

## Greeting



**Shigeo Okabe**

Graduate School of Medicine,  
The University of Tokyo

### From Program Supervisor

#### The Paradigm Shift in Brain Science

With a network of some 100 billion neurons, the human brain processes a huge amount of information and performs complex functions that make us unique. Conventional research methods have only had limited success in understanding the mechanisms of this intricate information processing network. When taking measurements at the neuron level, only a small number of cells can be examined at one time. Conversely, activity of a large brain area can be estimated or averaged activities of local neuronal population with their numbers in a range of several hundred thousand. It was thought by most scientists until recently that it was impossible to realize brain-wide analyses of network activity at the level of single neurons.

Fortunately, however, several new technologies have been developed in quick succession in recent years that enable us to analyze the whole brain network at the level of single neurons. These include: technology that enables analysis of the brain structure at the resolution of electron microscopy; imaging technology that makes the brain transparent and records its entire structure on a cellular level; and technology that controls activity of specific neurons with light. Stimulated by these new technologies, neuroscientists think that it is time for a major paradigm shift in brain science with its goal of elucidating the full mechanisms of the brain.

In 2013, US President Obama announced the launching of the BRAIN Initiative (Brain Research through Innovative Neurotechnologies), a large-scale national research project on a par with the Apollo Program to send humans on the moon. The BRAIN Initiative is targeted at accelerating the development and application of innovative technologies to revolutionize our understanding of the neural network of the whole human brain. In the same year, the Human Brain Project (HBP) was launched in Europe to develop database platforms bringing together the expertise from various kinds of brain research.

In parallel with these projects in the US and Europe, Japan has been formulating its own project based on three objectives: to focus on studies of non-human primate brains that will directly link to better understanding of the human brain; to elucidate the neural networks involved in such brain disorders as dementia and depression; and to promote close cooperation between basic and clinical research related to the brain. Dubbed Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS), this new project was just launched in fiscal 2014 and will focus on new technologies and clinical research. In this program, challenging goals will be achieved through long-term research carried out by linking core research institutions nationwide.

As the program supervisor for this massive project, we will work to expand cooperation among a broad range of institutions to apply novel ideas and technologies that will pioneer new frontiers in brain science. We are hopeful that this will lead to fundamental understanding of neural network that realizes cognitive functions unique to human, improved diagnosis of the damaged network caused by brain disease, and improved diagnosis and treatment of psychiatric and neurological disorders.



**Tetsuya Matsuda**

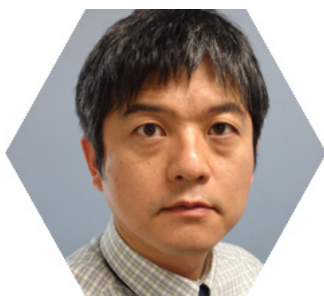
Brain Science Institute,  
Tamagawa University

## From Program Officers

In the 20 years since the large-scale neuroscience research project launched in the 1990s, the function of an organ that has been referred to as the “black box” of the body, has gradually been elucidated. The brain network of over a hundred billion neurons, and an understanding of the brain requires clarification of not only the function of each cell, but also how those activities are transmitted throughout the network. To achieve these goals, it is necessary to investigate the structural links between brain neurons, to create an accurate diagram of neural circuits, and to understand the principles under which signals are transmitted within this circuit. Due to technological limitations, research at this detailed level has not progressed much to date. However, with recent innovations in experimental measurement technologies, the time has come to tackle this research. The “Brain Mapping Neurotechnologies for Disease Studies (Brain/MINDS)” was launched to address precisely this goal.

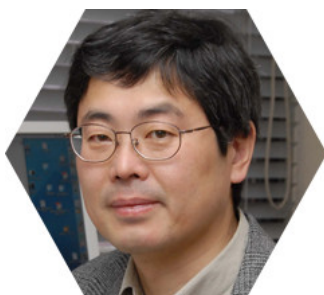
One of the topics of neuroscience research anticipated by the people in Japan is the elucidation of the mechanisms of neurological disorders such as dementia and depression. Although previous neuroscience research pursuing the elucidation of these disorders has produced results, further pathological elucidation of psychiatric and neurological disorders requires a deeper understanding of brain functions at the neural circuit level, which is the goal of this project. Also, to achieve a deeper understanding of neural circuits specific to psychiatric and neurological disorders, promotion of research under systems involving multiple parties – from basic to clinical research – is essential.

New large-scale brain projects are underway not only in Japan, but also in the United States, Europe, and Australia. In that context, given the developments in each of the countries and our collaborative relationships, it is important to leverage the strength of neuroscience research in Japan to move forward using an “all-Japan” structure. My own role is to provide guidance and advice such that the involved researchers all come together to advance toward the goals of this project. As program officers, our intentions are to fulfill our responsibilities to meet the expectations of the public towards neuroscience research under the direction of the program supervisor. Thank you very much for your understanding and support.



**Toshihisa Ohtsuka**

Graduate School of Medicine/  
Faculty of Medicine, University of Yamanashi



**Watanabe Masahiko**

Department of Anatomy  
Hokkaido University School of Medicine

## From Project Leaders

It is my great pleasure that we could inaugurate the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) project, supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Japanese Medical Research and Development, AMED. My name is Hideyuki Okano, one of the Project Leaders of Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS).

As you know, there is a globally increasing interest in the brain mapping projects, including The Brain Research Advancing Innovative Neurotechnologies (BRAIN) Initiative project in USA, Human Brain Project (HBP) in Europe, and Brain/MINDS in Japan. These brain mapping projects aim to map the structure and function of the human brain, and ultimately understand the vast complexity of the human brain. In Brain/MINDS, we focus our attention on

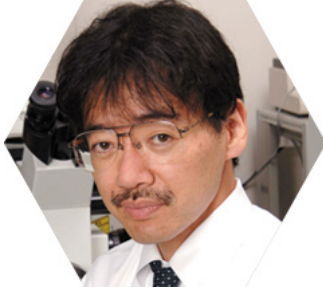


**Hideyuki Okano**

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marmoset (*Callithrix jacchus*), a new world small monkey, for structural and functional mapping of brains. This primate has numerous advantages for brain mapping, including a well-developed frontal cortex, compact brain, and availability of transgenic technologies. Brain mapping of common marmoset is an ambitious project, requiring extensive technological innovations. If we could obtain detailed information of structural and functional mapping of entire marmoset brains, those will enormously contribute to our understanding in the human brains and their



**Atsushi Miyawaki**

RIKEN Brain Science Institute

The history of science is a chain of advances in technology and knowledge that have always complemented each other. Technological innovations bring about new discoveries and are bred by other discoveries. In the Brain Integrated Neurotechnologies for Disease Studies (Brain/MINDS) project, a big group has been conceived of scientists who are inclined towards developing technological innovations in brain science. These innovations include, for example, optogenetics, a growing suite of techniques that combine optical and molecular genetic methods to manipulate neural activity using genetically encoded tools and are becoming popular in neuroscience, where the central challenge is to understand the mechanisms by which neurons process and integrate synaptic inputs and how these mechanisms are modified. In recent years, also, one of the most surprising innovations in neuroscience would be the new trend in optical imaging of brain tissue for the visualization of structures and molecules in situ. I hope that our efforts in the Brain/MINDS project will promote the progress of neuroscience as we address the expanding needs of this field.

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## Mission and Objectives

One of the important characteristics of Brain/MINDS will be that we pay considerable efforts in the mapping the brains of a small new world monkey, the common marmoset (*Callithrix jacchus*), since research on the non-human primate brain is essential for understanding the human brain and for developing knowledge-based strategies for the diagnosis and treatment of psychiatric and neurological disorders. Furthermore, common marmoset has the following advantages for brain mapping; i) Its frontal lobe is more developed than in other commonly used animals – more similar to humans; ii) The brain is compact (approximately 8 grams) and is suitable for comprehensive analysis of the neural circuit. iii) Marmosets can be genetically modified and manipulated. The objectives of Brain/MINDS can be categorized into the following three major groups (A-C):

**Structure and functional mapping of the non-human primate brain (particularly the marmoset brain):** In the Group A, as regards the structural (anatomical) mapping of the common marmoset, we will examine macroscale, mesoscale and microscale mappings by utilizing MRI-based diffusion tensor imaging (DTI), stereotactic tracer injections followed by light microscopic observations and A new method of serial EM (developed by Prof. Jeffery Lichtman at Harvard University), respectively. Transgenic techniques of common marmoset would contribute to mesoscale mapping in a cell-type specific approach. We will examine the functional mapping of the marmoset brain by resting state fMRI. As outputs of brain functions, behavioral and cognitive test batteries of common marmoset will be established.

**Development of novel, cutting-edge technologies that support brain mapping:** In the Group B, B1) High-resolution, wide-field, deep, fast and long imaging techniques for brain structures and functions, B2) Development of new techniques for controlling neural activity, and B3) Development of neuroinformatics for integrating heterogeneous and multi-scale data will be investigated. In B3, we are planning to cooperate with INCF, HBP and Allen Institute for Brain Science for generating database in the common formats.

**Human brain mapping and clinical research:** Here, we aim to map control and patients-derived human brains. In the Group C, three clinical research teams will be organized, including Neurodegenerative Disease Research Team, Psychiatry Disease Research Team and Vascular and Neuro-rehabilitation Research Team. These clinical research teams will generate multi-center patients-derived database of MRI and other biomarkers and will make feedbacks to marmoset researches.

Reciprocal translation among the Groups A, B, C will be examined to determine causal relationships between the structural/ functional damage of neuronal circuits and disease phenotypes and to eventually develop innovative therapeutic interventions for these diseases. It is obvious that extensive international collaboration will be required to achieve the goals of the project.