

NEUROSCIENCE

THE POWER OF THE INFANT BRAIN

An understanding of formative periods of intense learning

during childhood suggests strategies for correcting neurological

and psychiatric disorders later in life

By Takao K. Hensch

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WHAT'S ON YOUR MUSIC PLAYER? IF YOU'RE OLDER THAN 30 YEARS, it probably includes songs from your teenage years. Childhood and adolescence are the most impressionable period of a person's life. The earliest memories and experiences are essential in shaping character—and they profoundly influence everything that comes next. “The habits we form from childhood make no small difference, but rather they make all the difference,” Aristotle proclaimed more than 2,000 years ago.

The latest findings from brain science are lending a new appreciation to the proverb. New discoveries made during the past 15 years spell out more clearly how the brain begins to wire itself in infancy and toddlerhood—and how to tinker with brain circuits to treat the most serious neurological and psychiatric illnesses.

The brain builds the right connections during intervals of intense development—some lasting months, others years—that are known as critical periods. Most occur in infancy, but some arrive as late as the teenage years. Neuroscientists have already identified critical periods for vision, hearing, language and various forms of social interaction. During a critical period, the child brain enters into an intimate pas de deux with the outside world. Incoming photons and sound waves serve as cues for the brain's molecular machinery to lay down and select the links among brain cells that will last into adulthood and old age.

If a critical period occurs too soon or too late or if it fails to begin or end when it should, the consequences can be dire. A child might be left partially blind or become susceptible to conditions such as autism. A baby with, say, a hereditary cataract in one eye that keeps her from seeing her surroundings will lose sight because the connections among brain cells will not have wired up properly during a critical period that begins in infancy and tapers off gradually before ending at age eight. Once it is over, the child has an extremely limited chance of developing normal vision through that eye.

The original discovery of these formative stages came more than 50 years ago. (Torsten N. Wiesel and the late David H. Hubel received a Nobel Prize for some of the work in 1981.) For many years afterward, the conventional wisdom held that critical periods were fleeting and that once they ended, there was no way of going back. Recently new molecular tools for studying critical periods have overturned many of the prevailing ideas. Experiments in animals—and even some human studies—have demonstrated that a critical period might be reopened to repair broken brains well afterward.

The implications point to a startling possibility. We may one day be able to tweak chemical switches that reinstate pivotal intervals and let the brain rewire itself to treat neurological and psychiatric disorders ranging from amblyopia (lazy eye) to psychosis. An understanding of what happens in the baby brain may inspire more than the design of new drug treatments. It may also give educators, psychologists and policy makers a fundamental understanding of the basic process of child development or the consequences of parental neglect that will allow them to tailor schooling to fit the capabilities of each child at a particular stage of brain growth.

TRIGGERS AND BRAKES

THE BRAIN CHANGES ALL THE TIME, not just in infancy. Neuroscientists call it plasticity. When you learn how to juggle or use a

IN BRIEF

The child brain develops vision and other abilities during “critical periods,” when the brain is primed to undergo lasting change in response to sensory and social stimuli.

Critical periods open at defined times during the course of childhood and adolescence to allow the molding and shaping of neural connections—a property known as brain plasticity.

Growing understanding of the molecules that both start and stop critical periods has let scientists gain a measure of control over their timing, restoring plasticity even in adulthood.

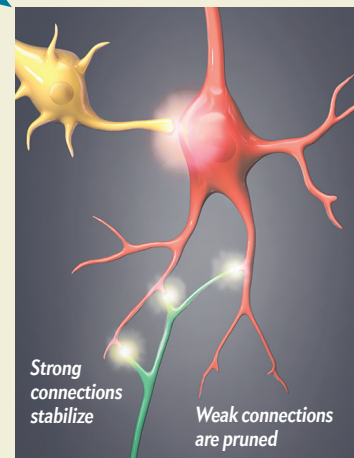
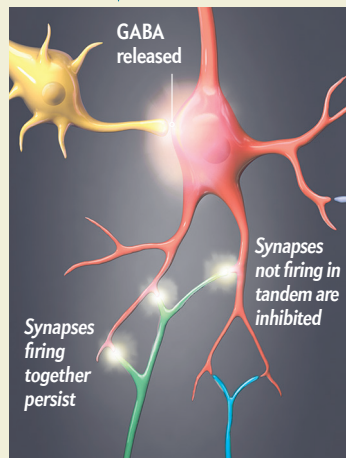
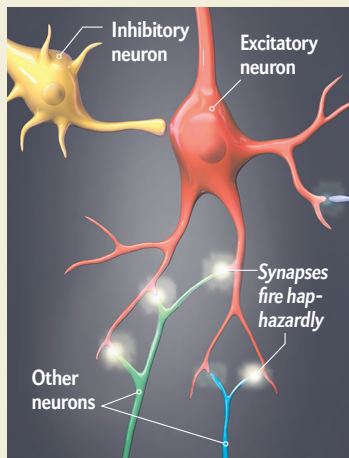
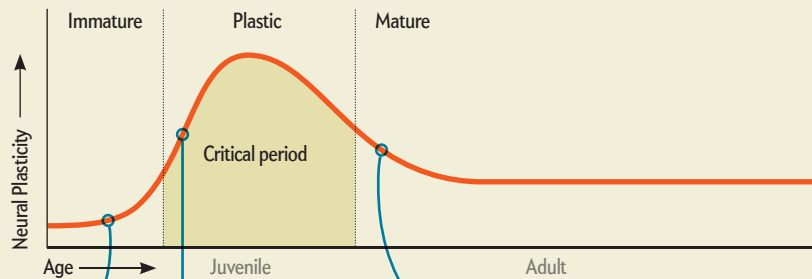
Regulating the biology of early development may one day allow drugs or medical procedures to restart critical periods later in life to correct early developmental problems.

A Young Brain's Window on the World

A rite of passage in early life—the critical period—takes place when the brain uses sights, sounds and the rest of the sensory inflow from a child's surroundings to guide the neurodevelopmental process. During one such interval, the incoming visual imagery appears to calibrate the brain's cortex with the outside world. Visual stimuli determine which neuron wires to another to best respond to input from the eyes.

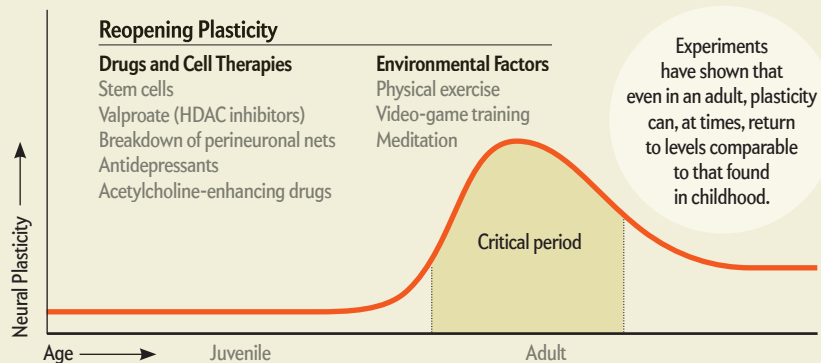
Bringing On Change

Neurons in the immature brain are highly active, firing in haphazard patterns. The neurotransmitter GABA orchestrates the brain plasticity of a critical period, in which only synapses that fire together survive, while those that do not are inhibited and eventually pruned. Once the critical period ends, the capacity to pare back synapses diminishes.



A Restart

Understanding of the molecular processes in the brain that bring about the plasticity of the critical period has enabled scientists to use drugs or behavioral measures, such as physical exercise, to demonstrate that the brain's connections can be molded at much later ages than once thought possible.



new phone app, subtle alterations occur at synapses, the sites where nerve signals travel between neurons. Mastering a new skill brings about biochemical changes in a neuron that results in either stronger or weaker transmission across synapses. This simple type of plasticity persists throughout a lifetime. A person can always learn new things.

During the critical periods of early childhood, however, especially momentous changes take place. A baby begins life with a thick overgrowth of synapses that must be pared back to do their job properly. The necessary structural changes—the culling of synapses—happen during the critical period.

Scientists who study critical periods often home in on the

visual system because it is relatively straightforward to manipulate. Shortly after birth, the visual cortex, located at the back of the head, begins to react to the flood of incoming light channeled from the eyes and the optic nerve.

What the eyes see stimulates cells in the visual cortex. Some of them then fire at the same time, resulting in new synapses forming between them—a process that gave rise to an oft-repeated adage: “Cells that fire together, wire together.” Out-of-sync synapses that do not communicate in unison get clipped back. The critical period to connect the visual system of the infant brain ends after a few years, and the resulting wiring plan usually remains in place for a lifetime.

Scientists who study the neurobiology of child development want to learn how to gain a measure of control over the timing of critical periods to potentially correct missed opportunities or mistakes made in wiring up a developing nervous system. They have looked for a set of molecular switches—triggers and brakes—that mark the beginning and end of these intervals.

One key discovery has come from inspecting an important signaling molecule in the brain. The neurotransmitter GABA (short for gamma-aminobutyric acid) is best known for tamping down the firing of nerve cells. Our laboratory initially found that GABA—together with some companion molecules—plays a key role in determining when a critical period starts and stops. Indeed, we found one type of GABA-producing neuron, the parvalbumin-positive large basket cell, that very likely orchestrates the entire process.

On the face of it, a parvalbumin neuron would seem ill suited to take on this task of kicking off a critical period. GABA's typical role is to quiet neural activity. Why, then, should it trigger one of the most intense events in child development? What happens, it turns out, is that the neurotransmitter brings order to an otherwise chaotic scene.

During a baby's earliest months, the brain is always on. Neurons—aptly named excitatory cells—fire haphazardly, like people in a crowd all talking at once. It is only when the critical period begins that some semblance of structure is imposed. GABA emitted from parvalbumin cells tells the excitatory cells to quiet down and stop talking nonsense. They do so by extending long tendrils called axons that form connections. The axons wrap like a basket around nearby excitatory cell bodies, the central part of a neuron. Their reaching out tamps down excitatory cells' overheated activity, enabling the target cells to emit sharp and clear signals—attaining what we call an excitatory-inhibitory balance.

Our research looked carefully at this process in the visual system of rodents. We began by genetically tinkering with mice to lower their GABA levels. As a consequence, the critical period did not begin when expected. Later, when we administered a benzodiazepine drug, such as Valium, that increases GABA signaling, the critical period got back on track.

The experiment showed that we could, in principle, control precisely when critical periods begin or end and how long they last. This realization has far-reaching implications for treating neurodevelopmental disorders. Animal studies from a number of labs have now shown that either perturbed genes or environmental stress can upset the fragile balance between excitation and inhibition and start a critical period at the wrong time. Researchers have begun to focus on whether correcting the timing of critical periods might one day prevent or treat autism,

schizophrenia or other neurological disorders by restoring the desired equilibrium.

BACK TO THE FUTURE

IT WILL TAKE YEARS, perhaps decades, of research before some of the most ambitious techniques tested in lab animals reach patients. Understanding critical periods, though, has also led to some compelling ideas for using drugs already on the market to restore a modest amount of plasticity in the adult brain.

A long-term goal would turn back the biological clock and restart a critical period. A lab at the University of California, San Francisco, tried to do this in rodents by transplanting embryonic cells that give rise to GABA-producing neurons in older brains after birth. After the transplant, another critical period began but only when these cells reached one month of age, indicating that timing was under the control of specific genes. When our lab deleted such timing genes in young animals, the start of even the normal critical period was delayed.

Another equally challenging approach to restoring plasticity would be to remove the brakes that prevent a critical period from restarting. One check on plasticity resides in a latticework of cartilagelike molecules called a perineuronal net. It wraps around the parvalbumin neurons as they mature, bringing to an end the critical period and thus preventing synapses from undergoing further structural changes.

The perineuronal net consists primarily of chondroitin sulfate proteoglycans, a molecular complex of proteins studded with sugars. Brakes on plasticity disappear when enzymes eat away at these molecules. A British-Italian team rescued aged rats with amblyopia after injecting such an enzyme, a chondroitinase, into their brain, which then dissolved the perineuronal net. At that point, a new critical period opened. The rats received the needed visual stimuli they had missed as pups, which enabled them to recover good vision.

Researchers at the Friedrich Miescher Institute for Biomedical Research in Basel adopted a similar approach. They first trained rats so that they responded fearfully to a particular stimulus—cowering, for instance, when a bell rang. Memories of frightening experiences are stored in cells of a brain area called the amygdala. Elimination of the perineuronal net around these cells initiated a critical period. The animals then successfully underwent a new training regimen that conditioned them to no longer be afraid when exposed to the stimulus, just like an infant rat.

The safety of a procedure that requires injection of an enzyme deep into the brain would come under intense scrutiny by the U.S. Food and Drug Administration—and so will not likely receive approval anytime soon. A number of existing drugs, however, may be able to enhance brain plasticity to some degree. Our lab has been involved in a collaboration to conduct a small pilot study that has shown that a generic drug for epilepsy and bipolar disorder enables an adult to learn new things almost as easily as a child does.

In the study, we used a drug that lifted another brake on brain rewiring. The drug—an HDAC inhibitor—works by turning off an enzyme that tightly coils up DNA, preventing the making of proteins that promote brain plasticity. We wanted to see if inducing plasticity would let a group of adults acquire perfect pitch—a skill that usually needs to be learned before the age of six through exposure to music. Healthy men in their 20s who



TETRIS THERAPY with a special version of the video game taps into brain plasticity to enable both eyes to work in tandem, improving vision in a subject with amblyopia, an impairment in which one eye exhibits stronger visual acuity than the other.

received the drug were trained to distinguish tones in three octaves. None of them suddenly developed perfect pitch just by taking the drug, but by the end of the two-week training, they did perform significantly better at identifying these tones than did a placebo group of comparable size.

Commonly available drugs that increase the presence of other neurotransmitters—acetylcholine, serotonin and other molecules that indirectly control the rate of firing of neural circuits—may also help restore plasticity. Acetylcholine causes neurons to emit a sharply defined signal in moments of arousal. It does so by adjusting the balance between excitation and inhibition in much the same way that a critical period does.

Boston Children's Hospital is undertaking a clinical trial to determine whether a drug to treat Alzheimer's disease, called donepezil, which increases availability of acetylcholine, may restore normal vision to young adults with amblyopia by overcoming a brake on plasticity. Added acetylcholine means more of it can bind to its receptors on neurons. That limits the ability of a plasticity-inhibiting molecule—Lynx1—to dampen the activity of those receptors. Our previous studies have shown that removing this chemical relative of a snake toxin rekindles plasticity.

Acetylcholine is not the only neurotransmitter that may help treat amblyopia. Administering antidepressants such as Prozac that increase the levels of serotonin has alleviated amblyopia in rat experiments. In some cases, drugs may not even be needed. Action video games or meditation may also promote a heightened state of plasticity—and are being explored as possible treatments for amblyopia, attention-deficit/hyperactivity disorder and other conditions.

Researchers who work on critical periods often find themselves asking why these limits on learning exist in the first place. The ability to learn, say, Chinese as an adult as easily as a child

does would provide an obvious benefit to all members of our highly social species. Why, then, have the brains of humans and many other animals evolved to limit their own malleability? Is there some inherent danger to reopening a critical period when we want to learn a new skill? After all, is not genius “nothing more nor less than *childhood recovered at will*,” as French poet Charles Baudelaire once wrote?

Restricting plasticity may have ultimately evolved to protect brain cells. The high metabolic demands of parvalbumin cells generate free radical molecules that can damage brain tissue—one reason the perineuronal net may have evolved. A postmortem examination of the brains of patients with schizophrenia and other mental illnesses shows an overall loss of perineuronal nets and related neural brakes on plasticity.

Alzheimer's may provide a clue to the perils of unbridled plasticity. Higher-order brain areas, such as the associational cortex, responsible for complex cognitive functions, have evolved to remain plastic throughout a lifetime. These regions are

less endowed with chondroitin sulfate proteoglycans that shut down critical periods, and they are also the first to experience the deaths of cells in this neurodegenerative disease.

Philosophical arguments also emphasize the inadvisability of letting the brain change too much. Opening and closing critical periods as desired may benefit treatment of neurological diseases. But an individual's basic identity is also shaped during these formative times. As humans develop ever more ingenious technological means to alter their environment, they will be tempted to find new ways to enhance plasticity in adulthood to adapt to the rapid-fire changes around them. If rekindling plasticity is not undertaken with the utmost care, the rewiring of the brain could threaten to undermine one's sense of self. Such vexing trade-offs should not be forgotten as we are lured into creating technologies that allow us to recapture the plasticity of childhood as adults to better adapt to the demands of a protean modern world. ■

MORE TO EXPLORE

Neurodevelopment: Unlocking the Brain. Jon Bardin in *Nature*, Vol. 487, pages 24–26; July 4, 2012. www.nature.com/news/neurodevelopment-unlocking-the-brain-1.10925

Re-Opening Windows: Manipulating Critical Periods for Brain Development. Takao K. Hensch and Parizad M. Bilimoria in *Cerebrum*. Published online August 29, 2012. <http://tinyurl.com/pyg9jic>

Balancing Plasticity/Stability across Brain Development. Anne E. Takesian and Takao K. Hensch in *Changing Brains: Applying Brain Plasticity to Advance and Recover Human Ability*. Edited by Michael M. Merzenich et al. Elsevier, 2013.

FROM OUR ARCHIVES

Baby Talk. Patricia K. Kuhl; November 2015.

scientificamerican.com/magazine/sa