ADVERTISEMENT FEATURE

BUILDING BETTER MIND MAPS

Innovative techniques for analysing brain function and structure are revealing remarkable details of neural architecture, providing NEW LEADS FOR DIAGNOSING AND TREATING BRAIN DISEASE.

Although the human brain has been an object of scientific fascination for centuries, we are just scratching the surface in terms of our understanding of its functionality and complexity. We have a good understanding of the general functional areas of the brain, but exactly how this interconnected network of neurons process and transmit information to give rise to thought and memory remains a highly active area of research.

Studying how the brain functions at the fundamental physiological level is one of the most challenging fields of research, requiring new methods for experimentation and detection of brain activity at the neuronal scale. Recent advances in brain-imaging techniques and understanding of the brain's fine structure, have made it possible to explore brain function in new ways. This is revealing discoveries with implications for brain health and artificial intelligence.

BRAIN/MINDS AND BEYOND

Two of several large-scale, national brain research projects launched in recent years around the world, Japan's Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) and Strategic International Brain Science Research Promotion Program (Brain/MINDS Beyond) projects aim to investigate the neural circuits underlying higher brain functions. They are national initiatives with dozens of participating institutions, each specializing in a particular area of brain study.

One area bringing new insights into the brain's architecture is the study of non-human primates at the University of Tokyo and the National Institutes for Quantum Science and Technology (QST).

"When it comes to understanding the human brain and disorders that can affect it, only other primates share our higher functions, such as a hierarchical visual cortex and a highly developed prefrontal cortex responsible for executive function and decision making," explains Takafumi Minamimoto, who leads the Neural Systems and Circuits Group of the Department of Functional Brain Imaging at QST.

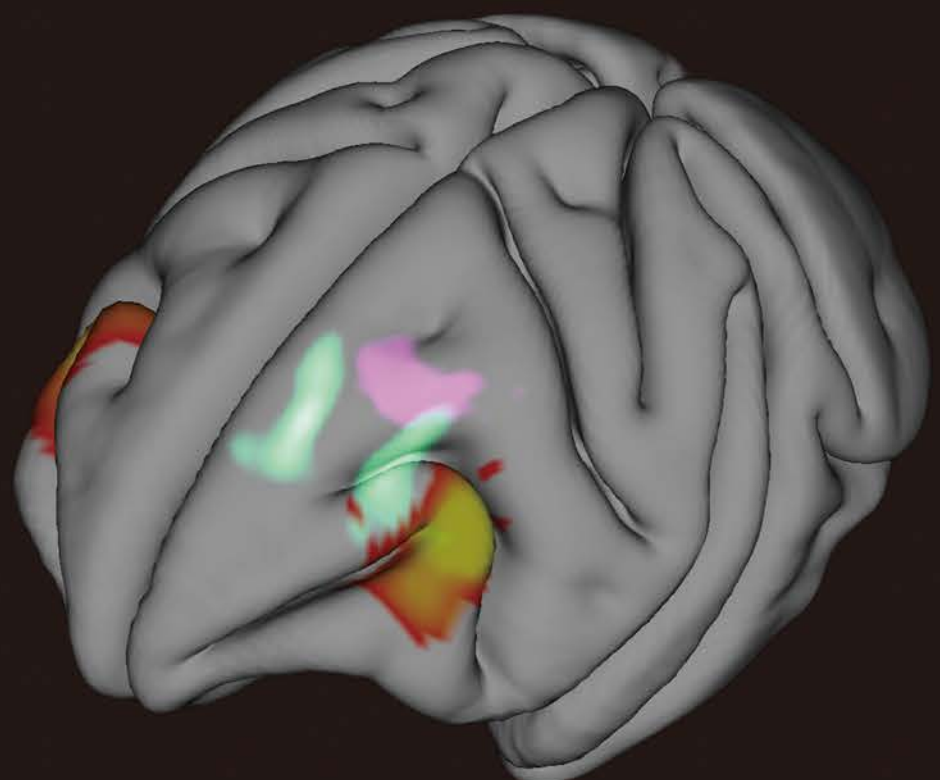
"Primate brain research is challenging and costly, but indispensable. It allows us to gain deeper insight into brain function that can help us understand and treat human brain disorders."

Minamimoto's team is focusing on developing higher precision methods for analysing brain function. Their greatest achievement has been the development of a chemogenetic method to turn off brain activity at the single-neuron level, combined with positron-emission tomography (PET) — an imaging technique for specific molecules. This has made it possible to visualize not only the activity of primate neurons, but also its connection to other brain areas[1].

"With chemogenetics, we inject a harmless viral solution into a specific area of the brain to genetically modify neurons to make them sensitive to a suppressor chemical," explains Minamimoto. "We can then inject the suppressor to turn off the modified neurons for hours at a time."

The team has recently developed a 100-fold more effective suppressor chemical[2], allowing them to inject tiny doses of this suppressor to selectively affect individual groups of neurons and their axon connections. They have used this technique to silence specific connections to discover the circuit pathways responsible for working memory and decision making.

The approach is also promising for treatment for brain disorders in humans. For example, as a potential model for treatment in humans, the group recently reported that chemogenetics can suppress seizures in macaques[3].



▲ Positron emission tomography (PET) image of a monkey brain, showing critical nodes in the neural pathways involved in working memory and decision making

THE VISUAL SYSTEM

Another team, at the University of Tokyo and led by Kenichi Ohki, is researching how visual information is processed in primates, which have a highly developed and hierarchical visual cortex. The group's research on marmosets uses a high-sensitivity calcium imaging technique that can visualize how specific parts of the brain respond to different stimuli.

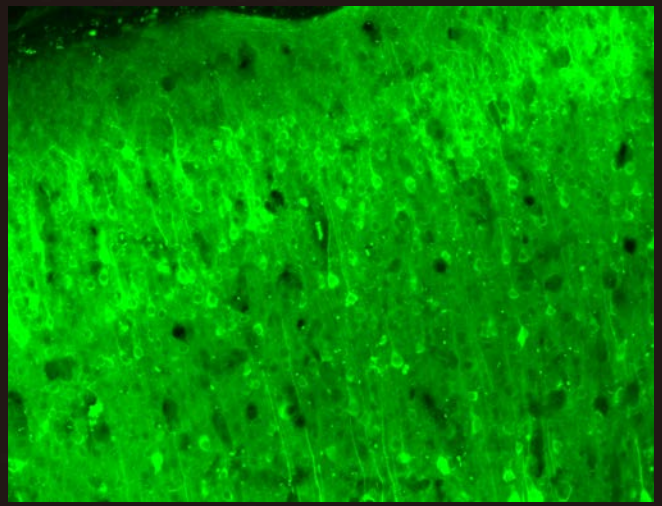
"Calcium imaging is a long-standing technique for observing brain function in mice, but it wasn't sensitive enough to visualize discrete groups of neurons in primates with the same quality as in mice," says Ohki. "In collaboration with Tetsuo Yamamori in RIKEN, We developed an improved method that significantly increased the expression of the fluorescent protein GCaMP6 in the primate brain, which, when combined with laser-based, two-photon imaging, allows us to visualize neuron activity in amazing detail."

The visual system makes up more than half of the cerebral cortex in primates, and it consists of an elaborate hierarchy of information processing stages. There are discrete areas that process patterns and angles, for example, and Ohki's research has shown that neurons fire in coordinated patterns sensitive to these different stimuli, with different cellular-level functionality.

"IT ALLOWS US TO GAIN DEEPER INSIGHT INTO BRAIN FUNCTION THAT CAN HELP US UNDERSTAND AND TREAT HUMAN BRAIN DISORDERS."

"One of the fascinating findings of our work is that the hierarchy of the visual system seems to process noise in the opposite direction to how artificial neural networks typically process noise," says Ohki. "It would be interesting to construct an artificial neural network that enables such a method of noise processing in the primate visual system."

Ohki's research group is looking in detail at how noise is processed in these cortico-cortical connections, which appear to be fundamental to how the brain functions in primates. These connections can also explain the plasticity of the brain and how different areas can be enrolled for information processing if the primary connection is impeded.



▲ Neurons in a marmoset brain captured using the fluorescent protein GCaMP6.

"For example, we've found that the development of the visual system occurs in the neonate as a result of wave-like activity across the retina, which stimulate the thalamo-cortical connections that build this hierarchical structure," Ohki says[4].

Without these stimuli, connections cannot develop from the primary visual cortex to the higher visual cortex. On the other hand, if these connections do not develop, one would expect alternative connections to be made from other areas, such as the somatosensory cortex to the higher visual cortex. Ohki suggests this might also explain how blind patients use the visual cortex to 'read' braille despite it being a tactile function.

"Our findings from primate studies are providing valuable insights into human neuropsychiatric disorders, particularly those related to miscommunication in the brain. Our techniques will be useful for guiding specific research and translating the knowledge from primates to humans," says Minamimoto.

"We hope to share this knowledge and technology with the world and collaborate with other groups to help advance this important field of brain research." ■

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