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Scientists reveal brain circuit mechanisms underlying arousal regulation

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Credit: Human Brain Project

Adjusting a specific deep-brain circuit's firing frequency immediately and dramatically alters rats' forebrain activity and alertness levels, Stanford University School of Medicine investigators have shown.

The findings, to be published online Dec. 10 in *eLife*, hold direct

implications for an increasingly widespread therapeutic approach called deep-brain stimulation. They point to DBS's potential for restoring consciousness in minimally conscious patients and countering other cases of impaired consciousness. The findings also highlight the importance of determining optimal stimulation frequencies for DBS devices used across a wide range of brain disorders and demonstrate a method for making those determinations.

The research suggests that a brain structure can be like a radio whose different stations, operating at different frequencies and playing different kinds of music, variously attract or repel different "listening audiences."

DBS involves the insertion of an electrical-signaling device into a specific area of the brain. It has provided therapeutic benefits to patients with disorders ranging from Parkinson's disease and essential tremor to major depression and obsessive-compulsive disorder.

"The methods we employed for tracking the circuitry of arousal regulation in the brain can guide DBS research on all of these disorders, and others," said the study's senior author, Jin Hyung Lee, PhD, assistant professor of neurology, of neurosurgery and of bioengineering at Stanford. "The brain structures that we showed to be critical in regulating arousal, and the connections between them, are virtually the same in rats and humans, so we have high hopes of seeing our findings, as well as our methods, translated into clinical trials."

Lead authorship is shared by postdoctoral scholar Hyun Joo Lee, PhD, and graduate students Jia Liu, Andrew Weitz and Zhongnan Fang.

Another of the study's coauthors is Nicholas Schiff, MD, professor of neurology and neuroscience at Weill Cornell Medical College in New York City. In a case study published in 2007, Schiff and his colleagues

demonstrated that electrically stimulating the central portion of the thalamus—a deep-brain relay station routing inputs from the senses to myriad cognitive-processing centers throughout the cerebral cortex—could restore consciousness in a patient who'd been in a minimally conscious state for six years.

"But there was no way to know how it worked," said Lee. "Electrical stimulation nonselectively triggers firing in all kinds of nerve cells close to the electrode tip, including those in nearby but irrelevant tracts. It can't be used to pinpoint the circuit, or circuits, in which electrical stimulation is exerting its beneficial effect, much less to elucidate exactly how."

Interplay of brain structures

In the new study, Lee's group tracked the interplay among distinct structures throughout the entire brain—among them the thalamus, the somatosensory cortex and the zona incerta—and showed how this interplay regulates arousal states. To do this, they combined several approaches, including optogenetics, whole-brain functional magnetic resonance imaging, electroencephalography and single-unit electrophysiology. This combination allowed Lee and her associates to excite or inhibit specific nerve cells at will in a cluster of nerve cells in the central thalamus of rats, while simultaneously observing resulting activity throughout the cerebral cortex.

Optogenetics entails installing light-sensitive proteins on the surface of selected nerve cells so that these cells, and only these cells, can be either excited or inhibited by specific frequencies of laser light delivered via a surgically implanted optical fiber. Whole-brain fMRI, with a resolution of less than one-fiftieth of an inch in each dimension, simultaneously monitors nerve activity levels in multiple brain regions. Single-unit electrophysiology—inserting microelectrodes into the brain and

recording individual nerve cells' electrical activity—lets researchers zero on circuits within zones of interest that have been flagged by the more global but less specific whole-brain fMRI technique.

The Stanford scientists experimented on otherwise normal laboratory rats that had been bioengineered so certain excitatory nerve cells in the central thalamus featured light-sensitive proteins on their surfaces. Laser light could be delivered through optical fibers to cause central-thalamic nerve cells containing those proteins to fire. The researchers stimulated the rats' brains with laser pulses at three different frequencies —10, 40 and 100 hertz. In each case, the stimulation proceeded in the form of 20-second bursts, once a minute, for six minutes, roughly mimicking the standard DBS cycle.

At all three frequencies, activity in the central thalamus increased. But the effects on brain areas receiving inputs from it were frequency-dependent: As shown by whole-brain fMRI, much more brain tissue in the frontal cortex was activated at 40 and 100 hertz than at 10 hertz. Stimulating the central thalamus at 10 hertz actually suppressed activity in the somatosensory cortex, a brain region that receives inputs from the central thalamus and is essential to maintaining alertness. The researchers validated this by monitoring individual somatosensory-cortex nerve cells using single-unit electrophysiology.

The suppression of somatosensory-cortex nerve cells at 10 hertz implied that inhibitory nerve cells from somewhere else must be intervening, and that their behavior was frequency-dependent.

The investigators next focused on the zona incerta, a structure below the thalamus consisting mostly of inhibitory nerve cells and known to send signals to the somatosensory cortex. This time, the researchers stimulated the central thalamus at 10 hertz and at 40 hertz while watching the effects in the zona incerta via single-unit electrophysiology

and monitoring the forebrain with electroencephalography. They found that 10 hertz stimulation elicited electroencephalographic and electrophysiological waveforms characteristic of sleep or unconsciousness far more pronouncedly than 40 hertz stimulation did.

Effect of high versus low frequency

Reasoning that the central thalamus was communicating with the zona incerta, Lee's group further bioengineered the test animals so that blue light would still fire up their excitatory central-thalamic nerve cells, but yellow light would shut down the inhibitory nerve cells in their zona incerta. Continuously stimulating these rats' central thalamic area with blue light, the researchers by turns suppressed or permitted zona incerta activity by switching the yellow laser on or off.

As expected, yellow light suppressed nerve-cell activity in the zona incerta, releasing the somatosensory cortex from the suppression observed earlier in the 10-hertz optogenetic stimulation of the central thalamus. Flicking off the yellow light switched on zona incerta nerve-cell activity, with suppression of activity in the somatosensory cortex resuming. The zona incerta was acting as a frequency-dependent circuit-breaker.

In a behavioral experiment, the researchers optogenetically stimulated the central thalamus of sleeping rats. At 10 hertz, the sleeping animals froze, in a manner suggestive of the behavioral arrest seen in people suffering from an absence seizure, which causes a brief lapse of awareness often characterized by a blank stare. (The condition is more common in children than adults.) At 40 or 100 hertz, the animals instantly woke up and started busily exploring their environments. EEG evinced waveforms associated with loss of consciousness in the 10 hertz case and of arousal at the higher frequencies.

The study's results mark a conceptual shift from a chemical-deficit-or-excess notion of brain disorders to a more nuanced information-processing theory of how the brain works and, when it isn't working well, why not.

More information: Jia Liu et al. Frequency-selective control of cortical and subcortical networks by central thalamus, *eLife* (2015). DOI: 10.7554/eLife.09215 , elifesciences.org/content/4/e09215

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