Brain works best when cells keep right rhythms

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It is said that each of us marches to the beat of a different drum, but new Stanford University research suggests that brain cells need to follow specific rhythms that must be kept for proper brain functioning. These rhythms don't appear to be working correctly in such diseases as schizophrenia and autism, and now two papers due to be published online this week by the journals *Nature* and *Science* demonstrate that precisely tuning the oscillation frequencies of certain neurons can affect how the brain processes information and implements feelings of reward.

"A unifying theme here is that of brain rhythms and 'arrhythmias'," said Karl Deisseroth, MD, PhD, associate professor of bioengineering and of psychiatry and behavioral sciences and senior author of both papers.

An arrhythmia is what cardiologists call a seriously irregular heartbeat. The new findings suggest that, like the cells that keep the beat of the heart (or the coxswain on a rowing team that calls out the rhythm of the strokes), certain brain cells can orchestrate oscillations that ultimately help govern behavior of other cells that are guided by those rhythms.

The brain's bit rate

In the *Nature* study, which will be published online April 26 along with a companion paper from MIT on which Deisseroth and graduate student Feng Zhang are also authors, Deisseroth's team focused on neurons in mice that produce a protein called parvalbumin. Some researchers have

suspected that these neurons drive "gamma" brain waves that oscillate at a frequency of 40 times a second (or Hertz). These waves, according to the hypothesis, might affect the flow of information in the brain. To date this could never be proved because no one could selectively control the neurons and see the resulting effect on the information flow, or oscillations.

"This has been a fundamental mystery. We have these cells that could be crucially involved in high-level, complex information processing and we see these oscillations that are happening, but people don't really know how to put all this together," Deisseroth said. "But this is exactly the kind of thing now that we can address using optical methods."

That's because Desisseroth's group has developed a technique, called optogenetics, in which specific cells can be genetically engineered to be controlled by pulses of visible light. The team did this with parvalbumin neurons in mice and found that by exciting or inhibiting them, they could produce or suppress "gamma" waves and see a marked change in the "bit rate" or quantity of information flowing through brain circuits.

"What we found is that if you crank the parvalbumin neurons down, you see fewer of these 40-Hertz oscillations. If you crank them up you see more of these gamma oscillations," Deisseroth said. "That's the first real proof that these neurons are indeed involved in generating these gamma brain waves.

"Then we found that we could quantify in bits the effect of oscillations on information flow through neural circuits and we found that the oscillations specifically enhance information flow among different cell types in the frontal cortex of these mammals." Deisseroth added. "The final outcome of this is that parvalbumin neurons and gamma oscillations work together to enhance the flow of real information in the brain."

The potential link to disease comes from the fact that in autism the gamma oscillations appear to be present at the wrong intensity, while in schizophrenia there appear to be too few parvalbumin neurons.

"This is a new perspective relevant to both schizophrenia and autism, conditions in which information comes in but it isn't necessarily processed correctly," Deisseroth said.

The paper's first authors were Zhang and psychiatrist Vikaas Sohal, MD. Postdoctoral researcher Ofer Yizhar, PhD, also contributed to the work. The research was funded by the university and several foundations including the National Institutes of Health, the McKnight Foundation, the Coulter Foundation and the William M. Keck Foundation.

Feeling reward

In the *Science* paper, which will be published first online April 23 in *Science* Express, Deisseroth led a team of researchers at Stanford and the University of California-San Francisco in investigating the effect of controlling the oscillations of neurons that emit the brain chemical dopamine. The group, made up of neuroscience, bioengineering and psychiatry researchers, wanted to see if varying the oscillations led freely-behaving mice to sense varying levels of reward.

To conduct the experiment, they optogenetically engineered dopamine neurons in a specific area of the brains of the mice. Then they placed the mice into a box with three chambers in a row. At first, none of the mice had a predictable preference for which chamber to occupy. Then the researchers exposed them to two days of conditioning in which their engineered dopamine neurons were exposed to high-frequency pulses of light while in a chamber on one end, and low-frequency pulses while in the chamber on the other end. Specifically, the mice were split into two groups in which the different stimuli were associated with opposite ends

of the box.

At the end of the experiment, the mice were placed in the middle chamber and exposed to no further light pulses. Each of the mice preferred to return to whichever chamber it was in when its dopamine neurons were subjected to the high-frequency light pulses, indicating that firing dopamine neurons at high-frequency rhythm correlates with stronger reward learning.

"We tested different rhythms in the dopamine neurons and we found that lower-frequency rhythms were much less effective, but the high-frequency bursts were powerfully effective in giving rise to this behavioral effect of reward," Deisseroth said. "Understanding more about these dopamine neurons has implications not only for drugs of abuse that directly access these feelings of reward, but also for depression because in depressed people, one of the most prominent and debilitating symptoms is the inability to enjoy things."

In some sense, the papers suggest that people who aren't thinking clearly or feeling happy might just be out of step, or rather have brain cells that quite literally don't have rhythm.

The other Stanford authors of the *Science* paper are lead authors Zhang and graduate student Hsing-Chen Tsai; medical research associate Antoine Adamantidis, PhD; and psychiatry and behavioral sciences professor Luis de Lecea, PhD. The UCSF researchers are Garret Stuber, PhD, and Antonello Bonci, MD. The research was supported by several fellowships and foundations including the National Institutes of Mental Health and Drug Abuse, as well as the Keck and McKnight foundations.

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