David H. Hubel and Torsten N. Wiesel's Research on Optical Development in Kittens [1]

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During 1964, David Hubel and Torsten Wiesel studied the short and long term effects of depriving kittens of vision in one eye. In their experiments, Wiesel and Hubel used kittens as models for human children. Hubel and Wiesel researched whether the impairment of vision in one eye could be repaired or not and whether such impairments would impact vision later on in life. The researchers sewed one eye of a kitten shut for varying periods of time. They found that when vision impairments occurred to the kittens right after birth, their vision was significantly affected later on in life, as the cells that were responsible for processing visual information redistributed to favor the unimpaired eye. Hubel and Wiesel worked together for over twenty years and received the 1981 Nobel Prize for Physiology or Medicine for their research on the critical period for mammalian visual system development. Hubel and Wiesel's experiments with kittens showed that there is a critical period during which the visual system develops in mammals, and it also showed that any impairment of that system during that time will affect the lifelong vision of a mammal [2].

In 1959, David Hubel and Torsten Wiesel met in John Hopkins Medical School in Baltimore, Maryland, where they worked in Stephen Kuffler's neuroscience lab. That same year Kuffler and the staff of his laboratory moved to Harvard Medical School in Boston, Massachusetts. While working in Kuffler's new lab at Harvard, Hubel and Wiesel conducted a series of experiments on cats and kittens as models for humans [3], and in the 1970s they repeated the experiments on primates. Their collaboration lasted for over twenty years, during which time Hubel and Wiesel elucidated details about the development of the visual system.

During the 1960s, scientists did not fully understand the development of the visual system, although Kuffler and his laboratory staff studied it closely. Researchers had yet to discover the connection between the retina, a layer of light sensitive cells on the backside of the eye, and the visual cortex of the brain. As of 2017, scientists know that the visual system consists of the eye, the optic nerve, the lateral geniculate body, and the visual cortex of the brain. The retina of the eye has rods and cones that receive visual stimuli that include colors and the forms of objects. That information is sent to the brain through the optic nerve. In the brain, the optic nerves from each eye cross at the optic chiasm, which is a cross formed by the optic nerves on the bottom of the brain. The right optic nerve becomes the left optic tract and the left optic nerve becomes the right optic tract. The optic tracts further carry the visual information into the brain and end at lateral geniculate body in the thalamus, which is a small part of the brain that serves as a relay for sensory information from the eyes to the brain. The lateral geniculate body has geniculate cells that are at a midpoint between the eye and the visual cortex. After that, the information is transferred to the visual cortex, which is the largest area of the brain that is responsible for interpreting visual information and is located on the outer backside of the brain called the occipital lobe. The visual cortex has cortical cells that are responsible for processing and interpreting visual information.

In 1964 at the time the article was published, surgeons operated on individuals with congenital cataracts, a disorder in which the lens of the eye is clouded upon birth, later in those individuals' lives rather than at birth. Those individuals required intensive treatment after surgery, as there was still impairment to vision in the affected eye. Hubel and Wiesel questioned why their vision remained impaired. Hubel and Wiesel hypothesized that there was a time period during which the visual nerve cells develop and that if the retina did not receive any visual information at that time, the cells of the visual cortex redistribute their response in favor of the working eye. By 1964, Hubel and Wiesel performed a set of experiments to test their hypothesis. Other researchers had studied the behavior and vision of animals after they were raised in the dark, but Hubel and Wiesel were the first to study animal behavior after physically suturing one of the eyes, thus further reducing the visual input to the retina.

For the purpose of the experiment, Hubel and Wiesel used newborn kittens and sutured one of their eyes shut for the first three months of their lives. The sutured eye did not get any visual information and received 10,000 to 100,000 times less light than the normal eye. That meant that there was no visual information for the retina of the sutured eye to record and thus the visual cortex could not receive any input from that eye. Hubel and Wiesel used four kittens for the experiment.

After three months, Hubel and Wiesel opened the sutured eyes, and recorded the changes. They found a noticeable difference in cortical cell response. The researchers recorded the activity of the visual system in each kitten by inserting a tungsten electrode into the sedated kitten's visual cortex of the brain, which let them monitor the activity of each cortical cell separately. The tungsten rod detected electrical activity or inactivity in the cortex, which indicated whether or not the visual cortex retrieved information from the previously sutured eye. By recording electrical activity in the kittens' visual cortex, Hubel and Wiesel observed how the cells of the visual cortex reacted to different stimuli from both eyes and whether or not there was a difference in the signals from the previously sutured eye and the normal eye.

Next, Wiesel and Hubel showed the kittens different patterns of light to stimulate the cortical cells. Normally, about eighty-five

percent of cortical cells respond identically to both eyes in a mammal [2] with normal vision and only fifteen percent of those cells respond to one eye only. However, when Hubel and Wiesel performed the experiment on kittens with previously sutured eyes, they found that one out of eighty-four cells responded to the previously sutured eye and the other eighty-three cells responded to the normal eye only. That meant that the cortical cells redistributed to favor the normal eye, as it was their only source of visual information during the early development of the kitten. The researchers also noted that all kittens who had one of their eyes sutured had some cortical cells that did not respond to any stimuli at all. The researchers concluded that those cells were likely only associated with the previously sutured eye. Because those cells did not respond at all to any visual stimuli, they had not regenerated and could not be used again. That meant that some cortical neuron [4] function can be fully lost if a vision impairment occurs during visual system development.

Hubel and Wiesel also performed a simple vision test on the kittens. They put an opaque barrier on one eye of the kitten and monitored the kitten's movement. They later repeated the same procedure for the other eye. The researchers noted that when the kittens were allowed to see with the previously sutured eye, they were uncoordinated and showed no signs of vision. However, the normal eye functioned properly and the researchers noted no impairment. Those findings meant that the previously sutured eye had lost its vision function and was not able to recover upon being open, which provided further evidence that previous vision deprivation affects long-term vision. Hubel and Wiesel concluded that an abnormality occurred somewhere within the visual pathway from the eye to the brain that caused the cortical neurons to redistribute and function only with the normal eye.

Hubel and Wiesel investigated where in the vision pathway the abnormality of vision cells came from. They sought to know whether the abnormality was a cortical or a geniculate abnormality, as that information would reveal how the vision pathway works. Another question that they asked was whether or not depriving the kittens of light or form (sight of object) caused the abnormality in the vision pathway. Their research aimed to explain how the deprivation of either one related to the continuous vision impairment in children after surgery. Hubel and Wiesel also questioned if the kittens' visual system reacted to the visual impairment the same way the system of an older or an adult cat would. Their findings sought to explain whether the connections made by the visual system before birth were innate or developed after birth. Finally, Hubel and Wiesel questioned whether the neural connections would deteriorate if an impairment was present, or whether the neural connections could not develop in the presence of an impairment. To answer those questions, Hubel and Wiesel performed multiple experiments with kittens and adult cats.

Following the vision tests, Hubel and Wiesel sought to answer where the abnormality occurred and how it worked. They checked the lateral geniculate body, which is a transfer site in the thalamus that receives visual information from the retina and transfers it to the occipital lobe of the brain. The cells in the lateral geniculate body normally respond more to one eye than the other. The vast majority of the geniculate cells that were associated with the previously sutured eye were intact and worked properly. However, upon analyzing those cells with a microscope [5], Hubel and Wiesel found that the cross sectional area of the lateral geniculate body had shrunk an average of forty percent and that some geniculate cells were smaller and contained little substance inside. That meant that the cells were not being used nearly as much as they could have been, causing the entire area to atrophy. The lateral geniculate body atrophied because it was receiving only half of its normal visual information, but it continued to transfer visual information from the eye to the brain. The researchers found no other physical abnormalities anywhere along the visual pathway. Hubel and Wiesel concluded that the abnormality that caused vision loss of the sutured eye likely occurred somewhere in the cortex of the brain, which was the last stop in the visual pathway.

Next, Hubel and Wiesel investigated whether the visual impairment in the kittens was caused by the deprivation of light or the depreciation of viewing forms. Light refers to colors as well as light or dark perception of the eye, while form refers to recognizing shapes of different objects. To determine the cause of the visual impairment, the researchers took the newborn kittens and put an opaque barrier over one of their eyes, which reduced the incoming amount of light to only ten to one hundred times. However, the barrier did not allow the kittens to distinguish forms or shapes. The results indicated that cortical cells only responded to the open eye, but the morphological changes in the lateral geniculate body cells were significantly reduced. Those findings suggested that cortical cells redistributed due to form deprivation, while the morphological abnormalities of the lateral geniculate body were due to light deprivation.

Next, Hubel and Wiesel investigated whether those visual effects would be replicated in older kittens that had already experienced vision. For that purpose, they sutured the eye of kittens shut at nine weeks of age for one month. Upon opening the eye, the researchers found that the distribution of cortical cells between eyes was still largely in favor of the open eye. However, there was almost no difference to the lateral geniculate body size. That, once again, established that the source of abnormality was cortical and not geniculate.

The researchers also tried the experiment with adult cats. They observed after visually depriving adult cats for several months, that the cats did not display any changes in cortical cell distribution or changes in the morphology [6] of their lateral geniculate bodies. Hubel and Wiesel concluded that younger kittens were most at risk for developing cortical abnormalities and, thus, blindness. That risk declined with every month of life and was almost non-existent in adults. Hubel and Wiesel found that there was a period at the beginning of kitten's life when the ability to view light and forms was most important for development.

Finally, Hubel and Wiesel researched whether visual pathway connections were present at birth and deteriorated with disuse or whether they did not develop if not used early on. To determine that, they experimented with three more kittens. The

researchers closed the eye of one of the kittens when the kitten was eight days old, which is about the time that eyes first start to open in kittens. They closed the eyes of the other two kittens after one to two weeks of age. The researchers studied the electrical connections in the brain at birth for all three kittens and found that their cortical cells responded to visual stimuli similarly to those in adult cats. This observation meant that the cortical cells had some ocular dominance. However, the cats could recognize the stimuli from both eyes. Hubel and Wiesel studied the same electrical connections in the brain later, after reopening the sutured eyes, and found that they had deteriorated and that cortical cells had redistributed in favor of the normal eye yet again. Hubel and Wiesel concluded that the neural pathways in the visual system are present at birth and deteriorate with disuse.

Hubel and Wiesel's experiment helped uncover how the visual system develops in mammals. First, they found a critical period during which the visual system developed and learned that the deprivation of vision during that time could impair vision forever. The conclusions of Hubel and Wiesel's experiment led surgeons to operate on congenital cataracts as soon as the infant was diagnosed. In 1981, Hubel and Wiesel received a Nobel Prize for Physiology or Medicine for their research on the development of the visual system.

Sources

1. Hubel, David H., and Torsten N. Wiesel. "Effects of monocular deprivation in kittens." *Naunyn-Schmiedebergs Archiv for Experimentelle Pathologie und Pharmakologie* 248 (1964): 492–7. http://hubel.med.harvard.edu/papers/HubelWiesel1964NaunynSchmiedebergsArchExpPatholPharmakol.pdf [7] (Accessed September 10, 2017).

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