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CRITICAL PERIOD REGULATION

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■ **Abstract** Neuronal circuits are shaped by experience during critical periods of early postnatal life. The ability to control the timing, duration, and closure of these heightened levels of brain plasticity has recently become experimentally accessible, especially in the developing visual system. This review summarizes our current understanding of known critical periods across several systems and species. It delineates a number of emerging principles: functional competition between inputs, role for electrical activity, structural consolidation, regulation by experience (not simply age), special role for inhibition in the CNS, potent influence of attention and motivation, unique timing and duration, as well as use of distinct molecular mechanisms across brain regions and the potential for reactivation in adulthood. A deeper understanding of critical periods will open new avenues to "nurture the brain"—from international efforts to link brain science and education to improving recovery from injury and devising new strategies for therapy and lifelong learning.

INTRODUCTION

Critical periods in development have been recognized by biologists for nearly a century. Chemicals applied at particular times to a developing embryo produce specific malformations, with the most rapidly growing tissues being most sensitive to the change in conditions (Stockard 1921). Stimulated by the external world, the postnatal nervous system responds further to natural sensory experience. Time windows exist when brain circuits that subserve a given function are particularly receptive to acquiring certain kinds of information or even need that instructive signal for their continued normal development. Beginning with the behavioral observations of Konrad Lorenz (1958), this concept has profoundly influenced not only biologists but also psychologists such as Freud, philosophers, physicians, policy makers, parents, and educators. The mechanisms, power, and inherent hazards presented by these special phases in brain development carry a social impact far beyond basic neuroscience.

Although critical periods have been well documented for sensory systems, one concern is that the concept is being used too broadly for too many types of learning,

without rigorous demonstration that such windows exist. The purpose of this review is to identify key principles emerging from the study and regulation of known critical periods (Table 1). It should be stated at the outset that transiently heightened levels of brain plasticity after birth do not preclude the possibility for lifelong learning. A critical period is an extreme form of a more general sensitivity, when neuronal properties are particularly susceptible to modification by experience. Through a deeper understanding of these exceptional developmental stages, we hope to gain insight into the process, as well as to design better strategies by which the older brain can learn.

This review presents evidence from each sensory modality, as well as higher order, multimodal brain systems (Table 1). Although, to date, the depth of study in each area varies widely, the seeds of a general theory are evident. Nine facets of critical periods can now be distinguished and guide the discussions to follow:

First is the functional competition between inputs. Genetic specification admirably determines much of the basic structure and function of the nervous system. But, the environment and physical characteristics of the individual into which the brain is born cannot be encoded in the genome. A process by which neurons select their permanent repertoire of inputs (or maps) from a wider array of possibilities is required for proper brain function. Indeed, the tailoring of neuronal circuits custom fitted to each individual is the main purpose of critical periods.

Second is the particular role for electrical activity. Neurons communicate by the transmission of nerve impulses as a reflection of external stimuli or spontaneous, internal states. The various inputs from which the nervous system can choose during the critical period are ultimately encoded in the discharge of action potentials. Most cellular models of plasticity are now based on the ability to potentiate or depress transmission at individual synapses through their pattern of activation. Whether competing spike trains actually instruct who the "winner" shall be, or merely "permit" other processes to adjudicate, is a fundamental question that must be addressed for each system.

Third is a structural consolidation of selected pathways. Early experience specifies a neural commitment to one of a number of possible patterns of connectivity. The magnitude and permanence of anatomical changes—from dendritic spine motility to large-scale rewiring—distinguish developmental plasticity from adult learning. A critical period may be defined in systems where structural modification becomes essentially irreversible beyond a certain age. Continued growth maintains sensitivity to environmental influence throughout life.

Fourth is the regulation of critical period onset and duration not simply by age, but rather by experience. If appropriate neural activation is not provided at all, then developing circuits remain in a waiting state until such input is available. Alternatively, enriched environments may prolong plasticity. In other words, the critical period is itself use-dependent. Understanding the cellular mechanism of this effect will greatly influence strategies for lifelong learning.

Fifth is the unique timing and duration of critical periods across systems. Not all brain regions develop with the same time course. There are both rostro-caudal

TABLE 1 Known critical periods and molecular mechanisms across systems (see text for references)

System	Age	Confirmed regulators	Delay[a]	Species[b]
Neuromuscular junction	<P12	ACh	+	mouse
Climbing fibers (CBL)	P15–16	NMDA, mGluR1, G_q, PLCβ, PKCγ	nd	mouse
LGN layers	<P10	Retinal ACh, cAMP; MAO-A, NO, MHC-I, CREB	nd	mouse, ferret, cat
Ocular dominance	P3 weeks-months	GABA, NMDA, PKA, ERK, CaMKII, CREB, BDNF, tPA, protein synthesis, NE, ACh	+	cat, rat, mouse, ferret
Orientation bias	<P28	NR1, NR2A, PSD95	+	cat, mouse
Whisker-barrel map formation	<P7	NR1, MAOA, $5HT_{1B}$, cAMP mGluR5, PLCβ, FGF8	nd	mouse
Whisker RF tuning	P14–16		nd	rat
Tonotopic map (cortex)	P16–50	ACh	+	rat
Absolute pitch	<7 years		nd	human
Taste/olfaction	none	GABA, mGluR2, NO, neurogenesis	+	mouse
Imprinting	14–42 hrs	Catecholamines	+	chick
Stress/anxiety	<P21	Hormones, $5HT_{1A}$	nd	rat, mouse
Slow-wave sleep	P40–60	NMDA	+	cat, mouse
Sound localization	<P200	GABA, NMDA	+	barn owl
Birdsong	<P100	GABA, hormones, neurogenesis	+	zebrafinch
Human language	0–12 years		nd	human

[a]Potential for critical period delay by altered experience. +, yes; nd, not determined.

[b]Primary species for elucidation of molecular mechanism.

gradients of maturation across modalities and hierarchical levels of processing within a given pathway. Intuitively, the critical period for one stage cannot begin unless its input from a preceding stage is ready. Cascades of critical periods and their cumulative sequence at different ages and levels of processing shape each brain function as the relevant neural pathways develop to a point where they can support plasticity.

Sixth is a diversity of molecular mechanisms across systems or even at various stages along the same pathway. Simply being regulated by neuronal activity in the neonatal brain, or contributing to popular plasticity models does not automatically establish a molecule's role in the critical period. The detailed mediators of plasticity will vary for individual connections and impede the search for canonical plasticity factors (Table 1). Moreover, the initial formation of maps during ontogeny may use molecules differently from the neuronal remodeling of established circuits.

Seventh is a particular role for inhibition in the central nervous system (CNS). Apart from certain rare instances where competing inputs directly impinge upon the same identifiable target cell, most neuronal circuits in the brain are intricately interconnected. In these tangled forests, inhibitory interneurons are rapidly emerging as a vital arbiter of neuronal plasticity (Hensch & Fagiolini 2003). Indeed, they may generally contribute to the onset, offset, or expression of critical periods throughout the brain.

Eighth is the potent influence of attention and motivation. As any teacher can attest, attention in a classroom setting is perhaps the most critical determinant of whether learning succeeds; so too at the neuronal level, where arousal state is translated into the level of aminergic and cholinergic transmission. These modulatory systems may be more actively engaged in the infant brain, allowing the seemingly effortless plasticity not seen in adults. Rekindling attentional mechanisms offers a key to critical period regulation.

Finally, it is the potential for reactivation in adulthood that confirms the very existence of critical periods. Depending on whether neuronal growth is rigidly limited to a critical period, different strategies for therapy, recovery from injury, and continuing education will apply to distinct brain regions.

PRIMARY MODALITIES

Motor Systems

Both in the periphery and in the brain, appropriate critical period development is prerequisite to proper motor control and coordinated movement later in life. Competition among multiple motor axons for a single target muscle fiber eliminates synapses at the neonatal neuromuscular junction (Sanes & Lichtman 1999a). The accessibility of this classic preparation makes it the prototypical synaptic model of critical period plasticity in the nervous system. Direct visualization of the

interaction and removal of supernumerary motor axons during the first two postnatal weeks in rodents outlines a progression of synaptic events from reinforcing functional efficacy to eventually consolidating its structure (Lichtman & Colman 2000, Walsh & Lichtman 2003). The period of refinement is slowed or accelerated by the chronic blockade or enhancement of neuromuscular activity, respectively (see Thompson 1985).

In contrast, junctions initially form in the total absence of neurotransmission, as seen in mice lacking the acetylcholine-synthesizing enzyme, choline acetyltransferase (ChAT) (Brandon et al. 2003). Conditional deletion of ChAT in a small subset of axons elegantly demonstrates that better excitation of the target muscle fiber biases the competition in favor of the genetically enhanced inputs (Buffelli et al. 2003). All synapses at which branches of the same two axons compete proceed to the same outcome (Kasthuri & Lichtman 2003). More extensively branched motor units are at a competitive disadvantage, as their larger size dilutes the limited resources at individual terminals. Moreover, a similar stage of synapse elimination is reached concurrently (with the same "winner" at each site), indicating that the pace of rearrangement is highly stereotyped once initiated.

Competition thus occurs globally rather than locally, driven by presynaptic activity that is directly adjudicated by the postsynaptic muscle fiber. In the CNS, it is difficult to similarly isolate inputs onto individual target cells. Climbing fiber axons from the brainstem inferior olivary nucleus terminating onto cerebellar Purkinje cell bodies are one rare example. Multiple climbing fibers present at birth are pruned to a powerful one-to-one relationship over the first few weeks of life (Crepel 1982). As for the neuromuscular junction (Lichtman & Colman 2000), a growing disparity in potency of synaptic excitation precedes eventual elimination (Hashimoto & Kano 2003), with the postsynaptic cell deciding which input to retain.

Blockade of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor defines a remarkably sharp two-day (P15–16 in mice) critical period for climbing fiber refinement (Kakizawa et al. 2001). This is curious because the Purkinje cell itself is devoid of functional NMDA receptors (Farrant & Cull-Candy 1991). It is likely that NMDA receptor–mediated mossy fiber excitation of underlying granule cells and their parallel fibers provides a permissive level of tonic activation to Purkinje cells that is required for the process. Subsequently, a molecular cascade including type 1 metabotropic glutamate receptor (mGluR) activation coupled to $G_{q\alpha}$-type G proteins, phospholipase Cβ (PLCβ), and the γ-isoform of protein kinase C (PKCγ) is recruited, as revealed by the systematic analysis of poly-innervation by climbing fibers in gene-targeted mice (Hashimoto et al. 2000, Ichise et al. 2000, Kano et al. 1995).

Finally at the neocortical level, refinement is influenced by appropriate sensory feedback during early life. Trimming the whiskers on a rat's snout from birth (but not as an adult) produces a significantly smaller, contralateral motor area that evokes abnormal patterns of movement (Huntley 1997). The basis for such crossmodal effects is likely to be complex.

Visual System I: Retino-Geniculate Connections

The visual system has long been favored for developmental study because there are only two discrete inputs into the system. Proper binocular fusion and stereoscopic vision depend on the correct processing of information from the two eyes (Daw 1995, Wiesel 1982). Multiple critical periods have been defined based on the timing when activity deprivation is effective in disrupting binocular representations along the pathway. There is a logical sequence of critical periods, ending earlier for functions dealt with at lower levels of the system.

The convergence of right- and left-eye input begins in the dorsal thalamus of mammals. Rather than crossing the optic chiasm, ventro-temporal ganglion cell axons are directed ipsilaterally by early expression of the Zic2 transcription factor in the retina (Herrera et al. 2003). Initially, overlapping nasal axons from the opposite eye gradually segregate within the lateral geniculate nucleus (LGN), resulting in the formation of layers or eye-specific domains (Wong 1999). Spontaneous neuronal discharge underlies this process, which occurs well before eye-opening and visual experience. In particular, rhythmic bursts of synchronized activity propagate across the neonatal retina of ferrets and rodents. Blockade of these waves driven initially by cholinergic amacrine cells—either by antagonist injection or targeted disruption of nicotinic receptor subunits—prevents lamina formation and defines the first critical period in the visual stream (Penn et al. 1998, Rossi et al. 2001). Despite the absence of layers, patchy segregation still occurs (Huberman et al. 2002, Muir-Robinson et al. 2002), demonstrating a distinct process that may reflect additional mechanisms such as later glutamatergic waves in the retina (Wong et al. 2000).

The segregation of input is clearly competitive and instructed by retinal activity, as seen when binocular innervation is forced in the tectum (Constantine-Paton & Law 1978, Ruthazer et al. 2003). Increasing the frequency of retinal waves in one eye by elevating cyclic AMP expands that eye's representation in the LGN at the expense of the normally active input (Stellwagen & Shatz 2002). At these monosynaptic connections from ganglion cells, it is reasonable to expect mechanisms of synaptic long-term potentiation (LTP) to be directly engaged (Sanes & Lichtman 1999b). Signaling by major histocompatibility complex (MHC)–related molecules is important (Huh et al. 2000). These may interact with LTP mechanisms in more complex ways, such as retrograde signaling or stimulus frequency dependence (Boulanger et al. 2001), or through unrelated processes, such as neurite outgrowth and adhesion, that remain to be clarified.

The cyclic AMP response element binding protein (CREB) is briefly upregulated in the LGN during the critical period for layer formation in mice. Gene-targeted disruption of CREB impairs segregation (Pham et al. 2001). In this context, monoamines play an interesting transient role in the visual thalamus unrelated to their later function in arousal. Excess serotonin (5-HT) in monoamine oxidase (MAO-A) knockout mice prevents segregation (Upton et al. 1999). Postysnaptic CREB levels could then be adjusted indirectly through 5-HT receptors.

After the eyes open, another round of synapse elimination reduces down to a powerful few multiple ganglion cell contacts onto each thalamic relay cell (Chen & Regehr 2000), similar to the neuromuscular junction or climbing fiber system. This pruning can contribute to the establishment of physiological properties such as ON- and OFF-center responses (Wong 1999). The LGN sublaminae into which these cells are typically sorted also fail to form when retinal activity is blocked earlier. Here, NMDA receptors play a role (Hahm et al. 1991), as does nitric oxide (Cramer et al. 1996).

Visual System II: Cortex

Over forty years ago, Wiesel & Hubel (1963) first described the loss of responsiveness to an eye deprived of vision in the primary visual cortex of kittens, providing the premier physiological model of critical period plasticity. Rapid functional effects of monocular deprivation (MD) are soon accompanied by anatomical rewiring of horizontal connections and thalamic afferents (Antonini & Stryker 1993, Trachtenberg & Stryker 2001). Altogether, these processes follow competitive interactions between the two eyes for the control of cortical territory (Daw 1995, Wiesel 1982). Although the present review focuses on plasticity due to abnormal vision during the critical period, note that the synaptic rearrangement underlying the initial formation of ocular dominance columns has recently been proposed to be genetically predetermined (Crowley & Katz 2002). To date, no such eye-specific molecules have been found. Instead shadows cast by individual retinal blood vessels or early manipulation of intracortical spread of activity are reflected in columnar architecture consistent with a competitive segregation process (Adams & Horton 2002, Hensch & Stryker 2004).

If both eyes are sutured during the critical period, no imbalance of input occurs, and the relative ability to drive visual responses is unchanged. Conversely, strabismus causes the two eyes never to see the same visual field, leading to an instructive decorrelation of retinal activity and loss of binocular responses. When the cortical target is silenced by inhibitory $GABA_A$ receptor agonists or blockade of excitatory NMDA receptors (Bear et al. 1990, Hata & Stryker 1994, Hata et al. 1999), the more active afferents serving the open eye are paradoxically instructed to retract, allowing the better-matched, deprived-eye connections to remain.

As a direct consequence of shifts in cortical ocular dominance, the weakened input becomes amblyopic: Visual acuity is strongly reduced and contrast sensitivity blunted even when no physical damage to the retina exists (Daw 1995, 1998; Dews & Wiesel 1970; Maurer et al. 1999). Importantly, the loss of behavioral visual acuity occurs only during a transient developmental critical period reflecting that measured by single-unit electrophysiology (Hubel & Wiesel 1970, Prusky & Douglas 2003). The rules of activity-dependent competition and timing have been confirmed across a variety of species (Berardi et al. 2000, Gordon & Stryker 1996). Interestingly, critical period duration is tightly correlated with average life expectancy. In all cases, plasticity gradually peters out rather than ceasing abruptly.

In rodents and cats, plasticity is low at eye opening, peaks around four weeks of age, and declines over several weeks to months (Daw 1995, Fagiolini et al. 1994, Gordon & Stryker 1996, Hubel & Wiesel 1970). In humans, amblyopia is set by the age of eight (see Daw 1995). Notably, the critical period is not a simple, age-dependent maturational process but is rather a series of events itself controlled in a use-dependent manner. Animals reared in complete darkness from birth express a delayed onset profile with plasticity persisting into adulthood (Fagiolini et al. 1994, Iwai et al. 2003, Mower 1991).

It is attractive to think of the loss of deprived-eye input as a long-term depression (LTD) or gain of open-eye input as LTP (see Heynen et al. 2003). But, manipulations based on advancing knowledge of their molecular mechanism have frustratingly failed to influence plasticity in vivo (Daw 2003, Bartoletti et al. 2002, Hensch 2003, Renger et al. 2002, Shimegi et al. 2003). For instance, endogenous brain-derived neurotrophic factor (BDNF) prevents LTD in the visual cortex (Jiang et al. 2003) but does not block the loss of deprived-eye input in transgenic mice overexpressing it (Huang et al. 1999). Conversely, early LTP and LTD that remain in the presence of protein synthesis inhibitors are inadequate to sustain shifts of ocular dominance in vivo (Frey et al. 1993, Taha & Stryker 2002). Such mechanistic dissociations between plasticity in vitro and in vivo have also been reported for hippocampal learning (Martin et al. 2000, Sanes & Lichtman 1999b). A role for LTP/LTD models is obviously not ruled out but rather placed at a secondary stage in the critical period process.

Excessive emphasis on homosynaptic mechanism provides incomplete insight into the competitive nature of ocular dominance plasticity (Miller 1996) and can be misleading for two reasons. First, it neglects the anatomical consequences of MD. Second, unlike motor axons competing for a single target muscle fiber, sensory input to the neocortex must be integrated by complex local circuit interactions in vivo. By treating the visual cortex as a monosynaptic connection from the eyes, one loses sight of its physiological function, namely vision. Although measures of subthreshold synaptic activity are residually sensitive to sensory manipulation in older animals (Sawtell et al. 2003), it is the ability to fire cortical action potentials through either eye that accurately reflects the visual capabilities of the system and defines the critical period (Daw 1995, Dews & Wiesel 1970, Prusky & Douglas 2003).

An unbiased perspective on intrinsic local circuit behavior has proven more fruitful (Hensch & Fagiolini 2003). Molecular cascades set in motion by a unique excitatory-inhibitory balance may lead to a structural consolidation that eventually terminates the critical period. Pharmacological attempts to disrupt the balance grossly hyperexcite or shut down the cortex (Hata & Stryker 1994, Ramoa et al. 1988, Shaw & Cynader 1984, Videen et al. 1986), yielding little insight into the normal function of local circuits during plasticity. Instead, by taking advantage of gene-targeting technology, gentle titration of endogenous GABA release or subtle prolongation of glutamatergic currents yields a similar shift of balance in favor of excitation that disrupts ocular dominance plasticity in the same way.

Mice carrying a deletion of the 65-kDa isoform of glutamic acid decarboxylase (GAD65), found primarily in inhibitory terminals (Soghomonian & Martin 1998), exhibit a significant reduction of stimulated GABA release and show no shift in responsiveness toward the open eye following brief MD (Hensch et al. 1998). Accentuated excitation, by preventing the natural developmental switch of NMDA receptor subunit composition, also weakens the response to MD (Fagiolini et al. 2003). Composed of a principal NR1 subunit and distinct modulatory NR2 partners, NMDA current decay is truncated by the insertion of NR2A subunits after eye opening (Nase et al. 1999). Synaptic NMDA responses remain prolonged in the absence of NR2A, yielding increased charge transfer (Fagiolini et al. 2003). Nevertheless, the critical period ends normally, contrary to expectation from an LTP view that predicts greater plasticity when NMDA receptor function is enhanced (Fox 1995, Tang et al. 1999).

Restoration of plasticity to both GAD65 and NR2A knockout mice by acute infusion of benzodiazepine agonists demonstrates a decisive role for excitatory-inhibitory balance (Fagiolini et al. 2003, Hensch et al. 1998). Drugs like diazepam selectively increase the open probability and channel conductance of a limited subset of $GABA_A$ receptors in a use-dependent manner, since they are inert in the absence of synaptic GABA release (Cherubini & Conti 2001, Sieghart 1995). Benzodiazepine binding sites are not associated with thalamocortical axons or other subcortical inputs (Shaw et al. 1987), making detailed local circuit analysis possible (Fagiolini et al. 2004).

A competitive outcome of MD can readily be understood by strategically placed inhibition. Specific spike timing–dependent windows for synaptic plasticity rely upon physiologically realistic, millisecond-scale changes in the temporal order of pre- and postsynaptic action potentials (Bi & Poo 2001, Froemke & Dan 2002). Inhibitory regulation of spike-timing could then instruct the direction of plasticity (Song et al. 2000). In contrast, classical models of LTP induced by changes in mean firing rate are indiscriminately blocked by benzodiazepines (Trepel & Racine 2000). Among the vast diversity of GABAergic interneurons in neocortex, parvalbumin-containing cells target the axon initial segment and soma (DeFelipe 1997, Somogyi et al. 1998), where they can control spike initiation (Chandelier cells) or back-propagation (basket cells), respectively, required for synaptic plasticity in the dendritic arbor.

Maturation of parvalbumin-positive interneurons parallels critical period onset (Del Rio et al. 1994, Gao et al. 2000), and when accelerated by transgenic overexpression, BDNF shifts the critical period earlier in time (Huang et al. 1999). Large basket cells, in particular, extend a wide, horizontal axonal arbor that can span ocular dominance columns in cat visual cortex (Buzas et al. 2001). Moreover, these electrically coupled networks of fast-spiking cells offer a system exquisitely sensitive to timing (Connors 2004, in this volume; Galaretta & Hestrin 2001). Only $GABA_A$ receptors containing the $\alpha 1$ subunit drive visual cortical plasticity and are preferentially enriched at somatic synapses opposite parvalbumin-positive large basket cell terminals (Fagiolini et al. 2004, Klausberger et al. 2002). Taken

together, specific inhibitory circuits may be ideally suited to detect and discriminate synchronized signals coming from the eyes.

Excitatory-inhibitory balance determines the neural coding of sensory input and tightly regulates prolonged spike discharge in both GAD65 and NR2A mutants. In the former, this is observed throughout life, and the critical period awaits diazepam treatment even in adulthood (Fagiolini & Hensch 2000). Dark-rearing from birth also impedes the normal maturation of inhibition and naturally delays critical period onset (Morales et al. 2002, Mower 1991), which can be prevented by brief diazepam infusion in the dark (Iwai et al. 2003). Conversely, premature ocular dominance shifts can be triggered in wild-type animals by diazepam as early as eye opening (Fagiolini & Hensch 2000, Fagiolini et al. 2004). Thus, critical period machinery lies dormant until set in motion by proper excitatory-inhibitory levels. Homeostatic scaling of synaptic input to maintain this balance observes a critical period by cortical layer in visual cortex, potentially contributing to ocular dominance plasticity in supragranular layers (Desai et al. 2002).

To fully saturate plasticity requires several days of experience (Gordon & Stryker 1996), whereas it is triggered by less than 48 h of diazepam treatment (Iwai et al. 2003). Accordingly, a cascade downstream of excitatory-inhibitory balance leading toward protracted structural consolidation is gradually being elucidated (Figure 1). Both protein synthesis and extracellular proteolysis via the tissue-type plasminogen activator (tPA)-plasmin axis are required for even brief MD to be effective (Mataga et al. 2002, Taha & Stryker 2002). These are well-positioned downstream of NMDA and $GABA_A$ receptors, calcium-calmodulin-dependent protein kinase II (CaMKII), protein kinase A (PKA), extracellular-regulated protein kinase (ERK), and CREB, which have all been found to affect ocular dominance shifts measured electrophysiologically (reviewed in Berardi et al. 2003). Ultimately, deprivation produces an age-limited increase in dendritic spine motility then rearrangement of thalamo-cortical axons (Antonini & Stryker 1993, Majewska & Sur 2003).

A role for neurotrophic factors may be found at multiple stages (Figure 1). Whereas gene-regulated overexpression promotes critical period onset (Huang et al. 1999), exogenous infusion of BDNF blocks both anatomical and physiological plasticity of excitatory connections (Hata et al. 2000, Jiang et al. 2003, Riddle et al. 1995). BDNF may first establish the proper milieu for plasticity by promoting the maturation of GABA circuits, then later participate directly in the plasticity process of neurite outgrowth or survival (Huang & Reichardt 2001, Berardi et al. 2003). For instance, an increase of proteolytic activity by tPA in visual cortex observed after a few days of MD may be triggered by BDNF in cortical neurons (Fiumelli et al. 1999, Mataga et al. 2002).

Similarly, the multifaceted actions of PKA upon both excitatory and inhibitory transmission must be considered carefully before interpreting its role in ocular dominance plasticity (Beaver et al. 2001, Heynen et al. 2003, McDonald et al. 1998). Moreover, behavioral state potently influences plasticity and can tap into the cAMP cascade (Figure 1). Brief MD produces ocular dominance shifts within

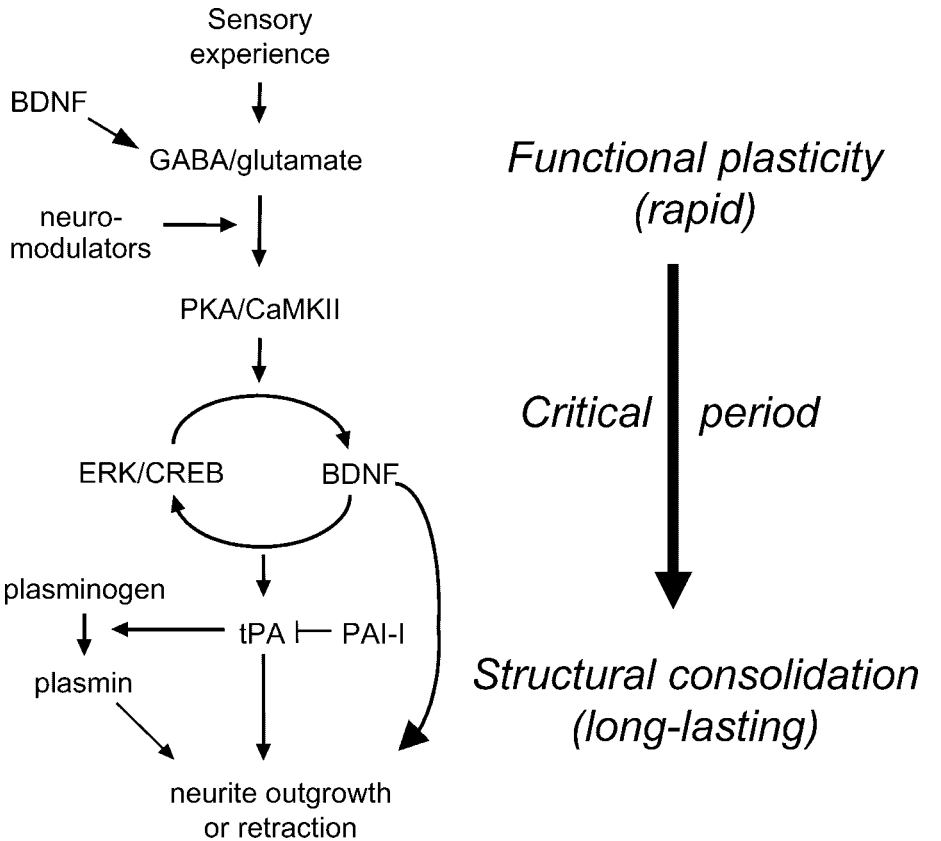

Figure 1 Identified molecular regulators underlying critical period plasticity in the primary visual cortex. A cascade of events, leading from functional excitatory-inhibitory balance to structural change, is delineated. See text for references.

two days in kittens (Mower 1991) but fails to do so under anesthesia (Imamura & Kasamatsu 1991). Conversely, interposed slow-wave sleep enhances the pace of plasticity (Frank et al. 2001). Neuromodulation lies in diffuse projections of norepinephrine and acetylcholine, whose pharmacological depletion prevents plasticity during the critical period (Bear & Singer 1986) and activation partially restores it to adults (Imamura et al. 1999, but see Beaver et al. 2001).

Sensitivity to sensory experience may ultimately disappear as the ability of neurites to navigate the extracellular matrix (ECM) is reduced. A decline in dendritic spine motility in vivo mirrors the end of the critical period in visual cortex (Grutzendler et al. 2002). Active growth inhibition by CNS myelination (Schwab & Caroni 1988) is also age-dependent in cortex (Daw 1995, Schoop et al. 1997). Conversely, injection of immature astrocytes rejuvenates adult cat visual

cortex (Muller & Best 1989), perhaps by providing a permissive substrate or otherwise creating a favorable environment for plasticity through releasable nerve growth factors (Gu et al. 1994). Taken together, such evidence indicates that the refractoriness of mature neuronal substrates to change may be "consolidated" in the extracellular milieu.

To reactivate plasticity in the visual cortex would then require drastic disruption of ECM structure. Chondroitin sulfate proteoglycans are key components that condense around neuronal somata and dendrites in the form of perineuronal nets near the end of the critical period (Celio et al. 1998). Degradation of these structures by repeated local chondroitinase injection reveals shifts of responsiveness toward the open eye following MD in adult rats (Pizzorusso et al. 2002). Intriguingly, mature, fast-spiking, parvalbumin-positive neurons are predominantly encapsulated by perineuronal nets (Hartig et al. 1999). To reopen the critical period, a resetting of its original GABAergic trigger may be needed. Cortical or bilateral retinal lesions by photocoagulation also produce enlargement and shifts of receptive field location in the adult primary visual cortex (Gilbert 1998). Rapid disruption of local excitatory-inhibitory balance may be followed by protracted outgrowth of horizontal intracortical connections over months.

Various response properties apart from ocular dominance emerge along the visual stream, and each has its own critical period. For instance, orientation and direction selectivity precede that of ocular dominance (see Daw 1995). In general, a property processed at higher levels of the system has a critical period that lasts longer than one processed at a lower level. Perceptual learning in the adult visual system can be highly specific for certain stimulus configurations (Karni & Sagi 1991), predicting changes in the responses of neurons in primary visual cortex (Gilbert 1998). However, neurons early in the processing stream fail to exhibit strong effects (Ghose et al. 2002). Extensive training on an orientation discrimination task does not alter selectivity of neurons in V1 or V2, but rather is mirrored by responses at later stages (V4) of the macaque visual cortex (Yang & Maunsell 2004). Consistent with this plasticity hierarchy, neurons in inferotemporal cortex at the highest level of the ventral stream may be substantially influenced into adult life by visual experience (see Kobatake et al. 1998). Although V1 comprises a stable representation in adults, plasticity may be progressively less constrained at subsequent cortical levels.

Finally, molecular mechanisms underlying experience-dependent plasticity of individual response properties need not overlap. Whereas the NR2A subunit and its anchoring postsynaptic density protein (PSD95) are dispensable for ocular dominance, they are essential for orientation preference to develop (Fagiolini et al. 2003). Targeted disruption of tPA or GAD65 has no influence upon the competitive segregation of retino-geniculate axons at earlier stages (Y. Tsuchimoto, A. Rebsam, S. Fujishima, M. Fagiolini, T.K. Hensch, submitted), and nitric oxide is unimportant for later ocular dominance plasticity in neocortex (Ruthazer et al. 1996). Moreover, simply because a molecule is regulated by activity does not mean it is required for plasticity, as shown for the immediate early gene *zif268*

in primary visual cortex (Mataga et al. 2001). Molecules first identified by subtractive screens in one area will need to be verified individually in other regions by restricted conditional manipulation.

Primary Auditory System

Lasting effects of early auditory experience have long been suspected (see Human Language, below), but their critical periods have only recently been defined in the primary auditory pathway (see Sound Localization). Synapse elimination during the first week of rodent life in the brainstem lateral superior olive results in a two-fold sharpening of functional topography when glycine/GABA synapses are still excitatory (Kim & Kandler 2003). A massive tonotopic map refinement is manifest later in auditory cortex between P16 and P50 in two ways (Chang & Merzenich 2003). Preference for high-frequency tones is converted into a more balanced representation from low to high values, while total cortical surface area contracts. Selective exposure to a particular frequency during this time yields a competitive overrepresentation in the final map. When no particular tone stands out in a uniformly noisy environment, then the critical period is delayed and rapidly appears even in adulthood once the noise is removed.

The functional consequence of intense auditory training is seen in the brains of musicians who are exposed to music before the age of seven. A significantly greater left hemisphere asymmetry of planum temporale activation arises in those who develop absolute pitch (Schlaug et al. 1995); an increased cortical representation of piano tones in highly skilled musicians also exists that is not seen for pure tones (Pantev et al. 1998). Similar enlargement of the cortical representation of the fingers of the left hand (except thumb) in string players, anterior corpus callosum, and cerebellar activation further reflects their unique dexterity (Elbert et al. 1995, Schlaug et al. 1995). Age of commencement of musical training is important to develop these changes.

As in visual cortex, an unexpected late developmental peak of GABA neurons (P60 in ferrets) is observed that is higher overall in auditory cortex. In particular, the proportion of parvalbumin-containing neurons remains immature until late (Gao et al. 2000), which may provide an important substrate for critical period plasticity. Large-scale changes in primary auditory cortex can be rekindled in the adult rat when tones are paired with electrical stimulation of the basal forebrain (Kilgard & Merzenich 1998). Acetylcholine release within cortex increases the salience of concomitantly presented stimuli, yielding map refinements that rival those occurring passively during the critical period (Chang & Merzenich 2003). Tapping these attentional mechanisms may improve function more effectively when treating learning disorders or injury with therapy or cochlear implants (Merzenich et al. 1996).

Somatosensory System

Major topographical reorganization persists in the adult somatosensory system. Consistent with the behavioral improvement following perceptual learning in

primates, a trained skin region can activate a cortical area up to three times larger than untrained fingers (Recanzone et al. 1992). Both the thalamus and cortex are extensively reshaped by somatosensory deafferentation (Jones 2000), in contrast to retinal lesions that produce few changes in the LGN (Gilbert 1998). Sensory stages that first embody a response property are more likely to observe a critical period. Tactile stimuli are represented selectively at peripheral sensory receptors, whereas orientation or binocular tuning is first found in cortex. Hence, even across modalities in blind subjects, the tactile response to Braille reading extends into primary visual cortex only if vision is lost within a critical period of 14–16 years (Sadato et al. 2002).

Evidence for critical periods in the somatosensory system is found in the enticing point-to-point anatomy representing rodent whisker mosaics at all levels of the neuraxis. The formation of cortical "barrels," long immune to pharmacological disruption of neuronal activity (O'Leary et al. 1994), is regulated by a variety of molecules revealed by gene targeting (Erzurumlu & Kind 2001). Global removal of the NMDA receptor is lethal at birth yet sufficient to disrupt barrellette structures in the brainstem (Iwasato et al. 1997). Conditional NR1 subunit deletion restricted to the neocortex yields viable animals with a similar degradation of most of the S1 barrel field (Iwasato et al. 2000). Targeted disruption of a group of molecules related to cAMP signaling also produces 'barrelless' mice, including MAO-A, 5-HT_{1B} receptor, adenylate cyclase, mGluR5, and PLCβ (reviewed in Erzurumlu & Kind 2001, Lu et al. 2003). Instead, ectopic overexpression of fibroblast growth factor 8 (FGF8) can produce additional, ectopic barrel domains (Fukuchi-Shimogori & Grove 2001).

Critical period plasticity in response to sensory manipulation appears distinct from the initial formation of barrels. Direct damage to the whisker follicle is required to produce gross changes in the nascent barrel field. The anatomical shrinkage of deprived cortical barrels is strictly limited to whisker cauterization before the end of the first postnatal week (Van der Loos & Woolsey 1973). Unlike barrel formation, however, this plasticity does not require NMDA receptor function because whisker cautery causes barrel shrinkage even in cortex-specific NR1 knockout mice (Datwani et al. 2002). As in the visual cortex, the critical period ends regardless of NMDA receptor kinetics owing to NR2A subunit expression (Lu et al. 2001). When vibrissae are carefully removed, rather than ablated, a similar critical period is detectable by electrophysiological techniques (Fox 1992). The area of cortex driven by stimulation of the spared whisker enlarges, while the anatomical map retains its layout. Functional plasticity decreases rapidly in layer 4 between P0 and P4 and is NMDA-sensitive (Fox et al. 1996), mirrored by a declining ability to induce NMDA-dependent forms of LTP or LTD at thalamo-cortical inputs (Crair & Malenka 1995, Feldman et al. 1998).

Total whisker deprivation during a sharp critical period in the second postnatal week (P12–14) produces profoundly abnormal layer 2/3 receptive fields (Stern et al. 2001). Both the onset of active whisking (Welker 1964) and emergence of mature inhibition (Kiser et al. 1998) anticipate this plastic period, which further

corresponds to a peak in experience-dependent motility of dendritic spines on pyramidal cells (Lendvai et al. 2000). However, direct analogy to ocular dominance cannot be made because the competitive situation of partial whisker deprivation has not been tested.

In contrast, expansion of spared whisker responses persists in upper cortical layers throughout life (Fox 1992), involving αCaMKII and CREB (Glazewski et al. 1999, 2000) and an LTD-like depression within the principal barrel of deprived whiskers (Allen et al. 2003). The direction of map plasticity is surprisingly modulated by the whisking experience. Active exploration of novel environments during learning paradoxically contracts the spared input (Polley et al. 1999). Interestingly, whisker trimming can regulate cortical GABA receptor binding at any age (Fuchs & Salazar 1998), which may permit the strong competitive plasticity throughout life. Abnormal lateral inhibitory interactions between trimmed and intact inputs also arise within thalamus (Simons & Land 1994). Early disuse of the whiskers can nevertheless have latent effects, degrading receptive field plasticity later in adulthood (Rema et al. 2003).

Taste/Olfactory System

Olfactory preferences learned early in life will affect the sexual behavior of adult rodents and are mediated by type 2 MHC in mice (Fillion & Blass 1986, Yamazaki et al. 1988). As opposed to these pheromonal actions, unilateral naris closure for one to six months can cause the deprived olfactory bulbs to atrophy even in adult mice (Maruniak et al. 1989). Conversely, taste deprivation or selective taste exposure during the suckling period produces no differences on adult preference for flavored solutions (Bernstein et al. 1986). As in the whisker-barrel system, direct damage to the receptors on the tongue at P2 is required to alter the formation of the gustatory pathways that process particular tastes (Lasiter & Kachele 1990). Such evidence indicates no clear developmental critical period for taste and olfaction.

The potential for strong olfactory plasticity throughout life is behaviorally adaptive. In the well-known "Bruce effect," a pheromonal memory is formed in female mice at the time of mating that programs spontaneous abortion when a novel male intruder appears (Brennan et al. 1990). This process requires nitric oxide and mGluR2 activation that disinhibits mitral cells (Kaba et al. 1994, Kendrick et al. 1997). Within 4 h after parturition, ewes learn to recognize the odor of their lamb. Activation of muscarinic acetylcholine receptors is important for memory formation during a critical period of less than 16 h postpartum (Ferreira et al. 1999). A mother rodent's ability to recognize and nurture her young reflects a boost in new neurons that are integrated into the olfactory bulb (Shingo et al. 2003). Neurogenesis rates jump during pregnancy by 65%, peaking near the seventh day of gestation and again after delivery.

Constant neurogenesis may hold a key to olfactory plasticity throughout life and offers an exception to prove the rule about inhibition in other systems. Neural stem cells migrate from the subventricular zone and connect to the established circuitry

in the olfactory bulb (Carleton et al. 2003), where they are activated in response to smells. The new neurons are GABAergic granule cells, which sharpen the evoked pattern of neural activity through lateral inhibition of mitral cells (Yokoi et al. 1995). Mutant mice with deficient olfactory neurogenesis, and therefore relatively few granule cells, have difficulty with odor discrimination but not memory (Gheusi et al. 2000)—reminiscent of the inability to discriminate unbalanced visual input prerequisite to ocular dominance plasticity (Hensch et al. 1998). Both odor enrichment and the hormone prolactin during pregnancy trigger neurogenesis (Rochefort et al. 2002, Shingo et al. 2003).

MULTIMODAL FUNCTIONS

Imprinting

The classic example of a sharp critical period, famously described by Lorenz (1958), is the imprinting of certain precocial birds on a parental figure within hours after hatching. This is a complex behavior that integrates many sensory modalities including vision, taste, olfaction, and audition. It is now known to be a two-step process consisting of a predisposition to approach stimuli with characteristics of the natural mother followed by actual learning, or filial imprinting (Bolhuis & Honey 1998). Neonatal human infants too are predisposed to find face-like stimuli more attractive than nonface-like stimuli, but gradually learn through experience in the first months of life to finely discriminate human faces while grouping others (monkeys) into one general category (Pascalis et al. 2002).

Many sorts of nonspecific stimuli are capable of inducing the predisposition. Chicks reared in darkness without such experience (e.g., handling, running on a wheel, exposure to taped maternal calls) fail to develop a predisposition to approach a bird-like figure (see Bolhuis & Honey 1998). Critical period onset can be delayed by a catecholaminergic neurotoxin, DSP4. Whereas lesions to the intermediate and medial hyperstriatum ventrale (IMHV) have no effect on predisposition, the IMHV is crucial for learning the ensemble of characteristics belonging to one object, which is imprinting. Spine density of IMHV neurons following imprinting is reduced by half, which suggests that synapse elimination may end plasticity (Scheich 1987).

Stress and Anxiety

Harlow (1959) identified the importance of maternal care on developing social behavior in infants. Rhesus monkeys isolated at birth and supplied with dummy mothers invariably choose cloth-covered figures over uncomfortable wire mesh constructions equipped with a functional nursing bottle (Harlow & Zimmermann 1959). Monkeys raised in this way eventually grow up to become uniformly poor mothers, neglecting and punishing their offspring. More than food reward, the quality of maternal care is a crucial nutrient for the development of complex social

behavior (Scott 1962). Recent research with rodents has provided insight into the neurobiological underpinnings of such effects.

Rat mothers engaged in high licking and grooming behaviors raise pups that have higher synaptic density, BDNF content, mature NMDA receptors, and spatial learning scores in the hippocampus (Liu et al. 2000), as well as greater tolerance to stress as adults (see Meaney 2001). Reduced hippocampal spatial learning and elevated anxiety in the mature offspring of poor mothers can be rescued by fostering to good mothers or enriched environments (Francis et al. 2002). Moreover, female pups raised by good natural or foster mothers grow up to become good mothers. These effects also become hardwired into better-functioning glucocorticoid systems in these rats (Meaney 2001). Early postnatal experience may thus overcome genetic predispositions.

Anxiety-like behavior results from appropriate serotonin receptor activation during a critical period of early postnatal life (Gross et al. 2002). Whereas global deletion of the 5-HT_{1A} receptor subtype yields increased anxiety in the adult mouse (Sibille et al. 2000), its conditional restoration in the hippocampus and cortex (but not brainstem raphe nucleus) rescues the phenotype. However, the receptor must be activated between P5 and P21 in order to be successful, demarcating a critical period for the development of lifelong anxiety behavior in mouse. Appropriate 5-HT_{1A} receptor activation may ultimately regulate $GABA_A$ signaling (Sibille et al. 2000). Therapeutic intervention for anxiety by serotonin agonists is most effective in chronic paradigms that recognize this critical period (Hen & Gordon 2004, in this volume).

Sleep

Both the amount and quality of sleep changes with age. Initially, rapid-eye movement (REM)-like sleep states predominate, followed by the emergence of slow-wave sleep (SWS), which eventually occupies most of adult sleep (Jouvet-Mounier et al. 1970, Roffwarg et al. 1966). Increasing evidence points toward a replay of daily events during these sleep states for the consolidation of memories (Maquet et al. 2003). Indeed, SWS enhances critical period plasticity in the visual system (see above). Conversely, sleep itself is shaped by experience (Miyamoto et al. 2003). During a critical period from P40 to P60 in cats and mice, total visual deprivation reduces the slow-wave EEG activity selectively in visual cortex, yielding regional inhomogeneities of sleep quality over the brain surface. Sleep plasticity reflects the degree of NMDA receptor activation, and its recovery after dark-rearing reveals a delay of the critical period by the absence of experience. If sleep function includes neuronal replay for brain plasticity, then its own developmental plasticity reveals an intricate interplay between systems.

Sound Localization

Sound localization is a complex task that beautifully exhibits several aspects of critical period development (Knudsen et al. 2000). A map of auditory and visual

space must be perfectly aligned within the barn owl tectum for appropriately targeted flight. Shifting the visual scene with displacing prisms causes a mismatch between receptive field position and interaural time differences (ITD) from a sound source. If prisms are mounted during a critical period in early life, birds can learn to remap (over 6 to 8 weeks) their ITD representation to best fit the new visual environment. Large-scale adaptation is possible only in juvenile birds, gradually declining by 150 days after birth. Interestingly, in this system critical period closure can be delayed by sensory and social enrichment (Brainard & Knudsen 1998).

A predisposition for the normal alignment of sensory maps is present throughout life, upon which newly acquired ITD maps are superimposed. The new connections are mediated by NMDA receptors (Feldman et al. 1996) and accompanied by two structural changes: sprouting of excitatory inputs in the adaptive direction for the learned ITD and formation of novel GABAergic circuits that actively suppress the competing, unused map (DeBello et al. 2001, Zheng & Knudsen 1999). In this way, critical period plasticity can etch multiple maps in the developing tectum, which coexist into adulthood even after the prisms have been removed. These early learning experiences are thus not forgotten, as restoring the same goggles to previously trained birds smoothly switches ITD maps at an age when plasticity typically does not occur (Knudsen 1998). Early experience can thus expand the repertoire of neural substrates available throughout life and offers an explanation why, for instance, early language learning in humans is so effective (see Human Language).

A potential for reactivating plasticity after the critical period has recently been tested using incremental training in the adult (Linkenhoker & Knudsen 2002). Rather than a single, large prismatic displacement ($>20^\circ$), which is normally ineffective in mature barn owls, several smaller steps ($\sim 5^\circ$) produce gradual ITD adjustments that accumulate over time. Eventually, large shifts are attained on the order of juvenile levels, which subsequently become accessible to single, large displacing prisms. Whether structural changes occur in the adult remains to be seen, but the findings indicate that lifelong learning is possible through the right training regimen.

Birdsong

The three-step process by which certain birds acquire a single, stereotyped song highlights the serial nature of multiple critical periods underlying a complex brain function (Doupe & Kuhl 1999). Young birds first memorize the song of a tutor during a sensory acquisition phase, followed by sensorimotor practice when the bird actively matches its own vocal output to the memorized template. These two phases may overlap somewhat (zebra finch) or be separated by several hundred days (swamp sparrows), indicating the length of memory (Brainard & Doupe 2002). Learning ends in song crystallization when note structure and sequence become highly stereotyped. Seasonal singers repeat this process annually, whereas other species such as the zebra finch learn one song for life during a cumulative critical period over the first 100 days posthatching.

The neurobiological substrate has focused on hypertrophied brain nuclei present in the male zebra finch, as females do not learn to sing (see Mooney 1999). Two pathways are delineated from the higher vocal center (HVc), which receives the auditory information: An anterior forebrain pathway (AFP) subserves song learning, and a ventral motor pathway through the nucleus robustus archistrialis (RA) produces vocalization. Normal song development depends upon an intact AFP because lesions to the lateral portion of the magnocellular nucleus of the anterior neostriatum (LMAN) result in abnormal song in normally tutored pupils. Cells in LMAN acquire precise response tuning to the bird's own song (Brainard & Doupe 2002) and exhibit a decline in dendritic spine density with development (Wallhausser-Franke et al. 1995). Surprisingly though, no AFP nucleus tested so far has emerged as an obvious repository of the tutor's memory trace.

Young birds raised in isolation (with no tutor) or deafened (with no auditory feedback) produce abnormal vocalizations as adults (Brainard & Doupe 2002). Isolation also delays the critical period for learning beyond the normal chronological age, which too is disrupted by LMAN lesions. As in other sensory systems, attention has fallen upon maturational changes of NMDA receptors in LMAN with similar conclusions (see White 2001). Receptor incorporation of NR2A subunits and shortening current decay times are delayed by isolation rearing, but the typical decline in NMDA receptor number is not. Moreover, current kinetics eventually accelerate even in isolation, failing to explain the delayed learning still possible thereafter (Livingston et al. 2000).

A potential site of sensorimotor integration lies in RA (see Mooney 1999), where the two pathways meet upon individual cells. Interestingly, LMAN axons innervate RA first, utilizing mainly NMDA receptors, perhaps to guide the later-arriving HVc axons at song onset, after which LMAN inputs are pruned by half (Doupe & Kuhl 1999, Mooney & Rao 1994). During the ensuing sensorimotor phase, GABA cell number peaks in the RA of males but not females (Sakaguchi 1996). Here again, an optimal excitatory-inhibitory balance may be required to correctly compare distinct aspects of the bird's own song with a memorized internal template. Indeed, the plasticity of individual song details (syllable phonology versus sequences) may be differentially delayed by masking noise throughout this period (Funabiki & Konishi 2003).

Termination of the critical period is strictly linked to hormonal control of sexual maturation (Brainard & Doupe 2002). Testosterone reduces density of dendritic spines in LMAN and prematurely crystallizes song, whereas castration yields inconsistent song throughout life (see White 2001). Seasonal learners have waxing and waning hormone levels. In addition, neurogenesis differs across species. Male canaries learn new song elements every year and their HVc shrinks (during nonbreeding periods) and enlarges accordingly (Alvarez-Buylla et al. 1988). Zebra finches add large numbers of neurons to their HVcs only when they are young and learning their one courtship song for life. Adult song can still degrade over months after deafening (see Brainard & Doupe 2002). Interestingly, the double insult of

concurrent LMAN lesion prevents this slow decay, revealing a lifelong role for the AFP in auditory feedback.

Singing is a well-characterized behavior that varies between species. Song length, spectral complexity, and periodic structure reflect geographical area, much like human language (Brainard & Doupe 2002). When given a choice within a range of tutors, young birds show an innate predisposition for conspecific song—learning is more rapid and accurate (Doupe & Kuhl 1999, White 2001). Attentional and motivational factors further influence sensory acquisition, as demonstrated by a higher degree of copying by birds trained to actively peck a key in order to hear a tape of a tutor's song. Intriguingly, birds learn best when playback is limited to 30 seconds daily, and more exposure leads to less copying (Tchernichovski et al. 1999). Expression of the immediate early gene *zif268* is also highest for conspecific song and reflects the amount of copying but declines when the same song is repeatedly presented (Bolhuis et al. 2000, Mello et al. 1995).

The expression of *zif268*, though not necessarily involved in plasticity itself (Mataga et al. 2001), vividly reveals the behavioral state of the animal (Tononi & Cirelli 2001). Norepinephrine gates the auditory response from HVc to RA naturally as birds fall asleep to allow neuronal replay (Dave & Margoliash 2000). Directed singing in waking toward a companion activates the AFP differently from when the bird is singing alone (Hessler & Doupe 1999, Jarvis et al. 1998), and learning from a live tutor is more potent than tape learning (Doupe & Kuhl 1999, White 2001). Neuromodulation by social context reflects the ultimate aim of singing: communication.

Human Language

Synaptogenesis (Huttenlocher & Dabholkar 1997) and metabolic changes (Chugani 1998) differ with age across brain regions in the human infant. Each of these predict separate critical periods for various brain functions, but evidence is largely limited to anecdote except for language acquisition. Lenneberg (1967) originally proposed that a critical period for language ends around puberty. Intense debate has since centered on whether native languages are truly crystallized or merely interfere with second-language learning later in life. Although detailed cellular and structural substrates are difficult to identify in humans, developmental psychology and advanced brain-imaging techniques are revealing developmental milestones that may underlie a critical period.

Full-term neonates already exhibit left-hemisphere dominance (by optical topography) for normal speech (Pena et al. 2003) and segregate concurrent streams of sound (as detected by electrical mismatch negativity, MMN) like adults (Winkler et al. 2003). Functional MRI confirms the precursors of adult cortical language areas at three months of age (Dehaene-Lambertz et al. 2002). A baby's speech then emerges through a series of stages much like the different types of vocalization (subsong, plastic song, full song) observed in birds (Doupe & Kuhl 1999).

Exploiting statistical properties of language input (see Kuhl 2000), the auditory perceptual map is refined by six months of age to eliminate nonnative phoneme distinctions (like "r" from "l" in Japanese). Interestingly, vowel sound discrimination can be taught even during sleep (Cheour et al. 2002). Once vision matures sufficiently, by ten months, information about the speaker's face is combined with the concurrent acoustic signal, leading to perceptual illusions such as the McGurk effect (dubbing mismatch). Ultimately, the cumulative critical period for language ends with the ability to properly discriminate subtle grammatical errors by the age of 12 years (Newport et al. 2001). Other linguistic features, such as semantics, can be learned throughout life.

Bilingual subjects reveal a sequential neural commitment to competing stimuli. Originally sensitive to all speech sounds, the MMN is observed only for native language contrasts after 12 months of age (Cheour et al. 1998), reflecting the great difficulty to hear, as well as to produce, nonnative phonetic distinctions later in life. Interference effects are minimal before adolescence and several different languages can be acquired, perhaps by switching inhibition of unused maps (see barn owl discussion above). Functional MRI reveals, when both languages are learned before age 11, overlapping regions of Broca's area are activated, whereas second languages acquired later must employ two distinct areas (Kim et al. 2002). Age of acquisition also affects the cortical representation of grammatical (but not semantic) processes (Wartenburger et al. 2003).

Social context is instrumental. In the rare cases when children have been raised in isolation, or in children with autism, language skills and social deficits are tightly coupled (Leonard 1998). Conversely, in normal nine-month-old American infants, limited (5 h) exposure to Chinese speakers spaced over one month prevents the loss of Mandarin speech sound distinctions (Kuhl et al. 2003). The reward of a live tutor is essential, since similar exposure to taped instructors has no rescuing effect. From personal anecdote, learning is further facilitated if each tutor speaks exclusively one of the two languages rather than both.

Training paradigms based on exaggerated acoustic cues characteristic of motherese, multiple instances by many talkers, and mass listening experience may succeed to incrementally rewire the brain of adults as it already has for learning-disabled children (Kuhl 2000, Temple et al. 2003). By paradoxically overcoming our "mature" cognition, we may one day learn new skills more naturally and efficiently, as our children do so effortlessly during their critical periods.

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