I'll take that brain to go: Advancements in the transport of human brain samples and epilepsy research

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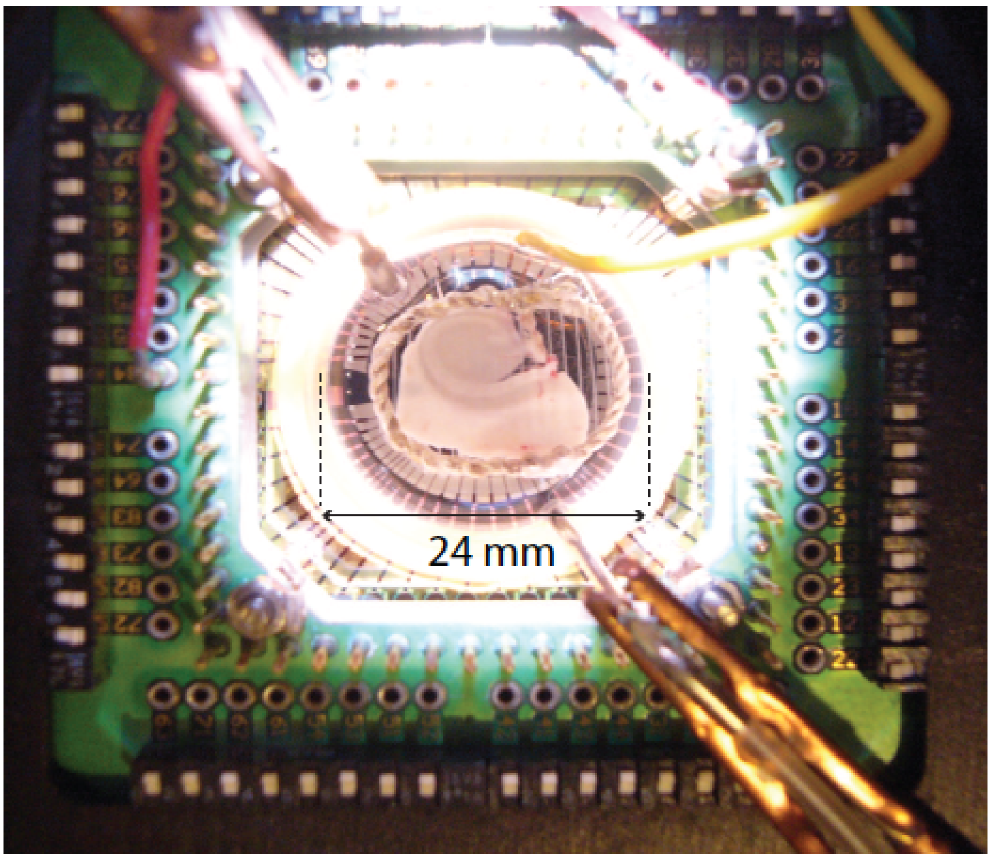


An epileptic human hippocampal slice submerged in the multi-electrode array recording chamber developed by the USC Viterbi research team for experiments in recording epileptic seizures. Credit: USC Viterbi School of Engineering

USC biomedical engineers, neurologists and neurosurgeons develop new methods to advance the study of human brains and epilepsy Studying the human brain is logistically complicated. Living samples of the complex and sensitive organ are limited and difficult to preserve, which means that research on them must be conducted quickly before they expire. Furthermore, the electrodes currently used to record neural activity are largely unsophisticated.

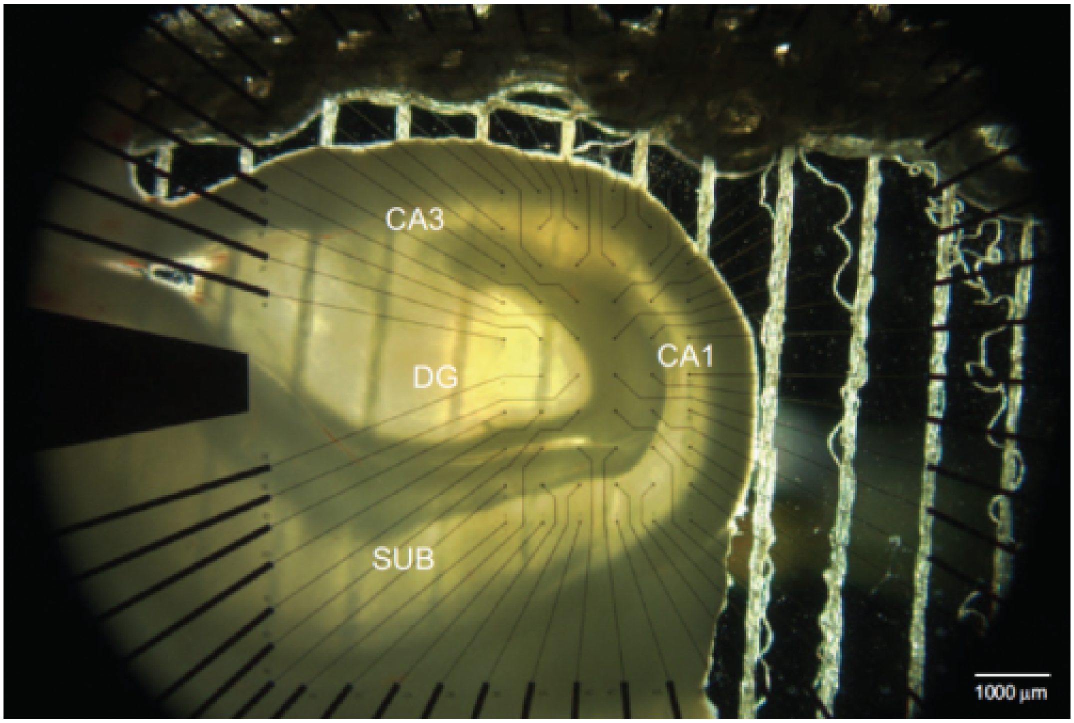
These factors complicate the study of epilepsy to determine its causes, prediction and prevention. However, a team researching epilepsy at the USC Viterbi School of Engineering has developed new methods to overcome these obstacles: a "to go" box that transports human brain samples to research labs in good condition, and a multi-electrode array (MEA) that provides an in-depth understanding of epileptic seizures.

Epilepsy is a neurological condition that causes repeated seizures that are sometimes contained within the hippocampal regions of the brain. The human brain contains two hippocampi, which aid in spatial navigation and convert short-term memories into long-term ones. If left untreated or if the patient does not respond to medication, epileptic seizures can cause permanent damage to the hippocampi. In 30 percent of cases the patient does not respond to pharmacological therapy, and may undergo surgery to have one hippocampus removed in an attempt to reduce their probability of seizure. For most patients, surgical removal of the seizure focus provides complete control of seizures, but for some it's still not enough.

"We still don't know exactly what causes epileptic seizures or how we can prevent them effectively," said USC Viterbi biomedical engineering research associate Min-Chi Hsiao, lead and corresponding author of the study. "The first step is to figure out where exactly in the brain these seizures are taking place. Then we can interpret the neural activity and figure out how to prevent seizures or stop them once or even before they begin." The first step was to obtain human brain samples. With help from surgeons at the Keck School of Medicine of USC, Hsiao and his team obtained brain tissue samples removed from living patients with epilepsy who underwent surgery to remove one of their hippocampi. Then, like many researchers in their field, they faced the daunting task of preserving and transporting the samples safely back to their lab on campus 7 miles away from the hospital, a 25-40 minute trip depending on Los Angeles traffic.

To hurdle this logistic obstacle, the team developed and fabricated a customized transport system to sustain the viability of the hippocampal slices. Their Mobile Oxygen-Temperature Sustaining (MOTS) system included compartments with mesh bottoms to contain each separate slice, which were then sealed into a glass container filled with a sucrose solution. During slicing, transportation and testing, oxygen-rich gas was bubbled through the solution in which the slices were immersed. For the ride to campus, the whole kit was placed in a Styrofoam container of crushed ice to maintain a steady temperature of 4 degrees Celsius. Hsiao believes that MOTS could be adapted to transport other kinds of human brain tissue used in research.

The team's next challenge was to develop a method to study seizures in-depth. In researching the causes of epilepsy, seizure activity is typically induced in a brain sample, and the resulting neural impulses are recorded using an electrode inserted into the slice. This single electrode, however, provides very limited information from only one spot of the hippocampus. Although some researchers are now experimenting with several electrodes, the USC Viterbi team utilized a planar MEA system with dozens of electrodes. "Ours is the first application of planar multi-electrode arrays (MEAs) to study human hippocampal tissue," said Hsiao. "Using the 10 x 6 MEA, we discovered that seizures can be induced and sustained in three different subregions of the hippocampus: dentate gyrus (DG), Area CA1, and subiculum (SUB)."



The 10 x 6 multi-electrode array developed by the USC Viterbi research team for experiments in recording epileptic seizures in human brain slices. Credit: USC Viterbi School of Engineering

They found that 60 electrodes configured in a 10 x 6 array enabled them to record neural activity from a broad cross-section of the hippocampus simultaneously. This MEA also allowed them to simultaneously record activity from different hippocampal subregions, something that had never been accomplished before. Before this, doctors and researchers knew that seizures originated in the hippocampus, but did not know in which subregions the onset was occurring. The team's experimental model has now shed light on how to profile seizures. Furthermore, in experiments with the MEA, the team also found that specialized stimulation could temporarily suppress a seizure in a brain slice.

In monitoring seizures with the new MEA, the team discovered that different patients experienced seizing in different subregions of the hippocampus, including the DG, CA1, and SUB. The team did not record seizures occurring in subregion CA3 of the hippocampus, but this may be due to surgical difficulties which can compromise the quality of the CA3 region.

The team's next step will be to create a stimulation paradigm that can be used to determine seizure characteristics of each patient. The eventual goal is to use the depth electrode in live patients in order to develop a personalized optimal stimulation pattern to treat each individual.

"A lot of research is being done on seizure detection or prediction," said Hsiao. "We are looking for the clues to optimally preventing seizures. Once the loop is closed perfectly, we will be able to predict a seizure in a patient and stop it beforehand."

The study, published online in the *Journal of Neuroscience Methods* on September 22, was co-authored by multiple faculty from the Keck School of Medicine of USC and USC Viterbi, including neurosurgeon Charles Liu, neurologist Christianne Heck, biomedical research associate professor Dong Song and biomedical engineering professor Theodore Berger.

Berger, director of USC Viterbi's Center for Neural Engineering, also conducts research with basic neuroscience researchers at USC, institutions such as the California Institute of Technology, and the Keck School-based USC Neurorestoration Center, which develops novel strategies for the restoration of neurological function by connecting on-going efforts in neural engineering. Research is applied to patients through clinical programs at Keck Medicine of USC, Rancho Los Amigos National Rehabilitation Center, Los Angeles County + USC Medical Center and other affiliated medical centers. Liu and Heck are the director and co-director of the USC Neurorestoration Center, respectively.

"This research has the potential to improve upon the FDA-approved concept of treating epilepsy by neuromodulation, but at a much higher resolution by applying specific algorithmic electrical stimulation at the level of the circuit," said Liu, professor of neurosurgery and neurology at the Keck School. "It is an example of the collaboration between the Center for Neural Engineering at USC Viterbi and the USC Neurorestoration Center at Keck to develop transformational therapies directly in human tissue by taking advantage of unique opportunities afforded by our clinical practice."

Provided by University of Southern California