PRESS RELEASE

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New Study Helps in Finally Breaking the "Silence" on the Brain Network

Scientists chemically suppress areas of the brain and then image brain activity to reveal how this triggers other complex operational networks

Studying the complex network of operations in the brain not only helps us understand its working better, but also provides avenues for potential treatments for brain disorders. But linking the brain network to actual behavior is challenging. In a new study, researchers have discovered that pinpointed suppression or "silencing" of certain areas of monkey brains using genetically engineered drugs can be used to reveal changes to their operational network and the subsequent behavioral effects.

Scientists have been studying the human brain for centuries, yet they have only scratched the surface of all there is to know about this complex organ. In 1990, the face of neuroscience changed with the invention of functional magnetic resonance imaging (fMRI). fMRI works on the idea that when a certain area of the brain is being used, it experiences an increase in blood flow. This technique has been used to study neurological activity in the brains of myriad animals and humans as well, providing valuable information on cognitive and movement-based functions.

fMRI has also revealed that "activating" a certain part of the brain has effects on other anatomically or functionally connected regions. Trying to solve this "network" of operations in the brain is one of the key issues in neuroscience.

In a recent study (https://doi.org/10.1016/j.neuron.2021.08.032), a research team—including Toshiyuki Hirabayashi and Takafumi Minamimoto from the National Institutes for Quantum Science and Technology (QST)—has shown that gene-targeting drugs in macaque monkeys can cause multifaceted behavioral effects via the altered operation of relevant brain networks, thus opening a critical path towards understanding the network of operations underlying higher functions in primates (monkeys, humans etc.). "*Our technique will allow us to study how disturbances to the functional brain network lead to certain symptoms. This will help us to work backwards to clarify the network mechanisms behind brain disorders with similar symptoms, thus leading to new treatments,*" reveals Dr. Toshiyuki Hirabayashi, principal researcher at QST, who led the study.

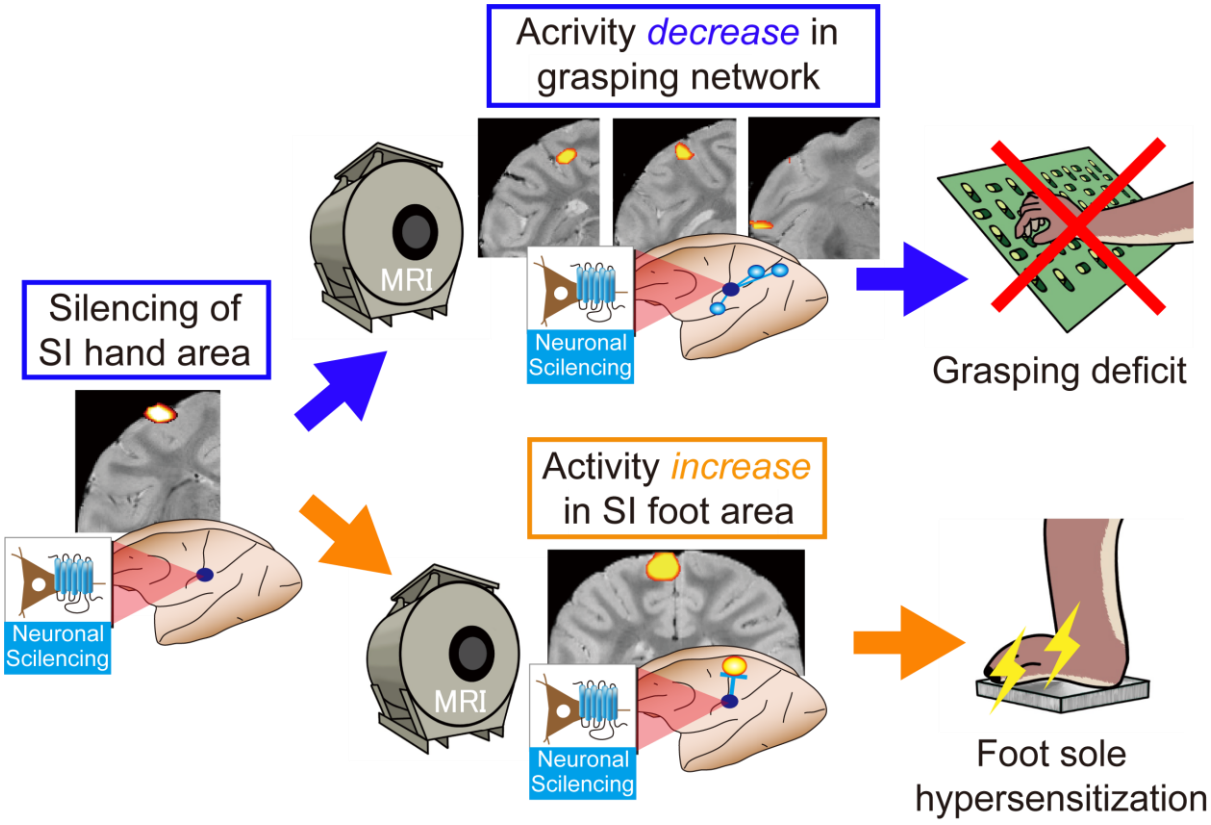
Conventional approaches to activating or suppressing areas of the brain include electrical stimulation or the injection of a psychoactive substance called muscimol, but recent research has focused on using genetic techniques of targeting due to how specific they are. Called chemogenetics, these techniques rely on artificial drugs that are designed to specifically bind to genetically induced artificial protein called "receptors." The drugs bind to the receptors, and thus influence physiological and neurological processes in the brain,

spinal cord, and other parts of the body where the receptors are genetically expressed. Combining chemogenetics with fMRI enables non-invasive visualization of network-level changes induced by local activity manipulation. But, unlike the recent study, chemogenetic fMRI studies so far have focused on a resting state, which might not provide the most useful results when trying to study task-related or sensory-related activities.

For their investigation into functional brain networks, the research team studied the effects of fMRI guided chemogenetics on hand-grasping in macaques. To do this, they first studied the part of the brain that is responsible for precise finger movement, and then silenced (suppressed) it for one hand using a "designer receptor exclusively activated by designer drugs" (DREADD). They then gave the monkeys with silenced hand-grasping skills a task that involved picking up food pellets from a board consisting of small slots. They found that the monkeys could pick up pellets well with the non-silenced hand, which was on the same side of the body as the silenced brain region. But they struggled with using the affected hand, which was on the opposite side. The scientists also saw that the designer drug caused a reduced fMRI signal from "downstream" areas of the monkey brains, providing insight into the rest of the network dysfunction underlying the altered hand-grasping behavior. Finally, they saw that silencing the hand sensory region caused unexpectedly elevated activity in the foot sensory region with an increased sensitivity in the foot on the opposite side of the body, which further suggested that portions of the network have inhibitory effects on other parts of the system.

These findings demonstrate that targeted chemogenetic silencing in macaques can cause stimulatory and inhibitory, i.e., bidirectional changes in brain activity, which can be identified using fMRI. Furthermore, chemogenetics offer a minimally invasive way to repeatedly manipulate the same location on the brain without causing damage to the brain tissue, making the approach beneficial for the study of the functional brain network. According to Dr. Hirabayashi, *"Applying chemogenetic fMRI to higher brain functions in macaques like memory or affection will lead to translational understanding of causal network mechanisms for those functions in the human brain."*

With developments like these, it is easy to see humankind having a clearer picture of the workings of the human brain soon!



Schematic representation of the targeted silencing experiment.

The scientists found that silencing the brain area (SI) for hand sensation surprisingly increased activity in the brain area for foot sensation.

Image courtesy: Toshiyuki Hirabayashi from National Institutes for Quantum Science and Technology

Research Article

"Chemogenetic dissection of the primate prefronto-subcortical pathways for working memory and decision-making"
ToshiyukiHirabayashi[1,5], YujiNagai[1], YukikoHori[1], Ken-ichiInoue[2,3], IchioAoki[4], MasahikoTakada[2], TetsuyaSuhara[1], MakotoHiguchi[1], TakafumiMinamimoto[1]
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About National Institutes for Quantum Science and Technology, Japan

The National Institutes for Quantum Science and Technology (QST) was established in April 2016 to promote quantum science and technology in a comprehensive and integrated manner. The new organization was formed from the merger of the National Institute of Radiological Sciences (NIRS) with certain operations that were previously undertaken by the Japan Atomic Energy Agency (JAEA).

QST's mission is to raise the level of quantum and radiological sciences and technologies through its commitment to research and development into quantum science and technology, the effect of radiation on humans, radiation emergency medicine, and the medical use of radiation.

To ensure that research and development delivers significant academic, social and economic impacts, and to maximize benefits from global innovation, QST is striving to establish world-leading research and development platforms, explore new fields, and serve as a center for radiation protection and radiation emergency medicine.

Website: https://www.qst.go.jp/site/qst-english/

About Dr. Toshiyuki Hirabayashi from National Institutes for Quantum Science and Technology, Japan

Dr. Toshiyuki Hirabayashi is a Principal Researcher in the Department of Functional Brain Imaging at the National Institutes for Quantum Science and Technology (QST), Japan. He obtained his Ph.D. from the University of Tokyo School of Medicine in 2006. He then joined his alma mater as a research associate in 2007, continuing to university lecturer by 2013. In 2015, he became a senior researcher at the National Institute of Radiological Sciences (NIRS), which later became QST. Dr. Hirabayashi's research interests include functional neural circuits, memory retrieval, and fMRI/electrophysiology with chemogenetics in macaques. In 2014, he was awarded a Japan Neuroscience Society Young Investigator Award.

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