Gamers map neural circuit that “sees” motion

May 4, 6pm ET (US)

EyeWire, the world’s first game to map the brain, has published a new wiring diagram for a neural circuit in the retina. The finding appears in the May 15 issue of *Nature*, and suggests a new solution to a problem that has eluded neuroscientists for 50 years: how does the retina detect moving visual stimuli? The wiring diagram supports the idea that certain kinds of retinal neurons—bipolar cells and starburst amacrine cells—are wired together to form a time-delay neural network that computes the direction of a moving stimulus. Computer simulations of time-delay neural networks are already used in artificial intelligence applications like speech recognition.

The wiring diagram was reconstructed from extremely high resolution images of a mouse retina acquired using serial electron microscopy. A similar approach was used in the 1970s and 80s to reconstruct the full wiring diagram, or connectome, of the roundworm *C. elegans*. “We are excited by our discovery because it demonstrates how connectomics can yield information that is critical for understanding the functioning of the mammalian central nervous system,” explained Sebastian Seung, professor at the Princeton Neuroscience Institute and Department of Computer Science. Seung is currently transitioning to Princeton after 15 years on the faculty at the Massachusetts Institute of Technology.

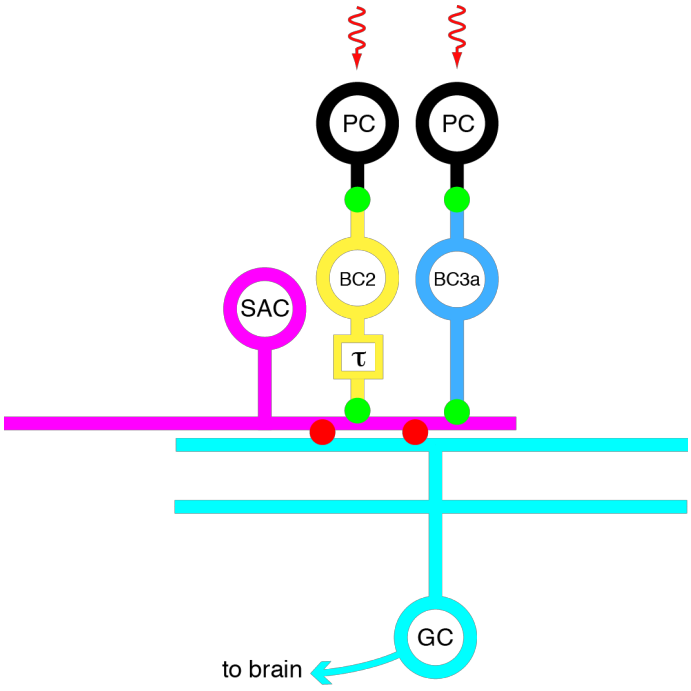
Visual perception starts in the retina

One might think that the only function of the eye is to capture an image and send it to the brain. The retina, the sheet of neural tissue at the back of the eye, does indeed sense incoming light, but this is just one of its many capabilities. The retinal neurons that send signals from the eye to the brain are called ganglion cells. In 1964, neuroscientists discovered types of ganglion cells that detect moving stimuli. Each neuron is activated by motion in a specific direction (up, down, left, or right), but not by motion in the opposite direction. This phenomenon is known as “direction selectivity,” and its discovery demonstrated that the visual perception of motion already starts in the retina. Perhaps the retina evolved this capability because perceiving motion is so crucial for survival, as in the examples of a person jumping away from an oncoming car, or a frog striking at a buzzing fly. Although half a century has passed since the original *description* of direction selectivity in the retina, a satisfactory *explanation* of this phenomenon has been difficult to achieve.

Following the trail

Explaining how the brain works is obviously challenging. Sophisticated and uniquely human faculties like language are still mysterious. However, it may be surprising to hear that the visual perception of motion, a seemingly trivial capability of many animals, has not yet been explained. The workings of the mind, whether simple or complex, depend on the transmission of information along “neural pathways.” A pathway traverses branches of neurons, which are like the “wires” of the brain, and also jumps from neuron to neuron across synapses. A major barrier to understanding the nervous system is that its pathways remain largely uncharted, even in the retina.

All pathways in the retina start with photoreceptors, the cells that sense incoming light. All pathways end with ganglion cells, the output neurons of the retina mentioned above. It has been difficult or impossible for neuroscientists to follow pathways through the retina, all the way from the input to the output. EyeWire has helped accomplish just that for two newly discovered pathways relevant for motion detection. The result is a new wiring diagram including four broad classes of retinal neurons: photoreceptor, bipolar, amacrine, and ganglion cells.



The wiring diagram is restricted to specific types of neurons within these classes. The ganglion cells (GC) are the direction-selective types that were discovered in 1964. The amacrine cells are of the starburst type (SAC), which was discovered in the 1980s. The bipolar cells (BC) are of Types 2 and 3a, discovered in the 2000s. The wiring of bipolar to starburst amacrine cells was previously unknown. By uncovering this wiring, the present study finally traces two pathways all the way through the retina, one pathway through the Type 2 bipolar cell and the other pathway through the Type 3a bipolar cell.

Play a game for science

The new wiring diagram was extracted from extremely high resolution images of a mouse retina. The most difficult step of this process was the 3D reconstruction of starburst amacrine cells. EyeWire enlisted volunteers to help by playing an online game resembling a 3D coloring book. The “lines” of the coloring book were the boundaries of neurons. Players traced the branches of starburst amacrine cells through the retina by coloring the interiors of cells, while staying inside the boundaries of the cells.

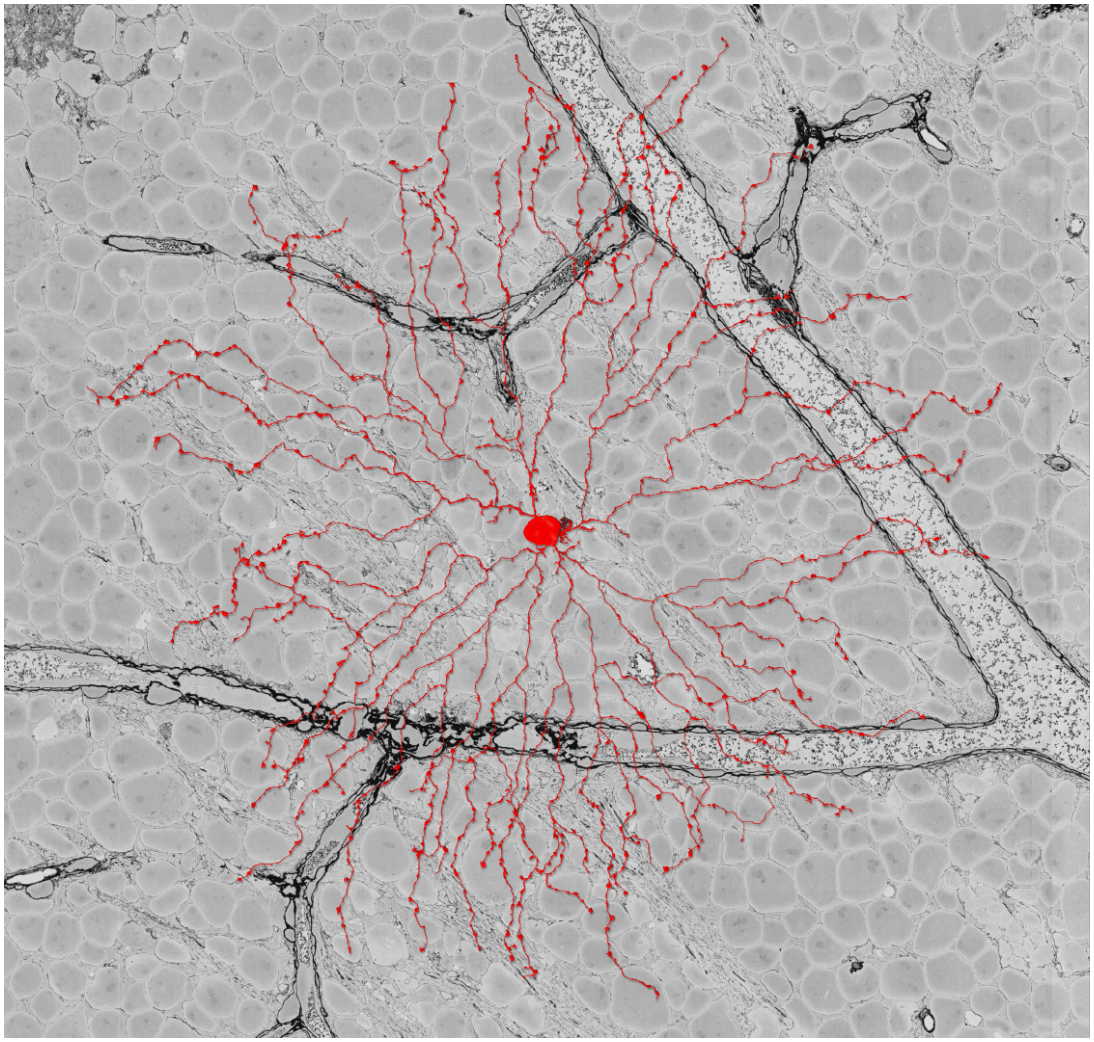
Starburst amacrine cells are some of the most difficult neurons to reconstruct, because their branches are so thin. The power to reconstruct these neurons was “unlocked” for EyeWirers who passed a challenging test of accuracy. The usernames of EyeWirers (2,183 in total) who contributed starburst reconstructions are listed as coauthors in the Supplementary Information of the *Nature* paper.

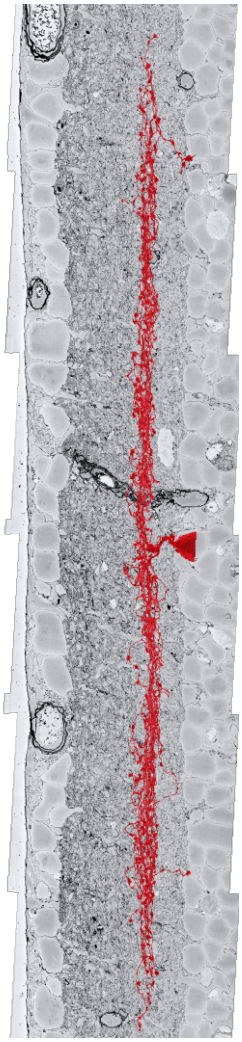
EyeWire has registered over 120,000 players from more than 100 countries. Most players have little or no formal training in neuroscience. Now anyone, anywhere, can participate in neuroscience research by playing a game of coloring neural images. This breaking down of barriers is part of a larger trend termed “citizen science,” “open science,” or “Science 2.0.” Amy Robinson, Creative Director of EyeWire, expresses her enthusiasm for this new approach to discovery: “Crowdsourcing has the potential to recapture and propagate wonder for this amazing world in which we live. Participants learn, they contribute, they participate in something bigger than themselves—it's uniting and empowering.” crazyman4865, a top scoring EyeWirer and creator of several EyeWire add-ons, is pleased by the discovery, remarking “and they say games are a waste of time.”

Oxford University astrophysicist Chris Lintott, one of the fathers of online citizen science and director of the Zooniverse, says that the “acid test of any citizen science project is whether it actually produces science—and it’s fabulous to see the first results from EyeWire which add neuroscience for the first time to the list of subjects to which the distributed power of the crowd has made important contributions. The results are a testament to EyeWire’s careful design and the enthusiasm and ability of the community it gathered.”

The star of the show

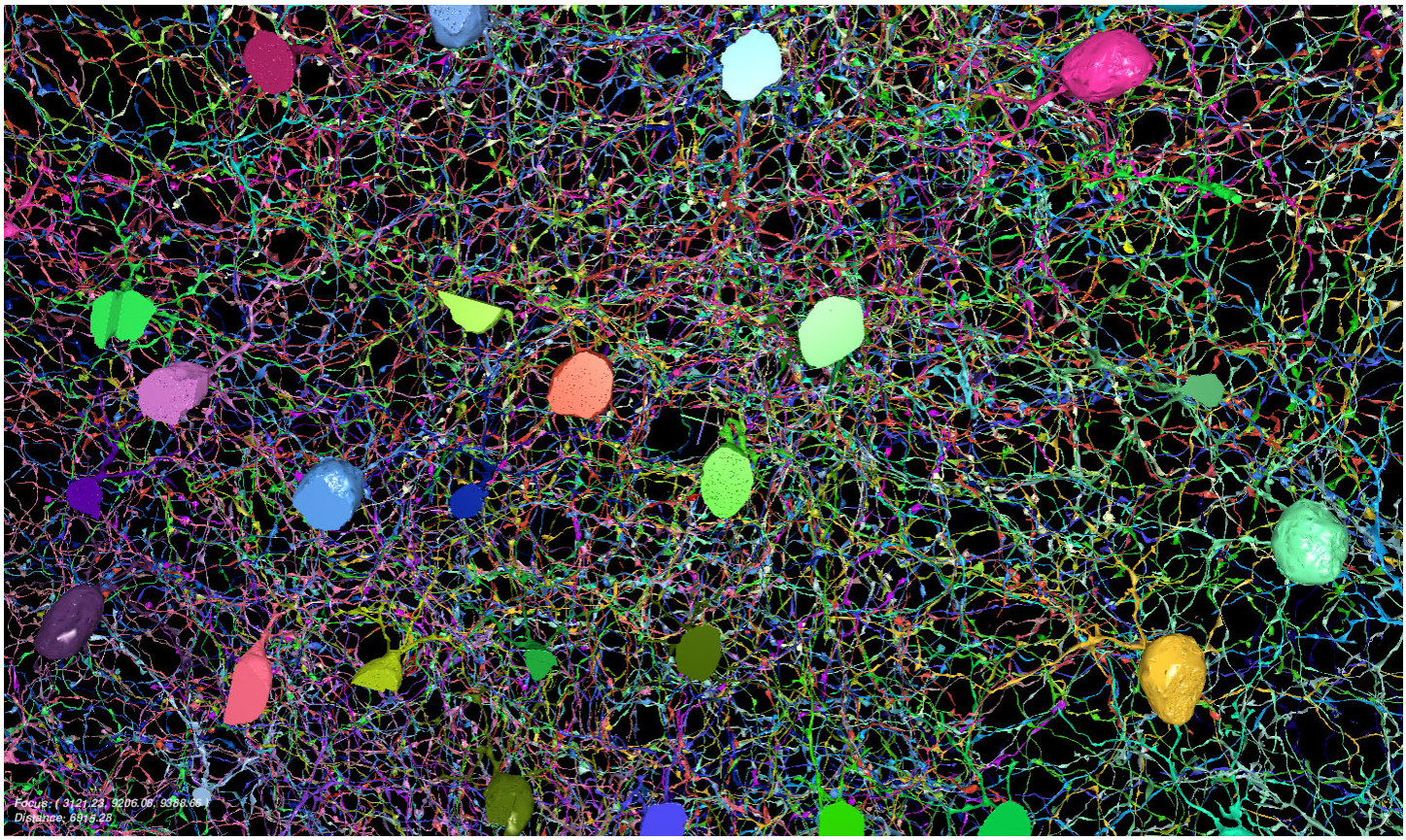
Two views of a real starburst amacrine cell (red) are shown below, along with high resolution images of the retina (grayscale) that were used for reconstructing the cell. The left view shows many thin branches extending from a centrally located “cell body,” which contains the nucleus and DNA. The whole image is about 0.3 mm across. The right view shows that the cell is flat like a pancake, and after rotation by 90 degrees corresponds to the cartoon representation of the starburst amacrine cell in the wiring diagram above. The starburst amacrine cells of this study were reconstructed from a mouse retina. Analogous cells have also been found in the human retina, so the present study is likely relevant to human visual perception.





In 2002, it was discovered that each branch of a starburst amacrine cell exhibits direction selectivity. Each branch is activated by a stimulus that moves outward from the center of the cell towards the tip of the branch, and is not activated by a stimulus that moves inward. In the anthropomorphic jargon of neurophysiologists, each branch is said to “prefer” motion in the outward direction.

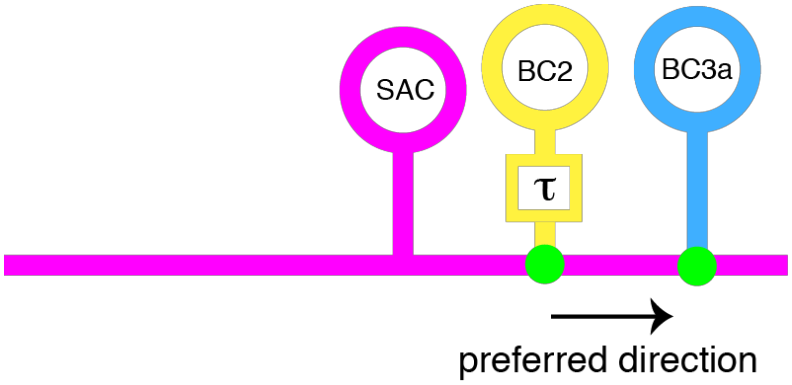
The views above are a bit misleading, because starburst amacrine cells actually overlap densely, rather than occurring in isolation. Their branches weave a tangled carpet, so that there are branches with many preferred directions at any location in the retina, as shown below.



It is now accepted that direction selectivity first emerges in starburst amacrine cells, and is then passed on to ganglion cells (see wiring diagram above). But the mechanism by which direction selectivity first emerges has remained unclear.

A time-delay neural network

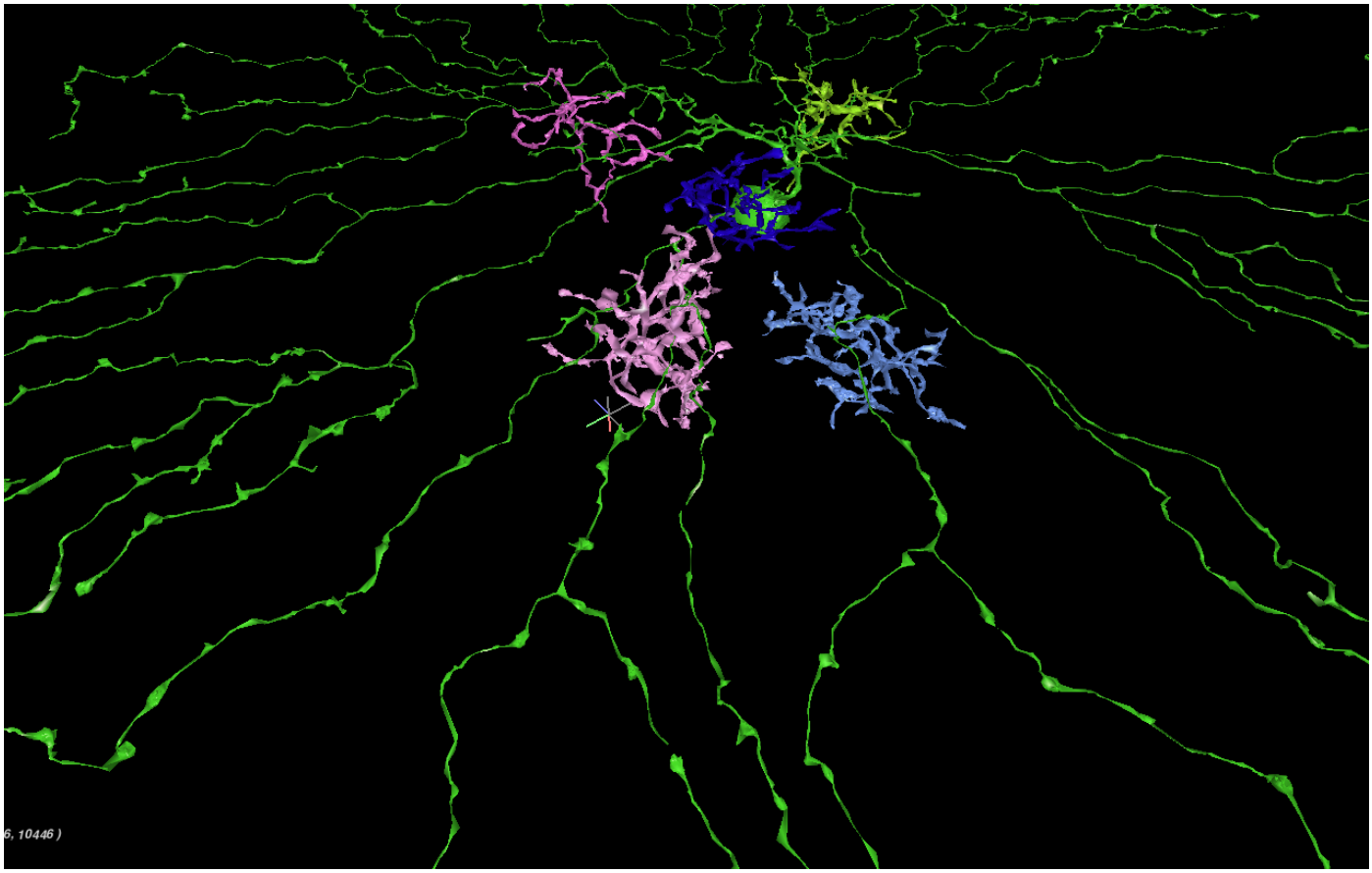
A new answer to this question is suggested by the part of the wiring diagram involving bipolar cells and starburst amacrine cells.



Type 2 bipolar cells (BC2) tend to connect with starburst amacrine cell (SAC) branches at locations near the cell body, while Type 3a bipolar cells (BC3a) prefer locations far from the cell body. The new answer also depends on a fact discovered in 2013, that BC2 responds to visual stimuli more slowly than BC3a. The time delay is indicated in the wiring diagram by the Greek letter “tau,” and is estimated to be around 50 milliseconds.

If a visual stimulus starts out near the cell body and moves outward (“preferred direction”), it activates BC2 first and BC3a second. Because of the time delay, the BC2 and BC3a signals reach the SAC at the same time. Together the signals are strong enough to activate the SAC. On the other hand, if a visual stimulus starts out far from the cell body and moves inward, it activates BC3a first and BC2a second. Because of the time delay, the signals reach the SAC even further separated in time. By itself, each signal is too weak to activate the SAC.

The above wiring diagram is a cartoon based on reconstructions of real starburst amacrine cells and bipolar cells, a few of which are shown below.



Technologies for neuroscience

EyeWire is the culmination of many years of technology development. The high resolution images of the retina were provided by coauthor Winfried Denk of the Max Planck Institute of Medical Research in Heidelberg, Germany. The images were acquired using serial block face scanning electron microscopy, a technology developed by Denk over more than a dozen years.

EyeWire appears simple on the surface, but its operation depends on sophisticated techniques from computer science that were developed in the laboratory of Sebastian Seung at MIT. EyeWire combines the gameplay of many people to produce 3D reconstructions of neurons. “Crowd wisdom” techniques are used to make the reconstructions more accurate than any single person could achieve. Rather than coloring neurons completely manually, players color more rapidly by interacting with an artificial intelligence based on a “deep learning” convolutional network.

The paper also contains a mathematical model of the neural circuit for motion detection that is based on the new wiring diagram. This model was studied in collaboration with coauthors from Qualcomm Research.

Structure yields clues about function

In his award-winning book *Connectome*, Sebastian Seung previously argued that neural wiring diagrams are crucial for understanding how the brain works and why it malfunctions. This view has aroused controversy, some of which can be seen in a 2012 public debate held at Columbia University between Seung and NYU neuroscientist Tony Movshon. Skeptics say that a static wiring diagram is not helpful for explaining dynamic brain function. In fact, the present work on retinal motion detection demonstrates that a wiring diagram can be critical for the perception of a dynamic stimulus.

Richard Masland, professor of ophthalmology at Harvard Medical School and one of the original discoverers of starburst amacrine cells, says “this is a very nice piece of work. It shows exactly the kind of question that the high resolution images of electron microscopy can answer. It is also a demonstration of how unexpected new truths can emerge from structural neurobiology.”

The retinal connectome

EyeWire is on the road to finding the *complete* wiring diagram or connectome of the retina, which will become an indispensable resource for visual neuroscientists. At the same time, the present study demonstrates that even a small part of the connectome is already helpful for understanding retinal function. According to Jinseop Kim, coauthor of the study and postdoctoral researcher at MIT, “Common misunderstandings about connectomics are that the goal is to blindly draw the complete wiring diagram of the entire brain, or that the real research can start only after the connectome is complete. Neither is true. We are unveiling the mysteries of neural circuits little by little on our way towards the connectome.”

About EyeWire

The EyeWire community includes volunteers around the world who cooperate with the laboratory of Sebastian Seung. EyeWire and the development of its computational technologies were supported by the Gatsby Charitable Foundation, the Howard Hughes Medical Institute, the Human Frontier Science Program, an anonymous donor, and the National Institutes of Health.

EyeWire Contacts

Amy Robinson <neurons@mit.edu>, Creative Director
Sebastian Seung <seung@mit.edu>, Scientific Director