NEWS

Laser technique pins source of brain waves linked to autism

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Researchers have for the first time identified the type of neurons that produce gamma rhythms, the high-frequency brain waves that are thought to go awry in autism and schizophrenia. The work was published online 26 April in two reports in Nature[1,2].

For this work, the researchers used 'optogenetics', a relatively new technique in which they **genetically engineer cells to respond to light** and record the resulting electrical patterns formed in the brain.

The brain makes different kinds of waves, or oscillations, when groups of neurons fire together at various frequencies. Gamma oscillations, for example, arise when cells fire together at about 40 times per second. These fast rhythms are known to occur when people pay attention to the most relevant aspects of their surroundings — such as a person talking to them — and ignore distractions like background music.

A few studies have linked gamma rhythms to autism. In 2007, for example, Swedish researchers used electroencephalography — an **indirect way to measure electrical patterns of brain circuits** — to show that an excess of gamma waves predicts the severity of developmental delay in boys with autism[3].

"It's been very interesting from the autism standpoint to consider what these oscillations are doing," says **Karl Deisseroth**, associate professor of bioengineering at Stanford University and lead investigator on one of the studies. "If your gamma power becomes too substantial, you might have certain types of information flow while excluding other types. That can affect which stimuli you pay attention to."

Until now, researchers did not know which brain cells generate the gamma waves, but several in vitro studies and computer simulations had pointed to fast-spiking 'parvalbumin' neurons, named

for the protein found exclusively inside these cells[4]. Parvalbumin neurons are inhibitory, meaning they release chemicals that silence other neurons, and are found throughout the brain.

Because available techniques could not target specific cell types in living animals, however, researchers had not been able to prove that parvalbumin cells, when firing in synchrony, cause gamma rhythms in human brains.

Optogenetics, a technique Deisseroth invented in 2005, involves inserting genes that code for opsin — a light-sensitive protein — into a subgroup of neurons in freely moving mice. Scientists can then trigger those cells to fire by delivering pulses of laser light through a surgical shunt into the targeted tissue.

Active circuits:

In the first study, led by Massachusetts Institute of Technology's **Christopher Moore**, the researchers targeted cells expressing parvalbumin in the barrel cortex, a brain region in rodents that is active when the animal's whiskers are touched. The scientists found that stimulating the parvalbumin neurons in one area of the barrel cortex increases the occurrence and intensity of gamma waves recorded in nearby cells.

In the second study, Deisseroth's group showed that gamma activity sharpens the electrical signals passing through cells of the prefrontal cortex, a brain area involved in, among other functions, focusing attention and making decisions.

"The studies laid the groundwork for a set of tools that I think have great potential for understanding the role of gamma oscillations in autism," says **Tony Zador**, professor of neuroscience at Cold Spring Harbor Laboratory, who was not involved with either study.

Gamma rhythms are known to travel over large distances in the brain. Some researchers have proposed that abnormalities in such long-range connections could underlie autism[5]. Although the new studies focused on recording the waves in cells close to the source neurons, Zador says future studies could help understand the effect of far-reaching gamma waves.

Gamma waves are also known to help establish the proper balance of excitation and inhibition in the brain, disruptions in which have been linked to autism.

A 2008 study of 21 children with autism, for example, suggested that the autistic brain is overactive after repeated clicking sounds, which might explain the increased sensitivity of some children with autism to loud noises[6]. Another study, published last year, found that inhibitory circuits are impaired in a mouse model of autism[7].

Moore's new work also links inhibition to sensory perception: activating parvalbumin cells

decreases the animals' normal brain response to sensory stimuli, such as their whiskers being touched.

Intriguingly, that response depends on when during the gamma wave the whisker is touched: responses diminish at the peak of the wave, but return to normal levels after the rhythm has decayed.

"The exact timing of when I flash that light, tap your finger, or play that sound relative to this ongoing rhythm matters a lot," Moore says. "Not only can we induce this gamma rhythm, but we can actually show how it changes transmission of information in the brain."

Optogenetics can also be used to stimulate specific behavior, according to another study Deisseroth's group published online 23 April in Science[8].

Using light to selectively activate neurons involved in reward and addiction, the researchers showed that the activation can be used to train mice to prefer being in one chamber over any others. In this way, laser light can become as motivating as a food or drug reward.

Other researchers are also trying to capitalize on the technique's potential in autism research. For example, Zador and his collaborators have found that several mouse models of autism **share defects in neural circuitry**, and plan to use optogenetics to stimulate subgroups of neurons in those circuits.

"Optogenetics manipulation is the biggest contribution to systems neuroscience in a decade, easily," Zador says. "We hope to figure out what deficits at the level of neuronal circuits represent the 'final common pathway' for the genetic lesions associated with autism."

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