

Harnessing the Childhood Brain to Treat Alzheimer Disease, Autism, and Mental Illness

Bret S. Stetka, MD | March 10, 2016

Editor's Note:

In his recent Scientific American article, "Critical Ingredients for Brain Development,"^[1] Harvard Medical School neurology professor Dr Takao K. Hensch asks his readers, "What's on your music player?," answering, "If you're older than 30 years, it probably includes songs from your teenage years." He then goes on to quote Aristotle: "The habits we form from childhood make no small difference, but rather they make all the difference."

Hensch's piece—as well as his research—explores the potential clinical use of tapping into, or reigniting, the human brain's so-called "critical periods," intervals of neuronal plasticity that occur as we develop and that explain why it's easier to pick up certain tasks and skills during infancy and childhood. Medscape recently spoke with Hensch about his work and about how critical period manipulation could help treat neurologic, psychiatric, and developmental illnesses.

Medscape: To start, how do you define a critical period in the brain?

Dr Hensch: We consider a critical or sensitive period to be a time window when environment is particularly potent in shaping brain function. Essentially, it's a heightened level of plasticity in response to the environment.

Medscape: How long has this concept been around?

Dr Hensch: The term "critical period" was used about 100 years ago initially in response to embryogenesis and susceptibility to chemical insults in early development. There were vulnerable moments when teratogens and other chemicals could affect development. The critical period idea in terms of experience and gene-environment interaction really took off in the mid 1900s with imprinting studies of Konrad Lorenz and Nikolaas Tinbergen, who won the Nobel prize for studying chicks imprinting on their mother figure.

These were behavioral observational studies, and it really became a neurobiological question with the work of Hubel and Wiesel, who were studying the developing visual system and actually started recording changes in brain areas for those functions.

Medscape: It seems that visual system development often serves as a prime example of critical periods in the brain.

Dr Hensch: That's right. Amblyopia or the enduring loss of visual acuity as a result of something as innocuous as a lazy eye—so in the absence of any damage to the retina—leads to a massive rewiring in the visual cortex if it happens early in life but not later in life. There is no cure for amblyopia. It's a bona fide neurodevelopmental disorder, and it has consequences for depth perception but also for quality of life. It was something that could be studied in animals at great detail.

Medscape: This concept explains why it's easier to acquire new skills, such as learning a new language or sport, as a young person. Is that correct?

Dr Hensch: Yes. The idea was adopted by a number of fields, including psychology and linguistics. The anecdotal observations from Aristotle's time onward that it's easier to acquire new skills earlier than later in life started to leverage the idea that circuits in the brain would be plastic to a different degree in different time periods.

Reopening Critical Windows as Therapy

Medscape: Have critical windows been demonstrated neurobiologically in addition to observationally?

Dr Hensch: Yes. If you take the example of language, you have to break it down into its component parts. The acquisition of full-blown language with all of its beautiful grammar and vocabulary and semantics is a multistep process. It starts with the ability just to hear your native speech sounds versus nonnative speech sounds. That's already starting at birth, this process of "pruning," or perceptual narrowing, as the psychologists call it.

Infants are born with the ability to hear speech sounds of any language, frankly. Through a very quick process of neuronal pruning in the first several months after birth, kids in Japan stop hearing differences in the letter R and the letter L, whereas in the United States, they would keep that discrimination. Increasingly, there are neurophysiologic signatures being reported that go along with that. This is just the first step of the multistep process, which then involves matching visual input from the speaker's facial features to match the sounds they make, all the way up to learning a second language efficiently.

Medscape: Can you tell us about your research and the work of some other groups trying to essentially reopen these critical windows?

Dr Hensch: I'd say that initially we're trying to understand how these windows come about in the first place, and in doing so we are trying to understand if it's possible to reopen them. If we know that critical periods are windows of biological time, then the questions become pretty straightforward. What determines when they start? What determines how long they are? What turns them off?

Medscape: With the ultimate goal being some sort of therapeutic application?

Dr Hensch: Yes. That's right. If neurodevelopmental disorders are seen as altered trajectories of development, maybe we could recorrect those trajectories before it's too late. Or, if a kid has passed through these windows, or an adult has a brain injury when their brain is no longer in this highly plastic state, we could use this information about critical period biology to reopen it or increase plasticity as a therapeutic.

Medscape: In which specific conditions do you think this might hold some promise?

Dr Hensch: Frankly, I think most mental illnesses actually are a reflection of neurodevelopmental issues. The most obvious ones are actual developmental disorders like autism. I'll tell you the reasoning behind this in a minute, but a seemingly normal start to development often goes off track after a few years. Later-emerging illnesses like schizophrenia could very well be altered critical period timing, in this case perhaps closure or failure-to-close plasticity.

I can tell you about why we came up with this view. It's relying entirely on our cellular work and now using initially sensory areas like visual cortex. We've identified mechanisms that trigger and turn off these critical periods. Of note, many of these molecules are linked through genome-wide association studies to autism or schizophrenia. It becomes interesting to think that these fundamental mechanisms, which normally set up the nervous system, are somehow skewed. You have critical periods either happening too early or too late or failing to close, as I mentioned.

The Role of Neurotransmitters in the Control of Critical Periods

Medscape: Can you discuss the role of neurotransmitters such as GABA in controlling critical windows?

Dr Hensch: The neurotransmitter work was the first powerful demonstration that critical periods are not set in stone and determined simply by age. They reflect the biology of the brain, which is changing quite dynamically in those early months to years.

Basically, there are two types of neurons: excitatory and inhibitory. Excitatory neurons vastly outnumber the inhibitory ones. For decades, Hubel and Wiesel and others have focused on the excitatory neurons. Using gene targeting in mice

or pharmacologic approaches to perturb the excitatory networks directly has not been so straightforward in terms of affecting this critical period timing.

When we turned our attention to the inhibitory system, this whole process started to open up. If you create a mouse or raise animals in dark rooms so that visual experience never happens, the inhibitory circuits fail to develop fully, and in those animals, the critical period fails to begin, even though they might grow up to become an adult in age. We know it hasn't begun because we can rescue the animals by boosting inhibition with common drugs, like Valium® (diazepam) or other benzodiazepines that act via GABA. This was very interesting and suggested that maybe the natural critical period indicates that vision in mice develops about 1 month after birth. There's a significant amount of time when visual experience is happening. There are about 10 days of visual experience after the eyes open in these animals when plasticity doesn't kick in. It's a sort of "pre-critical" period. In fact, you can trick the system by giving drugs that enhance inhibition, like benzodiazepines, and the critical period starts earlier than normal, suggesting that the machinery for plasticity is there; it's just waiting to be tapped by the right level of inhibition. This bi-directional control over when a critical period happens has immediate implications for autism and a variety of conditions because the development of inhibitory circuits is consistently affected in at very least monogenic forms of autisms.

People now talk about excitatory/inhibitory balance, and when this balance is achieved, plasticity is possible. Even the experiment that I just described to you of giving benzodiazepine to a mouse before its critical period is something that happens in humans, or has happened in humans, when young infants are treated for a seizure, for example, or some other condition where inhibition might be faulty. Although treating the condition might be of immediate concern, there's a second issue here that enhancing inhibition prematurely can flip the switch and turn on these critical periods.

Drug Therapy Applications in Reopening Critical Periods

Medscape: Your lab and others have actually tested the influence of existing drugs on critical periods, including histone deacetylase (HDAC) inhibitors and the Alzheimer disease medication Aricept® (donepezil). Can you speak to these studies?

Dr Hensch: Those came about from the other side of the critical periods. If GABA and inhibitory circuit maturation trigger the window, what closes the window? We found that for many years, people just speculated that plasticity factors, whatever they might be, simply disappear or decline with age. We focused on the possibility that maybe the brain wants to actively stabilize itself and put on brake light factors to prevent too much rewiring, which is what the brain really wants to do. It's an adaptive machine. Those two examples you mentioned come directly from this idea.

We did an unbiased transcriptomic screen of factors that might come up with age, and one top hit was a molecule that dampens acetylcholine receptor function.^[2] If you knock out this molecule from a mouse, they have an open-ended critical period. They remain plastic throughout life. So, we wanted to translate that to human use, and we speculated that if a molecule comes up in our brain that dampens cholinergic transmission if we give donepezil, which is a cholinesterase inhibitor, you might be able to override that brake by keeping cholinergic tone high a little bit longer.

In fact, when we treat wild-type animals past their critical period with donepezil, we get a reopening of plasticity and recovery from amblyopia. We've moved that into a pilot clinical trial at Boston Children's Hospital, where we are treating amblyopic human participants past the age of 10 years, which is the end of their critical period, when the traditional treatment—patching the good eye—is no longer effective. We are finding that we see improvements in their visual acuity when they are taking this drug. Valproic acid has the same idea, but it lifts a different brake—an epigenetic brake.

Medscape: There was also an interesting study looking at critical periods and perfect pitch. What did this work find?

Dr Hensch: That was a valproic acid study.^[3] Basically, we noticed that now there are many ways in which we can move the timing of the critical period around premature GABA or delaying GABA function. Of note, whenever we

shifted the onset, the closure followed after a finite period of time. So, it seemed almost as if we were triggering a gene program, which then runs to completion. We took this idea and felt that maybe we could reopen the gene program by reopening the chromatin.

HDAC enzymes are involved in deacetylating chromatin and keeping it tightly wound to prevent gene transcription. If we give an HDAC inhibitor to an adult animal, sure enough, you can reopen a window of plasticity, and again, in mice, recover from amblyopia.^[4] Donepezil and valproic acid, are commonly used and already clinically approved for other purposes. We were able to run that study where we gave healthy adults, well past the critical period for pretty much everything, the valproic acid and paired it with training on a variety of critical period-type tasks. We found improvement on naming of notes without a reference tone.^[3]

Nondrug Approaches to Reopening Critical Periods

Medscape: It sounds like there are some promising pharmacotherapeutic avenues, but your *Scientific American* article also alluded to some potential nondrug approaches, like meditation and even video games, that might be able to tinker with the critical windows.

Dr Hensch: Yes. This involved thinking more deeply about what these drugs are doing. I told you about this biological motivation in animal studies that suggested that there are mechanisms in place to dampen cholinergic transmission, which is normally high during moments of arousal or tension. You can imagine noninvasive ways to heighten the tension. Video games are designed to do that. In the case of visual functional restoration, it might be the perfect storm. The video games are designed to be attention-grabbing. Neuromodulators like acetylcholine are secreted at high levels. It's paired with a game that is dependent on depth cues, so you're training the system in a condition where the brain is permissive for plasticity. Dennis Levi at University of California Berkeley School of Optometry and Daphne Maurer at McMaster University in Canada are doing this—having amblyopic individuals play action video games because they drive these neuromodulatory systems and pairing it with a first person shooter-type game, using depth cues, to hit targets.

Meditation is just another version of the same. Meditation is a way to control your attention or arousal state. There are no religious overtones here. We're just talking about the act of meditating and focusing your attention. It creates that kind of neurochemistry in your brain, and the issue then becomes, well, do you need to pair it with some kind of training of a function that you hope to change?

That, I think, is the major message from the valproic acid study as well.^[3] Taking one of these drugs is not enough to make your brain change; you have to pair that plastic state with intensive training. That's pretty much what kids do, too. They're in a plastic state, but they have to work at it to learn a language or a motor skill. We think that there may come a day where clever use of technology or meditation might be able to create this in a drug-free manner.

Drawbacks to Critical Window Tinkering and the Evolution of Stability

Medscape: What are the potential drawbacks of manipulating critical periods?

Dr Hensch: Critical periods shape who we are, the languages we speak, the preferences we have, the skills we have, and so on. If there were some magic bullet that allowed us to reopen a critical period, in the extreme, you might think that you would erase all of that or make all of your identity vulnerable to being reshaped. However, most people are hoping for add-on benefits that would alter personalities. I think the two approaches I just talked about are providing a window for adding on.

There are more extreme manipulations that can be done in animals but not yet in humans because they involve altering an extracellular matrix—for example, physically loosening up the neural circuitry. That has also been shown to allow circuit rewiring. A big question for the field is: With these multiple ways to reopen a critical period, to what extent are we really rewiring the anatomic connections, or are we tweaking the system as it is, and maybe there is some limit

to the amount of plasticity because we've all come through a critical period that set up the circuitry in the first place?

Medscape: Evolutionarily speaking, why wouldn't it be advantageous to have and maintain plasticity in our brains throughout adult life?

Dr Hensch: Evolutionarily, it's quite costly to make all of these brake-like factors throughout our adult life, but they are redundant and highly conserved. There must be some merit to stabilizing your neural circuits after a period of adaptation to your environment.

I think it worked for most animal species because their ability to change their environment is pretty limited. A mouse or a cat would live in a very restricted area. Once they've adapted to it in the first few weeks of life, they're good to go. But humans in the past century or so have really ramped up the ability to change their environment. You can get on a plane and be in a country that speaks a totally different language, and we're really testing the limits of our own biology.

I think the clearest example of this might be mental illness. The prevalence of mental illnesses in humans might, in fact, be an example as we get older and life span increases of having not enough or too much plasticity. I'll give you two examples to finish.

The first example is schizophrenia. Schizophrenia emerges relatively late in adolescence or into the 20s. The parts of the brain that are finishing or in their critical period then are prefrontal areas; and so, in fact, you see schizophrenia as a prefrontal kind of disorder with executive function and working memory-type issues. Many genes have been linked to schizophrenia. If you take a step back and look at the big picture, there are genes involved in excessive spine pruning or plasticity of circuits. There was a paper on this in *Nature* just a few weeks ago.^[5]

Other genes that are compromised are myelin-related genes, which are some of the brakes that would normally limit plasticity. Myelin is full of factors that prevent structural rewiring of circuits. This could be a disorder where the critical period doesn't quite close in time, and this may have a temporary advantage, so you may see heightened plasticity in the early stages of psychosis. There are anecdotally, of course, many observations of geniuses like John Nash, who had their brilliant insights as their psychosis was starting. Eventually, too much plasticity can be pathologic. What happens when you get too much pruning? The gray matter is a little thinner. You get a compromised inhibitory network. This eventually manifests as schizophrenia.

The second example that I think is also very intriguing is Alzheimer disease. Alzheimer disease is well known to affect the higher-order associational cortices first. It's a "last in, first out" pathology. Those are the parts of the human brain that have evolved to remain plastic longer and give us our advantage as a species to be able to acquire new experiences over a lifetime. Even at a molecular level, it's clear now that those are the parts of the brain that have fewer of these molecular brake-like factors. As human life span has increased, it might be that we are witnessing a consequence of too much plasticity again. The parts of the brain that degenerate first or are vulnerable to Alzheimer degeneration are those areas that are plastic longer.

Circling back to the mouse work, when we looked at the knockout mice that are missing that cholinergic brake, those animals are plastic longer. But actually at around 10 months of age, they start to develop a degenerative pathology. It could be that giving these animals a longer window to rewire their circuitry makes the system vulnerable to damage and oxidative stress, for example. These are just some ideas that suggest that stability is protective.

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