Critical Periods in Vision: Why my Friend Was Wearing an Eyepatch.

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Abstract
Our brain is plastic: it changes and adapts in response to our environment. While some circuits in our brain remain plastic during our whole life, others are capable of plasticity only at a certain age, and for a limited amount of time. These confined periods of intense development are called critical periods. Through the example of the visual system, we will explore the concept of critical periods in the brain, how they were discovered, what causes them, and how they contribute to the brain development in health and pathology.

Keywords
Critical period, Vision, Amblyopia, Monocular deprivation, Primary visual cortex, Ocular dominance

Peer Review
This work has undergone a double-blind review by a minimum of two faculty members from institutions of higher learning from around the world. The faculty reviewers have expertise in disciplines closely related to those represented by this work. If possible, the work was also reviewed by undergraduates in collaboration with the faculty reviewers.
**Introduction**

It was the third day of first grade. I had just started my new school hundreds of miles away from my old friends, my old home, and warm weather. It didn't help that the other kids already seemed to know each other. I had spent the past two recesses sitting alone reading. It wasn't until my third recess that I made my first friend. I was sitting alone re-reading one of my favorite books, when a girl came up behind me.

“What are you reading?” She asked. Startled, I slammed my book closed and looked up to see who had interrupted me. She looked nice enough—big smile, two braids and an eye patch?

“Nothing.” I say, “Just my book.”

“Oh, that’s cool. Why aren’t you playing?” She asks.

“Why aren’t you playing?” I ask back.

“I don’t like playing with the other kids. They call me pirate.”

“Oh. That’s mean. You can play with me if you want.” I smile at the girl with the eyepatch and she smiles back. And that was the beginning of our beautiful friendship. It didn’t occur to me then that meeting my friend with the eyepatch would give me my first introduction to a widely studied neuroscientific topic: **critical periods**.

What is a critical period?

The brain is the main organ responsible for our actions. Sensory organs, such as the eyes, ears, and skin, relay cues from the outside world to the brain. Our brain then processes this sensory information, makes a decision on how our body should react, and sends commands to the rest of the body. For example, if I see a cookie on the kitchen table, my brain will probably make me salivate, walk to the table, and grab the cookie. The brain adapts our behavior to the environment, defines how we respond to things, and makes us who we are.

Not only does the brain use our senses to make decisions, it can also adapt and learn from previous experiences, a phenomenon called **plasticity**. While some brain regions remain plastic during the entirety of an individual's life, others are capable of plasticity only at a certain age, and for a limited amount of time. These periods of increased sensitivity to sensory stimuli are called critical periods. More precisely, a critical period is a period during which sensory experience can significantly shape brain development (Katz, 1999). In brain regions that have a critical period, exposure to sensory stimuli during the critical period is “critical” for brain circuits to grow properly.

The existence of critical periods in the brain was first suggested in the 1950s by neurologist Wilder Penfield who hypothesized that there is an ideal time frame for individuals to learn a second language. According to Penfield, after this ideal time frame, language acquisition becomes extremely difficult (Singleton & Lengyel, 1995).

**Why was my friend wearing an eyepatch?**

But what do critical periods have to do with my friend wearing an eyepatch? My friend has a condition called **amblyopia**, also known as lazy eye. This means she has poor vision in one eye. Amblyopia can be caused by strabismus (the misalignment of the eyes), refractive errors in one or both eyes, or visual obstruction (Nabel & Morishita, 2013). These factors cause an imbalance of representation of the two eyes in the brain.

In order to better understand the consequences of such an imbalance, we first need to look at how the brain processes visual cues. As you probably know, our brain contains a special type of cell called neurons. Neurons, unlike other cells in our body, are electrically excitable, meaning that they generate small electrical pulses to communicate...
with each other. A special type of neurons, called sensory neurons, are responsible for sampling information from the outside world. The sensory neurons of our eyes are called photoreceptors. The retina, at the back of our eyeballs, is covered with tightly packed photoreceptors, much like the pixels of a camera sensor. Photoreceptors detect light, convert it to electrical impulses, and send these signals to the brain, so we can ultimately process the things we see (Figure 1A).

Visual information from both eyes travels through nerves and eventually reaches a brain region called the lateral geniculate nucleus (LGN) (Figure 1A). In other words, the LGN is the first brain relay of vision. Visual signals from the left and right eyes remain separated as they reach the LGN (Figure 1B). The LGN maintains this separation when it sends information to the primary visual cortex (V1), in the occipital lobe, at the back of our head. This projection pattern creates discrete regions at the surface of V1 that preferentially respond to one eye or the other, also known as ocular dominance columns (Figure 1B). Ocular dominance columns are necessary for V1 to process visual cues in an ordered fashion. Therefore, improper development of these columns usually leads to impaired vision.

How do ocular dominance columns develop in the brain? To answer this question, two scientists, David Hubel and Torsten Wiesel, conducted various experiments investigating the impacts of monocular deprivation in cats (Wiesel & Hubel, 1965). They found that when a cat undergoes monocular deprivation at a young age, the ocular dominance columns of the patched eye disappear, in favor of the unpatched eye (Figure 1C). However, in the adult cat, monocular deprivation has no influence on V1 columns (Figure 1D). From these experiments, Hubel and Wiesel concluded that (1) visual stimulations are necessary for the development of ocular dominance columns, and (2) there are periods of time in which the brain is more responsive to these stimulations. Hubel and Wiesel had described the first example of a critical period in the brain.

Now let’s get back to my friend. In normal vision, there is an even distribution of right and left ocular dominance columns in V1. However, in individuals with amblyopia, one of the eyes is weaker and therefore sends fewer visual inputs to the brain (Nabel & Morishita, 2013), just like monocular deprivation in Hubel and Weisel’s experiments. This results in fewer ocular dominance columns responding to the weaker eye. Thus, in individuals with amblyopia there is an overrepresentation of ocular dominance columns of the dominant eye. Due to this, amblyopia in children is often treated with monocular deprivation of the
dominant eye. Regular use of the eyepatch forces the overuse and strengthening of the weaker eye, ultimately allowing its representation in the brain (ocular dominance columns) to even out. Generally, optometrists recommend that children wear their eyepatch for at least two hours a day over the course of several months, however the precise treatment regimen is highly individualized and depends on amblyopia severity and patient age. Patients are advised to wear the eyepatch through daily activities whenever possible, and may sometimes be given additional exercises to complete while their dominant eye is covered (such as drawing/writing assignments). These exercises are intended to further strengthen the weaker eye. (Chen and Cotter, 2016).

In addition to an eye patch, alternative amblyopia treatments include atropine eye drops or Bangerter filters. Atropine eye drops—which are sometimes used to supplement eyepatch treatment—are applied to the dominant eye. Treatment with atropine eye drops results in blurred vision in the stronger eye, subsequently promoting the overuse/improvement of the weaker eye (Chen and Cotter, 2016; Holmes & Levi, 2018). Similarly, Bangerter filters are fitted into patients' glasses, and are intended to cover the stronger eye. These translucent filters have varying densities meant to impair vision in the stronger eye (Chen and Cotter, 2016).

That said, most amblyopia treatment regimens are only effective while the child is in the critical period of development for vision. Once the critical period is over, the child does not display the same sensitivity to sensory stimuli, and the optical correction strategies mentioned above will usually result in little to no shift of representation (Chen and Cotter, 2016).

**Are critical periods the same in everyone?**

The short answer is no—at least not for the visual system. In a 2018 study, a cohort of kids of different ages, all diagnosed with amblyopia, were prescribed a patch to wear for a fixed amount of time (Holmes & Levi, 2018). After wearing the patch, visual acuity in the weaker eye was reevaluated and compared across ages (Figure 2). Children showed various levels of improvement—this was true even for children who got their weaker eye patched at the same age. Importantly, all children wore their patch for the same duration in this study. If everyone had the exact same critical period, one would expect a similar level of improvement in individuals of the same age. But instead we see various degrees of visual improvements amongst individuals of the same age, generally supporting the conclusion that the critical period for vision is highly variable among individuals.

The critical period for vision typically lasts until about age seven. As mentioned, after this age, monocular deprivation becomes a significantly less effective treatment for amblyopia, although the exact time when the critical period closes differs between each person (Holmes & Levi, 2018).
What causes a critical period to “open” or “close” in the brain?

There are many different hypotheses regarding the biological mechanisms that cause critical periods in the visual system to either open or close. The critical period for a given system is thought to open in response to the essential inputs for that particular system (i.e., light for the visual system). This catalyzes a period of development in which neurons begin to make new connections based on environmental saliency (Katz, 1999).

In addition, critical periods initiate when there is a favorable balance between excitatory and inhibitory neurons. When there is an overabundance of excitatory neurons, this leads to synchronous firing, with no selective growth or development (Katz, 1999). However, when there are sufficient inhibitory neurons this allows for inhibition and only salient connections develop.

There are many different models to explain how critical periods close. One model proposes that extracellular matrix structures called perineuronal nets wrap around neurons in the brain, causing them to stabilize! Perineuronal nets restrict neurons, prevent new connections, and effectively halt the plasticity observed during the critical period (Nabel & Morishita, 2013).

What do critical periods look like in modalities other than vision?

Ok, so we’ve talked a lot about vision, but we have four other senses (sound, smell, touch and taste). Have critical periods also been observed in these modalities? Well, the answer is complicated. Vision is the most extensively studied modality with respect to critical periods, but emerging research suggests that we have sensitive periods for various other sensory functions (Voss, 2013).

Sensitive and critical periods are similar in that they are both developmental windows during which an organism experiences increased plasticity and sensitivity to its sensory environment (Voss, 2013). However, the critical period is considered a specific type of sensitive period. Deprivation of sensory input during the critical period can result in a permanent alteration of brain structure. This is exemplified in our earlier discussion of Hubel and Wiesel’s experiments. When cats underwent monocular deprivation during their critical period of visual development, this led to permanent changes in their brains and ultimately had permanent effects on their vision (Figure 1C). This same permanence is not observed in sensitive periods, which do not tend to result in irreversible structural organization in the brain (Voss, 2013).

However, although deprivation during the sensitive period may not result in a permanent change of function, once the sensory period of development for a specific sensory skill closes, it is extremely difficult for an individual to acquire that skill, as heightened plasticity and sensitivity to one’s sensory environment has largely waned.

We have sensitive periods for various things, and some of them are actually quite strange! For example, research suggests that we may have sensitive periods for absolute pitch (commonly referred to as “perfect pitch”) (Gervain et al., 2013), detecting differences between certain phonemes (word sounds) (Werker & Tees, 2005), and being able to distinguish and accept specific flavors of food (Harris & Mason, 2017).

Is there plasticity beyond the critical period?

Neuroplasticity is an extremely popular topic within neuroscience. This is partially because elucidating the mechanisms that underlie plasticity in the brain can provide crucial information about brain structure and development. Additionally, a better understanding of neuroplasticity can potentially help implement more sophisticated and personalized methods of injury treatment and prevention. Recent studies have therefore
investigated the mechanisms underlying plasticity and potential ways of prolonging plasticity beyond the critical and sensitive periods. A 2014 review by Hübener and colleagues suggests that there is indeed plasticity in the mature adult brain (Hübener & Bonhoeffer, 2014). The authors propose that plasticity in the adult brain is not altogether absent, but simply inactive and can potentially be reinvigorated using a combination of sensory stimulation and drug therapy (Hübener & Bonhoeffer, 2014). This combination may prompt structural reorganization in the brain.

That being said, different modalities may require different approaches. For example, fluoxetine, an antidepressant, has been shown to increase plasticity in the visual cortex of adult rodents (Hübener & Bonhoeffer, 2014). In humans, a drug called valproate is hypothesized to improve absolute pitch learning, even though the critical period of development for absolute pitch closes in childhood (Hübener & Bonhoeffer, 2014). While the mechanisms underlying the observed increase of plasticity in these two studies are not yet entirely understood, they suggest that it is possible to attain plasticity later in life.

However, it is important to note that the staggered development of the brain (i.e. timing of critical periods) is thought to be evolutionarily favorable/imperative for proper function (Katz, 1999). Thus, while the investigation of critical periods may inform future research and treatment, manipulating them may prove detrimental to survival and function.

Conclusion
The visual system provides insight into the underlying mechanisms and characteristics of critical periods. Research suggests that critical periods within the visual system are periods of plasticity that vary across individuals. Studies also indicate that humans have various critical and sensitive periods for different modalities and functions. Understanding how critical and sensitive periods work and when they occur, can allow us to effectively manipulate brain development and ultimately develop personalized treatment and support. This can be extremely helpful for individuals who have specific developmental or sensory impairments. It certainly helped my friend with her amblyopia—she hasn't worn an eyepatch in years! Future studies will hopefully continue to elucidate mechanisms underlying both critical periods and sensitive periods of brain development.

Competing interests
The authors have no competing interests to declare.

Authors’ contributions
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Glossary
- **Critical Period**: period during which the brain needs sensory inputs to grow properly. Not all brain regions have a critical period, and the time when the critical period opens and closes is different for different regions.
- **Plasticity**: the ability for the brain to adapt its circuits in response to a changing environment.
- **Monocular Deprivation**: when one eye is either covered with a patch or sutured, in order to deprive it from light. This is an experimental method used to study plasticity in animals, as well as a treatment for amplyopia.
- **Photoreceptors**: sensory neurons that detect light. There are two types of
photoreceptors in the human retina: rods and cones.

- **Ocular Dominance Columns:** clusters of neurons that preferentially respond to one eye in the visual cortex. In the primary visual cortex, ocular dominance columns normally develop during the critical period.

- **Neuron:** specialized cell that generates and transmits messages in the form of electrical impulses. Neurons communicate with each other through complex circuits in the nervous system.

- **Excitatory neuron:** a neuron that releases neurotransmitters that make receiving neurons more likely to fire/send signal.

- **Inhibitory neuron:** a neuron that releases neurotransmitters that make receiving neurons less likely to fire/send a signal.

- **Synchronous firing:** when neurons fire electrical impulses at the same time.

- **Sensitive period:** a period of time when an individual is more responsive to their sensory environment.

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