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RESEARCH NEWS

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Incredible Opportunity Leads to Discovery of Neurons that Detect Novel Objects

A rare opportunity to study patients with an intractable form of epilepsy has led to the identification of specific neurons in the human brain that respond to novel or familiar objects. The discovery was made using micro-thin electrodes that read electrical activity from single neurons inside the brains of patients who were undergoing treatment to determine the origin of their epileptic seizures.

The research by Howard Hughes Medical Institute scientists and their colleagues may help researchers understand how the human brain distinguishes new objects from more familiar objects, a skill crucial to survival.

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— Erin M. Schuman

The research group, which was led by Howard Hughes Medical Institute investigator Erin Schuman at the California Institute of Technology, reported their findings in the March 16, 2006, issue of the journal *Neuron*. First author Ueli Rutishauser of Caltech and co-author Adam Mamelak of Huntington Memorial Hospital and Cedars-Sinai Medical Center collaborated on the studies with Schuman.

Prior to these studies, researchers had only identified regions of the human brain involved in detecting novel images or objects using functional magnetic resonance imaging. Those studies yielded conflicting evidence about whether such neurons existed in the learning centers of the brain - the hippocampus and amygdala. The hippocampus is involved in learning and memory, and the amygdala helps to etch memories that are associated with emotions such as fear.

Additional evidence supporting the existence of such neurons had also come from earlier non-human primate electrophysiology studies in which researchers found that specific neurons would activate only upon presentation of novel stimuli. It has been known for a long time that animals are capable of learning about a stimulus from a single sensory experience, said Schuman, though neurons that show evidence of single-trial learning have long eluded detection. This study identified a population of neurons in the medial temporal lobe that might contribute to rapid behavioral learning, she said.

In the study published in *Neuron*, the researchers tested people who had a rare form of intractable epilepsy that could be treated only by surgically removing regions of the brain responsible for the seizures. As part of the diagnostic tests to pinpoint the origin of the seizures, the patients underwent placement of deep-brain electrodes. The patients permitted Schuman and her colleagues to thread bundles of microwires inside the diagnostic electrodes. These microwires were designed to detect activation of single neurons in the brain. Patients in the study agreed to undergo behavioral tests which allowed the researchers to make recordings of the brain as each patient was asked to consider a series of novel and familiar images.

These experiments are incredibly rare, said Schuman. There are only a handful of places in the world where it is possible to record the single-unit activity of neurons in a human brain while the subjects are performing behavioral experiments. However, she said, the benefits to science in studying humans while performing these tasks can be enormous.

In our studies, a big advantage is that humans can learn tasks very quickly, and we can provide verbal instructions, she said. That allows us to look at very rapid changes in neuronal responses that occur during single-trial learning; these types of studies have been impossible to conduct in experiments with higher primates such as apes because the animals require many, many trials to learn a task

Importantly, she said, the patients could be instructed to identify novel images. Furthermore, the precision of the microelectrodes enabled the researchers to detect whether one neuron was responding only to a novel stimulus, even as its neighboring neuron was responding to a familiar stimulus.

In the experiments — as the researchers recorded from the patients' brains — they asked the patients to look at a series of images of subjects such as planes, cars, bottles, animals, mountains or computers. They also asked the patients to remember the quadrant of the computer display in which the images appeared.

The researchers subsequently asked the patients to look at another series of images, both novel and familiar. To test the patients' recognition of the images, they were asked to identify which images were new and which were old. To test the patients' recollection of the images - a process distinct from recognition - the patients were asked to recall in which quadrant of the display the images had appeared.

This experimental design gave us the ability to distinguish clearly between recognition and recollection, said Rutishauser. There has been considerable debate in the field about whether the hippocampus is involved in recognition, and this design enabled us to test it.

We found two classes of neurons, which we called novelty detectors and familiarity detectors, he said. The novelty detectors only increased firing to new stimuli whereas the familiarity detectors increased firing exclusively to old stimuli, he said.

This finding is important, said Schuman, because it showed that the researchers were seeing general novelty detectors, and not just those that are active during one phase of the experiment or the other. Novelty detection is critical for animals to create associations between behaviorally relevant stimuli. The other important finding is that these experiments enabled us to identify for the first time, neurons in humans that show changes in responsiveness as a result of a single behavioral trial, she said. This is a landmark in that respect.

Schuman said one surprising observation was that the patients' successful recognition of a familiar image — as measured by the neuronal response — didn't necessarily mean they correctly recollected where they have seen it. Also, a failure to recognize an image didn't necessarily mean the appropriate neurons didn't fire.

When the subjects would make behavioral errors, and we looked at the corresponding neuronal firing pattern, we found that the neuronal firing actually indicated the correct response, she said. Thus, there is some sort of disconnect or failure at the connection between the information the brain has and how the subject decided to respond.

There are examples of this in real life, said Schuman. For example, I might not remember meeting somebody before, even though they might insist that we had met. But later, I might remember that I had, indeed, met them before. That indicates there existed a certain neural substrate for the information on that person, but at the time I saw them, I perceived them as a new stimulus, not a familiar stimulus.