# Invading the brain to understand and repair cognition

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People are using brain-machine interfaces to restore motor function in ways never before possible - through limb prosthetics and exoskeletons. But technologies to repair and improve cognition have been more elusive. That is rapidly changing with new tools - from fully implantable brain devices to neuron-eavesdropping grids atop the brain - to directly probe the mind.

These new technologies, being presented today at the Cognitive Neuroscience Society (CNS) annual conference in New York City, are mapping new understandings of cognition and advancing efforts to improve memory and learning in patients with cognitive deficits.

## Eavesdropping on neurons

"A new era" of electrophysiology is now upon us, says Josef Parvizi of Stanford University who is chairing the CNS symposium on the topic. "We have gotten a much sharper view of the brain's electrophysiological activity" using techniques once relegated to science fiction.

Over the past decade, scientists have gathered a wealth of new data via grids of sensors inserted into the top layers of the brain. "You can basically eavesdrop on each millimeter of the human brain in real-time using 300-400 sensors, recording simultaneously from a large mantle of the human brain." That data, combined with new data mining and processing techniques, has led to an explosion in studies involving humans.

"Just compare recent papers in humans and non-human primates," says György Buzsáki of New York University (NYU). "In the latter case, 2 or 3 subjects are used with typically fewer than 50 recording sites, and a typical papers is based on 100-200 neurons. In contrast, observations in humans report on dozens of patients and an order of magnitude more data than in monkeys."

Buzsáki, who is presenting at the CNS meeting today, has been working to understand the syntactical rules of the brain - how information is parsed, packaged and transmitted. He thinks the answer is in the self-generated rhythms of the brain. His work has found that nearly all brain rhythms are preserved through mammalian evolution. Despite a 15,000-fold brain volume increase from the smallest to the largest mammal, "the dynamics of brain rhythms vary remarkable little across species," he says.

In a new study, Buzsáki and colleagues have been studying epilepsy in rats, specifically looking at interictal epileptic discharges (IEDs). Distinct from epileptic seizures, IEDs can impair memory in epilepsy patients. The new results suggest that the IEDs hijack the physiological patterns connected to memory consolidation, including during sleep.

"Eliminating IEDs would be an ideal solution," Buzsáki says. Short of that, scientists may be able to decouple IEDs from electrochemical signals associated with memory consolidation.

To help support such interventions, Buzsáki has been working on a new tool for recording and stimulating signals from the cortex. The scalable system offers higher spatial resolution for the superficial cortex layers and, unlike the commonly used subdural grids, sits atop the brain rather than penetrating it.

"Young students of cognitive neuroscience are lucky to be in the midst of a new era where we have access to amazing new tools of science for eavesdropping on the population of cells with a superb temporal resolution," Parvizi says.

## Stimulating for memory deficits

"Brain disease is a growing socioeconomic problem," says Dejan Markovic of UCLA. Traumatic brain injury (TBI) and epilepsy alone affect millions of patients a year. Neuromodulation - adjusting the electrochemical signals at the neural level - offers a potential solution.

Today's technology is inadequate for treating complex diseases at the network level, Markovic says: "Drugs have very limited success, making the development of new neuromodulation technology for treating cognitive and psychiatric disorders a major medical and social priority."

Tackling this is a challenge, as the brain is a massively parallel, complex system: about 10 layers of cells sit between the regions of the brain that handle our senses and our cortex, where memories are stored. And each cell has thousands of connecting points to other cells with multiple branches. Since mapping out the basic neuroanatomy of neural cells in the late 1800s, scientists have worked to understand how these cells dynamically interact.

Some scientists think the secret is in short electrochemical pulses exchanged between neurons - the language of the brain. In work previously only possible in animals, scientists are now recording these signals directly from the brain and in some cases trying to stimulate the brain with those signals to help patients with cognitive deficits. Markovic - with an interdisciplinary team including Lawrence Livermore National Labs, UCLA, and UCSF and a grant through DARPA - is working on a platform technology for such brain stimulation.

Epilepsy patients commonly have electrodes implanted in their brain to help doctors pinpoint the location of their seizures. The team is using these already-implanted electrodes to record and stimulate the activity of single neurons and small neuronal populations during the patients' 2-3-week-long hospitalization. Some patients receive a chronic implant that uses surface and depth electrodes for sensing and stimulation. The project builds off past work demonstrating memory strengthening by stimulating the brain's entorhinal region, the gateway to long-term memory storage in the hippocampus.

As Markovic is presenting at the CNS meeting today, the team is starting animal testing of a new system and will test in humans sometime this year. Among their goals for this system are: a higher density electrode array to allow for more precise targeting on neurons, new recording circuits that vastly increase the volume of data captured, and a new wireless power and telemetry technology that allows for real-time data transmission from the brain. The hope is to develop a neuroprosthetic that could not only help patients with epilepsy and TBI but also those suffering from depression, anxiety, PTSD, and other neuropsychiatric disorders.

What makes cognition especially challenging as a target of this technology, as opposed to motor behavior, is that memory function is represented by sparse and partially overlapping neural networks consisting of millions of neurons, Markovic says. "Obviously, access to all these neurons with the interface and recording technology that we have today is not possible, and clinical neuroscientists have to work hard to make inferences from very limited data they can access," he says. "Our technology will greatly increase the efficacy of neuromodulation and enable access to broader patient population."

While the work of Markovic and his colleagues "may well be science fiction at this point," Parvizi says, "their research will definitely push the envelope, and all of us will benefit from it."

In this new era of big neural data, "new analysis and theory are needed to make sense of data leading to discoveries," says Xiao-Jing Wang of NYU. His work combines experimental data computational modeling of oscillations in the brain to understand the many feedback systems across different scales in space and time.

**More information:** Parvizi, Buzsáki, Markovic, and Wang are presenting in the symposium, "Human Intracranial Electrophysiology: A New Era," CNS annual meeting in New York City; Sabine Kastner (Princeton) is moderating a discussion panel following the talks. More than 1,500 scientists are attending the meeting from April 2-5, 2016.

Provided by Cognitive Neuroscience Society