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## Playing the Body Electric

**A combination of genetics and optics gives brain scientists an unprecedented ability to dissect the circuits of the mind**

By Christof Koch

Each new generation of astronomers discovers that the universe is much bigger than their predecessors imagined. The same is also true of brain complexity. Every era's most advanced technologies, when applied to the study of the brain, keep uncovering more layers of nested complexity, like a set of never ending Russian dolls. We now know that there are up to 1,000 different subtypes of nerve cells and supporting actors—the glia and astrocytes—within the nervous system. Each cell type is defined by its chemical constituents, neuronal morphology, synaptic architecture and input-output processing.

Different cell types are wired up in specific ways. For example, a deep layer 5 pyramidal neuron might snake its gossamer-thin output wire, the axon, to a subcortical target area while also extending a connection to an inhibitory local neuron. Understanding how the brain's corticothalamic complex creates any one conscious sensation necessitates delineating these underlying circuits for the 100 billion cells in the brain.

Bulk tissue technologies such as functional brain imaging or electroencephalography identify specific brain regions related to vision, pain or memory. Yet they are unable to resolve details at the all-important circuit level. Brain imaging tracks the power consumption of a million neurons, irrespective of whether they are excitatory or inhibitory, project locally or globally, and so on. For progress on consciousness, something drastically more refined is needed.

Furthermore, as our understanding of the brain grows, our desire to intervene, to help ameliorate the many pathologies to which the mind is prey, grows commensurately. Yet today's tools (drugs and deep-brain stimulations) are comparatively crude, with undesirable side effects.

To the rescue rides an amazing technology, a fusion of molecular biology with optical stimulation, dubbed optogenetics. It is based on some fundamental discoveries made by three German biophysicists—Peter Hegemann, Ernst Bamberg and Georg Nagel working on photoreceptors in ancient bacteria. These photoreceptors directly (rather than indirectly, like the ones in your eyes) convert incoming light in the blue part of the spectrum into an excitatory, positive electrical signal. The trio also isolated the gene for this protein, called channelrhodopsin-2 (ChR2). Bamberg and Nagel subsequently engaged in a fruitful collaboration with Karl Deisseroth, a professor of psychiatry and bioengineering at Stanford University, and Edward S. Boyden, now at the Massachusetts Institute of Technology.

The group took the ChR2 gene, inserted it into a small virus, and infected neurons with this virus. Many of the neurons took up the foreign instructions, synthesized ChR2 protein and inserted the photoreceptors in their membrane. In the dark, the receptors quietly sit there, with no discernible effect on their host cells. But illumination of the network with a brief flash (10 milliseconds) of blue light causes each of these bacterial photoreceptors to jolt their host cell a bit. Collectively, they reliably and repeatedly produce a spike in the membrane voltage. Spikes are the universal all-or-none pulses used by all but the tiniest nervous systems to communicate information among neurons. Each time the light is



turned on, the cells spike reliably, exactly once. Thus, an entire population of neurons can be manipulated by precisely timed stabs of light.

The biophysicists added another photoreceptor to their tool kit. It derives from a different type of bacterium, one living in dry salt lakes in the Sahara Desert. Shining yellow light on it yields an inhibitory, negative signal. Through the same viral strategy, both photoreceptor types were then introduced into neurons. Once the neuron stably incorporates both types into its membrane, it can be excited by blue light and subdued by yellow. Each blue flash evokes a spike, like a note sounding when a piano key is pushed down. But a simultaneous flash of yellow light can block that spike. Consider the “musical score sheet” recorded from one such neuron as it is played with light. This ability to precisely control electrical activity in one or more neurons is unprecedented.

But the benefits of this technology for discerning the circuits of the mind go much deeper, because the virus that carries the photoreceptor genes can also carry promoter sequences that express their payload only in neurons with the appropriate molecular address. So rather than exciting all the neurons in a particular neighborhood, it becomes feasible to focus on a subset that synthesize a particular neurotransmitter or that send their outputs to a specific place.

Deisseroth’s group exploited this capability by introducing ChR2 into a subset of neurons located in the lateral hypothalamus, deep inside the mouse brain. Here about 750 cells produce orexin (also known as hypocretin), a hormone that promotes wakefulness. Mutations in the orexin receptors are associated with narcolepsy, a chronic sleep disorder. As a result of the manipulation, almost all the orexin neurons, but none of the other intermingled neurons, carried ChR2 photoreceptors. Furthermore, blue light via an optical fiber precisely and reliably generated waves of spikes in the orexin cells.

What would happen if this experiment were done in a sleeping mouse? In control animals, a couple of hundred blue flashes awakened the rodents after about one minute. When the same light was delivered to animals carrying the ChR2 gene, they woke up in half the time. That is, ghostly blue light that illuminates the catacombs of the brain and causes a tiny subset of neurons with a known identity to produce electrical spikes wakes up the animal. With additional controls, the Stanford group proved that the release of orexin from the lateral hypothalamus was what drove this behavior. This exemplary study established a compelling causal link between electrical activity in a subset of the brain’s neurons and sleep-to-wake transitions.

A string of such beautiful, interventionist mice experiments over the past several years has revealed specific circuit elements involved in a variety of normal and pathological behaviors: depression, behavioral conditioning, Parkinson’s disease and cortical oscillations critical for attention, among others. They have even helped restore sight to mice blinded by degenerating retinas. ChR2 experiments have been carried out successfully in monkeys; experimental human trials for some psychiatric illnesses are being actively considered.

The import of optogenetics for consciousness is that it allows testing of a specific hypothesis about the neural basis of consciousness. For instance, to what extent is feedback from higher cortical regions to lower regions essential? Find out by training an animal in a task that depends on conscious sensation, then inactivate those circuit elements with light and observe the animal’s behavior.

Francis Crick, co-discoverer of the double helical structure of DNA, and I had hypothesized that the claustrum, a mysterious thin structure located below much of cortex, is critical for binding information across sensory modalities and making it accessible to consciousness. The challenge is to find an appropriate behavior that requires mice to combine information dynamically across modalities—say, touch and smell. Then excite or inhibit claustrum neurons while the animals execute the task to study the extent the structure is necessary for this behavior.

A judicious mix of recombinant DNA technology, protein and viral design, genomics, optical fibers, lasers and microinstrumentation will enable scientists to explore strange new theories that close the gap between the objective brain and the subjective mind, to boldly go where no one has gone before.