New spatial profiling approach maps out discoveries for future brain research

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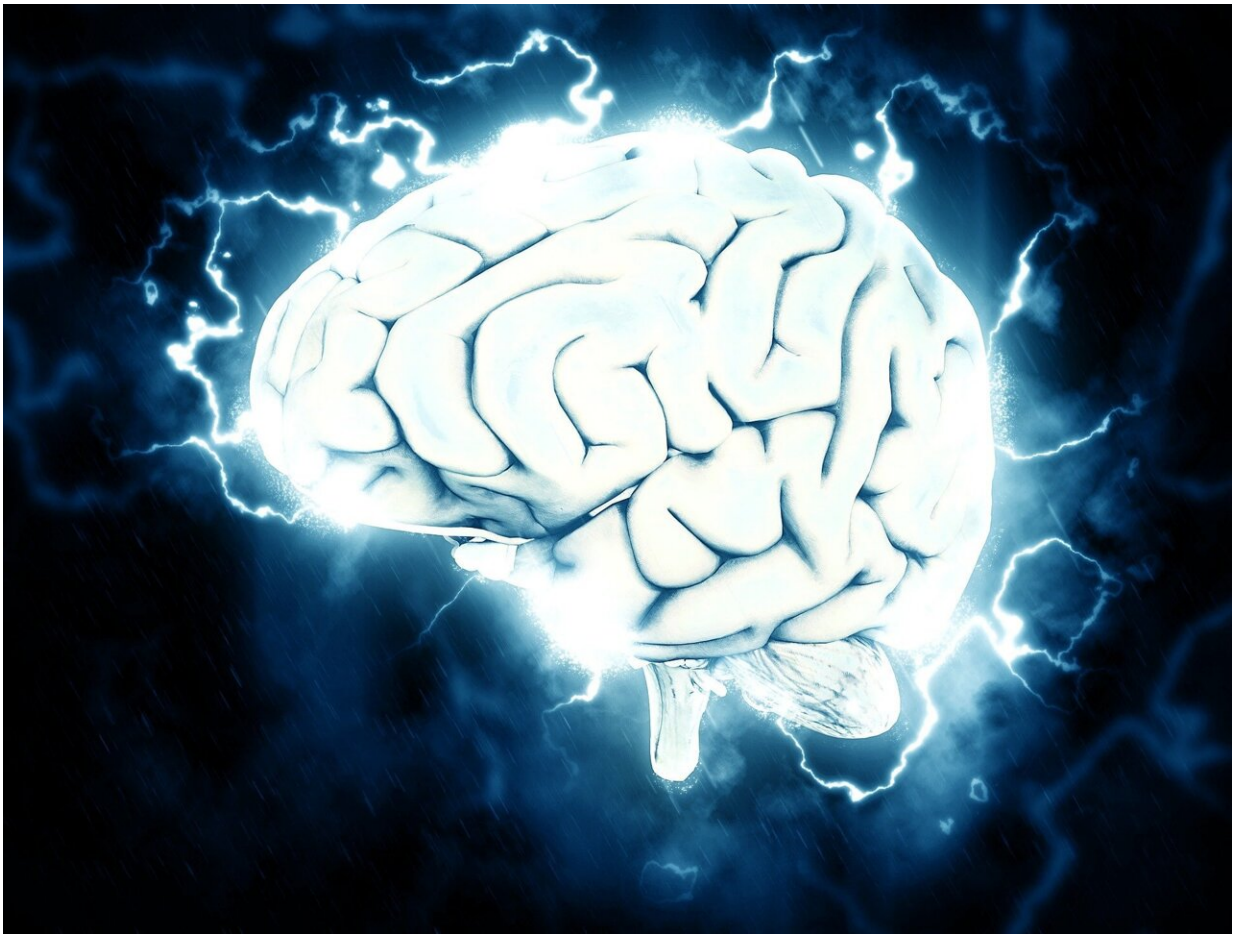

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An estimated one in six people suffer from a brain disorder worldwide,

according to the American Brain Foundation. Current research has provided some insight into cell communication inside the brain, but there are still a lot of unknowns surrounding how this crucial organ functions. What if there was a comprehensive map that took into consideration not just the biology of the brain, but the specific location where the biology occurs?

Researchers in the College of Engineering have developed a powerful, cost-effective method to do just that. Chang Lu, the Fred W. Bull Professor of Chemical Engineering, has been leading a research project that could be groundbreaking for brain research. The latest findings are published in the journal *Cell Reports Methods*.

The study features interdisciplinary research along with faculty in two additional departments within the College of Engineering: Xiaoting Jia, associate professor in the Bradley Department of Electrical and Computer Engineering, and Daphne Yao, professor in computer science and affiliate faculty at the Sanghani Center for Artificial Intelligence and Data Analytics

Their goal? Mapping and visualization of the brain biology at genome scale in the most cost-effective way possible to improve healthy functioning.

"Many of the facts about the brain are phenomenological, meaning that we know it happens, but we don't necessarily understand molecular activities underlying these events. I think this has been hindering the development of drugs," said Lu.

"Treating brain disorders has historically been done not by rational design, but by trial and error. By having a reference map that explains how different parts of the brain operate at a molecular level, this can help researchers begin to develop different treatment options."

What's new in brain mapping

Brain health is largely determined by gene activities in brain cells. When researchers talk about genetics, they are essentially referring to the DNA sequence and how it affects human health. For example, if something is wrong or altered within the sequence, then certain diseases can be diagnosed.

Research has revealed that there can be other chemical changes occurring in the brain that do not alter the DNA sequence, but change how other molecules interact with DNA. This change that influences gene activity without altering the DNA sequence is known as epigenomics, and it can be equally responsible for changing the gene activity inside the brain and causing various diseases.

Lu and his colleagues are interested in exploring how brain epigenomics can be altered in various brain regions in response to activity changes or specific conditions like seizures, epilepsy, addiction, or other mental diseases. The current process of brain mapping involves profiling single cells one by one.

While this approach offers high spatial resolution and presents important information about cell communication inside the brain, it is costly and tedious. Lu and his team have developed a more cost-effective approach to the spatial method: epigenomic tomography.

Epigenomic tomography involves the creation of a detailed map of the epigenome, or the genome-scale profile of the epigenetic change, across a large area and volume of the brain. Lu believes this is an important method for scientists to use to understand the genetic and environmental factors that affect the ways genes behave outside of DNA sequences.

"When a person has a seizure, struggles with addiction, or suffers from

any kind of brain disorder, they experience epigenomic alteration in the brain," Lu said. "Creating a reference map of the brain to display what healthy brain epigenomes look like across various regions can provide a helpful point of comparison for when the brain suffers a change, such as a seizure."

The future of drug development

Through their collaborative process, the research team was able to create a map that demonstrates when the brain is experiencing a seizure versus when it is experiencing normal activity. Here's their interdisciplinary approach:

- Divide the brain into small sections, about 0.5 mm in thickness. These sections are registered, meaning the researchers know where a particular section is from in terms of the location and region of the brain.
- Profile each one of the sections separately using their low-input technology developed in Lu's lab.
- Group features across these sections into clusters based on their spatial variation patterns using clustering algorithms with help from Yao.
- Create brain tomographies for both healthy and diseased brains, with assistance from Jia's model for investigating the effects of seizures and other brain disorders.

Once the digital tomography of the brain is reassembled, the researchers have a map that is characteristic of the brain's epigenome across a significant area. When the map changes, this reflects a significant change in terms of how the brain is performing at the epigenomic level, which Jia says is groundbreaking for understanding brain disorders.

"The missing piece to the puzzle is the fundamental understanding of the

seizure process at the molecular level across a spatially distributed brain region," said Jia. "Our method provides a powerful tool that allows us to investigate the molecular processes in the brain underlying seizure."

The results of their spatial epigenomic profiling will further help researchers understand how cells across various regions of the brain behave differently in terms of their epigenetic signatures. This cost-effective method also helps ensure that a sizable number of brain samples can be studied, something that yields statistical significance for the result.

Lu believes his team's brain mapping method could make a big impact on drug development for brain disorders. He said, "We hope more researchers will join us in terms of making progress on brain disorders. It's important research for people suffering from depression and addiction. That's a large percentage of our population."

Collaboration inside the lab

This interdisciplinary collaboration required specialties from all three departments. "Our findings wouldn't have been possible without the close collaboration across multiple disciplines," Jia said. "It's really exciting to see that epigenomic tomography facilitates the understanding of spatially dynamic processes across a large brain area underlying seizure, and I expect it can enable applications in a wide range of brain diseases in the future."

So what does research on the brain have to do with engineering? To Lu, this was the perfect project for a chemical engineer.

"The technology development part of this project is how you might traditionally think of engineering: solving a problem, designing an approach, and developing the technology. But I feel chemical engineers

are particularly equipped with the vast skill set of chemistry, biology, and data analysis. Each of these aspects are involved in this project, one way or another," said Lu.

The engineering expertise used in this project did not stop there. Yao used statistical algorithms to simplify and organize massive epigenomic data, making meaningful patterns stand out, such as how healthy and diseased brains' epigenomes differ.

"The amount of biological data generated in this project is huge, requiring the design of customized data processing methods tailored for this specific problem," Yao said. "It is super exciting to see clustering algorithms being used for biomedical research—something to brag about next time I teach machine learning."

More information: Epigenomic tomography for probing spatially-defined chromatin state in the brain, *Cell Reports Methods* (2024). DOI: 10.1016/j.crmeth.2024.100738. www.cell.com/cell-reports-meth … 2667-2375(24)00063-8

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