Sensitive Periods in the Development of the Brain and Behavior

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Abstract

■ Experience exerts a profound influence on the brain and, therefore, on behavior. When the effect of experience on the brain is particularly strong during a limited period in development, this period is referred to as a sensitive period. Such periods allow experience to instruct neural circuits to process or represent information in a way that is adaptive for the individual. When experience provides information that is essential for normal development and alters performance permanently, such sensitive periods are referred to as critical periods.

Although sensitive periods are reflected in behavior, they are actually a property of neural circuits. Mechanisms of plasticity at the circuit level are discussed that have been shown to operate during sensitive periods. A hypothesis is proposed that experience during a sensitive period modifies the architecture of a circuit in fundamental ways, causing certain patterns of connectivity to become highly stable and, therefore, energetically preferred. Plasticity that occurs beyond the end of a sensitive period, which is substantial in many circuits, alters connectivity patterns within the architectural constraints established during the sensitive period. Preferences in a circuit that result from experience during sensitive periods are illustrated graphically as changes in a ''stability landscape,'' a metaphor that represents the relative contributions of genetic and experiential influences in shaping the information processing capabilities of a neural circuit. By understanding sensitive periods at the circuit level, as well as understanding the relationship between circuit properties and behavior, we gain a deeper insight into the critical role that experience plays in shaping the development of the brain and behavior. ■

INTRODUCTION

Learning that occurs during sensitive periods lays the foundation for future learning. A classical example is that of filial imprinting (Lorenz, 1937): During a limited period soon after birth, a young animal (mammal or bird) learns to recognize, and bonds with, its parent (Hess, 1973). The newborn cannot know the identity of its parent a priori, so it imprints on the individual that is consistently nearby and that satisfies best its innate expectations for the characteristics of a parent. Under unusual conditions, that individual may not even be of the same species. The learning that occurs during this sensitive period exerts a long-lasting influence on the development of the individual's social and emotional behavior (Immelmann, 1972; Scott, 1962).

The term ''sensitive period'' is a broad term that applies whenever the effects of experience on the brain are unusually strong during a limited period in development. Sensitive periods are of interest to scientists and educators because they represent periods in development during which certain capacities are readily shaped or altered by experience. Critical periods are a special class of sensitive periods that result in irreversible changes in brain function. The identification of critical periods is of particular importance to clinicians, because the adverse effects of atypical experience throughout a critical period cannot be remediated by restoring typical experience later in life. The period for filial imprinting, for example, is a critical period.

Most of us view sensitive and critical periods from the perspective of behavior. Many aspects of our perceptual, cognitive, and emotional capabilities are shaped powerfully by experiences we have during limited periods in life. For example, the capacity to perceive stereoscopic depth requires early experience with fused binocular vision (Crawford, Harwerth, Smith, & von Noorden, 1996; Jampolsky, 1978); the capacity to process a language proficiently requires early exposure to the language (Newport, Bavelier, & Neville, 2001; Weber-Fox & Neville, 1996; Kuhl, 1994; Oyama, 1976); and the capacities to form strong social relationships and exhibit typical responses to stress require early positive interactions with a primary care giver (Thompson, 1999; Liu et al., 1997; Leiderman, 1981; Hess, 1973). In each case, the experience must be of a particular kind and it must occur within a certain period if the behavior is to develop normally.

Although sensitive periods are reflected in behavior, they are actually a property of neural circuits. Because

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behavior results from information that has been processed through hierarchies of neural circuits, behavioral measures tend to underestimate the magnitude and persistence of the effects of early experience on neural circuits. Therefore, to define sensitive periods and to explore why they occur and how they might be manipulated, we must think about them at the level of circuits.

Examples of Sensitive Periods

To illustrate properties of sensitive periods, I will refer primarily to data from four systems that have been studied in some detail: the systems for (1) ocular representation in the cortex of mammals, (2) auditory space processing in the midbrain of barn owls, (3) filial imprinting in the forebrain of ducks and chickens, and (4) song learning in the forebrain of songbirds. The following is a brief introduction to each of these systems.

Ocular representation in the primary visual cortex of monkeys, cats, and ferrets is the most thoroughly studied of all systems that exhibit a sensitive period (Katz & Shatz, 1996; Daw, 1994; Fox & Zahs, 1994; Shatz & Stryker, 1978; Hubel & Wiesel, 1977). In this circuit, information originating from either the left or right eye is conveyed to cortical layer IV by axons from the thalamus. The connections of thalamic axons with neurons in layer IV are shaped powerfully by visual experience during the first months after birth. During this period, chronic closure of one eyelid (monocular deprivation) causes a selective elimination of connections from the closed eye and an elaboration of new connections from the open eye (Antonini & Stryker, 1993). As a result, the circuit in layer IV comes to be dominated by input from the open eye. After the period ends, the typical pattern of ocular representation cannot be recovered despite the restoration of visual input to both eyes (Wiesel & Hubel, 1965). Because of this last property, ocular representation in the visual cortex is an example of a critical period.

Filial imprinting in ducks and chickens is another example of a critical period. Within a few days of hatching, these animals imprint on auditory and visual stimuli that identify the parent (Bolhuis & Honey, 1998; Ramsay & Hess, 1954). Imprinting causes neurons in a particular nucleus in the forebrain (the intermediate and medial hyperstriatum ventrale) to undergo changes in architecture and biochemistry and to become functionally selective for the imprinted stimulus (Horn, 1998, 2004; Scheich, 1987). After the imprinting period ends, the preference for the imprinted stimulus does not change with subsequent experience.

Song memorization in songbirds occurs during a critical period in some species but throughout life in other closely related species. Songbirds memorize the song that they will sing (Konishi, 1985; Marler, 1970a). Normally, they learn the song of their father (when only the male sings). However, in the absence of a father's song, they will learn other song dialects or the songs of certain other species. Song learning is associated with architectural and functional changes in a forebrain nucleus (the lateral magnocellular nucleus of the anterior neostriatum) which is essential for song learning (Doupe, 1997; Wallhausser-Franke, Nixdorf-Bergweiler, & DeVoogd, 1995; Bottjer, Meisner, & Arnold, 1984). For some species, song learning occurs only during a limited period early in development, whereas for others song learning continues throughout life.

Auditory processing of spatial information in the midbrain of the barn owl is an example of a sensitive period that is not a critical period. The processing of auditory spatial information in barn owls exhibits an unusually high degree of plasticity in juvenile animals (Knudsen, 2002). A circuit in the external nucleus of the inferior colliculus, integrates information from various localization cues and forms associations between auditory cue values and locations in space. Neural connectivity is shaped powerfully by juvenile experience, as the circuit calibrates its representations of auditory cues to create a map of space that is accurate for the individual. Manipulations of the owl's hearing or vision (vision calibrates the representation of auditory cues in this circuit) during the juvenile period result in the acquisition of highly atypical representations of auditory cue values. However, typical representations of cue values can be acquired even after the juvenile period ends by restoring normal hearing and vision, and by providing the owl with a sufficiently rich environment (Brainard & Knudsen, 1998). Because of this last property, this period is not a critical period.

Opening of Sensitive Periods

Initial Conditions

Not all circuits are shaped during sensitive periods. In some circuits, the connectivity (pattern and strengths of connections) that exists in the mature circuit is established by innate mechanisms with essentially no contribution from experience (Figure 1A). This is the case for many circuits that are located near the sensory or motor periphery, such as in the retina or the spinal cord, or that operate automatically (Kania & Jessell, 2003; Dyer & Cepko, 2001; Meissirel, Wikler, Chalupa, & Rakic, 1997). Other circuits maintain a high degree of plasticity throughout life, such as in the basolateral nucleus of the amygdala, the molecular layer of the cerebellar cortex, or the CA1 region of the hippocampus (Medina, Christopher Repa, Mauk, & LeDoux, 2002; Malenka & Nicoll, 1999; Ito, 1984). In these circuits, the range of potential stable patterns of connectivity is broad and remains broad throughout the lifetime of the animal (Figure 1B).

Most circuits operate between these extremes. For these circuits, innate influences establish an initial pattern of connectivity that is preferred (a valley in the stability landscape; Figure 1C), but the pattern is not specified precisely. This kind of circuit may be shaped by

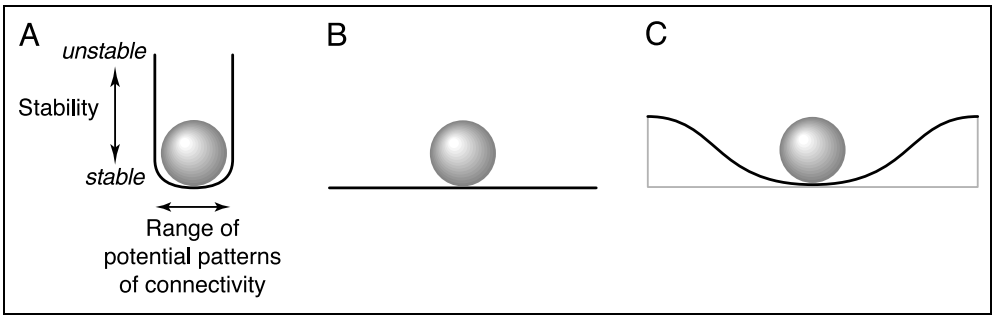

Figure 1. The constraints placed on different neural circuits by innate influences before experience exerts its effects, as represented by a stability landscape. The horizontal axis indicates the range of patterns of neural connectivity (strength and pattern of connections) that the circuit could acquire under any conditions. The vertical axis indicates the degree to which each pattern is stable. The thick line is the landscape showing the relative stabilities of the various possible patterns of connectivity and reflecting, therefore, the energy cost to change from one pattern of connectivity to another. The location of the ball in the landscape indicates the particular pattern of connectivity that exists in the circuit. (A) Circuit that is completely constrained by innate influences. The range of potential patterns of connectivity is narrow, and alternative patterns are not stable and, therefore, cannot be maintained. Examples are projections of photoreceptor cells onto bipolar cells in the retina or olfactory afferents onto glomeruli in the olfactory bulb. (B) Circuit with high capacity for experience-driven plasticity. The range of potential patterns of connectivity is broad, although defined by genetic determinants. All patterns are equally stable, so one pattern is not preferred over others. Examples are the molecular layer of the cerebellum, the CA1 region of the hippocampus and the basolateral amygdala. (C) Circuit that has the capacity to acquire a range of patterns, but prefers a certain range of patterns. Examples are the thalamic input to layer IV of the primary sensory cortex in mammals, the external nucleus of the inferior colliculus in owls, the lateral magnocellular nucleus of the anterior neostriatum in songbirds.

experience during a sensitive period. The degree to which experience can alter the innate pattern of connectivity varies greatly across different circuits and, for the same circuit, across different species. When a circuit can select from a large range of potential patterns of connectivity, the effect of experience can have an enormous impact on circuit connectivity. Conversely, when the range of potential patterns of connectivity is highly constrained by genetic influences, the effect of experience is correspondingly small.

Prerequisites

A sensitive period cannot open until three conditions are met. First, the information provided to the circuit must be sufficiently reliable and precise to allow the circuit to carry out its function (for high-level circuits, this may not happen until relatively late in development). Second, the circuit must contain adequate connectivity, including both excitatory and inhibitory connections, to process the information (Fagiolini & Hensch, 2000). Finally, it must have activated mechanisms that enable plasticity, such as the capacity for altering axonal or dendritic morphologies, for making or eliminating synapses, or for changing the strengths of synaptic connections. Experience that occurs before these three conditions are met will have no effect (positive or negative) on the circuit.

Timing of Initiation

The conditions required in order for a sensitive period to open may result from the progress of development or they may be enabled by the individual's experience. In several systems, intense impulse activity, of the kind that can result from experience, has been shown to trigger gene transcription and translation and to activate existing molecular cascades for processes that underlie plasticity (Zhou, Tao, & Poo, 2003; Kandel, 2001; Benson, Schnapp, Shapiro, & Huntley, 2000; Luscher, Nicoll, Malenka, & Muller, 2000). Conversely, depriving animals of adequate experience has been shown to delay the opening of certain sensitive periods (Doupe & Kuhl, 1999; Daw, 1997; Mower & Christen, 1985). Thus, either the progress of development or intense, experience-driven activity can trigger the onset of a sensitive period.

Complex behaviors may comprise multiple sensitive periods. Experimental evidence suggests that sensitive periods for circuits performing low-level, more fundamental computations end before those that affect circuits processing higher order aspects of sensory stimuli (Jones, 2000; Daw, 1997). For example, the sensitive periods for circuits responsible for binocular fusion and stereopsis end long before the sensitive periods for circuits that analyze complex objects (Le Grand, Mondloch, Maurer, & Brent, 2003; Rodman, 1994; LeVay, Wiesel, & Hubel, 1980). The same principle is likely to obtain for language, social development and other complex behaviors. This sequencing of sensitive periods is logical, because higher levels in a hierarchy depend on precise and reliable information from lower levels in order to accomplish their functions. Therefore, experience-dependent shaping of high-level circuits cannot occur until the computations being carried out by lower-level circuits have become reliable.

During a Sensitive Period

Properties of Sensitive Period Plasticity

Experience during a sensitive period customizes a developing neural circuit to the needs of the individual.

Experience provides precise information about the individual or about the environment that often cannot be predicted and, therefore, cannot be genetically encoded. For example, experience calibrates the circuits that process stereoscopic information to the exact separation and physical properties of the eyes (Jampolsky, 1978) and customizes circuits involved in processing speech sounds for the particular language(s) that will be spoken (Newport et al., 2001).

Only certain kinds of stimuli are able to shape a particular circuit during a sensitive period. The range of stimuli that can influence a circuit is determined by genetic predispositions that are built into the nervous system (Knudsen, 1999; Konishi, 1985; Hess, 1973; Immelmann, 1972). Within this potential range, some stimuli are preferred over others (Figure 1C). The predisposition of a circuit to be instructed by typical experience reflects both the selectivity of the circuit's various inputs, which themselves may be shaped during sensitive periods, as well as the innate connectivity of the circuit.

Mechanisms of Sensitive Period Plasticity

Axon elaboration and synapse formation as well as axon and synapse elimination are mechanisms that have been shown to alter circuit architecture during sensitive periods. During the development of a circuit, axons and dendrites are growing and connections between many pre- and postsynaptic neurons are being formed and broken over short periods (Niell & Smith, 2004). Experience that activates a circuit adequately can cause particular connections to be strengthened according to a Hebbian rule as follows: When the activity of a tentative, presynaptic element consistently anticipates (and, therefore, contributes to driving) the activity of a postsynaptic neuron, that synapse is stabilized and strengthened. The distribution of stabilized synapses shapes the growth patterns of axons and dendrites (Niell & Smith, 2004; Ruthazer & Cline, 2004).

Axon elaboration and synapse formation is associated with sensitive period plasticity in both the primary visual cortex in mammals and in the external nucleus in barn owls. In the primary visual cortex, experience with monocular deprivation causes thalamic axons conveying activity from the nondeprived eye to elaborate extensively in regions of layer IV that are typically occupied by axons representing the deprived eye (Antonini, Gillespie, Crair, & Stryker, 1998). In the external nucleus of the barn owl, novel axonal connections can be formed (DeBello, Feldman, & Knudsen, 2001) that allow highly atypical associations to be established between values of auditory localization cues and locations in space (Figure 2A). The capacity for axon elaboration in layer

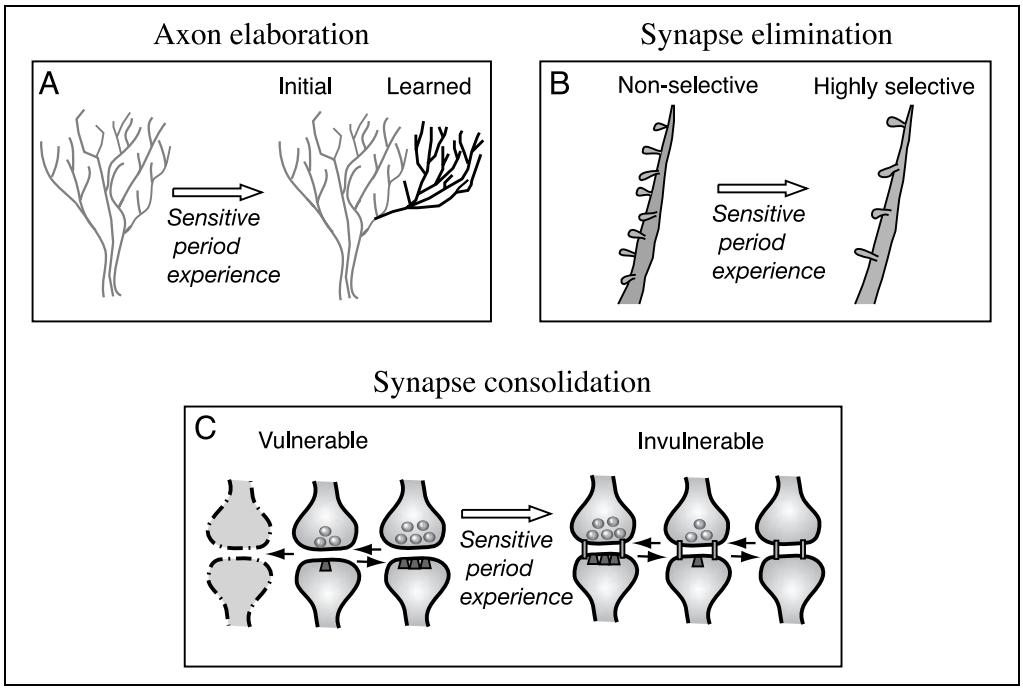

Figure 2. Mechanisms of architectural change that can underlie sensitive period plasticity. (A) Elaboration of a new axonal projection field, establishing novel connections as instructed by experience. The sketch represents data from auditory space analysis in the external nucleus of barn owls and ocular dominance in layer IV of the primary visual cortex in cats (DeBello et al., 2001; Antonini & Stryker, 1993). (B) Loss of dendritic spines, suggesting the selective elimination of unused synaptic inputs. The sketch represents data from filial imprinting in Guinea fowl and song memorization in zebra finches (Wallhausser-Franke et al., 1995; Scheich, 1987). (C) Hypothesis for synapse consolidation by CAMs. Repeated activation of this synapse and the postsynaptic neuron by experience during a sensitive period results in the insertion of CAMs (vertical bars cross-linking the synaptic membranes), which structurally consolidate the synapse, making it invulnerable to subsequent elimination. Changes in the efficacy of the synapse, due for example to experience after the end of the sensitive period, are still possible. Changes in the numbers of presynaptic vesicles (spheres in upper terminal) or neurotransmitter receptors (trapezoids in lower terminal) represent changes in the efficacy of the synapse. Consolidated synapses represent a permanent trace of the learning that occurred during the sensitive period.

IV of the primary visual cortex correlates with high levels of growth associated proteins and neurotrophic factors, particularly brain derived neurotrophic factor (BDNF), low levels of factors that inhibit axonal outgrowth, and the activation of a special subclass of glutamate receptor, the NMDA receptor (Huberman & McAllister, 2002; Katz & Shatz, 1996; McIntosh, Daw, & Parkinson, 1990). Some of these same factors have been shown to be present in other circuits during sensitive period plasticity (Horn, 2004; Mooney, 1999; Bottjer & Arnold, 1997).

Axon and synapse elimination is a second, potentially independent mechanism that can play a key role in shaping circuit architecture during sensitive periods. In layer IV of the visual cortex and somatosensory cortex, for example, synaptic connections that consistently fail to predict the activity of postsynaptic neurons are weakened and eliminated and axon branches are pruned (Feldman, 2001; Antonini & Stryker, 1993). The capacity to eliminate axons based on experience is apparent only during a sensitive period.

Selective synapse elimination during a critical period also shapes the architecture of circuits involved in filial imprinting in birds (Figure 2B). In ducks and chickens, auditory imprinting causes neurons in a particular forebrain nucleus (the medial hyperstriatum ventrale) to be activated strongly by the imprinted stimulus (Horn, 2004; Scheich, 1987). The dendrites of principal neurons in this nucleus exhibit about half the density of spines (sites for synapses) as the same class of neurons in individuals that have not imprinted on an auditory stimulus, and the synapses that remain have become more powerful. The inputs that are eliminated are presumably those that do not contribute to the representation of the learned stimulus (narrowing the range of potential patterns of connectivity).

Similar evidence (a decrease in dendritic spines) has been found in the song learning pathway in the forebrain of songbirds (Wallhausser-Franke et al., 1995), suggesting that an analogous mechanism may underlie their critical period for song memorization. Both of these behaviors, song memorization and filial imprinting in birds, are subject to critical periods that can end rapidly with appropriate experience (Hess, 1973; Marler, 1970b).

Synapse consolidation is a third mechanism that could underlie fundamental architectural changes that result from experience during sensitive periods. Unlike the first two mechanisms (axon elaboration and elimination), synapse consolidation has been implicated but not demonstrated to influence sensitive period plasticity. Cell adhesion molecules (CAMs) of different kinds can insert into synapses that have become functionally strong (potentiated) (Ehlers, 2003; Benson et al., 2000; Tanaka et al., 2000). CAMs are highly stable molecules that can cross-link pre- and postsynaptic membranes and anchor the synaptic membranes to the cytoskeleton. The hypothesis is that experience during a sensitive period potentiates specific synapses and that these synapses are structurally stabilized by the insertion of particular kinds of CAMs (Figure 2C). While other synapses remain vulnerable to elimination, these synapses become invulnerable to elimination, even if the functional efficacy of these synapses was to drop to zero (Figure 2C, right side).

This mechanism could account for the persistence of learning that occurs during sensitive periods. For example, in the external nucleus of the barn owl, multiple representations of auditory cues can be acquired through experience during the sensitive period. Multiple representations are associated with the acquisition of novel axonal projections into this nucleus (DeBello et al., 2001). Owls that have acquired alternative representations as juveniles are able to re-express those representations as adults (Knudsen, 1998). The increased capacity for plasticity in these individuals reflects the learning that occurred during the sensitive period. Moreover, a substantial portion of the axonal and synaptic changes (as assessed by bouton densities) that result from juvenile experience persist in adults (Linkenhoker & Knudsen, in press). The persistence of these synapses suggests that they have become relatively invulnerable to elimination, perhaps because they have been consolidated by a particular kind of CAM which inserts into synapses that drive postsynatpic neurons powerfully during the sensitive period.

The Unique Advantage of Initial Experience

Experience that occurs initially during a sensitive period has a unique advantage in shaping the connectivity of a circuit. Accumulating evidence about the development of synapses and circuits indicates that before a circuit has ever been activated strongly, it is in a state that favors change: excitatory synapses tend to be weak, synapses are occupied by subclasses of neurotransmitter receptors with relatively slow kinetics that favor plasticity, and inhibitory influences are weak and/or unpatterned (Luscher et al., 2000; Petralia et al., 1999; Hensch et al., 1998; Luhmann & Prince, 1991). Intense and repeated activation of a circuit, as can result from experience, alters these conditions dramatically. Synapses that participate in driving postsynaptic neurons become strong and less susceptible to further change due to the insertion of stabilizing proteins and different subclasses of neurotransmitter receptors (Si et al., 2003; Benson et al., 2000; Malenka & Nicoll, 1999). Synapses that do not participate in driving postsynaptic neurons are depressed and, possibly, eliminated (Bender, Rangel, & Feldman, 2003; Antonini & Stryker, 1993). Inhibitory networks become powerful and organized so that they suppress alternative patterns of excitation (Galarreta & Hestrin, 2001; Zheng & Knudsen, 2001; Hensch et al., 1998; Carandini & Heeger, 1994). Self-organizing forces,

acting according to the Hebbian rule, tend to reinforce already strengthened patterns of connections (Feldman, 2000; Martin, Grimwood, & Morris, 2000; Katz & Shatz, 1996; Miller, 1990; Bear, Cooper, & Ebner, 1987).

Although initial experience may have a uniquely potent effect in shaping patterns of connectivity, subsequent experience has the ability to cause further structural and functional changes that add to or counteract initial connectivity patterns, as long as the sensitive period remains open (Blakemore & Van Sluyters, 1974; Blakemore, Vital-Durand, & Garey, 1981). For example, cortical circuits that process speech information can acquire the capacity to process speech sounds of different languages with equal facility if the individual learns those languages at an early age (Newport et al., 2001; Doupe & Kuhl, 1999).

As with most forms of learning, behavioral and emotional state can have an enormous impact on the changes that result from experience during a sensitive period. Without adequate attention to the stimulus or arousal from the experience, plasticity does not occur in many circuits. Conversely, with heightened levels of attention and arousal, plasticity may occur at much later developmental stages in a given circuit. For example, long after juvenile songbirds no longer learn songs from a tape recorder, they can still learn songs from adult birds that interact with them while singing (Jones, Ten Cate, & Slater, 1996; Baptista & Petrinovich, 1986). In the sound localization pathway of barn owls, long after experience in individual cages no longer induces plasticity, exposure to more natural conditions results in substantial plasticity (Brainard & Knudsen, 1998).

Stability Landscape as a Metaphor for Sensitive Period Plasticity

The metaphor of a ''stability landscape'' illustrates graphically the functional implications of these cellular and molecular events for the future performance of a circuit. A stability landscape represents the range of possible connectivity patterns that a circuit might acquire and the degree to which any particular pattern is preferred. According to this metaphor, a sensitive period is a restricted period in the development of a circuit when experience readily alters the stability of particular patterns of connectivity.

Figure 3 illustrates the influence of experience on the landscape of a circuit. The ball begins at a low point in the center of the landscape, representing the intuitive notion that innate mechanisms establish an initial pattern of connectivity that is appropriate to process the neural activity that results from typical experience. Once a sensitive period begins, the particular spatio-temporal patterns of neuronal activity that result from experience (location of bold downward arrows in Figure 3) cause structural and functional changes, as described above, that can modify, refine, and reinforce this initial pattern. The changes may alter the range of patterns of connectivity that the circuit can acquire and they create high points and low points in the stability landscape. The pattern of connectivity that is instructed by experience becomes more sharply defined and highly preferred, even though the pattern may be atypical (Figure 3B).

Some circuits are able to acquire the capacity to express multiple stable patterns of connectivity (Figure 4A). When secondary experience instructs a new pattern of connectivity, extra energy must be expended to overcome the influences that stabilize the initial pattern (the ball must move up the slope of the landscape). Repeated experience that instructs the new pattern of connectivity refines and stabilizes the new pattern, creating a new low point in the landscape. For example, in the external nucleus of the barn owl, different kinds of experience during a sensitive period can establish multiple sets of associations between auditory cue values and locations in space and, once these alternative patterns have been acquired, the circuit can switch among them based on recent experience (Brainard & Knudsen, 1998; Knudsen, 1998). Analogously, some species of songbirds are able to learn multiple songs and humans are able to learn multiple languages with equal facility during a sensitive period (Doupe & Kuhl, 1999).

Other circuits are able to maintain only a single highly preferred pattern of connectivity (Figure 4B). For example, the circuits involved in imprinting acquire a strong preference for a particular stimulus, and the circuits involved in song memorization establish a template for just a single song, in some species of songbirds (Hess, 1973; Marler, 1970b).

Ending of Sensitive Periods

After a sensitive period has ended, many independent mechanisms that support plasticity continue to operate. The amount of plasticity that persists in a mature circuit varies widely, depending on the circuit's function. The plasticity that remains enables mature circuits to modify their patterns of connectivity within the enduring constraints established as a result of experience during a sensitive period.

A sensitive period ends when the mechanisms that were responsible for the unusually heightened state of plasticity no longer operate or operate with much lower efficiency. In the model, this is the point in development at which the circuit's landscape becomes resistant to change. After a sensitive period ends, change may still occur (as long as the period was not a critical period) but extra energy is required for a circuit to maintain a less stable pattern of connectivity (Figure 5). For example, in the auditory localization pathway of the barn owl, restoration of typical experience after the end of the sensitive period does not result in typical circuit performance unless the owl experiences a sufficiently rich

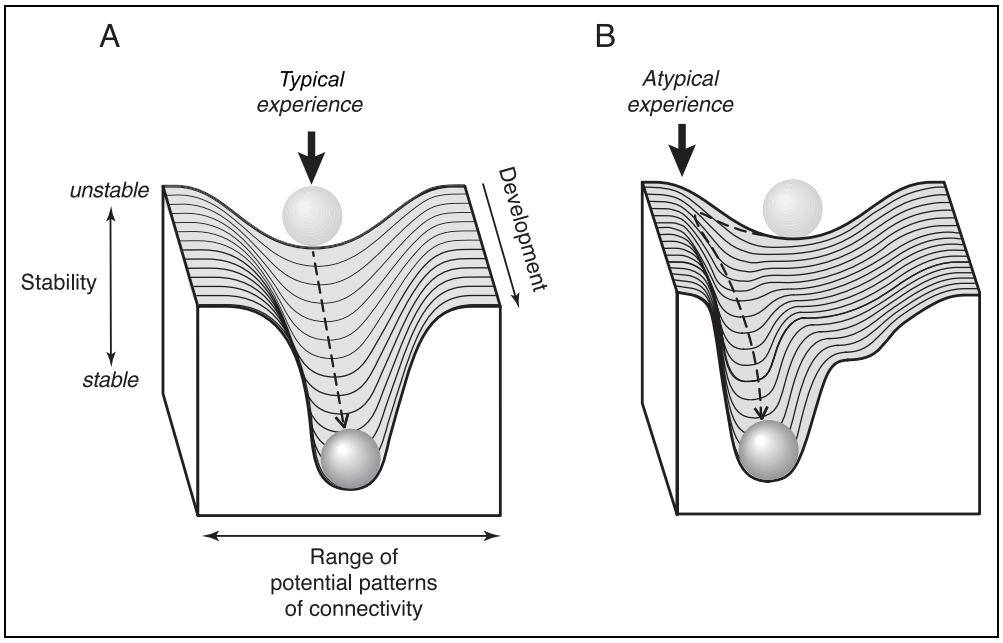

Figure 3. Stability landscape metaphors for the effects of typical (A) or atypical (B) experience on a neural circuit during a sensitive period. The horizontal axis indicates the range of patterns of neural connectivity that a circuit could potentially acquire; the vertical axis indicates the stability of each pattern of connectivity. Each contour line is the stability landscape for the circuit at a given point in development. Development progresses from top to bottom and may proceed quickly or slowly, depending on the circuit and the quality of the experience. The location of the ball on the landscape indicates the pattern of connectivity that exists at that point in development. The downward arrow indicates the pattern of connectivity that is instructed by experience. The dashed line represents the history of patterns of connectivity that the circuit attained over the course of development. Circuits begin with a genetically preferred pattern of connectivity (low area in the landscape) that is within a broader range of potential patterns. During a sensitive period, experience shapes fundamental aspects of a circuit's connectivity and, therefore, its stability landscape. (A) Effect of typical experience. When the pattern of connectivity that is instructed by experience is similar to the one that is established initially by innate influences, that pattern is further strengthened and stabilized. At the same time, the stability of alternative patterns decreases, due synaptic weakening and elimination of inappropriate synapses and to lateral inhibitory effects by the stabilized pattern. Thus, experience refines and reinforces the innate pattern of connectivity in the neural circuit. After the sensitive period ends, experience can alter the pattern of connectivity to a less stable pattern only by expending large amounts of energy. (B) Effect of atypical experience. Atypical experience drives the circuit's connectivity toward an abnormal pattern even though the pattern is initially energetically less favorable (the ball must move up the slope of the landscape). Once the circuit acquires this abnormal pattern, continuing atypical experience strengthens this pattern and it becomes the preferred pattern (low point in the landscape). The innately preferred, initial pattern usually maintains a relatively low point in the landscape (shoulder to the right of the low point), even though it has not been reinforced by experience. If the innate pattern is sufficiently robust and provides a stable alternative to the learned pattern, it can be attained after the end of a sensitive period as a result of restored, normal experience (Brainard & Knudsen, 1998).

environment (Brainard & Knudsen, 1998). After a critical period ends, alternative patterns of connectivity are no longer possible due to the properties of the circuit's stability landscape (Figure 6).

Many sensitive periods end gradually as a result of the progress of development, such as the adjustment of sound localization in barn owls or the acquisition of language proficiency in humans (Newport et al., 2001; Brainard & Knudsen, 1998). Sensitive periods that end exclusively as a function of developmental stage involve circuits that have the potential to learn multiple, stable patterns of connectivity during the sensitive period (Figure 4A).

However, some sensitive periods, specifically certain critical periods, have been shown to end rapidly once an individual is provided appropriate experience. Periods that can end rapidly involve circuits that have strong innate predispositions to be shaped by certain kinds of stimuli, such as the circuits for filial imprinting in birds and mammals and song learning in certain songbirds (Konishi, 1985; Hess, 1973). These circuits learn to respond to a particular stimulus (stimuli that identify the parent for filial imprinting or the song of a conspecific for song learning) and once the circuit acquires selectivity for that stimulus, subsequent experience has little or no effect.

A mechanism responsible for ending a sensitive period has not been demonstrated yet for any circuit. In the primary visual cortex, where the mechanisms have been studied in greatest detail, numerous factors correlate with the loss of plasticity in layer IV after the critical period (Berardi, Pizzorusso, & Maffei, 2000; Katz & Shatz, 1996; Fox & Zahs, 1994). If fundamental changes in connectivity patterns depend upon axonal or dendritic growth, the loss of any of the various mechanisms that enable neurite outgrowth would end a sensitive period (Lein & Shatz, 2001). If the fundamental changes require synapse formation or elimination, then the loss of key mechanisms that support these processes would end the sensitive period (Huberman & McAllister, 2002; Katz & Shatz, 1996; Fox & Zahs, 1994), and if the fundamental changes rely on structural stabilization of selected synapses by a particular CAM (Ehlers, 2003; Si et al., 2003; Kandel, 2001; Benson et al., 2000; Tanaka et al., 2000),

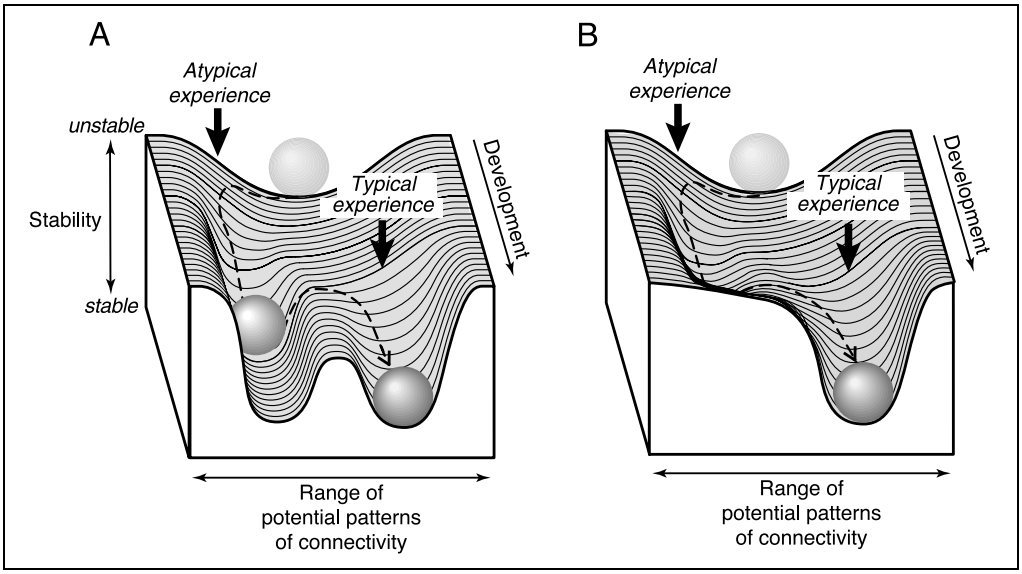

Figure 4. Stability landscape metaphor for the effects of atypical experience followed by restored, typical experience on a neural circuit during a sensitive period (see caption for Figure 3 for explanation of symbols). (A) Some circuits are capable of acquiring multiple low points in the stability landscape. Initial experience (atypical or first experience) instructs and strengthens one pattern of connectivity. A change in experience due, for example, to a change in the environment or to remediation of dysfunction (typical or second experience), causes the circuit to acquire a second stable pattern of connectivity. In some circuits, two or more stable patterns can coexist. After the sensitive period ends, this landscape allows the circuit to adopt either pattern of connectivity (move between low points in the landscape). Examples include the representations of auditory space cues in the barn owl, song learning in species of songbirds capable of learning multiple songs, and language learning in humans. (B) Some circuits can contain only a single stable pattern of connectivity. For these circuits, the stabilization of the second pattern (typical or second experience) involves the destabilization of the first pattern (atypical or first experience). Examples include thalamic projections to layer IV in the primary visual cortex, filial imprinting, and song learning in species of songbirds capable of memorizing only a single song.

the loss of the capacity to produce this molecule would end the sensitive period.

A host of mechanisms that impede changes in connectivity may also contribute to ending a sensitive period. Examples include a dramatic increase in the effectiveness of inhibitory circuitry (Zheng & Knudsen, 2001; Bear & Kirkwood, 1993), the myelination of axons (Keirstead, Hasan, Muir, & Steeves, 1992; Sirevaag & Greenough, 1987), the appearance of molecules that inhibit neurite outgrowth (Lee, Strittmatter, & Sah, 2003), and the stabilization of synapses by glia, extracellular matrix or proteoglycans (Ullian, Christopherson, & Barres, in press; Berardi et al., 2000). The capacity of experience to induce fundamental circuit changes could also be lost due to factors such as an age-dependent decrease in arousal or attention, a decrease in the release of neuromodulators, or a decrease in the responsiveness of neurons to these neuromodulators.

The various mechanisms listed above are not mutually exclusive and may well act in concert to restrict plasticity after the end of a sensitive period. Moreover, many of them could be triggered by repeated, strong activation of postsynaptic neurons in a circuit and, therefore, could contribute to a rapid closure of a sensitive period following appropriate experience. They could also arise gradually as a function of age or developmental stage.

A number of sensitive periods seem to end as animals approach sexual maturity, for example, heightened plasticity in the sound localization pathway in barn owls, song learning in some songbirds, and certain aspects of language learning in humans decline as juveniles approach adulthood (Newport et al., 2001; Knudsen, 1999; Immelmann, 1972). In songbirds, steroid hormones are known to exert a wide range of direct and indirect effects on neurons in the song pathway (White, Livingston, & Mooney, 1999; Bottjer & Arnold, 1997) that could stabilize connectivity in these circuits, making them resistant to further change by experience.

Absence of Relevant Stimulation Increases the Duration of Sensitive Periods

Under severely abnormal conditions, an individual may never be exposed to stimuli that are adequate to shape the innate properties of a neural circuit. Such complete absence of relevant stimulation prolongs the sensitive period. For example, juvenile songbirds that are kept in acoustic isolation, and are thereby prevented from hearing the songs of other birds, remain capable of memorizing the song of their species much later into development than birds that hear and memorize an abnormal song (Doupe & Kuhl, 1999). Analogously, in kittens that are reared in total darkness, layer IV of the primary visual cortex remains capable of a shift in its ocular dominance representation much later into development than in kittens reared in the light with one or both eyelids sutured closed (Mower, Caplan, Christen, & Duffy, 1985). In both of these systems, complete deprivation delays the closure of a critical period. Apparently, absence of relevant stimulation prevents the circuit from

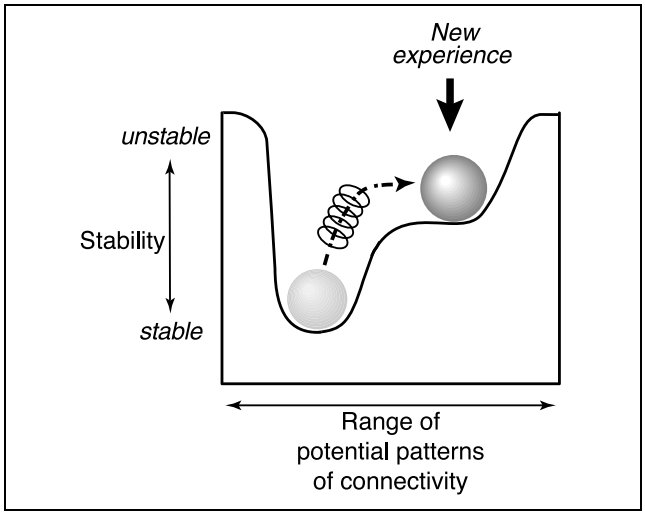

Figure 5. After a sensitive period has ended, attention, arousal, and/or reward, when coupled with new experience (downward arrow), can provide the energy needed (spring) to enable a circuit to acquire a less stable pattern of connectivity (dashed arrow), as long as the sensitive period is not a critical period (see Figure 6). Extra energy must continue to be expended in order to maintain this less stable pattern of connectivity in the circuit. When experience has caused an atypical pattern of connectivity to become the most stable (as shown), then an innately preferred pattern of connectivity (shoulder on the right of the landscape) requires the least additional energy to maintain, because innate factors usually help to stabilize this pattern.

ever being activated powerfully and, therefore, prevents the cellular and molecular transitions, discussed previously, that strengthen and consolidate synapses.

Even with complete deprivation, however, sensitive periods eventually end as a result of the progress of development. Under these conditions, circuits acquire highly abnormal patterns of connectivity and are unable mechanistically (the range of the landscape shrinks) or energetically (the slope of the landscape becomes too steep) to acquire a typical pattern of connectivity (Figure 6). In the case of songbirds that have never heard song throughout a critical period, adults sing highly abnormal (''isolate'') songs (Konishi, 1985; Marler, 1970b); in the case of primates or birds that have been deprived of interactions with an attentive primary car giver, they never respond appropriately to social signals offered by members of their own species (Thompson, 1999; Hess, 1973; Scott, 1962); in the case of humans who do not experience language during juvenile life, they become unable to acquire and use the principles of language (Newport, 1990; Curtis, 1977; Lenneberg, 1967).

From a clinical perspective, complete deprivation provides a means to prolong a critical period, thereby extending the time window when remediation of a disability or physical defect may still allow normal brain development. The danger, however, is that deprivation can lead to the consolidation of highly abnormal circuit connectivity. The highly abnormal patterns of connectivity that can arise from deprivation may result from homeostatic mechanisms, intrinsic to neurons and circuits, which attempt to maintain a minimal level of impulse activity in developing neural circuits. Under conditions of deprivation, a circuit is never activated strongly by experience. In response, homeostatic mechanisms cause the strength of inhibition in the circuit to decrease (Morales, Choi & Kirkwood, 2002), which increases the circuit's excitability. At the same time, other homeostatic mechanisms within excitatory neurons increase their excitability and sensitivity to synaptic input (Zhang & Linden, 2003; Turrigiano & Nelson, 2000). Consequently, the neurons begin to respond to abnormal patterns of input that otherwise would have been too weak to drive the circuit (the flanks in the stability landscape sink; Figure 7). If the circuit continues to respond to this input, the active connections, which previously were weak, begin to strengthen and

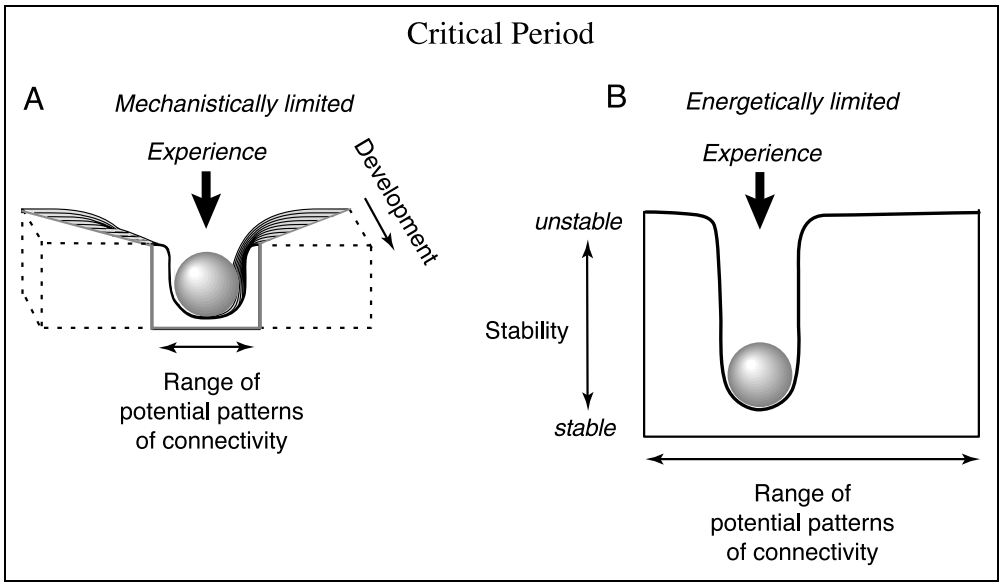

Figure 6. Stability landscape metaphors for critical periods. Experience during a critical period causes the pattern of connectivity to become irreversibly committed to the instructed pattern. (A) Mechanistically limited. Alternative patterns of connectivity no longer exist. (B) Energetically limited. Alternative patterns of connectivity cannot be maintained due to energetic constraints imposed by the effects of experience.

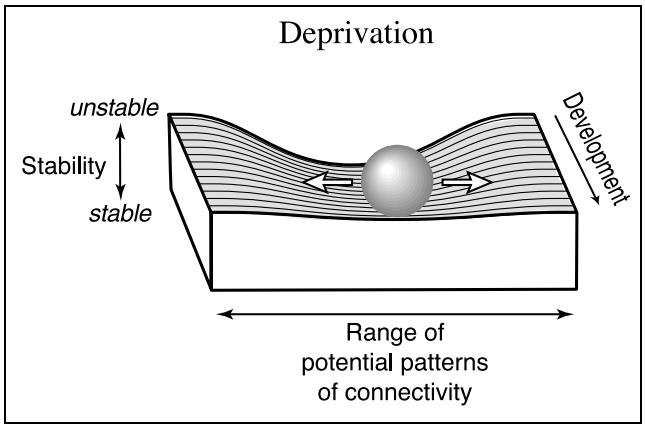

Figure 7. Absence of relevant stimulation causes a flattening of a circuit's stability landscape. Complete deprivation prevents the occurrence of the intense impulse activity that a circuit needs to drive changes in the landscape. Inadequate activation of a circuit causes homeostatic mechanisms to increase the excitability of the circuit and to diminish the normal advantage of the innately preferred pattern of connectivity, making the circuit vulnerable (horizontal arrows) to acquiring a highly abnormal pattern of connectivity.

stabilize. As the connections strengthen, homeostatic mechanisms now decrease the sensitivity of the neurons and, therefore, decrease their responsiveness to the unused normal inputs, and the circuit's connectivity consolidates an atypical pattern. If a critical period ends, the circuit is now committed to processing this abnormal information and/or processing information in an abnormal fashion.

Critical Periods for Circuits Versus Behavior

Behavioral analysis can demonstrate the existence of critical periods in the development of the brain. However, behavioral analysis tends to underestimate critical periods. The reason is that, in the hierarchies of circuits that produce complex behaviors, information is processed in series of circuits that operate in parallel. Circuits at higher levels in a hierarchy that remain plastic tend to obscure irreversible changes in circuits at lower levels (Trachtenberg, Trepel, & Stryker, 2000; Daw, Fox, Sato, & Czepita, 1992; Jones, Spear & Tong, 1984) as the higher level circuits are able to make adjustments that partially compensate for abnormal processing at lower levels. Thus, behavioral performance may improve with subsequent experience, even though circuits at some levels in a pathway have become irreversibly committed to processing information abnormally.

In addition, the parallel organization of information processing in the brain means that similar information can be derived from alternative pathways. For example, children who do not develop stereoscopic depth perception due to early strabismus may still acquire excellent depth perception using a variety of other cues. Only by testing specifically for stereoscopic vision is the deficit apparent (Jampolsky, 1978). Thus, because of the brain's capacity to tap alternative processing streams, behavioral performance may improve even though certain neural circuits have been irreversibly altered by experience. Again, irreversible changes in a neural circuit do not necessarily translate into irreversible changes in a complex behavior.

Because behaviors, such as language and social skills, result from the interactions of multiple hierarchies of neural circuits, each with its own developmental regulation, attempts to identify critical periods based on behavioral observations of different kinds or measured under different conditions are likely to lead to conflicting conclusions. A good example is the debate about critical periods in human language development (Newport et al., 2001; Doupe & Kuhl, 1999; Flege & Yeni-Komshian, 1999). Although it is convenient to talk about ''the critical period for language,'' this short-hand is far too simplistic and can lead to apparent contradictions. Language depends on a wide range of specialized sensory, motor, and cognitive skills that involve many neural hierarchies distributed throughout much of the forebrain. For example, the analyses of phonetics, semantics, grammar, syntax, and prosody are likely to be accomplished by distinct hierarchies of neural circuits. The functional properties of each of these hierarchies are shaped by experience with language. Whereas the hierarchy that underlies semantic analysis remains fully plastic throughout life, the hierarchy that underlies phonetic analysis contains neural circuits that pass through sensitive periods. The hierarchies that underlie the analysis of grammar and syntax also appear to contain circuits that are subject to sensitive periods (Newport et al., 2001; Weber-Fox & Neville, 1996; Neville, Mills, & Lawson, 1992). Thus, language development involves multiple sensitive periods that affect certain, but not other, aspects of this complex behavior.

To minimize contradictions in the interpretation of behavioral observations, it is essential to analyze behavior into elementary components that reflect, as closely as possible, the specific levels of neural processing that are shaped by experience. A similar principle holds true when characterizing critical periods in terms of brain physiology: Because critical periods act at the level of specific neural circuits, to avoid apparent contradictions it is essential to analyze a critical period in the circuit in which it occurs. For example, the critical period for ocular dominance representation in the visual cortex was analyzed initially by combining data recorded from all layers of the cortex (Hubel & Wiesel, 1965). Because the cortex comprises several levels of processing in the visual pathway, combining data across cortical layers led to differing characterizations of the critical period. We now understand that the critical period for ocular representation reflects predominantly the critical period for thalamic input to layer IV (Trachtenberg & Stryker, 2001; Antonini et al., 1998; Daw et al., 1992). Plasticity in

other layers persists much later into development, allowing them to respond to binocular experience by altering their connections in a way that partially compensates for an abnormal ocular representation in layer IV. With this realization, the search for mechanisms underlying the critical period for ocular dominance representation in the visual system has focused on layer IV of the primary visual cortex.

Can Critical Periods Be Re-Opened?

The question of whether a critical period can be reopened is of particular interest from a therapeutic standpoint. By definition, the effects of critical period experience on the performance of a circuit are permanent. That is, they persist for the lifetime of the animal. Changes in the environment or remediation of dysfunction that restores normal input to a circuit does not enable experience to restore normal function to that circuit after the critical period has ended. Although the mechanisms activated by attention and arousal have been shown to enable large changes in the connectivity of adult circuits (Kilgard & Merzenich, 1998), it is unlikely that the changes that have been induced involve the same range of cellular and molecular changes as those that occur during critical periods (Feldman, 2003; Francis, Diorio, Plotsky, & Meaney, 2002; Zhang, Bao, & Merzenich, 2001).

For normal experience to restore completely normal function after a critical period has ended, the factors that impose the energetic or mechanistic constraints on a circuit (Figure 6) must become, once again, modifiable by experience. Numerous factors probably contribute to the loss of plasticity after the critical period in most circuits, as in the primary visual cortex (Berardi et al., 2000; Katz & Shatz, 1996; Fox & Zahs, 1994). If so, then to reinstate the full capacity for plasticity that exists during a critical period would require the reactivation of an entire array of early plasticity mechanisms as well as the inactivation of the many factors that impede plasticity in mature circuits (Lee et al., 2003). In some circuits, however, a critical period may be controlled by one or a few key factors. This possibility is suggested, for example, for the circuits responsible for song learning in songbirds, in which plasticity is limited to a critical period in some species but not in other closely related species (Konishi, 1985). In such cases, reinstatement of critical period plasticity in adults may be feasible.

Although the full capacity for plasticity that exists during a critical period may not be able to be reestablished, it is possible to increase the plasticity of mature circuits dramatically through various experimental manipulations. For example, ocular dominance plasticity in the visual cortex has been increased in adult cats or rats by injecting fetal astrocytes, enzymatically degrading extracellular matrix proteoglycans, or by raising levels of BDNF, NE, or ACh (Huberman & McAllister, 2002; Pizzorusso et al., 2002; Lein & Shatz, 2001; Berardi et al., 2000; Greuel, Luhmann, & Singer, 1988; Bear & Singer, 1986). Another technique that increases functional plasticity in the cortex is electrical stimulation of the nucleus basalis, the source of the neuromodulator ACh in the forebrain. The nucleus basalis becomes active when individuals are aroused and attend to particular stimuli. Electrical stimulation of this nucleus while exposing adult rats to a particular sound frequency, for example, dramatically increases the representation of that frequency in the primary auditory cortex (Kilgard & Merzenich, 1998).

Interventions like these, when combined with appropriate experience and applied to the correct circuits, may have the potential to restore normal function to a circuit even though the critical period may not be able to be reopened. With increased understanding of (1) the fundamental components of behavior that are affected by critical periods, (2) the circuits in the underlying pathways where plasticity would enable the recovery of typical behavior, and (3) the mechanisms that control and limit plasticity in these circuits, acquisition of typical behavior in adult animals that have experienced atypical or deprived conditions during critical periods may be possible.

Concluding Remarks

The central nervous system requires instruction from experience during sensitive periods in order to develop properly. Sensitive periods in the development of complex behaviors (such as social behavior and language) reflect sensitive periods in the development of the neural circuits that underlie these behaviors. The effects of experience operate within the constraints imposed by genetics on a circuit. These effects include the capacity to guide changes in brain architecture and biochemistry and, in some circuits, to trigger and/or end sensitive period plasticity.

During a sensitive period, particular kinds of experience shape the connectivity of a circuit in fundamental ways, causing certain patterns of connectivity to become energetically preferred or mechanistically specified. Although plasticity persists after the end of a sensitive period, this residual plasticity alters a circuit's connectivity within the constraints that were established as a result of experience during the sensitive period.

Critical periods are a subset of sensitive periods for which the instructive influence of experience is essential for typical circuit performance and the effects of experience on performance are irreversible. A clinical issue that is of central importance is: for an animal that suffers from the adverse effects of chronic atypical experience throughout a critical period, can the critical period be reopened to enable the restoration of typical behavior at a later stage? Experimental evidence indicates that for most circuits a host of molecular and cellular changes

contribute to the reduction in circuit plasticity after a critical period has ended. It is unlikely that all of these changes could be reversed at a later stage in such a way that the full capacity for plasticity, that existed during the critical period, is reinstated. However, experiments have demonstrated that certain molecular and cellular changes can be reversed, and several interventions have been found that dramatically increase plasticity in adult circuits that are shaped by early experience. In principle then, if we are able to identify precisely which circuits are responsible for the components of behavior that have been affected adversely by atypical experience during a critical period, and we learn to manipulate the capacity for plasticity of key aspects of these circuits in adults, it may be possible to restore normal function to those circuits and, therefore, to restore typical behavior to individuals after the end of a critical period.

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