【Grant-in-Aid for Scientific Research (S)】

Broad Section D

Title of Project： Creation of Neurophotonics and Elucidation of Brain Funcitons

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Keyword：Bioimaging, neuroscience, laser

【Purpose and Background of the Research】

The question "what kinds of neural cells' collective activity realize our mental activity" always fascinates many people as an eternal object. To understand the emergent and the operating principles of brain function, functions of local neural circuits and its true nature -propagation and synchronization of neural activity between cells - are critically required to be clarified under a truly intact condition (*in vivo*). The collective action with network synchronization is deterministically crucial for realizing the function of local neural circuits. However, information transmission at neural synapses occurs stochastically at the molecular and cellular levels. To integrally understand brain function beyond this divergence, a cutting-edge method must directly visualize the population activity and quantitatively analyze the transmission process as it is.

【Research Methods】

The principal investigator has promoted *in vivo* two-photon excitation microscopy to measure the living brain and nervous system worldwide. Based on this, we will utilize optical technologies such as high-power compact laser light sources with variable wavelength, adaptive optics, and second harmonic generation. We are going to finally realize the world's first high-speed super-resolution optical imaging that visualizes biomolecule activities within deeper layers in biological tissues and morphological changes of living cells less-invasively.

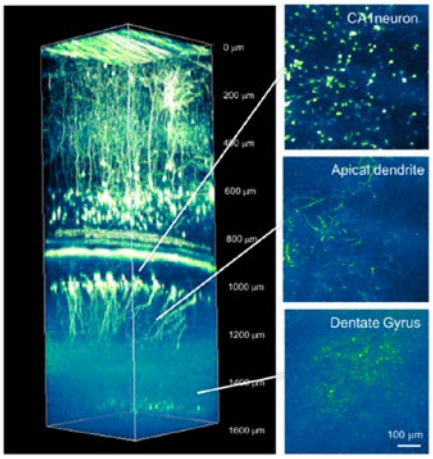

Fig.1: *in vivo* observation of mouse living brain

Using this innovative microscope, we will accurately visualize and analyze synchronous neuronal population activity and neurotransmitter exocytosis in the deep part of the mouse living brain in the "as is" state. Furthermore, we will track three-dimensional morphological changes of nerve cells and the dynamics of exocytosis in real-time, which will lead to an understanding of the signal transmission mechanism by the interaction between nerve cells and glial cells and the emergent principle of brain function.

【Expected Research Achievements and Scientific Significance】

This project will develop and improve novel microscopy, leading us to understand the essence of information transmission in the brain by analyzing multiple neural cell responses and synchronous changes in collective activity. The microscopy enables super-resolution imaging for revealing the nature of neurotransmission, incredibly deep in living organs. It will visualize biomolecular dynamics during the exocytotic process from the accumulation of exocytotic molecules at presynaptic terminals, neurotransmitter release at synapses to response in the posterior region, without damaging the neural circuits in the living brain. Besides, by combining it with localized photoactivation and/or administration of drugs, it will lead to developing a route leading to the elucidation of the molecular basis and treating diseases such as mental illness and diabetes.

As described above, the new "neurophotonics" promoted by this research project will contribute to life science innovations such as control of physiological functions by light and photocell therapy by advancing deep-body imaging.

【Publications Relevant to the Project】

· M. Inoue, *et al.*, "Rational engineering of XCaMPs, a multicolor GECI suite for in vivo imaging of complex brain circuit dynamics", ***Cell***, **177**:1346-1360.e24 (2019)

· K. Yamaguchi, *et al.*, "In vivo two-photon microscopic observation and ablation in deeper brain regions realized by modifications of excitation beam diameter and immersion liquid", ***PLoS ONE***, (2020)

【Term of Project】 FY2020-2024

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.nips.ac.jp/bp/