【Grant-in-Aid for Transformative Research Areas（A）】

Emergence of Brain Functions from the Dynamic Connectome（Dynamic Brain）

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Project Information	Project Number : 24A305 Keywords : neuronal circuit, brain development, learning and memory, connectome	Project Period (FY) : 2024-2028

Purpose and Background of the Research

●Outline of the Research

In the nervous system, much of the information processing is achieved by the wiring and synaptic connections between neurons. Therefore, most brain functions emerge from the entirety of synaptic connections between neurons (the connectome). In recent years, the connectome has been extensively studied using electron microscopy and optical microscopy. Optogenetics and pharmacogenetics have been utilized to identify the circuit elements in the brain. Such reductionist approaches have been powerful in identifying the circuit units. On the other hand, the combination of many elements can be more than just the sum of those elements, and such “emergent nature” of the neuronal circuits may be the origin of the brain functions. Interestingly, the emergent brain functions are not innate to our connectome. Our connectome is never created as a complete form from the beginning, but rather is created gradually as it evolves over time during development and learning.

Traditionally, research on synaptic plasticity in development and learning has focused on elementary processes. In contrast, to understand such emergent properties, it is important to capture synaptic plasticity across the entire neural circuit (e.g., **Figure 1**). In this research area, we aim to understand how synapses, neurons, and circuit structures change as a whole during brain development and learning, and what are the principles that give rise to emergent brain functions.

First, we will measure the entire neural circuit structure, the connectome, at multiple time points to elucidate the dynamic changes. Next, we will comprehensively measure the accompanying functional changes (calcium, glutamate, membrane potential, etc.). Then, based on quantitative analyses, we will clarify the structural changes that support emergent phenomena at the functional level, leading to the demonstration of these changes in mathematical models and reconstructed systems (**Figure 2**).

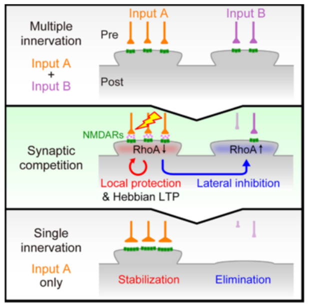

Figure 1 An example of heterosynaptic plasticity controlling developmental dendrite pruning

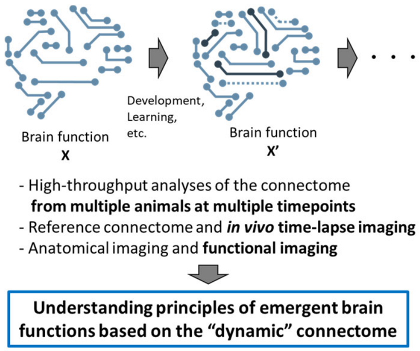

Figure 2 Direction of this research area

●Aim A01 “Emergence of neuronal functions”

A01 aims to study the relationship between quantitative properties of synaptic distribution, dendritic computation, and neuronal function based on emergent properties within a neuron.

●Aim A02 “Emergence of circuit functions”

A02 aims to study the emergence of brain functions based on the dynamic and quantitative properties of network structures.

●Aim A03 “Reconstruction of emergent brain functions”

A03 aims to understand the fundamental features of the emergent brain functions through reconstitution. We use both computer simulation and neuronal organoids.

In addition, our technical support team helps micro-connectomics using electron microscopy, meso/large-scale connectomics with fluorescence microscopy, large-scale functional imaging with ultra-wide-field two-photon microscopy, and computer simulation (**Figure 3**).

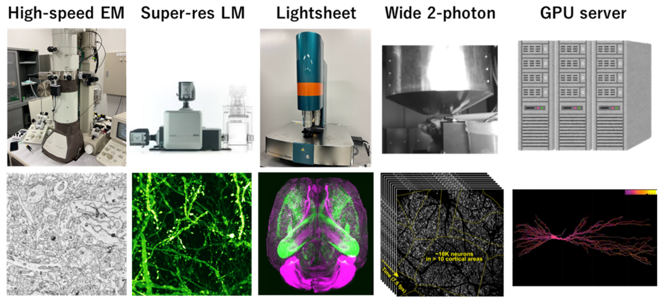

Figure 3 Activities of our support team

Expected Research Achievements

●Research aims of this research area

A01 aims to understand emergent functions at the neuronal level focusing on the control of synaptic strength and distribution, the regulation of spontaneous neural activity, and dendritic integration. A02 study emergent functions at the circuit level, focusing on stepwise circuit reorganization in motor learning, spatial learning, and song learning. In A03, we aim to reconstruct the emergent brain functions using neural organoids and simulations of membrane potentials and molecular activity.

●Expected outcomes

In this research area, we will elucidate the principles of the neuronal and circuit scales that give rise to brain function using cutting-edge approaches in the life sciences that integrates multiscale structural and functional imaging data. Our study will help us understand the development of brain function and disease, reconstruct them *in silico*, and lead to more rational decoding of brain function and therapeutic strategies. These techniques may eventually be integrated with AI technology to revolutionize society.

Homepage Address, etc.	Website: https://plaza.umin.ac.jp/dynamic-brain X (Twitter): https://twitter.com/dynbrain