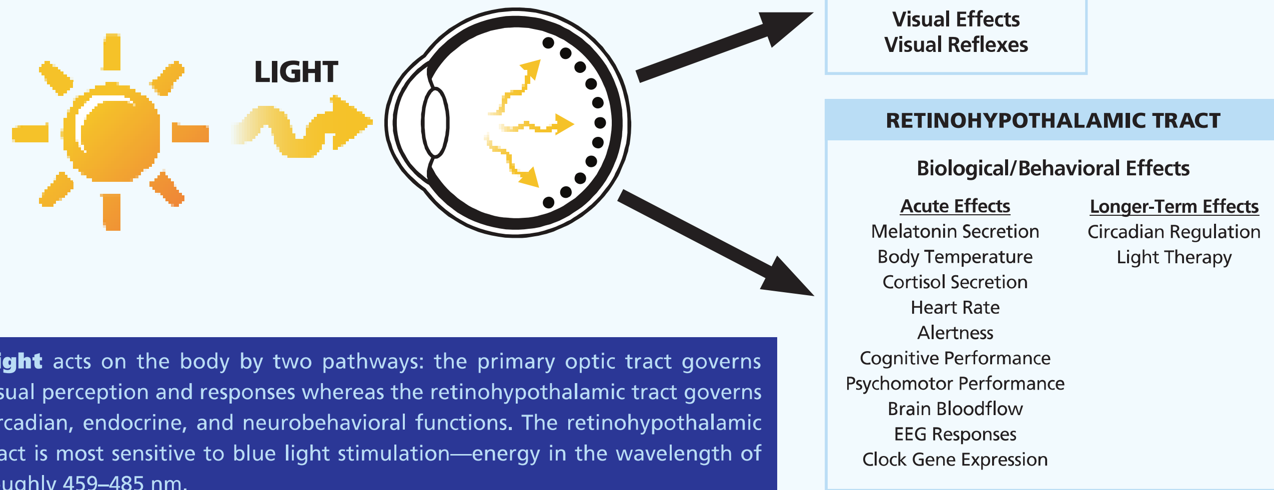
Light: An Influential Environmental Agent



Light acts on the body by two pathways: the primary optic tract governs visual perception and responses whereas the retinohypothalamic tract governs circadian, endocrine, and neurobehavioral functions. The retinohypothalamic tract is most sensitive to blue light stimulation—energy in the wavelength of roughly 459–485 nm.

Source: Benjamin Warfield and George Brainard/Thomas Jefferson University. Adapted by Matthew Ray/EHP.

During the 24-hour light/dark cycles, the researchers sounded a gong as they replaced light with darkness, to remind subjects of daily procedures such as collecting urine. But at some point, the gong malfunctioned; at the same time, one subject's circadian rhythm ran free. When the experimenters discovered this, they conducted new experiments that appeared to show free-running rhythms only in the gong's absence, says Czeisler. This finding convinced the researchers that social cues were critical to entraining the human circadian rhythm.

An incident 6 years later challenged that concept in Czeisler's mind. In 1976, Czeisler's advisor attended a closed meeting of some 18 top circadian scientists at the Max Planck Institute, and Czeisler, then a graduate student, tagged along. As the scientists toured an apartment in the bunker that was illuminated by table lamps, Czeisler asked a question that he says in retrospect seems ridiculous but that helped turn the field on its head. "What's it like when it's dark in here?" he asked. "'It *is* dark in here,' Dr. Wever responded," Czeisler says.

It turned out that by "dark in here" Wever meant the overhead fluorescents—which represented daylight when the researchers turned them on each morning—were turned off. The table, kitchen, and bathroom lamps, which subjects could control themselves, weren't believed to influence circadian rhythms. But apparently they did.

From 1980 to 1987, a series of papers came out that changed the field's thinking on how human circadian rhythms are entrained, says George C. Brainard, director of the Light Research Program at Jefferson Medical College of Thomas Jefferson University. One set of papers, the first of which was published by Alfred Lewy, then a staff psychiatrist at the National Institute of Mental Health, demonstrated convincingly that bright white light at an intensity of 2,500 lux could have an acute effect on suppression of melatonin secretion, which is a marker of circadian sensitivity. Lewy's work led to the use of bright light to treat mood disorders.

Czeisler's first paper on circadian entrainment appeared in the August 1981 issue of *Photochemistry and Photobiology*. He demonstrated that light/dark cycles, not social interaction, entrained the circadian rhythms in 2 male subjects living in a specially constructed apartment devoid of potential time cues. In one phase of the experiment, the subjects were told the light/dark cycles would be more or less random. In reality, the subjects selected their own cycles, as the researchers turned the lights off when the subjects went to bed and on when they awoke. Under these circumstances, the subjects' circadian rhythms ran free.

Subsequently, the researchers imposed 24-hour light/dark cycles, alternately advancing and retarding the clock—giving the subjects a light regime that was later or earlier, respectively, than the actual time—and then holding it constant. In each case, entrainment ensued.

In a paper published 8 August 1986 in *Science*, which Brainard calls a "landmark," Czeisler showed that exposure to carefully timed bright light over several days could reset the circadian rhythm very precisely, the way one might reset a watch, even when the subjects' bedtime was held constant.

Then, in the 1990s, some studies of circadian rhythm in blind people began showing results that begged big questions about unknown pathways for light perception. Some blind individuals, particularly those whose eyes had been removed, showed abnormal, free-running circadian rhythms with attendant sleep disorders, as one would expect for the sightless. Others who still had their eyes showed normal circadian rhythms. Czeisler was able to suppress melatonin secretion and shift circadian rhythm in the latter patients by exposing them to bright light. "That just blew us away," he says.

But it didn't blow away skeptical journal editors. One who rejected the paper said, "These people aren't really blind, they are lying," according to Czeisler, despite the subjects' failure to perceive a neuro-ophthalmologist's brightest light when he shined it directly into their eyes. After 5 years and 20 rejections, the *New England Journal of Medicine* published the paper 5 January 1995 after first making Czeisler test more subjects and cover both their eyes and their whole bodies, "just in case light might be penetrating some other body part."

The Story of a New Receptor

A major milestone came with the 1998 discovery of melanopsin retinal ganglion cells, a new type of photoreceptor in the eye. These cells provide signals to the suprachiasmatic