Out-of-sync brain waves may underlie learning deficit linked to schizophrenia

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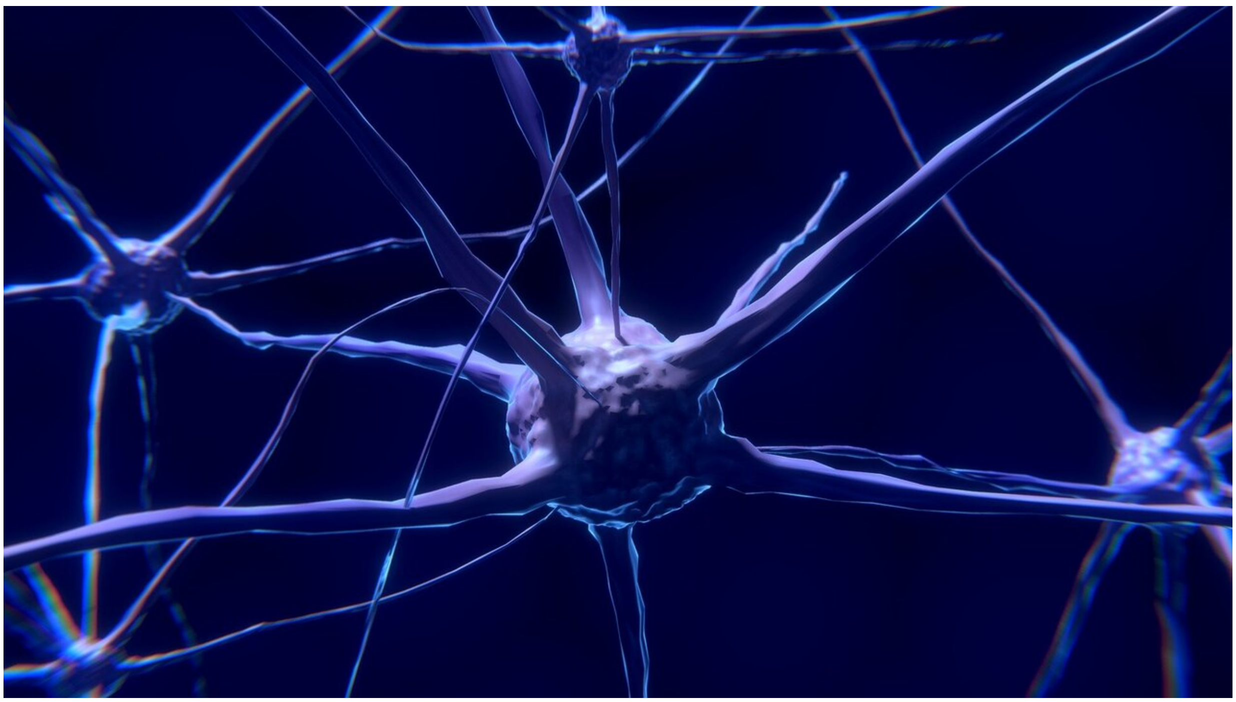

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A new UC San Francisco study has pinpointed a specific pattern of brain waves that underlies the ability to let go of old, irrelevant learned associations to make way for new updates. The research is the first to directly show that a particular behavior can be dependent on the precise synchronization of high-frequency brain waves in different parts of the brain, and might open a path for developing interventions for certain psychiatric disorders, including schizophrenia.

Swapping old rules for new ones is something we do constantly. It happens when you get a new phone, switch cars or update the software on your laptop—the first few times you try to turn on the headlights in a rental car, you might fire up the windshield wipers instead. But eventually, you get it.

Making such adjustments is critical for adapting as the world changes around us. But struggling to let go of old rules doesn't just sometimes make it difficult to complete day-to-day tasks. It might also contribute to certain forms of psychosis, like schizophrenia, by disrupting people's ability to reappraise and update distorted beliefs and delusions despite contradicting evidence and logic.

"Perseveration is a term we use to describe individuals sticking to something that's no longer appropriate," said Vikaas Sohal, MD, Ph.D., an associate professor of psychiatry and member of the UCSF Weill Institute for Neurosciences. "It's a problem in a lot of different neuropsychiatric conditions."

In the new study, published in *Nature Neuroscience* on May 25, 2020, Sohal and colleagues provide a glimpse of what might be happening in the brain when a breakdown in rule-shifting leads to perseveration. They found that the precise coordination of a specific kind of brain waves, called gamma waves, was key to learning to let go of an old rule and, instead, pay attention to cues that were previously irrelevant.

The work helps to clarify a long-standing debate about the significance of brain waves. For decades, scientists have been able to measure these coordinated, rhythmic neural activity patterns, which can take varying forms. For just as long, the significance of brain waves has been hotly contested. Some researchers have argued that brain waves have important functions, and that some cognitive disorders might be linked to certain brain waves going awry. Gamma waves, for example, which arise from neural activity with a regular rhythm between 30 and 120 cycles per second, have been hypothesized to be involved in attention and conscious thought. But other scientists disagree, claiming that brain waves are an irrelevant byproduct of neural activity.

Trying to figure this question out has been something like what an alien might experience if they just landed outside a football stadium, said Sohal. "Imagine you're outside the stadium trying to figure out what's going on just by the sound," he said. "Mostly, you're just hearing random noise. But every once in a while, you hear that noise synchronize in a cheer or some chants, and you wonder, 'Hey—does that mean something?'"

Instead of the noise of sports fans pouring out of a stadium, Sohal's team recorded the activity of neurons in different parts of the brain. Many past brain wave studies have relied on the faint electrical signals detectable in electroencephalogram (EEG) recordings made from the surface of the skull, but in the new study, the researchers put probes inside the brain to get a more precise look at the function of these oscillations. The researchers also used genetic engineering to pin a fluorescent activity indicator to neurons of a type that are ideal for capturing the fast-paced activity of gamma waves in areas of the brain important for cognition. Light flashes from these fluorescent tags indicated when the voltage of these neurons changed, allowing the team to visually track communication between the cells.

To see if gamma waves were linked to perseverative behaviors, the researchers designed a "mouse version" of the Wisconsin Card Sorting Task, a standard assessment tool that measures how human participants learn new rules on the fly, which tends to be challenging for people with schizophrenia. In the mouse task, researchers hid a reward under fine sand or coarse cat litter in one of two bowls, and gave each a distinctive smell, and left mice to figure out which odor marked the prize. Once the mice learned the task, researchers switched the rule on them by making the odor cue irrelevant, now cuing the reward only by whether the mice had to dig through sand or cat litter to reach it.

As mice learned to make the switch, the team observed an increase in gamma waves that were synchronized across both sides of the brain. When researchers knocked those waves out of sync by using light stimulation in mice with neurons genetically engineered to respond to it, the mice suddenly became very bad at this kind of learning. Perseverative errors shot up and the mice needed as many as twice the attempts to figure out the new cue for the reward.

"It seems like gamma synchrony is important for overcoming rule perseveration," said Sohal. "It fits with an emerging view that maybe communication between brain regions is impaired in schizophrenia and related disorders, which might give rise to certain symptoms."

Curiously, disrupting gamma synchrony did not throw off the mice's ability to learn new associations or flip a rule they had previously learned. When the scent of garlic stopped signaling a reward, for example, they were still able to reverse course and learn that the odor of coriander—which previously marked a cold trail—now coded for buried treasure. It was only when they had to switch from one kind of sensory cue to another (e.g., from scent to touch cues) that gamma synchrony really came into play, possibly because learning to drop that kind of perseveration may actually be much harder.

"It tells us there's something special about the type of learning that requires you to pay attention to something you were ignoring before," Sohal said.

Previous research, including in Sohal's lab, has suggested that deficits in gamma synchrony and the neurons that give rise to it might contribute to cognitive issues at the core of schizophrenia and Alzheimer's disease. A deeper understanding of normal gamma wave patterns and what happens when they are disrupted could eventually lead to help for patients who need it, said Kathleen Cho, Ph.D., a postdoctoral researcher in the Sohal lab and lead author on the paper.

"Treatments for these kinds of cognitive problems are underdeveloped, in large part because the relevant mechanisms are unclear," she added. "This study moves us towards a deeper understanding of how we might begin to treat this kind of neurological disruption."

More information: Kathleen K. A. Cho et al. Cross-hemispheric gamma synchrony between prefrontal parvalbumin interneurons supports behavioral adaptation during rule shift learning, *Nature Neuroscience* (2020). DOI: 10.1038/s41593-020-0647-1

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