109. R. W. Sperry, *Proc. Natl. Acad. Sci. U.S.A.* **50**, 703 (1963).
110. A. Gierer, *Development* **101**, 479 (1987).
111. F. Bonhoeffer and J. Huf, *Nature* **288**, 162 (1980); *EMBO J.* **1**, 427 (1982); *Nature* **315**, 409 (1985).
112. J. Walter, B. Kern-Veits, J. Huf, B. Stolze, F. Bonhoeffer, *Development* **101**, 685 (1987); J. Walter, S. Henke-Fahle, F. Bonhoeffer, *ibid.*, p. 909.
113. E. C. Cox, B. Muller, F. Bonhoeffer, *Neuron* **4**, 31 (1990).
114. H. Baier and F. Bonhoeffer, *Science* **255**, 472 (1992).
115. H. Nakamura and D. D. O'Leary, *J. Neurosci.* **9**, 3776 (1989).
116. M. Yamagata and J. R. Sanes, *Development* **121**, 189 (1995).
117. E. E. Ball, R. K. Ho, C. S. Goodman, *J. Neurosci.* **5**, 1808 (1985); H. Sink and P. M. Whitington, *Development* **113**, 701 (1991); S. Cash, A. Chiba, H. Keshishian, *J. Neurosci.* **12**, 2051 (1992); A. Chiba, H. Hing, S. Cash, H. Keshishian, *ibid.* **13**, 714 (1993).
118. A. Chiba, P. Snow, H. Keshishian, Y. Hotta, *Nature* **374**, 166 (1995).
119. J. Dodd and T. M. Jessell, *Science* **242**, 692 (1988).
120. Recent studies on signal transduction mechanisms in axon guidance include (*46*) and J. R. Atashi *et al.*, *Neuron* **8**, 831 (1992); W. Li, R. K. Herman, J. E. Shaw, *Genetics* **132**, 675 (1992); T. P. O'Connor and D. Bentley, *J. Cell Biol.* **123**, 935 (1993); D. Y. Wu and D. J. Goldberg, *ibid.*, p. 653; L. Aigner *et al.*, *Cell* **83**, 269 (1995); H. Y. Chang *et al.*, *Nature* **376**, 686 (1995); Y. Goshima, F. Nakamura, P. Strittmatter, S. M. Strittmatter, *ibid.*, p. 509; S. M. Strittmatter, C. Fankhauser, P. L. Huang, H. Mashimo, M. C. Fishman, *Cell* **80**, 445 (1995); E. Tanaka and J. Sabry, *ibid.* **83**, 171 (1995); M. F. VanBerkum and C. S. Goodman, *Neuron* **14**, 43 (1995); P. A. Garrity *et al.*, *Cell* **85**, 639 (1996).
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Synaptic Activity and the Construction of Cortical Circuits

L. C. Katz* and C. J. Shatz

Vision is critical for the functional and structural maturation of connections in the mammalian visual system. Visual experience, however, is a subset of a more general requirement for neural activity in transforming immature circuits into the organized connections that subserve adult brain function. Early in development, internally generated spontaneous activity sculpts circuits on the basis of the brain's "best guess" at the initial configuration of connections necessary for function and survival. With maturation of the sense organs, the developing brain relies less on spontaneous activity and increasingly on sensory experience. The sequential combination of spontaneously generated and experience-dependent neural activity endows the brain with an ongoing ability to accommodate to dynamically changing inputs during development and throughout life.

The mammalian central nervous system relies on precise synaptic circuits to function correctly. These circuits are assembled during development by the formation of synaptic connections between hundreds of thousands of neurons. Although molecular interactions direct the early formation of circuitry (*1*, *2*), this initial patterning is followed by a prolonged period during which massive numbers of new synapses are added. In this review, we consider how neuronal activity, by guiding synapse formation, elimination, and rearrangements, establishes adult patterns of connectivity and function. We argue that sensory experience, which historically has been viewed as the strongest force guiding circuit formation, is actually a special case of a more general role for neural activity, much of which can be generated spontaneously. We then examine possible mechanisms by which patterns of activity—either spontaneous or evoked by sensory experience—can be translated into patterns of synaptic connections.

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Sensory Experience and Circuit Formation in the Visual System

The role of sensory experience in the formation of neural circuits has been most thoroughly studied in the mammalian visual system. Most current concepts are based on the development of ocular dominance columns in the visual cortex. In carnivores and primates, thalamic inputs to the cortex arising from the lateral geniculate nucleus (LGN) segregate by eye within cortical layer 4 into a series of alternating stripes. These eye-specific stripes form the structural basis for the functionally defined system of ocular dominance columns that span all cortical layers. Early in development, ocular dominance stripes in layer 4 are absent (*3–5*). The LGN axons representing each eye are sparse and simple and overlap within layer 4. By the addition of large numbers of branches and synapses within the appropriate regions and elimination of the sparse collaterals initially present within inappropriate regions, LGN axon arbors gradually form dense, eye-specific patches (Fig. 1) (*6*). These anatomical rearrangements of the presynaptic axons are accompanied functionally by a corresponding change in the synaptic physiology of layer 4 neurons (*7*), the majority of which are initially activated by stimuli presented to either eye but finally come to respond to visual stimulation through one eye only.

The classic experiments of Hubel and Wiesel demonstrated the important role of visual experience in determining the organization of ocular dominance columns (*8*, *9*). If one eye is deprived, even temporarily, of vision by eyelid closure for several weeks in neonatal life, then most of the mature visual cortical neurons are responsive only to stimuli presented to the eye that remained open. Within layer 4, early eye closure greatly enlarges the patches of input from LGN axons representing the open eye, whereas those representing the closed eye are relegated to very small regions (*9*, *10*).

Local cortical circuits undergo similar anatomical rearrangements under the influence of sensory input. In cats, eye closure between 6 months and 1 year of age produces physiological shifts in the cortex's ocular dominance profile, but no anatomical change in the organization of LGN axon terminals (*11*, *12*). This implies that local connections—perhaps those between layer 4 and layer 2/3—remain plastic considerably longer than the longer range connections from the thalamus. In addition, local horizontal connections of pyramidal neurons in cortical layers 2 and 3, which in the adult cortex form periodic clusters of branches that link columns of similar orientation preference, can be altered in response to visual input [reviewed in (*13*)]: Prolonged visual deprivation results in the formation of large, poorly organized clusters (*14*). The clustering of horizontal connections can be altered by inducing strabismus, which prevents cortical neurons from receiving simultaneous inputs

from the two eyes (*15*).

These experience-dependent effects on the functional and structural organization of the visual cortex result from alterations in the amount or patterning (or both) of neural activity within the visual pathways. This is graphically demonstrated by the result of silencing inputs from both eyes by intraocular injections of tetrodotoxin (TTX, a blocker of voltage-sensitive sodium channels) while ocular dominance columns are normally forming. Eye-specific patches within layer 4 are absent (*16*) because LGN axons fail to restrict their terminal arbors and instead remain widely branched (*6*).

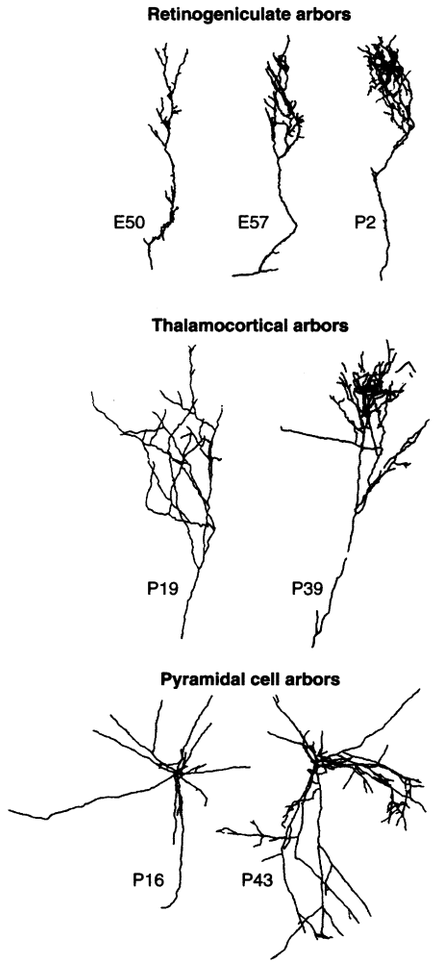

Fig. 1. Development of axonal arbors at different locations along the visual pathway. The terminal arbors of axons are shown at various embryonic (E) and postnatal (P) ages (in days) in cats. In all cases, the emergence of the adult pattern of connections is the result of considerable sprouting and proliferation of axon branches, accompanied by much more limited elimination of small collaterals at inappropriate locales. These morphological changes suggest that the strategy for forming adult circuits involves a local control of sprouting and synaptogenesis rather than selection from a large pre-existing repertoire [modified from (*25*)].

Spontaneous Neural Activity and Early Steps in Circuit Formation

The experiments considered above indicate that the final steps in the construction of cortical circuits require neural activity that is normally supplied by visual experience. However, visual experience alone cannot account for many features of visual system development. In nonhuman primates, for example, ocular dominance columns in layer 4 begin to form in utero (*3*) and are fully formed by birth (*17*). Thus, although visual experience can modify existing columns, initial formation of the stripes is independent of visual experience. Other features of cortical functional architecture, such as orientation tuning and orientation columns, are also present before any visual experience (*18*), as are crudely clustered horizontal cortical connections (*14, 19*). These findings suggest that early activity-dependent processes must operate before the onset of visually evoked activity.

One source of this activity is likely to be spontaneously generated waves of action potentials, which are present in the mammalian retina well before the onset of vision. Several weeks before eye opening, and even before maturation of the photoreceptors, mammalian ganglion cells spontaneously fire periodic bursts of action potentials (*20, 21*). Simultaneous recordings from hundreds of retinal ganglion cells (*21–23*) reveal that these bursts are correlated among neighboring cells and contribute to waves of neural activity that spread across restricted domains of the retina (Fig. 2) (*24*).

These endogenously generated patterns of activity may direct activity-dependent development of eye-specific layers in the visual thalamus. In the developing LGN, as in the formation of cortical ocular dominance columns, inputs from the two eyes are initially intermixed. The LGN layers form as ganglion cell axons remodel their branches (Fig. 1 and see below) and become restricted to appropriate layers (*25*), a process requiring neural activity (*26*). Retinal waves are present at the onset of LGN segregation (and probably earlier) and persist until just before eye opening—a time just after the eye-specific layers have formed within the LGN. As development proceeds, different functional classes of ganglion cells (ON and OFF cells) are recruited with different firing patterns into the waves (*27*), which may drive the formation of ON and OFF sublaminae in the LGN, a process that also requires activity (*28*).

Retinal waves provide highly correlated patterns of spontaneous neural activity that, long before the onset of vision, could also drive activity-dependent synaptic remodeling in central visual structures such as the visual cortex. But to do so, activity from the retina must be relayed across retinogeniculate synapses to drive LGN neurons to fire action potentials. Physiological recordings from an in vitro preparation indicate that spontaneously generated retinal activity indeed drives LGN neurons to fire periodic bursts of action potentials; in the absence of retinal inputs, LGN neurons are electrically quiescent (*29*). As blocking retinal activity later in development prevents ocular dominance column formation, retinal waves could also account for the segregation of LGN axons in the visual cortex that occurs in utero in primates.

Correlated spontaneous activity has also been observed in the firing of spinal cord motoneurons (*30*), as have coordinated calcium fluctuations in clusters of cells in the developing cerebral cortex (Fig. 2) (*31*). In the cortex, the activity of neighboring cells relies on second messengers passed through gap junctions (*32*), whereas coupling in the

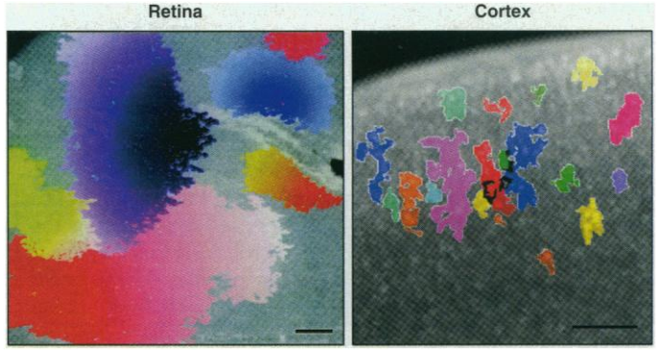

Fig. 2. Organized patterns of spontaneous activity in the developing retina and cortex. In the retina, waves of action potentials spread between cohorts of retinal ganglion cells, visualized here by calcium imaging. Each region represents a different event, and the intensity of the color indicates the direction of propagation. In the cortex, groups of neurons, indicated by the colored areas, undergo spontaneous changes in their intracellular calcium concentrations; unlike the retinal waves, these events propagate via gap junctions and do not require synaptic transmission and action potentials. Despite mechanistic differences, both phenomena produce highly correlated patterns of activity that are thought to be important in guiding circuitry formation. Scale bar, 100 μm. Left panel is from (*24*) and right panel is from (*86*).

retina requires synaptic transmission between amacrine and ganglion cells (*24*). Despite these mechanistic differences, both retinal waves and cortical domains define regions of correlated activity, and both could act to form circuits by reinforcing connections among coactive cells [reviewed in (*22*, *33*)].

What is the significance of spontaneously generated, correlated patterns of activity? Theoretical considerations and experimental evidence (*5*, *34*, *35*) indicate that the emergence of adult patterns of connectivity requires correlated neural activity among sets of inputs (either spontaneous or sensory-evoked), coupled with the ability of postsynaptic cells to detect such correlations. Correlated activation of ganglion cells in the two eyes, achieved by using electric shocks applied to both optic nerves simultaneously, prevents ocular dominance column formation (*36*); similarly, stroboscopic illumination (which presumably activates all retinal ganglion cells in approximate synchrony) blocks formation of tectal "ocular dominance" stripes in the dually innervated optic tectum of goldfish (*37*).

Any mechanism for translating activity into structural remodeling must also reinforce presynaptic inputs that are simultaneously active with the postsynaptic cell (*5*, *15*, *34*, *38*). This feature of synaptic enhancement is characteristic of "Hebb" synapses (*39*), which figure prominently in models of activity-dependent synapse formation in visual system development (*40*). These considerations have sparked considerable interest in the possible role of long-term potentiation (LTP), which coordinates pre- and postsynaptic activity.

Mechanisms of Synaptic Modification During Development

Despite evidence that coordinated patterns of neuronal activity influence the organization of circuits throughout the brain, the mechanisms by which activity is translated into long-term structural changes in connections remain obscure. Considerable speculation has focused on the role of synaptic mechanisms similar to LTP and long-term depression (LTD) in the hippocampus. In slice preparation of the CA1 hippocampal region, high-frequency trains of electrical stimuli—which result in the coordinated activity of pre- and postsynaptic elements—strengthen synapses for many hours. The induction of LTP in this region is dependent on the *N*-methyl-D-aspartate (NMDA) class of glutamate receptors, whose combined voltage and ligand dependency provide an elegant molecular mechanism for detecting the coordinate action of cohorts of synapses (*41*).

In the developing neocortex LTP may contribute to ocular dominance column segregation (*42*). As LTP requires the activation of NMDA receptors, several investigators have examined the effects of blocking NMDA receptors on the development of ocular dominance columns in visual cortex. The results of such experiments—which generally rely on infusing the NMDA blocker amino phosphonovaleric acid (APV) into visual cortex—remain controversial. Infusion of APV blocks the shift in ocular dominance elicited by monocular deprivation during the critical period (*43*), but it may also block all visual responsivity in the affected area (*44*). As blocking cortical activity in its entirety prevents ocular dominance column formation and deprivation-induced shifts (*45*), APV infusions alone cannot rigorously address whether NMDA-receptor–dependent LTP—as opposed to some other activity-dependent process—is normally involved in the development or modification of columns. Other forms of long-term synaptic enhancement that rely on voltage-gated calcium channels appear to be present in cortex even when NMDA receptors are blocked (*46*).

Nevertheless, the presence of LTP (and LTD) in the developing visual cortex, and the similarity of its properties to those of LTP at the CA3-CA1 synapse in hippocampus (*47*), makes it a plausible candidate as one of the mechanisms mediating cortical plasticity. For instance, LTP is easier to elicit in younger than in adult visual cortex (*48*); however, despite the presence of LTP in the visual cortex, the causal links between LTP and the anatomical and physiological rearrangements that occur in the developing visual system remain tentative. LTP is observed in visual cortex slices prepared from animals of every age, not just those in the critical period. This is not surprising, as the adult cortex, including visual cortex, continues to exhibit adaptive changes in response to changes in patterns of inputs (*49*).

Efforts to probe the relation between LTP and developmental rearrangements have exploited rodent systems, in part be-

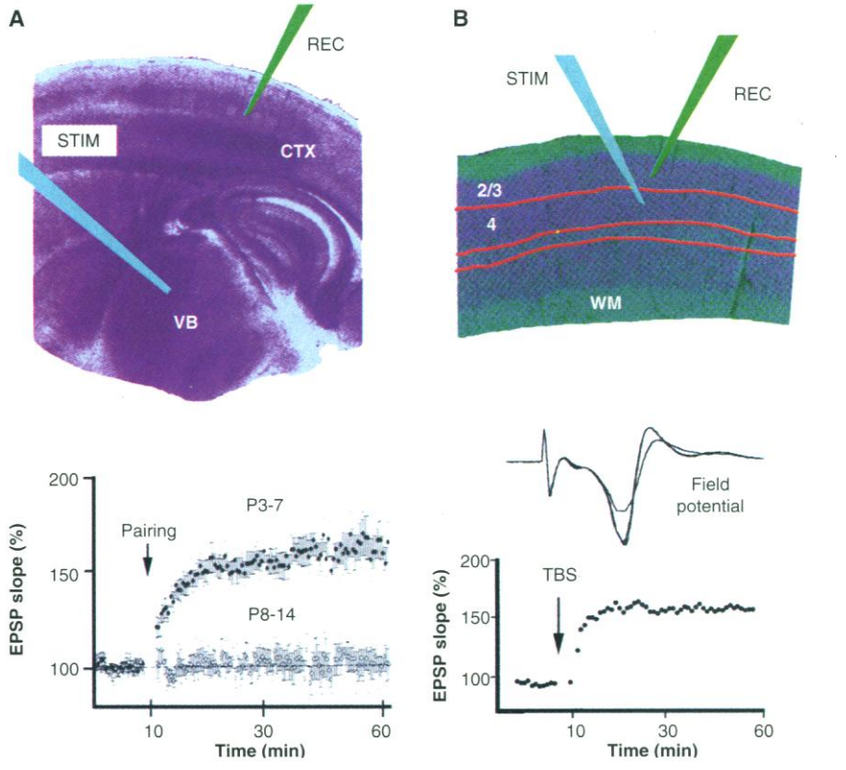

Fig. 3. Long-term potentiation (LTP) at two different synapses in the neocortex. (**A**) LTP of thalamocortical connections in the rodent somatosensory system is restricted to early postnatal life. The top panel shows the recording arrangement in a slice that includes intact connections between the thalamus (VB) and primary somatosensory cortex (CTX). Pairing stimulation of VB (STIM) with depolarization of recipient cells in layer 4 (REC) of cortex in young animals (age P3 to P7) leads to robust LTP; the same protocol in older animals (age P8 to P14) does not lead to synaptic enhancement (lower panel). (**B**) Intrinsic connections of the visual cortex can also undergo LTP. Stimulation with theta-burst stimulation (TBS) of layer 4 (in young and old animals) leads to robust enhancement of the extracellular field potential recorded in layer 3. This form of cortical LTP is remarkably similar to LTP observed in the hippocampus. EPSP, excitatory postsynaptic potential. (A) is modified from (*54*) and (B) is modified from Kirkwood and Bear (*52*).

cause of the availability of murine strains in which specific components of the LTP pathway have been disrupted by gene targeting. Unfortunately, rodents lack ocular dominance columns, but they do have a small region of visual cortex in which neurons are binocularly responsive. The rodent visual system responds similarly to that of carnivores and primates to visual deprivation: During a well-defined critical period, eye closure can shift the ocular dominance profile of binocular cells toward the nondeprived eye (*50, 51*). Unlike carnivores and primates, however, anatomical correlates of this shift, if any, have not been obvious. Rearing rats in the dark, which expands the time window during which eye closure can shift ocular dominance, also prolongs the period during which stimulation of the white matter can elicit LTP in layer 4, suggesting a link between LTP and physiological plasticity (*52*); LTP in other layers (such as between layers 4 and 2/3) is unaffected by dark-rearing. Similarly in cats, dark-rearing slows but does not prevent the formation of ocular dominance columns within layer 4, and it extends the physiologically defined period of susceptibility to monocular closure in other cortical layers (*12, 16, 53*).

The relation between LTP and neocortical plasticity has also been tested in the primary somatosensory cortex of rodents, in which clusters of thalamic afferents representing individual whiskers are grouped together into structures called barrels. Analysis of slice preparations that include both the somatosensory thalamus and the developing barrel cortex shows LTP between thalamic inputs and layer 4 cells to be restricted to a relatively early period in life, which suggests a role for LTP in developmental events (Fig. 3) (*54*). Furthermore, in mice in which NMDA receptors—and presumably LTP—have been inactivated (by gene-targeting deletion of the NMDA R1 subunit), subcortical portions of the somatosensory system develop abnormally. Unfortunately, these animals die shortly after birth, so the consequences of NMDA receptor inactivation on plasticity in the visual or somatosensory areas of neocortex cannot be evaluated. However, in the brainstem trigeminal nucleus of these animals, the normal pattern of whisker-related patches fails to emerge, indicating that the absence of functional NMDA receptors has altered the topographic specificity of this system (*55*).

In considering possible mechanisms for morphological rearrangements during development, it is worth noting that activity-dependent rearrangements occur at several noncortical locations without the benefit of either LTP or the NMDA receptor. For example, at the developing neuromuscular junction, the reduction in polyneuronal innervation occurs at a cholinergic synapse, and synaptic weakening of the "losing" input precedes the subsequent strengthening and growth of the winning input (*56*). Similar synaptic changes have been observed at neuromuscular synapses in cell culture (*57*). In the cerebellum, elimination of multiple climbing fiber inputs onto individual Purkinje cells—a process reminiscent of the reorganization that takes place in the ocular dominance column system—is prevented by deleting genes encoding protein kinase A, an enzyme not thought to contribute to hippocampal LTP (*58*). Evidently, the nervous system has evolved a myriad of strategies for developmental rearrangements, of which several may be operating in the developing visual system.

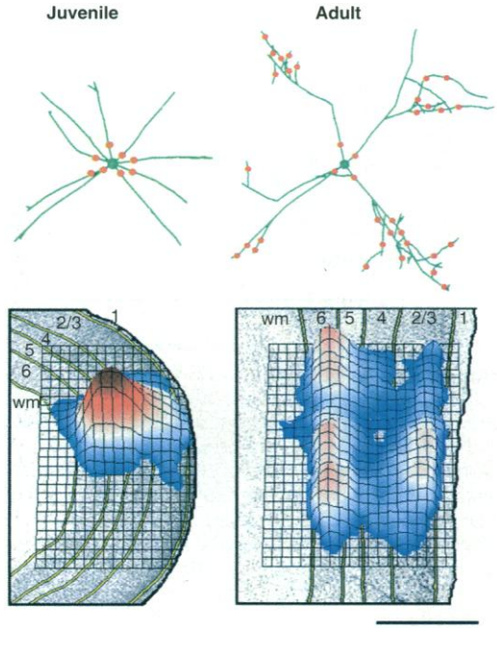

Fig. 4. Differences between the morphological and functional state of developing circuits in the visual cortex. In juvenile animals, intrinsic horizontal axon collaterals (top panels) extend for considerable distances (seen here in tangential view), but only form functional connections locally (red dots). Optical recordings (lower panels) of coronal slices of visual cortex similarly show that horizontal activation is restricted to a region considerably smaller than the extent of developing collaterals, implying that synapses along distal collaterals are weak or absent. In adult animals (right panels) axon terminals are found in distinct laterally placed clusters, and optical recordings with voltage-sensitive dyes demonstrate that these can supply functional connections. Wm, white matter. Scale bar, 1 mm. After (*66*).

The Role of Activity—Synapse Formation or Elimination?

Although some of the metrics for plasticity are physiological, others are morphological; only rarely are assessments of both criteria performed in the same experiment. Relating morphological and physiological changes is further confounded by the difficulty of determining the functional state of synaptic connections in developing systems. Morphological criteria for the presence of synaptic connections are often based on the properties of synapses in mature tissues; such criteria may not be appropriate in developing systems. Many assumptions about the mechanisms of circuitry formation are clouded by this issue. Counts of the numbers of identifiable synapses indicate that the number of synapses increases dramatically during early postnatal life in most mammalian species (*59*). However, such assessments cannot take into account the possibility that immature synapses, although capable of releasing neurotransmitter, may not be discernible morphologically.

At developing neuromuscular synapses in vitro (*60*), for example, growth cones form functional synapses within minutes after contacting a muscle fiber. Yet, other than the accumulation of a few presynaptic vesicles, these early synapses lack the diagnostic morphological correlates of the mature synapse. Similarly, in the developing mammalian retina, when the early spontaneous waves are present, whole-cell recordings from the retinal ganglion cells reveal robust synaptic currents generated by cholinergic amacrine cells (*24*); yet electron microscopic studies conclude that synaptogenesis within the inner plexiform layer has barely commenced (*61*). Given the extensive remodeling of growing axons and dendrites in the developing brain (*62*), nascent functional synapses probably form and remodel rapidly, making it imperative for models of activity-dependent plasticity to account for the dynamic and fragile nature of emerging connections. These considerations raise the issue of whether the rearrangements observed anatomically—such as the growth or retraction of axonal branches—reflect construction and removal of synapses, or simply changes in nonfunctional portions of an arbor. An important related issue is whether activity-dependent rearrangements reflect changes in the number and positions of synapses, as opposed to the strength or efficacy of individ-

ual synaptic connections.

The formation of layer-specific projections from the retina to the LGN illustrates some of these issues. Initially, axons from one eye form rudimentary branches in all regions of the LGN (25), which show little evidence of mature synaptic ultrastructure (63). Yet electrophysiological recordings demonstrate functional retinogeniculate connections (64, 65). As development proceeds, "inappropriate" synapses—and their morphological correlate, the fine collateral branches—disappear, whereas arborizations in the appropriate LGN layer increase in size and complexity (Fig. 1), a process that is accompanied by increasingly robust synaptic transmission (64). Thus, formation of the adult pattern of connections involves elimination of a limited number of immature connections in inappropriate locales, coupled with the elaboration and addition of many new connections in the appropriate layers. The process is conservative in the sense that the system does not make a large investment in building stable synaptic structure until after the decision to eliminate or retain a functional connection is made.

The formation of horizontal connections in the visual cortex provides another illustration that the anatomical and functional states of connections can differ at early stages of development. Localized photorelease of "caged" glutamate and optical recording demonstrate that despite the presence of unbranched axon collaterals that can extend for more than 1 mm, neurons exchanged functional inputs only with their close neighbors. The subsequent ability of collaterals to evoke activity at more distant sites coincides with the onset of axonal branching and the emergence of clusters (Fig. 4) (66). Thus, as for the developing retinogeniculate projection, there is no large, preexisting repertoire of synaptic connections from which a subset is selected on the basis of activity patterns (Fig. 1). The major events in intracortical cluster formation, as with the segregation of retinogeniculate axons into eye-specific layers, are conservative and involve the local addition of large numbers of active synapses, accompanied by axon branching. Hence, neural activity is likely providing cues that drive the formation of new synapses and axon branches, as well as cues that act to select and stabilize existing ones.

Are such considerations relevant to the classical paradigm of ocular dominance column formation? LGN inputs from the two eyes do initially overlap in layer 4, and physiologically neurons receive functional inputs from both eyes (7). On the basis of studies of individually labeled LGN axons (6, 67), it appears that ingrowing axons are initially very simple and sparse. Hence, during the period of overlap, axons have probably formed very few permanent connections. The subsequent emergence of segregated columns, like the development of layers in the LGN and horizontal connections in cortex, is likely to follow a similar strategy: loss of a relatively small number of inappropriate synapses, accompanied by a massive growth and sprouting in the correct column (Fig. 1). Indirect support for this notion comes from experiments in which brief monocular deprivation is performed. Even after periods of deprivation on the order of a few days, the collateral arbors of axons representing the deprived eye shrink dramatically, whereas those of the open eye expand (68). The changes after a few days are as robust as those occurring after many months of deprivation, suggesting that morphological plasticity is very rapid and potentially sufficient to account entirely for the rapid physiological change.

Neurotrophins and Activity-Dependent Development

One possible mechanism for translating patterns of activity into patterns of synaptogenesis and growth involves the local release of neurotrophins, which have become attractive candidates as retrograde signals in activity-dependent synaptic remodeling in the mammalian nervous system [reviewed in (69)]. One need only posit that groups of coordinately activated postsynaptic neurons release neurotrophins, and that only axon collaterals whose parent cell body has also been activated are capable of responding to the synaptogenic effects of the neurotrophins. This scenario does not require that developing collaterals have functional synapses along their length, but only that collaterals can respond to a synaptogenic factor when they are electrically active in its presence. This "constructionist" view of the role of activity (70) seems to account more plausibly for the development of these patterned connections than proposals based solely on large-scale regressive events.

In addition to controlling neuronal survival and differentiation during early development (71), neurotrophins modulate synaptic strength within minutes at developing neuromuscular synapses in vitro (72) in adult hippocampal slices (73) and in the developing mammalian visual system. In rodents, intraventricular administration of nerve growth factor (NGF) prevents the physiologically assessed shift in ocular dominance in favor of the nondeprived eye (50, 74) and blocks the anatomical shrinkage of the cell bodies of LGN neurons receiving inputs from the deprived eye (75). These actions of NGF may be mediated through the basal forebrain cholinergic system, which influences cortical plasticity (76), rather than by direct action on LGN axon terminals, as only the neurotrophin receptors TrkB and TrkC, but not TrkA (the high-affinity NGF receptor) are detectable in the LGN and cortex (77).

Ligands of TrkB—BDNF, NT-4, or both—are more likely to be involved in the activity-dependent control of LGN axon branching during development. Intracortical infusions of BDNF or NT-4, but not NT-3 or NGF, prevent the formation of ocular dominance columns in layer 4 (78); infusion of BDNF (but not of NGF) also alters the effects of monocular deprivation on the ocular dominance distribution (as assessed physiologically) of cortical neurons (79). Exogenous NT-4 (but not NT-3 or NGF), provided by local cortical injections of neurotrophin-coated latex microspheres, attenuates the shrinkage of LGN neuron cell bodies receiving input from the deprived eye during the critical period (80). And in an in vitro slice assay, McAllister *et al.* (81) found that BDNF, but not NGF or NT-3, elicited robust dendritic growth of postsynaptic cells in layer 4; BDNF was effective only in the presence of spontaneous activity (82). Thus, LGN axons may normally compete for an endogenous ligand of TrkB available within layer 4, and the availability of ligand from the postsynaptic cell or the ability of the presynaptic terminals to respond to it may be regulated by neural activity.

These results suggest a role for BDNF or NT-4 in activity-dependent synaptic remodeling during visual system development. Yet, as is the case for the role of LTP, many crucial links are missing. It is not known if the exogenously supplied neurotrophins indeed act directly on LGN axons. If ligands of TrkB are indeed involved, they should be expressed by layer 4 cortical neurons at the relevant developmental times and at levels regulated by neural activity in a highly local fashion. Neural activity does regulate global levels of BDNF messenger RNA (mRNA) expression in rat visual cortex (83); whether such regulation occurs with sufficient rapidity is unknown. BDNF mRNA has been detected within neurons of the primary visual cortex in cats, ferrets, and rats, but primarily within layer 2/3 and 5/6, not layer 4 (84); virtually nothing is known about NT-4 expression patterns in visual cortical neurons. It will also be crucial to determine whether the endogenous regulators of developmental plasticity are indeed neurotrophic factors.

A crucial unresolved issue is whether neurotrophins act in an instructive or a permissive fashion. Are neurotrophins released from the postsynaptic neuron in an activity-dependent manner, acting rapidly

to stabilize or enhance coactive presynaptic inputs, as is required by the models of visual cortical plasticity? Or are they simply permissive, setting the scene for activity-dependent competition? For instance, neurotrophin concentrations might modulate the threshold for synaptic plasticity in visual cortex (*47*, *85*). These questions must be addressed to establish a role for neurotrophins in activity-dependent synaptic rearrangements not only in the visual system but also elsewhere in the central nervous system during development. Whatever effects neurotrophins exert during synaptic development, it is exciting that 25 years after Hubel and Wiesel first described the effects of abnormal visual experience on the functional and structural organization of the mammalian visual system, we are on the verge of obtaining a satisfying mechanistic understanding of this developmental process, which is so essential for enabling the brain to learn about and adapt to the world.

REFERENCES AND NOTES

1. C. S. Goodman and C. J. Shatz, *Cell* **72**, 77 (1993); *Neuron* **10**, 1 (1993).
2. M. Tessier-Lavigne and C. S. Goodman, *Science* **274**, 1123 (1996).
3. P. Rakic, *Philos. Trans. R. Soc. London Ser. B* **278**, 245 (1977).
4. S. LeVay, M. P. Stryker, C. J. Shatz, *J. Comp. Neurol.* **179**, 223 (1978); S. LeVay, T. N. Wiesel, D. H. Hubel, *ibid.* **191**, 1 (1980).
5. C. J. Shatz *Neuron* **5**, 745 (1990).
6. A. Antonini and M. P. Stryker, *J. Neurosci.* **13**, 3549 (1993).
7. S. LeVay, M. P. Stryker, C. J. Shatz, *J. Comp. Neurol.* **179**, 223 (1978).
8. T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **26**, 978 (1963); *ibid.*, p. 1003; D. H. Hubel and T. N. Wiesel, *J. Physiol.* **206**, 419 (1970).
9. D. H. Hubel, T. N. Wiesel, S. LeVay, *Philos. Trans. R. Soc. London Ser. B* **278**, 377 (1977).
10. C. J. Shatz and M. P. Stryker, *J. Physiol.* **281**, 267 (1978).
11. N. W. Daw, K. Fox, H. Sato, D. Czepita, *J. Neurophysiol.* **67**, 197 (1992).
12. G. D. Mower, C. J. Caplan, W. G. Christen, F. H. Duffy, *J. Comp. Neurol.* **235**, 448 (1985).
13. L. C. Katz and E. M. Callaway, *Annu. Rev. Neurosci.* **15**, 31 (1992).
14. E. M. Callaway and L. C. Katz, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 745 (1991).
15. S. Löwel and W. Singer, *Science* **255**, 209 (1992).
16. M. P. Stryker and W. Harris, *J. Neurosci.* **6**, 2117 (1986).
17. J. C. Horton and D. R. Hocking, *ibid.* **16**, 1791 (1996).
18. T. N. Wiesel and D. H. Hubel, *J. Comp. Neurol.* **158**, 307 (1974); B. Chapman and M. P. Stryker, *J. Neurosci.* **13**, 5251 (1993); I. Godecke and T. Bonhoeffer, *Nature* **379**, 251 (1996).
19. J. C. Durack and L. C. Katz, *Cereb. Cortex* **6**, 178 (1996); E. S. Ruthazer and M. P. Stryker, *J. Neurosci.* **16**, 7253 (1996).
20. L. Galli and L. Maffei, *Science* **242**, 90 (1988).
21. M. Meister, R. O. L. Wong, D. A. Baylor, C. J. Shatz, *ibid.* **252**, 939 (1991).
22. R. O. L. Wong, M. Meister, C. J. Shatz, *Neuron* **11**, 923 (1993).
23. R. O. L. Wong, A. Chernjavsky, S. J. Smith, C. J. Shatz, *Nature* **374**, 716 (1995).
24. M. B. Feller, D. P. Wellis, D. Stellwagen, F. S. Werblin, C. J. Shatz, *Science* **272**, 1182 (1996).
25. D. W. Sretavan and C. J. Shatz, *J. Neurosci.* **6**, 234 (1986).
26. C. J. Shatz and M. P. Stryker, *Science* **242**, 87 (1988); D. W. Sretavan, M. P. Stryker, C. J. Shatz, *Nature* **336**, 468 (1988).
27. R. O. L. Wong and D. M. Oakley, *Neuron* **16**, 1087 (1996).
28. J. O. Hahm, R. B. Langdon, M. Sur, *Nature* **351**, 568 (1991); S. R. Bodnarenko and L. M. Chalupa, *ibid.* **364**, 144 (1993).
29. R. Mooney, A. A. Penn, R. Gallego, C. J. Shatz, *Neuron*, in press.
30. M. O'Donovan *et al.*, *J. Exp. Zool.* **261**, 261 (1992).
31. R. Yuste, A. Peinado, L. C. Katz, *Science* **257**, 665 (1992).
32. A. Peinado, R. Yuste, L. C. Katz, *Neuron* **10**, 103 (1993); R. Yuste, D. A. Nelson, W. W. Rubin, L. C. Katz, *ibid.* **14**, 7 (1995).
33. H. T. Cline, *Curr. Biol.* **1**, 275 (1991).
34. K. D. Miller, J. B. Keller, M. P. Stryker, *Science* **245**, 605 (1989).
35. G. Goodhill and S. Lowel, *Trends Neurosci.* **18**, 437 (1995); N. V. Swindale, *Comput. Neural Sys.* **7**, 161 (1996).
36. M. P. Stryker and S. L. Strickland, *Invest. Ophthalmol. Visual Sci.* (suppl.) **25**, 278 (1984).
37. L. L. Eisele, and J. T. Schmidt, *Neurobiology* **19**, 395 (1988).
38. Y. Fregnac, D. Shulz, S. Thorpe, E. Bienenstock, *Nature* **333**, 367 (1988).
39. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949).
40. D. V. Madison, R. Malenka, R. A. Nicoll, *Annu. Rev. Neurosci.* **14**, 379 (1991); R. Malenka, *Cell* **78**, 535 (1994).
41. M. F. Bear and R. C. Malenka, *Curr. Opin. Neurobiol.* **4**, 389 (1993); R. C. Malenka and R. A. Nicoll, *Trends Neurosci.* **16**, 521 (1993); M. Bear and W. Abraham, *Annu. Rev. Neurosci.* **19**, 437 (1996).
42. T. Tsumoto, *Prog. Neurobiol.* **39**, 209 (1992); Y. Komatsu, K. Fujii, J. Maeda, H. Sakaguchi, K. Toyama, *J. Neurophysiol.* **59**, 124 (1988); A. Artola, S. Brocher, W. Singer, *Nature* **347**, 69 (1990); M. F. Bear, *Prog. Brain Res.* **108**, 205 (1996).
43. M. F. Bear, A. Kleinschmidt, Q. Gu, W. Singer, *J. Neurosci.* **10**, 909 (1990).
44. K. D. Miller, B. Chapman, M. P. Stryker, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 5183 (1989).
45. H. O. Reiter and M. P. Stryker, *ibid.* **85**, 3623 (1988).
46. Y. Komatsu and M. Iwakiri, *J. Neurophysiol.* **67**, 401 (1992).
47. A. Kirkwood, S. M. Dudek, J. T. Gold, C. D. Aizenman, M. F. Bear, *Science* **260**, 1518 (1993).
48. N. Kato, A. Artola, W. Singer, *Dev. Brain Res.* **60**, 43 (1991).
49. J. A. Hirsch and C. D. Gilbert, *J. Neurosci.* **11**, 1800 (1991); A. Das and C. D. Gilbert, *Nature* **375**, 780 (1995); X. Wang, M. M. Merzenich, K. Sameshima, W. M. Jenkins, *ibid.* **378**, 71 (1995).
50. L. Maffei L, N. Berardi, L. Domenici, V. Parisi, T. Pizzorusso, *J. Neurosci.* **12**, 4651 (1992).
51. J. A. Gordon and M. P. Stryker, *ibid.* **16**, 3274 (1996).
52. A. Kirkwood, H.-K. Lee, M. Bear, *Nature* **375**, 328 (1995); A. Kirkwood and M. F. Bear, *J. Neurosci.* **14**, 1634 (1994).
53. M. Cynader and D. C. Mitchell, *J. Neurophysiol.* **43**, 1026 (1980).
54. M. Crair and R. Malenka, *Nature* **375**, 325 (1995).
55. Y. Li, R. S. Erzurumlu, C. Chen, S. Jhaveri, S. Tonegawa, *Cell* **76**, 427 (1994).
56. R. J. Balice-Gordon, C. K. Chua, C. C. Nelson, J. W. Lichtman, *Neuron* **11**, 801 (1993).
57. Y.-J. Lo and M.-m. Poo, *J. Neurosci.* **14**, 4684 (1994); Y. Dan and M.-m. Poo, *Curr. Biol.* **4**, 95 (1994).
58. M. Kano *et al.*, *Cell* **83**, 1223 (1995).
59. P. Rakic, J.-P. Bourgeois, M. F. Eckenhoff, N. Zecevic, P. S. Goldman-Rakic, *Science* **232**, 232 (1986).
60. E. Frank and G. D. Fischbach, *J. Cell Biol.* **83**, 143 (1979).
61. J. Maslim and J. Stone, *Brain Res.* **373**, 35 (1986); R. O. L. Wong, R. M. Yamawaki, C. J. Shatz, *Eur. J. Neurosci.* **4**, 1387 (1992); Y. Nishimura and P. Rakic, *J. Comp. Neurol.* **241**, 420 (1985).
62. M. E. Dailey and S. J. Smith, *J. Neurosci.* **16**, 2983 (1996); N. A. O'Rourke, H. T. Cline, S. E. Fraser, *Neuron* **12**, 921 (1994).
63. G. Campbell and C. J. Shatz, *J. Neurosci.* **12**, 1847 (1992).
64. C. J. Shatz and P. A. Kirkwood, *ibid.* **4**, 1378 (1983).
65. R. Mooney, D. V. Madison, C. J. Shatz, *Neuron* **10**, 815 (1993).
66. M. B. Dalva and L. C. Katz, *Science* **265**, 255 (1994); D. A. Nelson and L. C. Katz, *Neuron* **15**, 23 (1995).
67. A. Ghosh and C. J. Shatz, *J. Neurosci.* **12**, 39 (1992).
68. A. Antonini and M. P. Stryker, *Science* **260**, 1819 (1993).
69. D. Lo, *Neuron* **15**, 979 (1995); H. Thoenen, *Science* **270**, 593 (1995); T. Bonhoeffer, *Curr. Opin. Neurobiol.* **6**, 119 (1996); A. Ghosh, *Curr. Biol.* **6**, 130 (1996).
70. D. Purves, *Body and Brain* (Harvard Univ. Press, Cambridge, 1988).
71. A. M. Davies, *J. Neurobiol.* **25**, 2334 (1994); D. Kaplan and R. Stephens, *ibid.*, p. 1404; W. C. Snider, *Cell* **77**, 627 (1994); D. Lindholm, E. Castren, M. P. Berzaghi, A. Blochl, H. Thoenen, *J. Neurobiol.* **25**, 1362 (1994); M. Bothwell, *Annu. Rev. Neurosci.* **18**, 223 (1995); G. Lewin and Y.-A. Barde, *ibid.* **19**, 289 (1996).
72. A. M. Lohof, N. Y. Ip, M.-m. Poo, *Nature* **363**, 350 (1993).
73. H. Kang and E. M. Schuman, *Science* **267**, 1658 (1995); M. Korte *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 8856 (1995); S. L. Patterson *et al.*, *Neuron* **16**, 1137 (1996); A. Figurov, L. D. Pozzo-Miller, P. Olafsson, T. Wang, B. Lu, *Nature* **381**, 706 (1996).
74. G. Carmignoto, R. Canella, P. Candeo, M. C. Comelli, L. Maffei, *J. Physiol.* **464**, 343 (1993).
75. N. Berardi *et al.*, *Proc. R. Soc. London Ser. B* **251**, 17 (1993); L. Domenici, A. Cellerino, L. Maffei, *ibid.*, p. 25.
76. T. Kasamatsu and J. D. Pettigrew, *Science* **194**, 206 (1976); M. F. Bear and W. Singer, *Nature* **320**, 172 (1986).
77. K. L. Allendoerfer *et al.*, *J. Neurosci.* **14**, 1795 (1994); R. J. Cabelli *et al.*, *ibid.*, in press; R. B. Gibbs and D. W. Pfaff, *J. Comp. Neurol.* **341**, 324 (1994); J. P. Merlio, P. Ernfors, M. Jaber, H. Persson, *Neuroscience* **51**, 513 (1992).
78. R. J. Cabelli, A. Hohn, C. J. Shatz, *Science* **267**, 1662 (1995).
79. R. Galuske, D.-S. Kim, E. Castrén, H. Theonen, W. Singer, *Eur. J. Neurosci.* **8**, 1554 (1996).
80. D. R. Riddle, D. C. Lo, L. C. Katz, *Nature* **378**, 189 (1995).
81. A. K. McAllister, D. C. Lo, L. C. Katz, *Neuron* **4**, 791 (1995).
82. ——— *ibid.*, in press.
83. E. Castren, F. Zafra, H. Thoenen, D. Lindholm, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 9444 (1992); A. A. Schoups, R. C. Elliott, W. J. Friedman, I. B. Black, *Dev. Brain Res.* **86**, 326 (1995).
84. E. Lein, A. Hohn, C. J. Shatz, *Soc. Neurosci. Abstr.* **21**, 1795 (1995); P. Ernfors, J. Bengzon, Z. Kokaia, H. Persson, O. Lindvall, *Neuron* **7**, 165 (1991).
85. E. L. Bienenstock, L. N. Cooper, P. W. Munro, *J. Neurosci.* **2**, 32 (1982); M. F. Bear, *Neuron* **15**, 1 (1995); K. Deisseroth, H. Bito, H. Schulman, R. W. Tsien, *Curr. Biol.* **5**, 1334 (1995).
86. K. Kander and L. C. Katz, unpublished data.

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