New method classifies brain cells based on electrical signals

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MIT Professor Earl Miller. Credit: The Picower Institute for Learning and Memory

For decades, neuroscientists have relied on a technique for reading out electrical "spikes" of brain activity in live, behaving subjects that tells

them very little about the types of cells they are monitoring. In a new study, researchers at the University of Tuebingen and MIT's Picower Institute for Learning and Memory demonstrate a way to increase their insight by distinguishing four distinct classes of cells from that spiking information.

The advance offers brain researchers the chance to better understand how different kinds of neurons are contributing to behavior, perception and memory, and how they are malfunctioning in cases of psychiatric or neurological diseases. Much like mechanics can better understand and troubleshoot a machine by watching how each part works as it runs, neuroscientists, too, are better able to understand the brain when they can tease apart the roles different cells play while it thinks.

"We know from anatomical studies that there are multiple types of cells in the brain and if they are there, they must be there for a reason," said Earl Miller, Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences at MIT, and co-senior author of the paper in *Current Biology*. "We can't truly understand the functional circuitry of the brain until we fully understand what different roles these different cell types might play."

Miller collaborated with the Tuebingen-based team of lead author Caterina Trainito, Constantin von Nicolai and Professor Markus Siegel, co-senior author and a former postdoc in Miller's lab, to develop the new way to wring more neuron type information from electrophysiology measurements. Those measures track the rapid voltage changes, or spikes, that neurons exhibit as they communicate in circuits, a phenomenon essential for brain function.

"Identifying different cell types will be key to understand both local and large-scale information processing in the brain," Siegel said.

Four is greater than two

At best, neuroscientists have so far only been able to determine from electrophysiology whether a neuron was excitatory or inhibitory. That's because they only analyzed the difference in the width of the spike. The typical amount of data in an electrophysiology study—spikes from a few hundred neurons -only supported that single degree of distinction, Miller said.

But the new study could go farther because it derives from a dataset of recordings from nearly 2,500 neurons. Miller and Siegel gathered the data years ago at MIT from three regions in the cortex of animals who were performing experimental tasks that integrated perception and decision making.

"We recognized the uncommonly rich resource at our disposal," Siegel said.

Thus, the team decided to put the dataset through a ringer of sophisticated statistical and computational tools to analyze the waveforms of the spikes. Their analysis showed that the waveforms could actually be sorted along two dimensions: how quickly the waveform ranges between its lowest and highest voltage ("trough to peak duration"), and how quickly the voltage changes again afterward, returning from the peak to the normal level ("repolarization time"). Plotting those two factors against each other neatly sorted the cells into four distinct "clusters." Not only were the clusters evident across the whole dataset, but individually within each of the three cortical regions, too.

For the distinction to have any meaning, the four classes of cells would have to have functional differences. To test that, the researchers decided to sort the cells out based on other criteria such as their "firing rate"

(how often they spike), whether they tend to fire in bursts and how variable their intervals are between spikes—all factors in how they participate in and influence the circuits they are connected in. Indeed, the cell classes remained distinct by these measures.

In yet another phase of analysis the cell classes also remained distinguishable as the researchers watched them respond to the animals perceiving and processing visual stimulation. But in this case, they saw the cells play different roles in different regions. A class 1 cell, for example, might respond differently in one region than it did in another.

"These cell types are truly different cell types that have different properties," Miller said. "But they have different functions in different cortical areas because different cortical areas have different functions."

New research capability

In the study the authors speculate about which real neuron types their four mathematically defined classes most closely resemble, but they don't yet offer a definitive determination. Still, Miller said the finer-grained distinctions the study draws are enough to make him want to reanalyze old neural spiking data to see what new things he can learn.

One of Miller's main research interests is the nature of working memory—our ability to hold information like directions in mind while we make use of it. His research has revealed that it is enabled by a complex interplay of brain regions and precisely timed bursts of neural activity. Now he may be able to figure out how different classes of neurons play specific roles in specific regions to endow us with this handy mental ability.

And both Miller's and Siegel's labs are particularly interested in different brain rhythms, which are abundant in the brain and likely play a key role

for orchestrating communication between neurons. The new results open a powerful new window for them to unravel which role different neuron classes play for these brain rhythms.

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