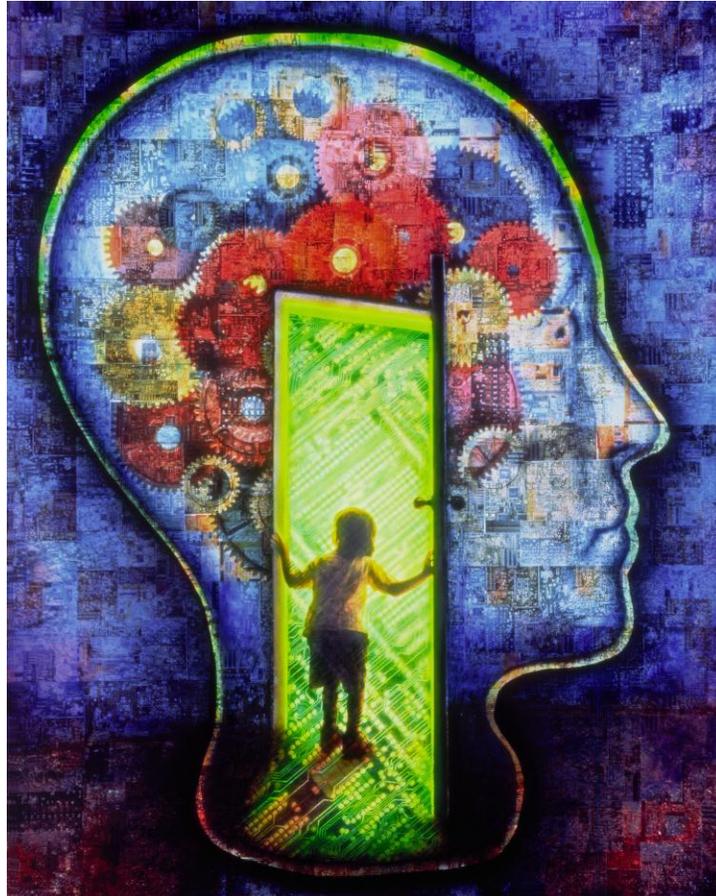


Re-opening Windows:
Manipulating Critical Periods for Brain Development
By Takao K. Hensch, Ph.D., and Parizad M. Bilimoria, Ph.D.



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Editor's note: The brain acquires certain skills—from visual perception to language—during critical windows, specific times in early life when the brain is actively shaped by environmental input. Scientists like Takao K. Hensch are now discovering pathways in animal models through which these windows might be re-opened in adults, thus re-awakening a brain's youth-like plasticity. Such research has implications for brain injury repair, sensory recovery, and neurodevelopmental disorder treatment. In addition, what we know today about these critical windows of development already has enormous implications for social and educational policy.

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Whether we realize it or not, nearly all of us have dreamed of enhancing brain plasticity, or the brain's capacity to change. This desire might become apparent when we visit a foreign country late in life and wish we could speak with the fluency of a native; when we hear an exquisite violin performance and wish we had learned to play as a child; or simply when we wish it were easier to break a bad habit.

The same desire permeates society's hope for advanced treatment of brain injury, where the diminished plasticity of the adult brain severely limits recovery. One example is stroke, a major cause of long-term disability for which there is currently no pharmacological treatment. Many stroke victims suffer muscle weakness or paralysis and have difficulty walking. Compounding these challenges are aphasias, or impairments in the ability to talk, read, write, and understand words or numbers. In a substantial number of cases, the aftermath of a stroke can make it impossible to live independently.¹⁻³

When we hope for stroke survivors to regain the abilities they've lost, we are essentially wishing that the neural circuits damaged by stroke could be rebuilt—in other words, that we could regain access to the heightened plasticity of a developing nervous system. This idea seems a bit fantastical. In recent years, however, neuroscientists have gained remarkable insights into the regulation of neural circuit plasticity. Data from animal studies now suggest that it may be possible to re-awaken youth-like plasticity in the adult brain.

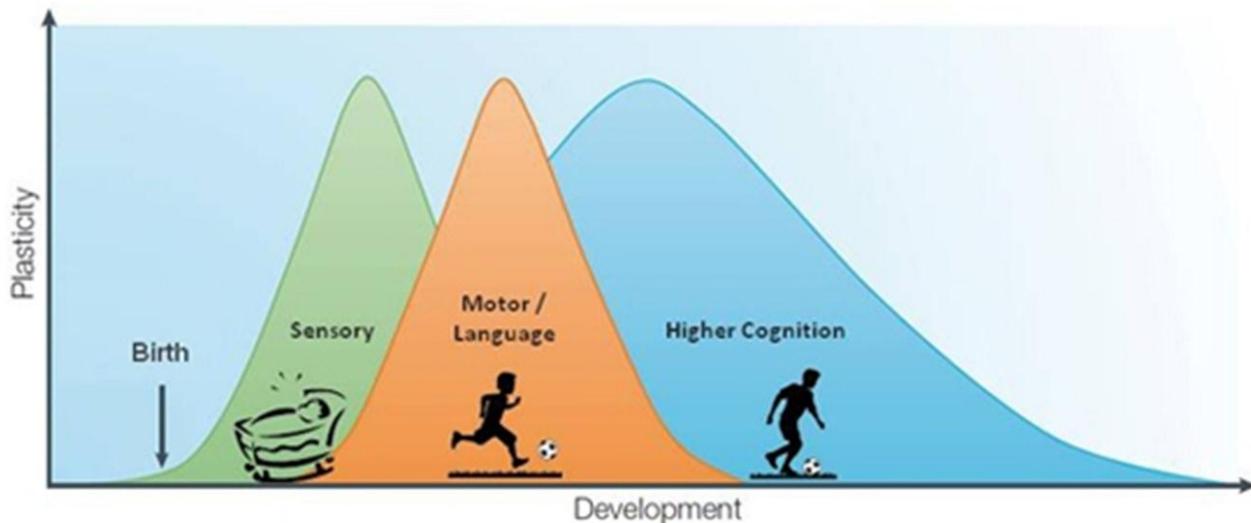
The ability to re-open plastic windows of brain development extends even beyond the dream of lifelong learning or recovery from brain injury. This research has the potential to affect a much broader array of neurological conditions, including mental illness. Here we discuss the fundamental discoveries leading up to these new capabilities, then consider both the therapeutic potential and the safety concerns that accompany the power to manipulate brain plasticity.

Defining Windows

Windows of heightened plasticity during brain development are called critical or sensitive periods (Figure 1). A critical period is the time when environmental input is required for the proper development of a particular brain circuit. If the circuit is left unstimulated, the brain function served by that circuit will be permanently compromised. Until recently, there were no interventions that could reverse this outcome. A sensitive period, less stringent than a critical period, is the time when environmental experiences have the greatest impact on brain circuitry.

The circuits in question can also be shaped by experiences later in life, but to a lesser degree.⁴ As indicated in Figure 1, there are different critical or sensitive periods for different brain circuits and the various functions that they underlie.

Fig 1: Windows of Plasticity in Brain Development



Adapted from Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience*, 6(11), 877–888.

Windows of heightened plasticity in brain development are called critical or sensitive periods. In humans, there are sensitive periods for the development of sensory pathways (vision, hearing), language, and higher cognitive function, as well as many other brain functions. Note that the peak of plasticity for each sensitive period is staggered throughout development.^{4, 6, 7}

More-complex or multifaceted brain functions, especially those in humans, tend to reflect cumulative sensitive periods rather than one critical period. Documented examples of sensitive periods in children include those for seeing, hearing, receptive language, speech production, and higher cognitive functions.^{5, 6} Currently, however, the best-understood windows of plasticity are critical periods controlling specific attributes of primary sensory modalities in animals, such as the representation of different tones in the auditory cortex or of left versus right eye inputs in the visual cortex. The latter, a property called ocular dominance, is also reflected in the cellular

architecture of the human brain known as ocular dominance columns—columns or stripes of neurons in the visual cortex that respond preferentially to left versus right eye inputs.^{4,7}

“Lazy Eye” as an Investigative Strategy

Studying the impact of visual deprivation in early life has yielded tremendous insights into the biology of critical periods. In 1981, neurobiologists David Hubel and Torsten Wiesel won the Nobel Prize, in part for demonstrating that proper visual system development requires visual experience. Motivated by observations that children who suffer early visual deprivation due to cataracts can have lifelong visual impairments, they studied the visual system in cats and monkeys. They identified a clearly defined window during which input through both eyes is required for vision to develop normally. Unlike adult animals, whose vision is unaffected by a period of visual deprivation, in young animals if one eye is kept shut (deprived) during the critical period for ocular dominance, the animal will develop amblyopia—poor vision in that eye. Strikingly, even when amblyopia develops, the covered eye itself is unharmed. Instead, the brain structures serving that eye shrink and the territory is taken over by cells favoring the other eye.⁸

Since Hubel and Wiesel’s discoveries, the impact of monocular deprivation on the visual cortex has become a classic system for investigating critical period plasticity, although now most such investigations are carried out in rodents. One of the greatest strengths of this system is that it models a condition common in humans. Crossed eyes or congenital cataracts leading to unequal visual inputs in childhood can cause amblyopia, a condition affecting two to five percent of the population, in which vision through one eye, the “lazy eye,” is poor despite the eye itself being perfectly healthy. Patching the better eye can restore the quality of vision through the lazy eye, but only if it’s done during the critical period.⁴

Inhibition as the On Switch

What controls the timing of critical periods? Early in postnatal life, the majority of neuron-to-neuron communication in the brain is excitatory. This means that at synapses—the sites of communication between neurons—the release of a neurotransmitter, or chemical messenger, from neurons on the sending end often intensifies the electrical activity of neurons on the receiving end. As the brain matures, however, inhibitory neurotransmission grows—the release of a neurotransmitter from one neuron dampens the electrical activity of its synaptic

partners. Studies of the mechanisms underlying amblyopia have revealed that once this rise in inhibitory neurotransmission reaches a certain threshold, the critical period turns on.⁹

Scientists first demonstrated the existence of an inhibitory threshold using gene disruption technology in mice to prevent the rise in GABA levels, the main inhibitory neurotransmitter of the central nervous system. When they deleted one of two versions of the enzyme that synthesizes GABA, the brain produced GABA at lower levels than normal. Under these conditions, shutting one eye early in development did not affect ocular dominance—critical period plasticity failed to begin. When researchers then administered a drug (a benzodiazepine, such as Valium, commonly used to treat anxiety in humans) enhancing the effects of GABA in the laboratory, critical period plasticity returned, and monocular deprivation affected ocular dominance as expected.¹⁰

Amazingly, benzodiazepine treatment can trigger the critical period for ocular dominance even after these GABA-deficient mice reach adulthood.¹¹ Benzodiazepines can also be used to trigger plasticity earlier than normal in non-GABA-deficient mice by prematurely elevating inhibitory neurotransmission before the normal onset of the critical period.^{11, 12} However, once the natural critical period has passed and inhibition is already mature, benzodiazepines cannot trigger a second window of plasticity in adulthood.¹¹ It seems that there is something intrinsically special about the initial maturation process of wiring inhibitory connections that controls the onset of critical periods—in fact, transplantation of embryonic inhibitory neuron precursors into the cortex of adult mice, unlike benzodiazepine treatment, does induce ocular dominance plasticity as the cells get plugged into the circuit.¹³

One particular type of inhibitory neuron appears to be pivotal for the timing of this critical period: the parvalbumin-positive large basket cell (PV-cell). PV-cells connect cells horizontally within a particular region. In the visual cortex, PV-cells emerge just ahead of the critical period for ocular dominance and control the width of ocular dominance columns.⁴ Also, they signal through the receptors that benzodiazepines bind to when accelerating the onset of critical period plasticity.^{12, 14}

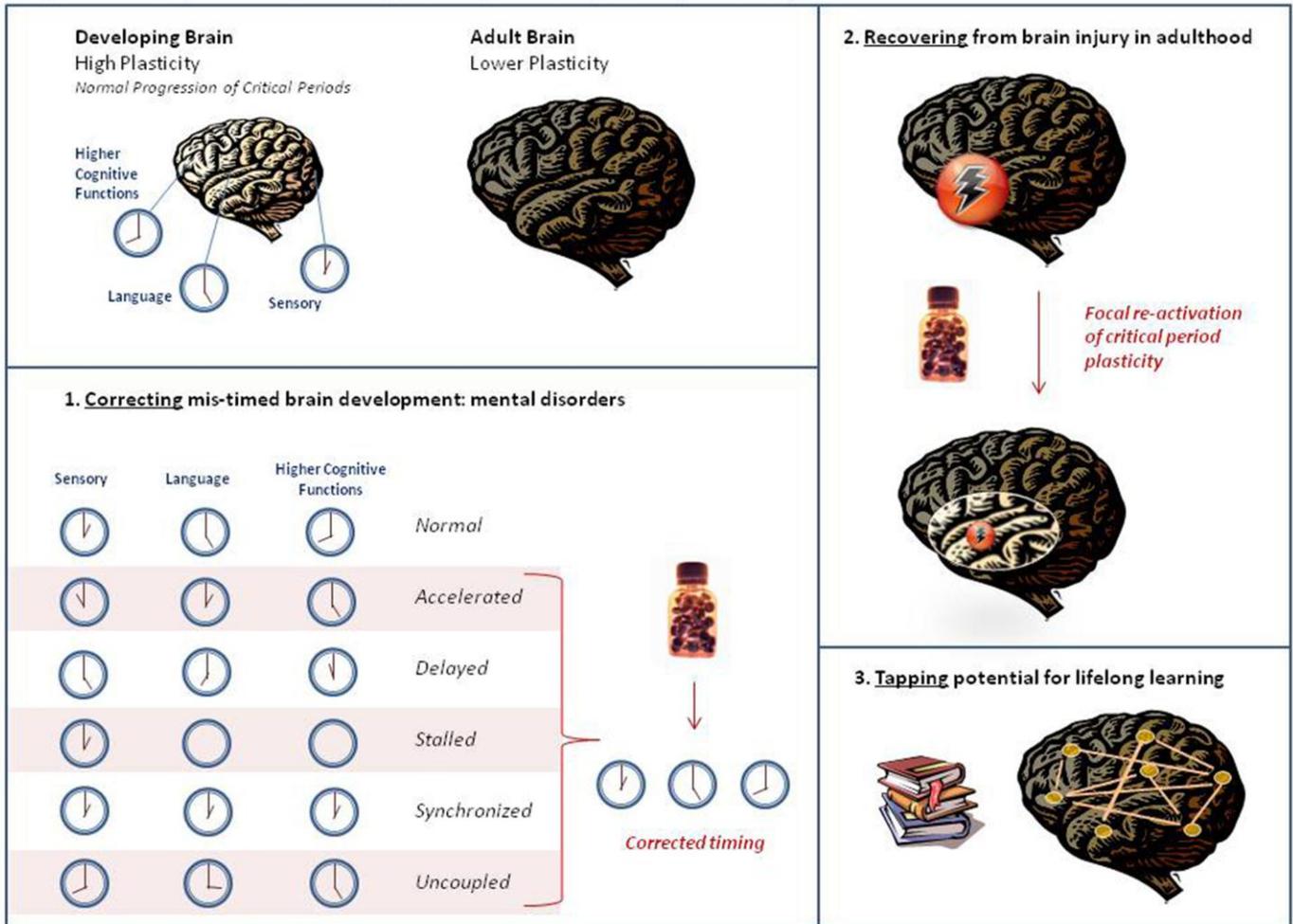
Excitatory/Inhibitory Balance

Researchers have proposed that excitatory/inhibitory (E/I) imbalance underlies the pathology of neurodevelopmental disorders such as epilepsy, autism, and schizophrenia.^{15, 16}

Several of the genes implicated in autism spectrum disorders (ASDs) are important for establishing or maintaining E/I balance.¹⁷ A meta-analysis of many mouse models of ASDs revealed that despite varying disease causes, a common deficit is present in neocortical PV-cells across the board.¹⁵ In addition, directly disrupting E/I balance in the mature prefrontal cortex of mice leads to social and cognitive deficits reminiscent of those occurring in psychiatric disorders.¹⁸ These and many other data linking E/I imbalance to mental illness suggest that studying the signaling pathways that regulate critical or sensitive period plasticity will have implications far beyond developmental neurobiology.

As suggested in Figure 2, alterations in the timing of sensitive periods (such as accelerated or delayed onset or stalled, synchronized, or uncoupled progression) could underlie various neurodevelopmental disorders, including autism and schizophrenia. By understanding the biological mechanisms that control sensitive period timing, such as E/I balance, we may one day be able to correct the roots of these disorders as mistimed development. Studying the biology of sensitive periods may also lead to strategies for tapping into sensitive period plasticity during adulthood, potentially as an avenue for promoting recovery from brain injury, or simply to enhance lifelong learning.

Fig 2: Consequences of manipulating critical period plasticity



The developing brain exhibits higher plasticity than the adult brain. During normal development, critical periods occur in a predictable temporal sequence, as depicted here with examples of vision, language, and higher cognitive function.

1. Following genetic disruption or pharmacological manipulation, certain critical periods may be accelerated or delayed. Critical periods might then become incorrectly synchronized or uncoupled from one another across the brain. Alternatively, the extended duration of one critical period may stall the onset of others. Interventions that restore the expected hierarchical progression of critical periods during brain development may then be useful in preempting mental illness.

2. In cases of stroke or other brain injuries suffered during adulthood, the main obstacle to treatment is believed to be the limited plasticity of the adult brain. Thus, a tantalizing treatment strategy would be to rekindle critical period plasticity in the damaged circuits.

3. The ability to tap into critical period plasticity during adulthood, likely through non-invasive means (such as incremental training, enriched environments, or educational video games), could also enhance the potential for lifelong learning.

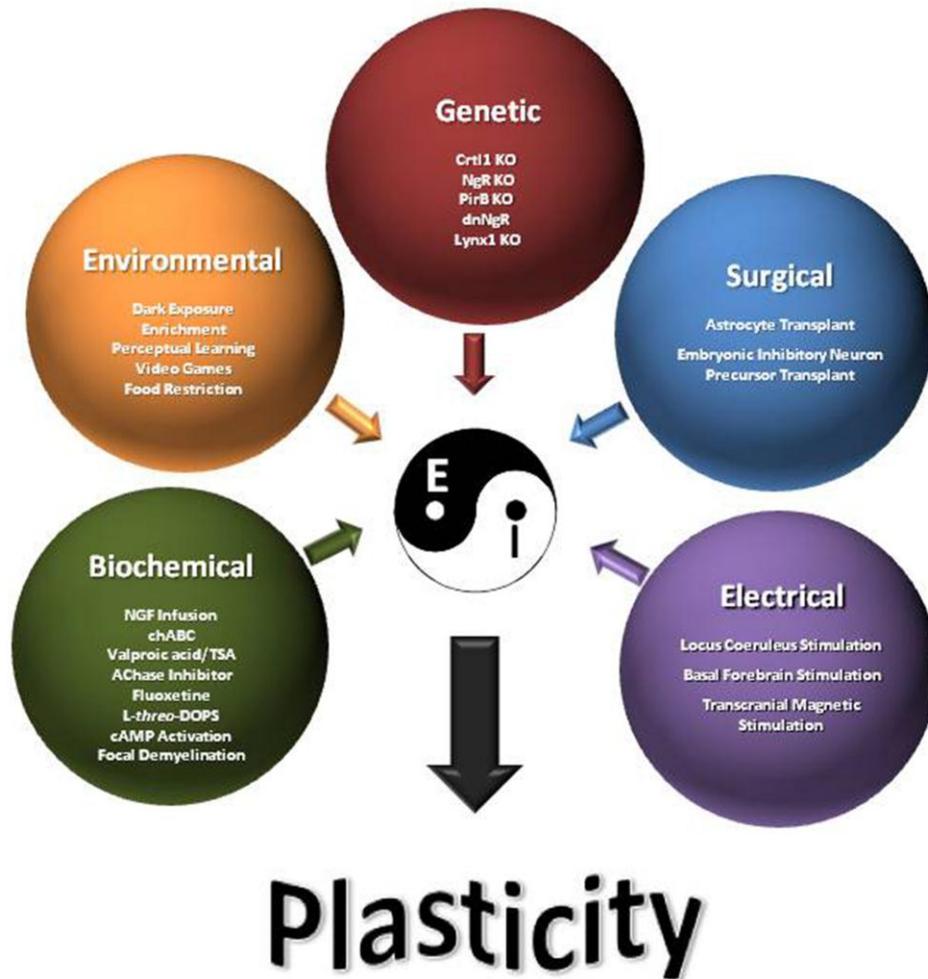
How might knowledge about E/I balance be used to design drugs that promote brain plasticity? As it turns out, there's already a drug that humans take—the famous antidepressant fluoxetine (Prozac)—that triggers youth-like plasticity in adult rats and might be working through E/I regulation.¹⁹ Chronic fluoxetine treatment reactivates ocular dominance plasticity in adult rats. If the rats have amblyopia, patching the good eye while the rat is on fluoxetine allows full recovery of visual acuity in the amblyopic eye. Clinical trials to test fluoxetine as a treatment for amblyopia in humans are already under way.²⁰ Also, the strategies for restoring vision in adults with amblyopia have recently been linked to interventions for stroke recovery—promoting plasticity in the adult brain being the common thread²¹—and there is some evidence that fluoxetine, when prescribed along with physiotherapy, promotes motor recovery in stroke victims.²²

Incredibly, just as exercise can replicate the benefits of antidepressants in humans suffering from major depressive disorder,²³ environmental enrichment can yield results similar to those of fluoxetine in rats suffering from amblyopia. In environmental enrichment, the rats' cages are larger and contain a variety of toys that are changed regularly, which scientists believe increases exploratory behavior and sensory-motor stimulation. Like fluoxetine treatment, environmental enrichment adjusts inhibition, allowing adult rats to recover from amblyopia when their good eyes are patched.²⁴ Caloric restriction in adult rats also adjusts inhibition and re-opens the critical period for ocular dominance, potentially through an increase in corticosterone levels.²⁵ More direct attempts to adjust E/I balance include the use of transcranial magnetic stimulation to the visual cortex of humans, which has been reported to improve visual acuity in amblyopic participants.²⁶

Another non-invasive intervention to engage plasticity beyond a critical period is incremental training. Barn owls have auditory space maps that align sound cues with visual information. These maps readily adapt to large changes in sensory experience early in life, and then later become resistant to reorganization. By modifying training protocols to feature more-gradual changes in sensory experience, researchers can significantly improve the capacity for learning in adult owls.²⁷ Along these lines, action video games have been used to train the amblyopic eye of adults for improved vision.²⁸ Together, these stories of fluoxetine, environmental enrichment, transcranial magnetic stimulation, and incremental training illustrate that many different paths can lead to enhanced brain plasticity after the critical period (Figure 3).

Biochemical, environmental, genetic, surgical, and electrical interventions can each re-awaken ocular dominance plasticity in adult animals.

Fig 3: Factors that affect critical period timing



Based on figures in Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., & Hensch, T. K. (2010). Removing brakes on adult brain plasticity: From molecular to behavioral interventions. *Journal of Neuroscience*, 30(45), 14964–14971.

As well as data from Spolidoro, M., Baroncelli, L., Putignano, E., Maya-Vetencourt, J. F., Viegi, A., & Maffei, L. (2011). Food restriction enhances visual cortex plasticity in adulthood. *Nature Communications*, 2, 320.

Diverse experimental manipulations—ranging from biochemical, genetic, and surgical interventions to environmental changes or electrical stimulation—are known to induce juvenile-like plasticity in the adult visual cortex. These manipulations are all thought to trigger plasticity via a common circuit mechanism: adjusting the balance of excitation/inhibition (E/I balance) in the brain.⁹

The more we understand how these paths to plasticity intersect at the level of E/I balance, the better interventions we will be able to design for promoting learning later in life and overcoming brain disease or injury. One common pathway may be brain-derived neurotrophic factor (BDNF). When levels of this growth factor are prematurely elevated in mice, PV-cells and

their inhibitory activity in the visual cortex develop at an accelerated pace. As a result, visual acuity develops precociously, and the critical period for ocular dominance ends earlier than normal.²⁹ Conversely, when rodents are raised in the dark and have lower levels of BDNF, plasticity is delayed.³⁰ If the expression of BDNF is uncoupled from visual experience via a genetic trick, however, the critical period proceeds normally even in the dark.³¹ Each of these then represents a novel therapeutic target to regulate the timing of plasticity.

Releasing the Brakes

It is also crucial to appreciate what restrains plasticity as the brain ages. Structural changes in the extracellular environment of neurons are a key factor. As PV-cells age, they become ensnared in perineuronal nets, protein-rich extracellular structures found throughout the nervous system, composed of molecules called chondroitin sulfate proteoglycans (CSPGs). Breaking down perineuronal nets was among the first experimental manipulations found to re-activate visual plasticity in adulthood. Repeatedly injecting an enzyme that degrades CSPGs into the visual cortex of adult rats restores the ability of visual experience to influence amblyopia long after the normal critical period for this type of plasticity.³²

Perineuronal nets in the amygdala, an area of the brain associated with emotion, act as brakes on fear memories. Readily erased during infancy, fears acquired after a critical period are difficult to extinguish—the basis for post-traumatic stress disorders (PTSD). Remarkably, degrading CSPGs in the amygdalae of mature mice makes fear memory labile again, such that it is possible to actually lose fear memories acquired in adulthood.³³ This finding nicely illustrates how the study of one specific critical period in the visual system can lead to the discovery of global mechanisms regulating other critical periods.

Another physical change that occurs at different stages of the brain's maturity is increased myelin formation—the wrapping of axons in white, fatty insulation that promotes intercellular communication. Like CSPGs, myelin and its associated proteins can strongly inhibit axon growth, and increased myelination is a major reason why neural circuits largely fail to regenerate with age. When a key mediator of myelin signaling, the Nogo receptor, is genetically deleted in mice, ocular dominance plasticity continues well past the normal critical period.³⁴ Recently, researchers found that immune system genes in the mature brain signal through the

same receptor complex to limit adult plasticity.³⁵ This suggests that myelination is important for closing critical periods of plasticity.

While the removal of structural “brakes” on critical periods of plasticity, like perineuronal nets and myelin, is far from clinical use, the lazy eye model has recently revealed a different kind of brake on attentional signals in the brain. Lynx1 is a negative regulator of the neuromodulator acetylcholine (ACh). Like perineuronal nets and myelin, Lynx1 accumulates as the brain matures. It binds to the nicotinic ACh receptor (the same receptor activated by nicotine in cigarettes) and reduces its sensitivity to ACh. When the Lynx1 gene is deleted in mice, nicotinic ACh receptor signaling is amplified, and adult mice recover from amblyopia spontaneously.³⁶ Researchers obtained similar results by enhancing ACh signaling pharmacologically, using an inhibitor of acetylcholinesterase, the enzyme that degrades ACh. Since acetylcholinesterase inhibitors are already safely prescribed to provide some relief from the symptoms of cognitive and functional decline, such as in Alzheimer’s disease,³⁷ a clinical trial to rescue amblyopia in younger people past their critical period is feasible.³⁸

Treading with Caution

The data discussed here certainly provide great hope for enhancing lifelong learning and treating brain injuries or disorders of a broad range. But it is imperative to act cautiously when translating laboratory findings into interventions for humans. There are biological, clinical, and ethical risks to consider.

To begin with, there must be a biological purpose for the natural reduction in plasticity that occurs as our brains mature. Consider, for example, what might happen if our environmental experiences were to forever have the same dramatic impact on neural circuits that they do during development: our brains would likely be in a constant state of flux, with new experiences frequently undoing the wiring laid down by previous experiences. We might not be able to retain any of the major lessons we’d learned. This sort of failure to stabilize neural circuits may well underlie the pathology of some neurodevelopmental disorders.¹⁶

Another key point to bear in mind is the hierarchical nature of critical periods.⁷ Shifting the timing for one neural pathway may affect all other circuits that lie downstream (Figure 2). If a circuit is highly plastic at a time when it would normally have been more stable, it will have a cascading effect in ways that may be hard to predict until we have better wiring diagrams of the

brain and deeper knowledge of how brain connectivity develops. The unwanted lasting effects of performance-enhancing drugs in sports have already taught us that faster is not always better.

An obvious concern, particularly for pharmacological interventions, is the danger of side effects. The inadvertent acceleration of critical periods in infants exposed to common drugs that alter E/I balance needs to be explored. Another example is highlighted with regard to treating stroke by manipulation of GABA (inhibitory neurotransmitter) signaling. Reducing an excessive form of inhibition that occurs after stroke promotes functional recovery in a rat model. However, doing this too soon might actually promote cell death and increase the severity of the stroke.³⁹ As is always the case in biology, the cells and molecules discussed in the context of critical periods have diverse functions, and targeting any of them is likely to yield complex results that may even be unrelated to plasticity. But as we understand more about the basic biology of the neural circuits underlying plasticity and their response to disease or injury, the design of safer and more targeted interventions becomes possible.

An Arena for Action

While research continues on the cellular and molecular mechanisms controlling critical period plasticity, and the safety and efficacy of fluoxetine or cholinesterase inhibitors are followed up in amblyopic adults, one arena that can see swift action is early childhood policy and programs. There is ample evidence that early childhood adversity—or toxic stress experienced during sensitive periods of brain development—has lifelong consequences for health, learning, and behavior.⁴⁰

Toxic stress occurs when the body's stress response systems are activated strongly, frequently, or for extended periods of time without reliable adult support. Examples of potential precipitants of toxic stress include extreme poverty, child abuse or neglect, parental substance abuse or mental illness, severe maternal depression, and exposure to violence.^{40, 41} In the absence of buffering support from adult caregivers, such stressors can trigger a toxic stress response that will have lasting effects on the architecture of brain circuits. Importantly, they may damage the development of brain regions critical to the regulation of emotion, including the amygdala, hippocampus, and prefrontal cortex.^{40, 42} The scars of toxic stress are even beginning to be identified at a molecular level as biochemical marks in the brains of suicide victims that correlate

with histories of child abuse⁴³ or changes in telomeres, the protective DNA caps on chromosomes, in children who endured severe neglect early in life.⁴⁴

Toxic stress in early life has been linked to a whole range of behavioral and health problems, many of which are interrelated. For instance, adverse childhood experiences increase the risk for engaging in harmful behaviors such as substance abuse, gambling, gang involvement, and violent crime. They have also been correlated with alterations in immune function and levels of inflammatory markers known to be associated with a variety of chronic illnesses, including cardiovascular disease, autoimmune disease, asthma, liver cancer, and depression.⁴⁰ Further, adverse childhood experiences have been linked to a number of cognitive deficits, including difficulties with memory and executive function, and affective deficits such as problems with reward processing and emotion regulation.⁴⁵

Despite our knowledge of sensitive periods of brain development and the overwhelming evidence of the broad spectrum of damage caused by early childhood adversity, it remains an ongoing challenge to translate this science into social policies that protect children.⁴⁶ It also remains a challenge to develop school policies that capitalize on our knowledge of sensitive periods as windows of heightened educational opportunity.⁴⁶ For instance, although there is clear evidence that children have the capacity to attain fluency in any language if they are exposed to it starting at birth, the teaching of second languages continues to be delayed until early adolescence, and bilingual programs for young children are insufficiently valued. Second, while educational reforms dedicate resources to the training, recruitment, and retention of K–12 teachers, they often do not invest sufficiently in preschool teachers. Other examples of the science-policy gap include the slow, bureaucratic nature of child custody cases during the sensitive periods of development of young children, the limited availability of family leave after the birth or adoption of a child, insufficient efforts to reduce high staff turnover in poorly funded child care programs, and limited support for working parents who are trying to balance child care with long hours at low-paying jobs.^{5,47}

Clearly, there is a need for greater respect, funding, and focus on early childhood education and well-timed interventions targeting early life adversity. Even if advances in our understanding of sensitive period plasticity one day make it possible to design more effective interventions for older children and adults—interventions that undo some of the damage to brain

circuits caused by adversity in early life—preventing or reducing adversity in the first place will remain the smartest strategy.

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