturbances in behavior for monkeys.
- By comparison, isolation of an older animal for a comparable period was found to be without such drastic consequences.
- Thus, under controlled conditions, the critical influence of early experience on later behavior can be confirmed.
1.2. Development of Visual Perception Requires Visual Experience

• Patients with congenital binocular cataracts removed after 10 years old had permanent deficits in visual acuity and difficulties perceiving shape and form.

• As a result, congenital cataracts are now usually removed in early childhood.
2. Development of Binocular Circuits in the Visual Cortex Depends on Postnatal Activity

**Figure 56–2** Afferent pathways from the two eyes project to discrete columns of neurons in the visual cortex. Retinal ganglion neurons from each eye send axons to separate layers of the lateral geniculate nucleus. The axons of neurons in the lateral geniculate nucleus project to neurons in layer IVC of the primary visual cortex. Neurons in layer IVC are organized in alternating sets of ocular dominance columns; each column receives input from only one eye. The axons of the neurons in layer IVC project to neurons in adjacent columns as well as to neurons in the upper and lower layers of the same column. As a result, most neurons in the upper and lower layers of the cortex receive information from both eyes.
2.1. Visual Experience Affects the Structure and Function of the Visual Cortex

• A monkey was raised from birth to 6 months of age with one eye-lid sutured shut. When the sutures were removed, the monkey was blind in the deprived eye. In addition, the cells in the visual cortex were altered (next slide).

• However, deprivation in adults, even for much longer periods of time, had no effect. Thus, the cortical connections that control visual perception are established within a critical period of early development.
A  Movement across the retina

Contralateral (right) eye

Ipsilateral (left) eye

B  Variation in responses of single cortical cells
**Figure 56-3** Responses of neurons in the primary visual cortex of a monkey to visual stimuli. (Adapted, with permission, from Hubel and Wiesel 1977.)

**A.** A diagonal bar of light is moved leftward across the visual field, traversing the receptive fields of a binocularly responsive cell in area 17 of visual cortex. Receptive fields measured through the right and left eye are drawn separately. The receptive fields of the two cells are similar in orientation, position, shape, and size, and respond to the same form of stimulus. Recordings (below) show that the cortical neuron responds more effectively to input from the ipsilateral eye. (F, fixation point.)

**B.** The responses of single cortical neurons in area 17 can be classified into seven groups. Neurons receiving input only from the contralateral eye (C) fall into group 1, whereas neurons that receive input only from the ipsilateral eye (I) fall into group 7. Other neurons receive inputs from both eyes, but the input from one eye may influence the neuron much more than the other (groups 2 and 6), or the differences may be slight (groups 3 and 5). Some neurons respond equally to input from both eyes (group 4). According to these criteria, the cortical neuron shown in part A falls into group 6.
C. Responsiveness of neurons in area 17 to stimulation of one or the other eye. The $C_1$ plot shows the responses of more than 1,000 neurons in area 17 in the left hemisphere of normal adult and juvenile monkeys. Neurons in layer IV that normally receive only monocular input have been excluded. The $C_2$ plot shows the responses of neurons in the left hemisphere of a monkey in which the contralateral (right) eye was closed from the age of 2 weeks to 18 months and then reopened. Most neurons respond only to stimulation of the ipsilateral eye.
Ocular dominance column

1. Inputs from the two eyes remain segregated in the lateral geniculate nucleus.

2. The geniculate input carrying information from the two eyes to the cortex terminate in alternating columns (ocular dominance column).

3. Later geniculate axons terminate on neurons in layer IVC of the primary visual cortex; convergence of input from the two eyes on a common target cell occurs at the next stage, in cells above or below layer IVC.
Sensory deprivation early in life alters the structure of the cerebral cortex.

**Figure 56–4** Visual deprivation of one eye during a critical period of development reduces the width of the ocular dominance columns for that eye. (Scale bars = 1 mm.) (Adapted, with permission, from Hubel et al. 1977.)

A. A tangential section through area 17 of the right hemisphere of a normal adult monkey, 10 days after the right eye was injected with a radiolabeled amino acid. Radioactivity is localized in stripes (**white areas**) in layer IVC of the visual cortex, indicating areas of termination of the axons from the lateral geniculate nucleus that carry input from the injected eye. The alternating unlabeled (dark) stripes correspond to regions of termination of the axons carrying signals from the uninjected eye. Labeled and unlabeled stripes are of equal width.

B. A comparable section through the visual cortex of an 18-month-old monkey whose right eye had been surgically closed at 2 weeks of age. Label was injected into the left eye. The **wider white stripes** are the labeled terminals of afferent axons carrying signals from the open (left) eye; the **narrow dark stripes** are terminals of axons with input from the closed (right) eye.

C. A section comparable to that in part B from an 18-month-old animal whose right eye had been shut at 2 weeks. Label was injected into the right eye, giving rise to **narrow white stripes** of labeled axon terminals and **wide dark stripes** of unlabeled terminals.
• Does sensory deprivation alter ocular dominance columns after they have been established or does it interfere with their formation?

• It is now clear that the mature pattern of ocular dominance columns in monkeys is not achieved until 6 weeks after birth. Only at this time the terminals of fibers from the lateral geniculate nucleus are fully segregated.

• Sensory deprivation during critical periods early in the postnatal life interferes with their formation.
Development of Ocular Dominance Columns

2 weeks

3 weeks

5.5 weeks

13 weeks
Figure 56–5  The development of ocular dominance columns. Autoradiographs of four stages in the postnatal development of ocular dominance columns in the visual cortex in a cat. The images show horizontal sections through columns in the cortex ipsilateral to an eye that was injected with a radiolabeled amino acid. The cells in the lateral geniculate nucleus that receive input from the injected eye become labeled by transneuronal transport. At 15 days after birth the terminals of labeled fibers are spread in a relatively uniform manner along layer IV and are intermingled with those of unlabeled fibers that convey signals from the contralateral eye. At 3 and 5.5 weeks some segregation of the terminals is visible, but only as modest differences in labeling density. At 13 weeks the borders of the labeled bands become more sharply defined as the fibers conveying inputs from each eye segregate. (Adapted, with permission, from LeVay, Stryker, and Shatz 1978.)
Normal development of ocular dominance columns

Development of ocular dominance columns after closure of one eye at different times

Birth
2 wk
3 wk
6 wk

Visual cortex layer IVC
Lateral geniculate nucleus
Figure 56–6 The effects of eye closure on the formation of ocular dominance columns. The top diagrams show the gradual segregation of the terminals of lateral geniculate afferents in layer IVC of the visual cortex under normal conditions (left) and when one eye is deprived of stimulation (right). The blue domains represent the areas of termination of inputs from one eye, the red domains are those of the other eye. The lengths of the domains represent the density of the terminals at each point along layer IVC. For clarity the columns are shown here as one above the other, whereas in reality they are side by side in the cortex. During normal development layer IVC is gradually divided into alternating sites of input from each eye. The consequences of depriving sight in one eye depend on the timing of eye closure. Closure at birth leads to dominance by the open eye (red) because at this point little segregation has occurred. Closure at 2, 3, and 6 weeks has a progressively weaker effect on the formation of ocular dominance columns because the columns become more segregated with time. (Adapted, with permission, from Hubel, Wiesel, and LeVay 1977.)
2.2. Patterns of Electrical Activity Organize Binocular Circuits in the Visual Cortex

- Synaptic connections are strengthened when pre- and postsynaptic elements are active together.
- Neighboring axons from the same eye tend to fire in synchrony because they are activated by the same visual stimulus at any instant.
- The synchronization of their firing means that they cooperate in the depolarization and excitation of a target cell (cooperation), thus maintaining the viability of those synaptic contacts at the expense of the non-cooperative synapse (competition).
Development of ocular dominance columns depends on competition

- Ocular dominance columns are not established if activity in retinal ganglion neurons is blocked by tetrodotoxin (a blocker for voltage-sensitive Na channel). When the two optic nerves are stimulated synchronously, ocular dominance columns still fail to form. Only when the optic nerves are stimulated asynchronously are the ocular columns established.

- Competition between two sets of afferent axons for the same population of cortical neurons drives their segregation into distinct target territories.
Figure 56–8  Ocular dominance columns can be experimentally induced in a frog by transplantation of a third eye. (Adapted, with permission, from Constantine-Paton and Law 1978.)

A. Three days before the transplant the right eye was injected with a radiolabeled amino acid. The autoradiograph in a coronal section of the hindbrain shows the entire superficial neuropil of the left optic lobe filled with silver grains, indicating the region occupied by synaptic terminals from the labeled (contralateral) eye.

B. Some time after a third eye was transplanted near the normal right eye the right eye was injected with a radiolabeled amino acid. The autoradiograph shows that the left optic lobe receives inputs from both the labeled eye and the transplanted eye. The normally continuous synaptic zone of the contralateral eye has become divided into alternating dark and light zones that indicate the sites of inputs from each eye.
A Inputs are normally segregated in the tectum

B Transplanted eye induces ocular dominance columns
3. Reorganization of Visual Circuits During a Critical Period Involves Alterations in Synaptic Connections
3.1. Reorganization Depends on a Change in the Balance of Excitatory and Inhibitory Inputs

- In the visual cortex of a monkey, the first physiological changes following closure of one eye occur in layers II/III and V (binocular neurons), but not in layer IV (monocular neurons).
- This implies that loss of cortical responsiveness to the deprived eye results from a circuit alteration rather than from a simple loss of thalamic input from the deprived eye.
Involvement of inhibition in the binocular region of mouse visual cortex

• In mice, closure of the contralateral eye during (but not before or after) the critical period for ocular dominance shifts the preference of binocular neurons to inputs from the ipsilateral eye.

• The critical periods can be advanced or delayed by manipulating γ-aminobutyric acid (GABA, an inhibitory neurotransmitter) signaling.

• Enhancing GABA: shift the critical period for monocular deprivation to an earlier developmental time. Delayed GABA: shift the critical period to a later developmental time.
**Figure 56-9** A critical period for ocular dominance plasticity is evident in mice. (Adapted, with permission, from Hensch et al. 2005.)

**A.** The visual cortex in mice contains a small region that receives thalamic (LGN) inputs from both eyes. In this binocular region most neurons are responsive to contralateral eye input, fewer respond to binocular inputs, and very few respond to ipsilateral eye input only.

**B.** When the contralateral eye has been closed during the normal critical period and then reopened, inputs from that eye are underrepresented and many more neurons respond to binocular or ipsilateral eye input. Eye closure before or after the time of the normal critical period does not elicit the same shift in responsiveness.
Deprivation before normal critical period

- Control

- Enhanced GABA

Deprivation after normal critical period

- Control

- Delayed GABA

*Shift the critical period for monocular deprivation to an earlier developmental time. (benzodiazepines)*

*Shift the critical period for monocular deprivation to a later developmental time. (genetically reducing GABA synthesis)*
A balance of intracortical excitation and inhibition is required for the reorganization during this critical period.

Figure 56–10  The timing of the critical period for ocular dominance plasticity in mice is sensitive to the level of GABAergic neurotransmission. Altering the status of GABA (γ-aminobutyric acid) synthesis and signaling shifts the period in which monocular deprivation can change the response properties of neurons in the visual cortex. Enhancing GABA signaling, through administration of benzodiazepines, shifts the critical period for monocular deprivation to an earlier developmental time. In contrast, delaying GABA signaling, by reducing GABA synthesis genetically and then administering benzodiazepines at a later time, shifts the critical period for monocular deprivation to a later developmental time. (Adapted, with permission, from Hensch et al. 1998.)
3.2. Postsynaptic Structures Are Rearranged During the Critical Period

- **Dendritic spines** are potential sites of synaptic plasticity. Spines are small protrusions from the dendrites of many cortical neurons on which excitatory synapses form.
- Being dynamic structures, their appearance and loss are thought to reflect the formation and elimination of synapses.
- Alterations in spine motility and number can be correlated with 3 known features of **critical periods**, as described in the next slide.
1. Rather than occurring in layer IV, the changes occur primarily in superficial and deep layers of the cortex, where **binocular cells** lie.

2. They occur only in the portion of the visual cortex that normally receives **binocular input**.

3. They fail to occur following eye closure in adult mice.
Figure 56–11  The motility of dendritic spines in the mouse visual cortex changes after one eye is closed. The dendrites of pyramidal neurons in the visual cortex have many spines, the density of which remains comparatively constant under normal conditions. Closure of one eye (contralateral in this example) during the critical period for binocular development enhances the motility of dendritic spines and over time results in an increase in the proportion of spines that receive synaptic input from the open eye. Similar changes in spine motility are not observed if the eye is closed after the critical period. (Reproduced, with permission, from Oray et al. 2004.)
3.3. Thalamic Inputs Are Also Remodeled by Their Target Cortical Neurons

- Neural activity of thalamic neurons regulates the secretion of neurotrophic factors by cortical neurons (target cells). Such factors may then regulate survival of some of the pre-synaptic thalamic neurons at the expense of others.

- One such factor, brain-derived neurotrophic factor (BDNF), is synthesized and secreted by cortical neurons.

- Administering excess BDNF or interfering with its receptor trkB may modify the formation of ocular dominance columns.
3.4. Synaptic Stabilization Contributes to Closing the Critical Period

• What opens the critical period and what closes it?
• Formation of myelin creates physical barriers to sprouting and axon growth. The state of myelination of axons occurs around the time the critical period closes.
• Candidates for closing the critical period include Nogo (next slide) and myelin-associated glycoprotein (MAG), both actively inhibit the growth of axons.
Figure 56–13  The critical period for monocular deprivation is extended in mice lacking Nogo signaling. The drawings show arborization patterns of thalamocortical axons carrying signals from contralateral and ipsilateral eyes to the binocular zone in visual cortex. Monocular deprivation during the critical period elicits a shift in ocular preference in neurons in the binocular zone in both wild type mice and mice mutant for Nogo or the Nogo receptor. After the normal critical period (at 45 days) monocular deprivation continues to elicit a marked shift in axonal input and ocular preference in mice mutant for Nogo-A or the Nogo receptor but not in wild type mice. The plot shows that elimination of Nogo signaling prevents closure of the critical period. (Adapted, with permission, from McGee et al. 2005.)
4. Segregation of Retinal Inputs in the Lateral Geniculate Nucleus (LGN) is Driven by Spontaneous Neural Activity In Utero

• The arbors of retinal ganglion cells from the two eyes are segregated into alternating layers in LGN like ocular dominance columns (next slide 83).

• Neuronal activity is essential for segregation. In the LGN, however, the segregation of inputs is complete before birth. Thus, vision cannot drive the neural activity essential for segregation.

• The axons of retinal neurons are spontaneously active in utero, well before the eyes open (slide 84/85).
**Figure 56–14** The terminals of retinal ganglion cells in the lateral geniculate nucleus become segregated during normal development. At early stages the terminals of axons from each eye intermingle. At later stages the inputs from the left and right eyes segregate into separate layers of the nucleus. In some species axons from one eye even segregate into functionally specialized sublayers (on and off layers in ferrets). (Adapted, with permission, from Sanes and Yamagata 1999.)
**Figure 56–15** Correlated waves of neural activity in the developing retina.

A. Microscopic visualization of the activity of retinal ganglion neurons in a flat-mounted preparation of mammalian retina. Spontaneous waves of neural activity are visualized by monitoring Ca\(^{2+}\) transients (**yellow domain**) after loading of cells with dyes that change their fluorescent emission spectrum with changes in intracellular Ca\(^{2+}\) concentration.

B. These still images from a movie sequence show the propagation of one Ca\(^{2+}\) activity focus (**yellow domain**) across the retina. Images were taken 1 second apart. Many cells within the activity focus are **activated synchronously** (Reproduced, with permission, from Blankenship et al. 2009).

C. Retinal activity waves recorded over time are superimposed in this image. Discrete waves are indicated in different colors; the origin of a wave is indicated by a darker hue. These waves originate in different retinal foci and spread in distinct, unpredictable directions. (Reproduced, with permission, from Meister et al. 1991.)
5.3. Distinct Regions of the Brain Have Different Critical Periods of Development

- The timing of critical periods varies between brain regions. Even within visual cortex, critical periods for organization of inputs differ among layers.

- The adverse effects of sensory deprivation for the primary sensory regions of the brains are realized early in postnatal development. However, social experience can affect the intracortical connections over a much longer period.

- Thus, certain types of learning (language, music) are optimal at particular stages of development.
**Figure 56–19** The timing of critical periods varies with brain function. (Reproduced, with permission, from Hensch 2005.)

**A.** In cats the critical periods for development of orientation or direction selectivity in visual neurons occur earlier than those for establishment of ocular dominance and slow-wave sleep oscillation.

**B.** In humans the timing of periods for development of sensory processing, language, and cognitive functions varies.
6. Critical Periods Can Be Reopened in Adulthood

• The **plasticity of critical periods** can be distinguished from **plasticity in adulthood** by its magnitude and by the ease with which it is triggered. Why?

• First, from postnatal life to adolescence, neural circuits can undergo fundamental changes in response to the animal’s experience. In mature circuits molecular and structural elements promote stability and impede plasticity.

• Second, in a developing circuit no particular pattern of connectivity is firmly entrenched, so there is less to overcome.