National Institutes for
QST Quantum and Radiological Science and Technology

PRESS RELEASE

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Novel Technique Decodes Mechanisms Controlling Executive Functions of the Primate Brain

Chiba, Japan - Researchers devise a new technique to identify specific neural pathways involved in executive functions of the brain

Executive functions allow humans to manage daily activities, which use working memory, and decision-making. However, how these functions are mapped in a primate brain like that of humans, had evaded researchers for a long time. A group of researchers in Japan have now devised a novel chemogenetic method to dissect the neural pathways involved in high-order executive functions. Their findings are published in a new article in *Science Advances*.

The human brain is a wonderfully enigmatic organ, helping to juggle multiple tasks efficiently to help us get through a long day! This feature, called executive function, seats primates like us at the pinnacle of evolution. The prospect of losing the spectacular flow of neural information in our brains because of an accident or disease is, thus, unnerving. In the event of such an unfortunate occurrence, to restore the brain to its previous working condition with full functionality—to reboot it, so to speak—would need a better understanding of the specific neural pathways involved in our daily activities that rely on working memory and decision-making—two important executive functions.

To achieve this objective, a group of researchers from National Institutes for Quantum and Radiological Science and Technology (QST), Japan, were hard at work at devising a technique they call "imaging-guided chemogenetic synaptic silencing" to decipher the specific neural pathways involved in high-order executive functions. In a pioneering study published in *Science Advances*, the researchers now report successfully delineating specific neural pathways involved in working memory and decision-making using this technique.

The group, led by eminent researcher Dr. Takafumi Minamimoto from the Department of Functional Brain Imaging, QST, focused on studying the dorsolateral part of the prefrontal cortex (dlPFC) in the monkey brain, to apply their novel technique, and further identify the neural pathways of interest. It is interesting to note this choice, not only because it is the brain region partially responsible for controlling executive functions, but also since this specialized region is only present in primates.

Importantly, the role of dlPFC is supported by brain regions like the dorsal caudate (dCD) and lateral mediodorsal thalamus (MDl) too. This intricate association is further explained by Dr. Kei Oyama, who is the first author of the study, as follows, "*The primate prefrontal cortex (PFC), especially its dorsolateral part (dlPFC), is well known to serve as the center of higher-order executive functions; it is uniquely developed in primates and underlies their distinctive cognitive abilities. These functions, however, do not solely rely on dlPFC neurons but also on their cooperative interactions with subcortical structures, including the dorsal caudate (dCD) nucleus*

and lateral mediodorsal thalamus (MDl)."

Next, the researchers wanted to understand the who-does-what for working memory and decision-making. Given that the dlPFC, MDI, and dCD neurons are connected, they selectively silenced specific neuronal synapses to disrupt the flow of information, and achieve just dlPFC-dCD and dlPFC-MDl projections, either unilaterally (involving just one side of the brain), or bilaterally (involving both sides). To achieve this, they made the dlPFC neurons express designer receptors exclusively activated by designer drugs (DREADDs). Further, the monkeys involved in the study were analyzed for behavioral changes, to understand the effect of chemogenetic silencing.

Interestingly, the researchers observed that silencing the bilateral dlPFC-MDl projections in the monkeys, but not their dlPFC-dCD projections, caused problems in the working memory related to their surroundings. On the contrary, silencing their unilateral dlPFC-dCD projections, but not their unilateral dlPFC-MDl projections, altered their preference in decision-making. These results reveal that the two higher-brain functions, working memory and decision-making, which are essential for our daily lives, are controlled by different neural pathways linking specific brain areas.

Overall, this study lays the foundation for further explorations of the intricacies of the complex primate brain. In this regard, Dr. Oyama explains the potential clinical and research applications of these findings, "*Many psychiatric disorders, including depression, are thought to be associated with disturbances in the transmission of neural information through neural circuits between specific brain regions. Our findings are expected to deepen our understanding of mental disorders and lead to the discovery of treatments and remedies. The successful development of a novel technique in our study will serve as a key technology for the next-generation of* researchers *to investigate primate brain functions, which will contribute to broad areas in life by dramatically deepening our understanding of the mechanism of higher-brain functions*."

The world will indeed wait with bated breath for future mysteries to unravel as explorations take researchers deeper into the labyrinthine maze that is the mind.

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Research Article

"Chemogenetic dissection of the primate prefronto-subcortical pathways for working memory and decision-making**"**

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About National Institutes for Quantum and Radiological Science and Technology

The National Institutes for Quantum and Radiological Science and Technology (QST) was established in April 2016 to promote quantum science and technology in a comprehensive and integrated manner. 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 and explore new fields.

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About Dr. Kei Oyama from National Institutes for Quantum and Radiological Science and Technology, Japan

Dr. Kei Oyama is a reputed researcher at the Department of Functional Brain Imaging. Specifically, Dr. Oyama is an active member of the Neural Systems and Circuits Research Group. He is an expert in different facets of behavioral and cognitive neuroscience, like learning and memory, behavior analyses, neuropharmacology, electrophysiology etc. His expertise is bolstered by around 20 publications in these fields, in reputed journals.

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