Essential brain circuit in visual development found: Study could lead to new treatments for amblyopia

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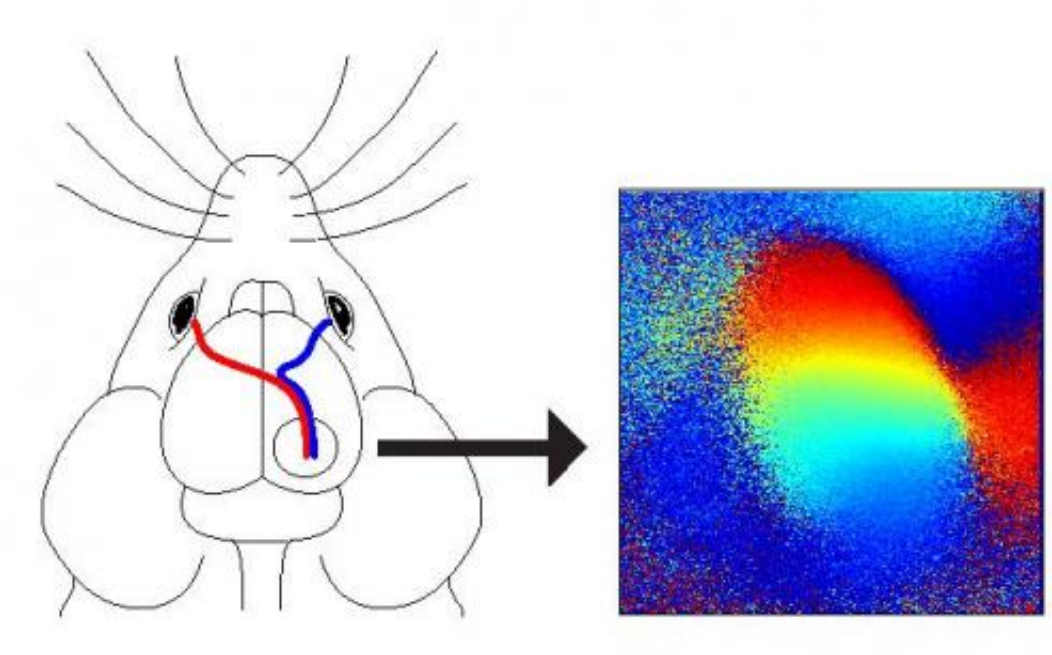

To trace the connections of the eyes to the brain in a mouse, different dyes can be placed into each eye. The left eye (red) and right eye (blue) mostly connect in separate territories. But they can both connect to the binocular zone (green-yellow). Amblyopia occurs when one eye is impaired and the other takes over this zone. Credit: Dr. Joshua Trachtenberg, UCLA.

A study in mice reveals an elegant circuit within the developing visual system that helps dictate how the eyes connect to the brain. The

research, funded by the National Institutes of Health, has implications for treating amblyopia, a vision disorder that occurs when the brain ignores one eye in favor of the other.

Amblyopia is the most common cause of visual impairment in childhood, and can occur whenever there is a misalignment between what the two eyes see—for example, if one eye is clouded by a cataract or if the eyes are positioned at different angles. The brain at first has a slight preference for the more functional eye, and over time—as that eye continues to send the brain useful information—the brain's preference for that eye gets stronger at the expense of the other eye.

Patching the strong eye can help correct amblyopia. But if the condition isn't caught and corrected during childhood, visual impairment in the weaker eye is likely to persist into adulthood.

"Our study identifies a mechanism for visual development in the young brain and shows that it's possible to turn on the same mechanism in the adult brain, thus offering hope for treating older children and adults with amblyopia," said Joshua Trachtenberg, Ph.D., an associate professor of neurobiology at the David Geffen School of Medicine, University of California, Los Angeles (UCLA). The study was published in *Nature*.

Within the brain, cells in a limited region called the binocular zone can receive input from both eyes. During brain development, the eyes compete to connect within this zone, and sometimes one eye prevails—a process known as ocular dominance.

Ocular dominance is a normal process and is an example of the brain's ability to adapt based on experience—called plasticity. But it can also set the stage for amblyopia. If one eye is impaired and can't effectively compete, it will lose space in the binocular zone to the other eye. Also, this competition takes place during a limited time called the critical

period. Once the critical period closes—around age 7 in kids—the connections are difficult to change. Some studies have shown, however, that it's possible to partially correct amblyopia in the teenage years.

"The new study identifies a key step in ocular dominance plasticity," Dr. Trachtenberg said. It was funded by the National Eye Institute (NEI) and the National Institute of Neurological Disorders and Stroke (NINDS), both part of NIH.

Much is known about the mechanisms behind ocular dominance. Fifty years of research on it has even led to a general theory of plasticity called the sliding threshold model. The new study tested a fundamental piece of this model that at first seems at odds with ocular dominance.

According to the model, plasticity can only proceed if the activity—or firing rate—of cells in the brain is above a certain threshold. Below this threshold, strong connections won't be made stronger and weak ones won't be eliminated. This is where it's difficult to fit ocular dominance to the model: If the binocular zone cells are only being driven by one eye, then their firing rate should drop by about half—below the threshold.

Working with the lab of Xiangmin Xu, Ph.D., at the University of California, Irvine, Dr. Trachtenberg and his team at UCLA investigated this problem in mice. To induce changes in ocular dominance, they temporarily patched one eye in young mice. After 24 hours, they removed the patch and recorded how the firing rate of binocular zone cells changed in response to vision through each eye.

They found that the cells' firing rates immediately dropped by half when vision was restricted to one eye, as expected. But over the next 24 hours, the cells responding to either eye—even the eye that had been temporarily patched—increased their firing rate back to the normal range.

The team's next goal was to explain the increased firing rate. "Since the signals from the patched eye to the binocular zone are reduced, we wanted to know what drives the increase," Dr. Trachtenberg said.

First, they investigated the possibility that the binocular zone cells were getting more stimulation from other parts of the brain, but that wasn't the case. Instead, the key turned out to be a brain circuit that normally inhibits the cells. When vision through one eye is impaired, the inhibition from that circuit gets weaker. This loss of inhibition restores the cells' firing rate to the range where their connections can be remodeled.

By manipulating this circuit, the researchers were able to prevent ocular dominance in young mice and induce it in older mice that were already beyond the critical period. If this circuit could be controlled in the human brain—for example, with a drug or with implants of the kind sometimes used to treat Parkinson's—it would open the door to correcting amblyopia years later than is currently possible, Dr. Trachtenberg said.

More information: Kuhlman SJ et al. "A disinhibitory microcircuit initiates critical period plasticity in visual cortex." *Nature*, August 2013. DOI: 10.1038/nature12485

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