Plasticity, Visual Input Triggers and Brainwaves Identified

The collaboration of scientists from different fields is paying off. Several new exciting studies are revealing more about the mechanism of plasticity and the roles of visual input and brainwave patterns in learning & memory.

Researchers have long been interested in factors that can trigger the brain's ability to learn and remember. In the August 8 issue of the journal Cell, neuroscientists at Children's Hospital Boston report that they've identified one such factor, a protein called Otx 2.

Otx2 helps initiate a critical period -- a window of heightened brain plasticity, when the brain can readily make new connections.

Takao Hensch, PhD, of the Neurobiology Program and Department of Neurology, the study's senior investigator, speculates that there may be similar factors from the auditory, olfactory and other sensory systems that help time critical periods. Timing is important, because the brain needs to rewire itself at the right moment -- when it's getting the optimal sensory input.

"If the timing is off, the brain won't set up its circuits properly," Hensch says.

Being able to control the timing of critical periods in different parts of the brain could possibly ameliorate developmental disorders such as autism, in which researchers believe critical periods may be inappropriately accelerated or delayed. Triggering a critical period can also help healthy people learn more readily – great news for NH students, and also applicable clinically in

those recovering from stroke or brain injury, for example.

Input Triggers

Interestingly, Hensch and colleagues found that the brain cells that switch on critical periods in the visual system (parvalbumin cells) don't actually make Otx2 themselves. Instead, Otx2 is sent by the retina. In essence, the eye is telling the brain, "The eyes are ready and seeing properly -- you can rewire now."

"The eye is telling the brain when to become plastic, rather than the brain developing on its own clock," says Hensch, who is also a professor at Harvard Medical School and at Harvard University's Department of Molecular & Cellular Biology. "The idea that this class of molecular messenger is passed from cell to cell is considered unorthodox in cell biology." This idea, however, has long been advocated by Dr. Alain Prochiantz of the Ecole Normale Superieure (Paris) and College de France, Hensch's collaborator and a coauthor on the study.

There must obviously be other triggers for plasticity, since blind people can still learn, and in the current study, Hensch and colleagues demonstrated that when mice are reared in the dark, thus getting no visual input, Otx2 remains in the retina. Only when the mice received full visual input did Otx2 begin to appear in the cortex, and only then did parvalbumin cells start to mature.

In other experiments, the researchers injected Otx2 directly into the cortex. The parvalbumin cells matured, even when the mice were kept in the dark. Finally, when Otx2 synthesis was blocked in the eye, parvalbumin cell functions failed to mature.

Otx2 has an unusual derivation: it is originally produced during embryonic development; without it, mice don't develop heads! Production then stops, but some days after birth, it reappears in parvalbumin cells. "The nervous system is recycling an embryonic factor to induce brain plasticity," says Hensch.

They Got Rhythm

Another research project at Stanford University reveals that parvalbumin cells themselves produce gamma brainwaves. 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 neurons can affect how the brain processes information and implement feelings of reward.

Although users of neurofeedback may have known this for some time, it could never be proved because no one could selectively control the neurons and see the resulting effect on the information flow, or oscillations.

"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.

“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."

The authors further showed that these brain rhythms regulate the processing of sensory signals. They found that the brain's response to a tactile stimulus was greater or smaller depending on exactly where the stimulus occurred within the oscillation cycle.

"It supports the idea that these synchronous oscillations are important for controlling how we perceive stimuli," says Moore, one of the researchers. "Gamma rhythms might serve to make a sound louder, or a visual input brighter, all based on how these patterns regulate brain circuits."

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."

In the Science paper, (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.

"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 the behavioral effect of reward," Deisseroth said.

Understanding more about these dopamine-producing neurons has implications for depression because one of the most prominent and debilitating symptoms is anhedonia (the inability to enjoy things).

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. This can partly explain the success of bio- and neurofeedback, music therapy and NMS in treating depression, as it is already known that the brain can 'copy' an example brainwave pattern and adopt it.

Sources

Because this research required a merger of expertise from neuroscience and molecular genetics, three different laboratories contributed to its completion. In addition to Tsai, Moore and Carlén of MIT, co-authors include Jessica Cardin, research affiliate at the McGovern Institute and the University of Pennsylvania, and Karl Deisseroth and Feng Zhang at Stanford University. Other co-authors were Konstantinos Meletis, a postdoctoral fellow at the Picower Institute, and Ulf Knoblich, a graduate student in MIT's Department of Brain and Cognitive Sciences.

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