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FOCAL POINT ON BRAIN SCIENCE IN JAPAN

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THE BEST MODEL TO UNLOCK THE SECRETS OF THE HUMAN BRAIN

With its focus on marmosets, Japan's national brain initiative has been generating invaluable data for UNLOCKING THE MYSTERIES OF OUR MINDS.

At the heart of Japan's national brain initiative, the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) project, lies a diminutive monkey — the common marmoset. It's this focus that distinguishes it from other national brain initiatives, and promises to offer a unique contribution to our understanding of the human brain.

Researchers in the field of neuroscience have made immense strides in the past two decades. "We're getting tantalizingly close to being able to address some of the core questions of neuroscience — how the brain functions as a whole entity, and how such a sophisticated organ can make decisions, produce emotions and generate consciousness," says Shigeo Okabe, the programme supervisor of the Brain/MINDS project, based in Tokyo. "We're entering a very exciting stage for neuroscience."

CLOSING THE GAP

But the vast majority of animal brain studies are conducted on rats and mice, which have brains that differ greatly from our own. This is a necessary consequence of the understandably stringent limits on the techniques that can be used to probe the living human brain. It's precisely this gap that non-human primates can help to fill, by providing a strategic stepping stone: their brains are more human-like than those of rodents, while the full range of analytic and imaging techniques applicable to rodents can also be used on them.

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A MARMOSET
Common marmosets offer a strategic stepping stone between the rodent and human brains. They underpin Japan's national brain initiative, which is called Brain/MINDS.

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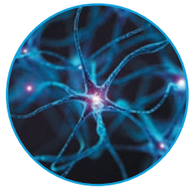
The marmoset brain is estimated to have about **636 MILLION NEURONS**, roughly nine times more than the mouse brain.



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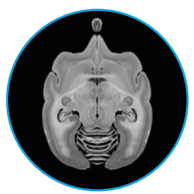
The marmoset brain is about 3 centimetres long and 2 centimetres wide and weighs about 8 grams (**ROUGHLY 2.0–2.5%** of the animal's total body weight).



"In the case of the other organs, mice and humans generally share very similar cell types and structures," explains Okabe, who is also a professor in the Graduate School of Medicine of the University of Tokyo in Japan. "But in the case of the brain, mice lack a large frontal cortex. So if you want to understand the neurocircuits in the frontal cortex of human brains, you have to turn to primates."

When Japanese neuroscientists thrashed out the direction their national brain project should take more than a decade ago, they seized upon this strategic role that primates can play. This focus on using primates to better understand the human brain is one of the three major objectives of Brain/MINDS, which launched in 2014.

The other two objectives — to elucidate the neural networks involved in such brain disorders as dementia and depression, and to promote close cooperation between basic and clinical research related to the brain — flow from that.

"Since the marmoset brain has quite similar structures to the human brain, we used this animal model to understand human disease," explains Okabe. "That's why the project has an emphasis on human disorders, especially dementia, which is of particular relevance to Japan's super-aged society."

Their broader range of behaviours is another advantage of marmosets over rodents. It can be quite difficult to distinguish a mouse with depression or dementia mouse from a healthy one, but the difference is much more apparent in marmosets. "It's very difficult to measure the extent of dementia or depression in mice models because of the limited number of the behavioural tests," says Okabe. "In contrast, marmosets are much cleverer, so we can use many different measures to assess their mental state, making such measurements easier and more precise."

The Brain/MINDS project has produced some impressive achievements in the past decade. For example, marmoset models for Alzheimer's and Parkinson's diseases have been realized and are now being used to further research in this area, with potential great future benefits for human sufferers of these conditions.

Unlike mouse models of Parkinson's disease, the marmoset model exhibits the characteristic motor symptoms that humans display. Another accomplishment is the development of fluorescence microscope with a huge field of view, capable of imaging 16,000 brain cells at a time. This microscope is being used to collect massive amounts of data on the marmoset brain. Finally, a new bioluminescent probe that allows the brains of moving marmosets to be imaged in three dimensions at a single-cell level has been produced.

BEYOND BRAIN/MINDS

An extension of the Brain/MINDS project was launched in 2018. Brain/MINDS Beyond, has three main objectives. One is to foster more international collaboration with groups working overseas. Another objective is to extend the work being done on marmosets to larger primates. "There is still quite a wide gap between the marmoset and human brain," says Okabe. "In Brain/MINDS Beyond, we're seeking to fill that gap by using larger primates like macaques."

Finally, Brain/MINDS Beyond has a strong emphasis on harnessing artificial intelligence to analyse the vast amounts of data being generated.

Okabe sees this as a strategic time in neuroscience, especially with many national brain projects nearing their conclusions.

"I think now is a time to reconsider what the critical problems in neuroscience are and what needs to be done to tackle them in the next stage," he says. "We have to focus on what specific subjects, tools and databases we need for the next decade. And we need to promote the next stage of international collaboration." ■

3

In 2009, marmosets became **THE FIRST PRIMATE FOR WHICH STABLE TRANSGENIC LINES**, containing genes from other species, were established.

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"We're entering a very exciting stage for neuroscience."

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