【Grant - in - Aid for Scientific Research on Innovative Areas(Research in a proposed research area)】
Biological Sciences

Title of Project: Constructive understanding of multi-scale dynamism of neuropsychiatric disorders

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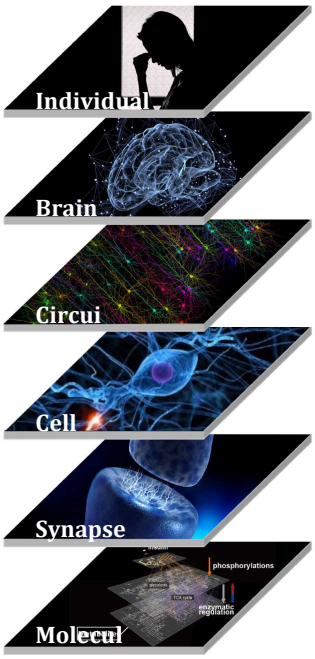
【Purpose of the Research Project】

Despite extensive recent efforts, the patho-genesis of psychiatric disorders remains poorly understood, mainly because their pathophysiology is a synergistic interaction between multiple genes variants and environmental factors. Thus, what we recently know as contributory factors for the diseases is the susceptible gene variants (Molecular layer), synaptopathy (Subcellular and Cell layer), alteration in neuronal circuits (Circuit layer), conceivably resulting in the behavioral manifestations (Individual layer). However, the understanding of each layer has been limited within a single layer, which hinders the integrative and causal mechanistic understanding of behaviors. Probably, each layer can affect one another, macroscale to the mesoscale and then to the microscale layer or vice versa. Thus, we deal with phenomena of intricate complexity of psychiatric disorders that are governed by various mechanisms integrated across multiscale layers.



【Content of the Research Project】

In this study, we aim at a constructive understanding of multiscale hierarchical nature of psychiatric disorders with use of recently available state-of-art techniques: hypothesis-free and comprehensive omics technologies and powerful simulation/analysis tools generate new types of heterogeneous data with a density and depth previously unimaginable, which can handle big data from multiscale layers ranging from molecules/ synapses/neurons/circuit (and ideally, all the way to behavior).

For instance, the role of genes identified by genetic analysis of families of psychiatric disorders as well as molecules identified by omics analysis of postmortem brain samples will be analyzed and subject to the construction of mathematical models. Using animal models of the candidate genes, a responsible neural circuit will be identified by behavioral and anatomical analyses. Within that neural circuit, responsible cell types will be identified using omics analysis and the mechanism for the emergence of behavioral changes will be pursued by manipulation of a specific neural circuit and by employing mathematical modeling of the responsible neural circuit. By using induced pluripotent stem (iPS) cells derived from patients with psychiatric disorders, neural cells and cerebral organoids will be generated and cellular pathology underlying mental disorders will be studied using omics analyses.

【Expected Research Achievements and Scientific Significance】

Through the series of studies as described above, a mathematical model of psychiatric disorders that incorporate multiple layer facets including molecular, cellular, circuit and behavioral levels, will be constructed and thereby we will aim at a constructive understanding of the multiscale phenomena of psychiatric disorders. One of the goals of neuroscience research is to elucidate how specific neuronal populations form functional neuronal circuits are altered in the disease state. Findings based on our strategy that would causally identify the contributory factors for the disease will provide the knowledge necessary to establish circuit-centric therapeutics as well as the rationale molecular (and chemistry) based drug designs.

【Key Words】 Psychiatric disorders, Multiscale, Constructive understanding, Optical manipulation, Modeling, Transomics

【Term of Project】 FY2018-2022
【Budget Allocation】 1,236,570 Thousand Yen
【Homepage Address and Other Contact Information】
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