Researchers decode retinal circuits for circadian rhythm, pupillary light response

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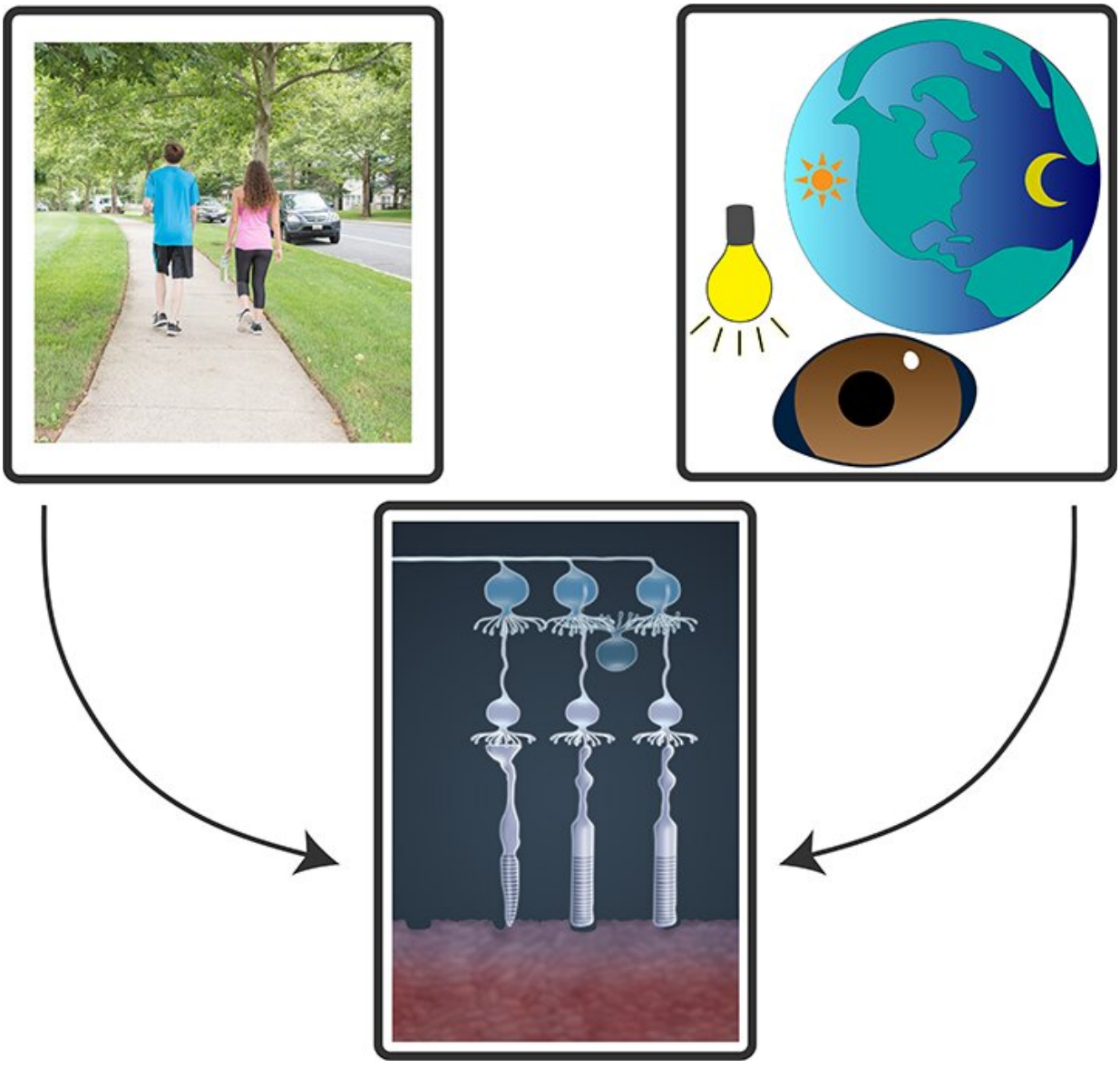

Image-forming and non-image-forming visual functions use distinct circuits in

the retina. Credit: National Eye Institute

The eye's light-sensing retina taps different circuits depending on whether it is generating image-forming vision or carrying out a non-vision function such as regulating pupil size or sleep/wake cycles, according to a new mouse study from the National Eye Institute (NEI) and the National Institute of Mental Health (NIMH). Published in *Cell Reports*, the findings could have implications for understanding how our eyes help regulate mood, digestion, sleep, and metabolism. NEI and NIMH are part of the National Institutes of Health.

"We know a lot about pathways involved in image-forming vision, but until now it remained unknown if and how non-image-forming visual behaviors rely on these same pathways in the eye," said Johan Pahlberg, Ph.D., head of the Photoreceptor Physiology Group at NEI and a senior author of the study.

Vision begins when light travels into the eye and hits the retina's light-sensing photoreceptors. The photoreceptors transfer signals through several layers of retinal neuron before those signals are sent to the brain. Light also triggers certain non-vision functions, such as controlling how much light enters the eye through the pupil (pupillary light reflex) and regulating the wake/sleep cycle (circadian rhythm). Circadian rhythm disruption has been linked to sleep problems, obesity, and other health issues.

To investigate pathways used by image-forming versus non-image-forming functions in the retina, Pahlberg and colleagues studied groups of mice that had been genetically modified to turn off one or more pathway links, or synapses, between photoreceptors and their next downstream neuronal neighbors, called bipolar cells. The group

investigated the roles of rod photoreceptors, which are sensitive to low light levels; cone photoreceptors, which see color; as well as three types of bipolar cells: rod bipolar cells, "on" cone bipolar cells, and "off" cone bipolar cells.

"On" cone bipolar cells react to increases in light, and "off" cone bipolar cells react to decreases in light. Cone photoreceptors can only communicate with cone bipolar cells, while rod photoreceptors have pathways to communicate with each of the bipolar cell types, depending on the level of light. Bipolar cells then communicate with other neurons in the retina, passing information to the optic nerve and on to the brain. Some mice in the study had no functional connections between rods and "on" bipolar cells, for example, or connections between cones and any bipolar cells, or lacked connections between rod and cone photoreceptors.

The researchers compared the mice's responses to visual stimuli while assessing pupillary light responses and monitoring their nocturnal wake/sleep cycle. They determined that while image-forming vision can use rod and cone photoreceptors, as well as all the types of bipolar cells, the same was not true for non-image forming functions. The pupil response relies exclusively on rod photoreceptors, while cones are unable to control this behavior. Meanwhile, both circadian rhythm regulation and the pupil reflex only use "on" bipolar cells pathways, relying on rod bipolar cells and "on" cone bipolar cells, but not "off" cone bipolar cells.

"We were really surprised to find that animals with only 'off' bipolar cells can't adjust to changes in the day/night cycle, but can still see and respond to visual events, meaning they have functional image-forming vision. It was really interesting to us that the non-imaging forming functions completely ignore information from the 'off' pathway," said Pahlberg. "We were equally surprised that rod photoreceptors, which are optimized for low light conditions, were still being used for the pupillary

response even when light levels were high. We really thought the rods would be maxed out at that point."

Pahlberg expects many of these findings in mice will hold true for humans, since the retinal circuitry is similar across mammals. Moving forward, he intends to explore other non-image-forming functions of the retina, like mood regulation, and see how else these different retinal circuits are being used.

More information: Corinne Beier et al, Divergent outer retinal circuits drive image and non-image visual behaviors, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111003

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