BRAIN-SCANNING METHOD MAY TRANSFORM TREATMENTS

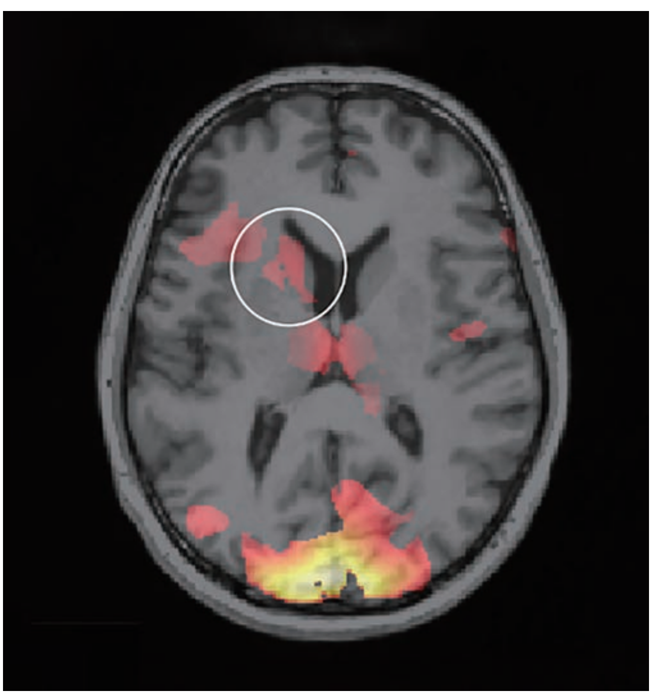
Advances in MRI imaging being driven by researchers in Japan could reshape the way we treat psychiatric disorders and HELP PEOPLE OVERCOME ANXIETY RELATED DISORDERS AND OTHER CONDITIONS.

A revolutionary, non-invasive therapeutic device for the brain was unveiled just over a decade ago. Called decoded neurofeedback (DecNef), and developed by a team led by Mitsuo Kawato of the Advanced Telecommunications Research Institute International (ATR) in Kyoto, Japan. It combines machine learning and brain scanning to identify and reward 'healthy' brain activity patterns that condition the brain to reject excessive fear, such as phobias and social anxiety.

DecNef was initially met with skepticism from some experts. But a number of successful studies with post-traumatic stress disorder (PTSD)[1] and animal phobias[2] are helping to support its use as a promising non-invasive technology for treating anxiety-related disorders. A sister technology, called functional connectivity neurofeedback (FCNef), is in the early phases of development. In contrast to DecNef, which targets specific brain regions, FCNef targets brain circuits — clusters of neurons that connect to perform a function.

HARMONIZED DATASET

To inform neurofeedback treatments such as DecNef and FCNef, clinical psychiatrist Kiyoto Kasai of the University of Tokyo is leading an initiative to establish a massive database of functional magnetic resonance imaging (fMRI) data.



▲ A functional magnetic resonance image (fMRI) of the brain of a psychiatric patient. The circle indicates a region of abnormal activity.

When completed and made available to researchers in 2024, the database will store more than 9,000 cases, making it "the world's most comprehensive by an order of magnitude for data collected with the aim of sharing across institutions," says Kasai. The initiative is part of Japan's Brain/MINDS Beyond Program, which was launched in 2018 to advance brain science research and enhance international collaboration.

Kasai says that by gaining a better understanding of brain circuits and their relationship with the conscious mind, it will be possible to obtain objective indicators for psychiatric diseases to aid diagnosis. However, the differences in these indicators between healthy subjects and those with disorders can be minute and nuanced. He notes that analyses of fMRI images from about 10,000 samples would be needed to distinguish susceptibility to disorders from normal human diversity.

Combining datasets from different medical facilities has remained a challenge internationally, as they have different MRI systems, and different imaging processes and other types of equipment. "For instance, the boundary between grey and white matter in the same person's brain would look different under different conditions," explains Kasai.

Before the Brain/MINDS Beyond Program, Kasai's team traveled to 12 sites in Japan to take MRI images of the same subjects in different facilities, using MRI machines from a range of brands and scanner types. The disparities in MRI images of the same subject helped the team devise methods of data conversion to make it possible to integrate datasets. They published the harmonized data on an open-access database.

The Brain/MINDS Beyond Program pushed these efforts further, including a collaboration with researchers in the United States' Human Connectome Project, so that imaging methodologies for next-generation MRI machines were standardized and usable across various vendors and scanners. The data is fully translatable between the Brain/MINDS Beyond Program and the Human Connectome Project, allowing for data use on an international scale. The team has also scaled up the number of subjects traveling between facilities to improve the harmonization of data.

Efforts for harmonization have led to intriguing findings about the role of brain parts and circuits. For example, in 2016, Kasai's team built on the results of a study by the ENIGMA schizophrenia project — an international consortium studying schizophrenia — and found that some patients with chronic schizophrenia were more likely to have increased volume on the left globus pallidus, a brain region that helps regulate voluntary movement[3].

▲ **An image of a patient's brain that shows the connectivity of neural fibres as predicted by a magnetic resonance imaging (MRI) technique.**

Subsequent research by Kasai and colleagues showed that the increase in volume can be apparent in early adulthood, before the onset of schizophrenic episodes[4]. "We expect such findings to inform early diagnosis and identification of at-risk groups," says Kasai. Plans are underway to use MRI data from the Human Connectome Project and the Asian Consortium on MRI in Psychosis to examine whether the same results could be generalized across populations.

INSIGHTS FROM PRIMATES

As a next step, comparing MRI images of human and other primate brains will help build animal models of psychiatric disorders. "Non-human primates enable studies of causality when validating functional connectivities associated with disorders. While mice are an important model organism for genomics, primates help model high-level cognitive abilities and the circuits related to them," says Takuya Hayashi of the RIKEN Center for Biosystems Dynamics Research in Kobe, Japan. The advance in MRI technology is allowing such research to flourish.

THE ULTIMATE GOAL IS TO IDENTIFY BRAIN STRUCTURES AND CIRCUITS THAT SERVE AS INDICATORS FOR HUMAN PSYCHIATRIC DISORDERS.

Hayashi aims to establish MRI technologies that visualize the anatomy, function and connectivity of non-human primates, particularly marmosets and macaques, at the same level of acuity as humans. The ultimate goal is to identify brain structures and circuits that serve as indicators for human psychiatric disorders.

"MRI technology for non-human primates, however, lags by a decade," says Hayashi, as MRIs had been developed with a focus on human medical needs. The sheer size difference of the brains makes it challenging to capture high-resolution MRI images in primates.

Marmoset and macaque brains, for example, are 200 times and 20 times smaller than ours. In a world first, Hayashi developed a system designed to receive radio frequencies for obtaining high-resolution MRI images in macaques, which include 24 channels that help capture clear images of the entire brain.

In addition to developing hardware, it is equally important to identify and map regions of the primate brain that correspond to regions of the human brain, adds Hayashi. Ultimately, he envisions a brain atlas with an array of additional information like genetics, cells and data from microscopes.

"Much like the way Google Maps includes information on traffic conditions, street views and reviews, the combination of macroscopic information, such as network and functional activity, with microscopic information, including genetics and cellular expression, will give rise to a database that generates accurate models in primates and is truly useful for understanding mechanism and treating human disease," says Hayashi.

High-resolution brain MRI systems for non-human primates that they have established through international collaboration with the Human Connectome Project has led to discoveries including

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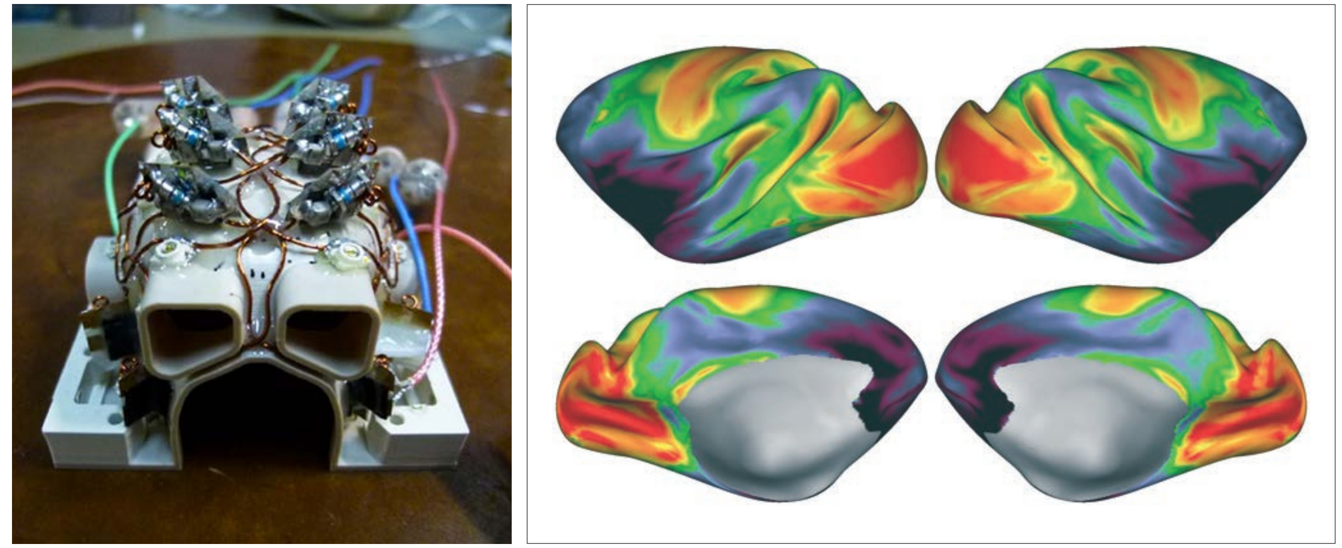

▲ **Headset for monitoring brain activity of marmosets. Magnetic resonance imaging (MRI) scans (right) showing cortical myelin of macaques.**

major functional networks associated with social behavior across species.

Kasai adds that a future challenge is to develop a database that integrates data of species with different levels of brain complexity, as well as to make the data accessible for international studies. In 2022, researchers at the University of Tokyo, RIKEN, the National Center of Neurology and Psychiatry (NCNP) and the National Institute for Physiological Sciences (NIPS) came together to form the Alliance for Brain-Related Database (ABReD) — a translational database of mice, marmosets and humans. "Once established, such types of databases will not only accelerate translational research using MRI images of the brain, but also research that crosses over to molecular and genetic mechanisms," he says.

NEUROFEEDBACK THERAPY

This MRI database of primates will help realize a more precise understanding of brain circuit mechanisms, which is crucial for bringing neurofeedback therapies like DecNef and FCNef, closer to real-world application.

Mitsuo Kawato of ATR, one of the developers of DecNef, says that FCNef may even show promise in treatments for depression, schizophrenia and autism spectrum disorder. "While healthy subjects show a negative correlation in the connectivity of the left dorsolateral prefrontal cortex and the left precuneus, it's the opposite for subjects with depression[5]," he says. "Symptoms of depression were reduced after the connectivity was normalized[6]."

For schizophrenia, some symptoms that occur in the acute stage, such as delusions and hallucinations can be treated with dopamine antagonist-type medications. "But we currently lack drug treatments for chronic patients who suffer from reduced cognitive ability, social withdrawal and a lack of energy," says Kawato.

"FCNef could be a powerful new tool for these psychiatric disorders, but we must exercise extreme caution on choosing circuits to target," says Kawato. "Improvements to MRI image quality and analysis are giving us more clues on brain circuit differences between healthy subjects and those with psychiatric disorders." But this is no easy task.

"When there are hundreds to choose from, how do you choose the right target? How do you set the criteria? These are questions we must address," adds Kawato.

There is still a lot of work that needs to be done before the technology can be applied in the clinic, but the long-term prospects are exciting. "We need more basic research and a more precise understanding of brain circuits before the technology can be applied in the real world," says Kawato. "However, when we know the precise functions of circuits, the technology holds vast potential for personalized psychiatry." The computer programs for neurofeedback developed at ATR have been shared with more than 20 research laboratories in the world, some of which have resulted in successful large-scale trials.

"Japan leads the world in the number of MRI machines per capita, so there is huge potential for MRI-image-assisted diagnosis and neurofeedback therapy to become widespread once the technology is ready," adds Kasai. With further international collaboration, the members in the Brain/MINDS Beyond Program will strive to make their technology more user friendly and get it out into the world to help as many people as possible. ■

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