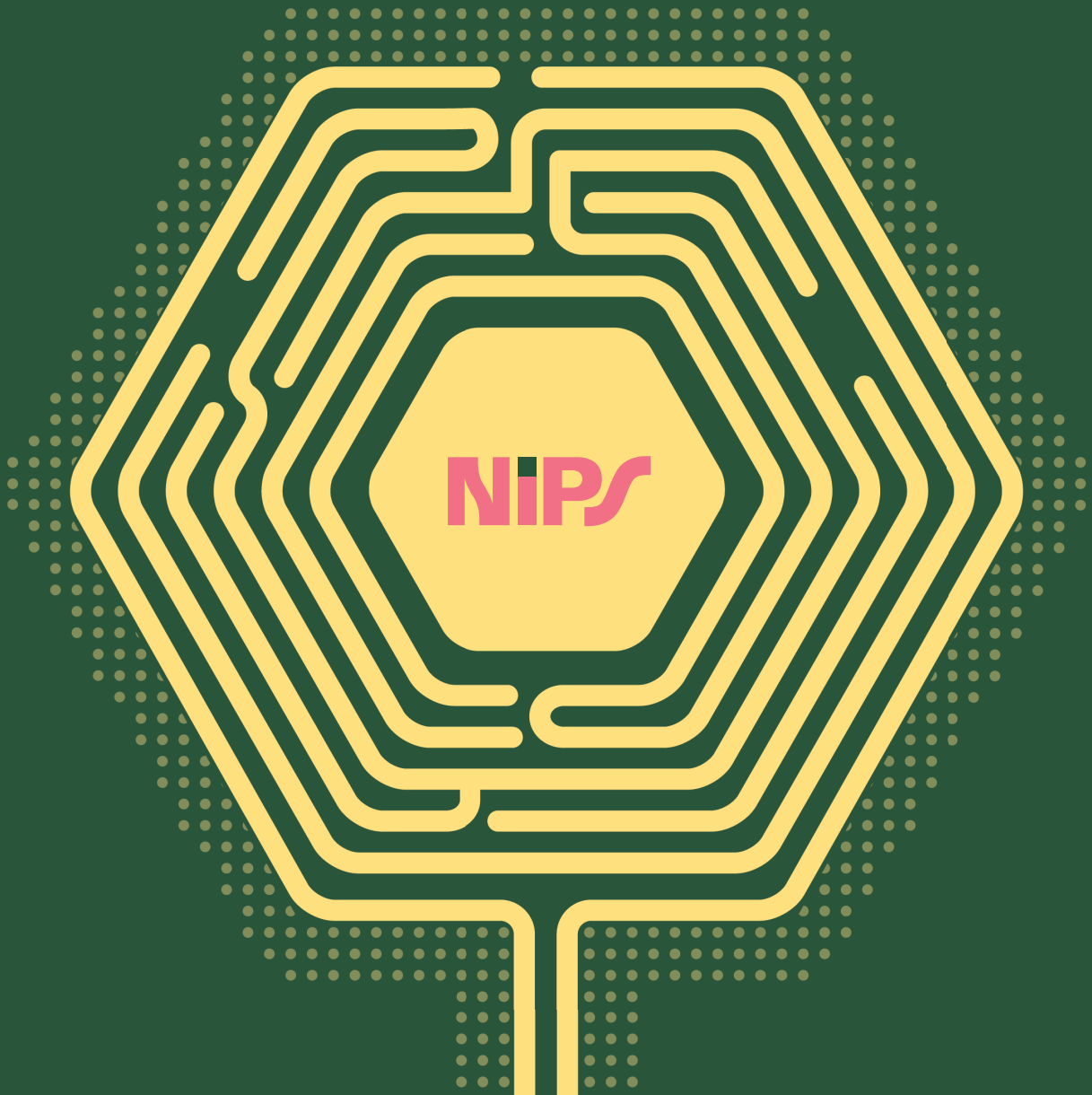
National Institutes of Natural Sciences

National Institute for Physiological Sciences 2023



C O N T E N T S

INTRODUCTION

The National Institute for Physiological Sciences (NIPS) is an inter-university research institute focused on research and education to understand human physiology. NIPS promotes collaborative studies amongst both National and International researchers and organizations to together help understand body functions and their mechanisms. Research at NIPS also provides further understanding of the fundamental mechanisms causing diseases, to enable new and improved treatments for these diseases and their symptoms.

A major focus of current research at NIPS is to understand the brain. Most developed in humans among all the creatures, the brain is critical for how we detect, respond and adapt to our environment, through the processes of sensation, motor control and learning and memory. However, the brain also directs our individual behaviors and desires, and how we communicate with each other socially through language and emotions. Furthermore, the brain also interacts with our visceral organ systems to regulate body homeostasis, and research at NIPS also aims to provide a comprehensive understanding of the mechanisms of body homeostasis through our research on the interaction between immune system and brain, on the regulation of the cardiovascular system, on whole body and cellular metabolism, on temperature control and on how we regulate our biological defenses against damage and pathogens. NIPS strives to advance our understanding of brain function and body homeostasis, from the molecular, cellular, organ, whole body and society levels, and we provide and develop cutting-edge research technology, including computational and mathematical approaches, to achieve these strategic goals.

The NIPS advocates the following three major missions.

The first mission of NIPS is to conduct cutting-edge research in the physiological sciences across various levels from the molecular and cellular through to organ systems, and to integrate this multi-level information to understand homeostasis in the living body. As research in life sciences has become diversified and "translatable", NIPS aims to conduct world-leading research focused on the basic medical sciences, especially physiology and brain sciences. To apply and develop rigorous basic research techniques necessary to answer fundamental questions is also part of our mission.

The second mission of NIPS is to play the role of a research hub. NIPS conducts collaborations with scientists at universities and research institutes to further strengthen and enhance research expertise in Japan at a leading global level. To achieve this goal NIPS also encourages collaborations with foreign researchers, and we provide and develop specialized and cutting-edge research techniques and equipment to facilitate these collaborations. NIPS provides advanced devices in areas including electron and laser microscopy for subcellular through to human imaging, and in transgenic animals and viral vectors. NIPS also supports advanced research workshops in various fields to help establish and support research collaborations, discussions and advances and sharing of knowledge. Through these activities NIPS is a hub for domestic and international research communities to intercommunicate and support each other. In 2022, it was decided to introduce a new 3T MRI in the supplementary budget of the AMED project related to NIPS. It will be installed in 2023. However, the current situation is that the budget for advanced equipment to be deployed at inter-university research institutes is extremely tight. We will negotiate with the government to install new research equipment and to update equipment. On the other hand, we maintain and provide fundamental experimental technologies such as electrophysiological techniques. In addition, in order to accelerate research collaboration with researchers from companies, we have appointed a person in charge of industry-university collaboration, and held the first social collaboration training course in 2022. At present, NIPS participates in a number of programs as their core organizations, such as JISEDAI-NOU Project, Japan-US Brain Research Cooperative Program, Advanced Bioimaging Support and Brain/MINS Beyond.

In 2022, we were suffered from a periodic spread of CONOD-19 infection, joint research, such as NIPS workshop and collaboration, has been recovered steadily. In addition, new collaboration at the center for the animal resources and collaborative study with researchers outside NIPS has started.

The third mission of NIPS is to provide advanced and thorough education for young scientists. NIPS is responsible for the 5-year PhD course in physiological sciences of SOKENDAI (The Graduate University for Advanced Studies). NIPS also provides further education for graduate students and young researchers from other universities and industries in Japan and internationally, through various research training programs that include the annual NIPS Training Course and via NIPS Internships. To further facilitate the interaction with the universities, the employment of 2 new professors under a cross-appointment system has been introduced at 2021.

To understand human body functions and to apply our extended knowledge to support human life is our ultimate goal. NIPS will make every effort to open our institute to every research community that can work together with us towards this goal. For this purpose, your understanding and support will be appreciated.

Director General

NABEKURA, Junichi

MD, PhD

1981 MD, Kyushu University, 1987 PhD, Kyushu University, 1987 Postdoc Researcher, Washington University, 1991 Assistant Professor, Tohoku University, 1993 Associate Professor, Akita University, 1995 Associate Professor, Kyushu University, 2003 Professor NIPS, 2013 Vice Director General, NIPS, 2019 Director General, NIPS and Vice President, NINS.

Specialty: Neurophysiology

Outlines of Institute

National Institute for Physiological Sciences (NIPS) is an Inter-university Research Institute for research and education on human physiology. NIPS researchers are investigating human body and brain functions as well as their mechanisms through joint studies with domestic and foreign scientists, and providing specialized techniques and large-scale equipment for shared use as well as education and training for graduate students and young scientists.

Organization

NAOJ, NIFS, NIBB, NIPS and IMS were reorganized into NINS by reason of enforcement of the National University Corporation Law.
The NIPS currently comprises 4 departments, 17 divisions, 4 centers, 18 sections, Research Enhancement Strategy Office and Technical Division.

Joint Research

As an inter-university research institute, NIPS conducts collaborative research based on proposals from domestic and foreign physiological scientists. Applications from domestic and foreign scientists are reviewed and controlled by the Inter-University ad hoc committee.

Graduate Programs

The NIPS carries out two graduate programs.

1.Graduate University for Advanced Studies

The NIPS is in charge of Physiological Sciences Program of Graduate Institute for Advanced Studies, SOKENDAI. The University provides 2 courses, 5-year Doctor Course and 3-year Doctor Course (transfer admission after master's course completion). The degree conferred on graduation is Doctor of Philosophy.

2.Graduate Student Training Program

Graduate students enrolled in other universities and institutes are trained to conduct researches for fixed periods of time under the supervision of NIPS professors and associate professors.

Exchange Programs

To activate international collaborations among physiological scientists in the Institute and foreign organizations, scientist exchange programs are conducted.

System management

Administrative Council, Education and Research Council and Executive Meeting are established at NINS to inspect significant matters of management, education, research and administration.
Advisory Committee for Research and Management in NIPS advises the Director-General on important matters in management of the Institute.

Administration

Administration of the institutes is managed at Okazaki Administration Center of NINS.

A Short History of the Institute

In 1960, many physiologists affiliated with the Physiological Society of Japan initiated a discussion on how to establish a central research institute for physiological sciences in this country.

In recent years, remarkable progress has been made in the life sciences throughout the world, particularly in the fields of molecular biology, cellular biology and physiology, and in areas concerning information processing and regulatory systems of higher animals. In view of these developments, there was a consensus among physiologists in Japan that a new type of research organization must be created, in parallel with the laboratories in universities, to pursue new approaches in the life sciences.

Through discussions among the physiologists, the following characteristies of such a new institute were considered to be of utmost importance.

1. Investigators from different fields should be able to collaborate on research projects in the life sciences with minimal restrictions.
2. Research communication among scientists from many fields should be closely coordinated.
3. Specialized, large-scale equipment required for multidisciplinary research, not routinely available in smaller laboratories of educational institutions, should be accessible, and proper training and maintenance should be provided. A Committee for the Foundation of a Physiological Institute was organized by Drs. MOTOKAWA K., KATSUKI Y., NATORI R., TOKIZANE T., INOUE A., UCHIZONO K., and many other leading physiologists in 1965. Thereafter, in order to establish such an institute, considerable effort was made by scientists and related government officials.
   The following time table describes the history leading to the foundation of the Institute:

Nov., 1967

The Science Council of Japan officially advised the then Prime Minister, SATO Eisaku, that the establishment of an institute for Physiological Sciences was important, and urgently necessary for the promotion of life sciences in Japan.

The Science Council of the Monbusho （the Ministry of Education, Science and Culture） reported to the Minister of Education, Science and Culture that two institutes for scientific research of biological sciences, namely, the Institute for Physiological Sciences and the Institute for Basic Biology, should be established as early as possible.

May, 1976

The Preparing Office and the Research Council for the establishment of Institutes for Biological Sciences were opened in the Monbusho.

May, 1977

The Institute for Physiological Sciences （Director-General: Prof. UCHIZONO K.） was officially established which, together with the Institute for Basic Biology, constituted the National Center for Biological Sciences （President: Prof. KATSUKI Y.）. Constituents of the Institute for Physiological Sciences at the time of inauguration were as follows.

Department of molecular physiology
Division of Ultrastructure Research
Department of Cell physiology
Division of Membrane Biology
Department of Information physiology
*Division of Neurobiology and Behavioral Genetics
Special Facilities for Physiological Research
Technical Division

Apr., 1978

In the second year the following laboratories were added:

Department of Molecular physiology
*Division of Intracellular Metabolism
Department of Information physiology
Division of Neural Information
Department of Biological Control System
Division of Neural Control

Apr., 1979

In the third year the following laboratories were added:

Department of Cell physiology
Division of Correlative Physiology
*Division of Active Transport
Department of Biological Control System
*Division of Cognitive Neuroscience

Apr., 1980

The following were added in the fourth year:

Department of Information physiology
Division of Humoral Information
*Division of Learning and Memory Research
Research Facilities
Division of Experimental Animals

Apr., 1981

A new organization, Okazaki National Research Institutes, comprised of three independent institutes (Institute for Molecular Science, Institute for Physiological Sciences, and Institute for Basic Biology) was established. Previously, these institutes had been managed independently. However, on 14 Apr. 1981, they were administratively amalgamated into one organization, and thereafter referred to collectively as the Okazaki National Research Institutes.

Apr., 1982

The following was added:
Department of Molecular physiology
Division of Neurochemistry

Apr., 1984

The following was added:
Department of Biological Control System
Division of System Neurophysiology

Apr., 1985

Prof. EBASHI S. was elected the Director-General of the Institute.

Oct., 1988

The Graduate University for Advanced Studies, SOKENDAI was founded and in the Institute the School of Life Sciences, Department of Physiological Sciences was established.

Jun., 1990

The following were added:
Department of Integrative Physiology
Sensory and Motor Function Research Project
Higher Brain Function Project
*Autonomic Function Research Project

Dec., 1991

Prof. HAMA K. was elected the Director-General of the Institute.

Apr., 1997

Prof. SASAKI K. was elected the Director-General of the Institute.

Apr., 1998

The following were added:
Department of Cerebral Research
Division of Cerebral Structure
Division of Cerebral Circuitry
Division of Cerebral Integration
A part of facilities in the complex of Physiological Research Facilities was reformed to the Center for Brain Experiment.

Apr., 2000

Division of Experimental Animals was transferred to the Research Facilities as shown below. Center for Integrative Bioscience

- Department of Strategic Methodology
- Department of Development, Differentiation and Regeneration
- Department of Bio-Environmental Science

Research Center for Computational Science
Center for Experimental Animals
Center for Radioisotope Facilities

Apr., 2003

Prof. MIZUNO N. was elected the Director-General of the Institute.
The following were added:
Department of Developmental Physiology
Division of Behavioral Development
Division of Homeostatic Development
Division of Reproductive/Endocrine Development
Division of Adaptation Development

Apr., 2004

Established National Institutes of Natural Sciences (NINS).
National Astronomical Observatory of Japan (NAOJ), National Institute for Fusion Science (NIFS), National Institute for Basic Biology (NIBB), National Institute for Physiological Sciences (NIPS) and Institute for Molecular Science (IMS) were integrated and reorganized into NINS by reason of enforcement of the National University Corporation Law.
In NIPS, Division of Neurochemistry in Department of Molecular Physiology was renamed to Division of Biophysics and Neurobiology, Division of Humoral Information in Department of Information Physiology was renamed to Division of Neural Signaling, Department of Biological Control System was renamed to Department of Integrative Physiology, Division of Cognitive Neuroscience was renamed to Division of Computational Neuroscience, and Center for Integrative Bioscience was renamed to Okazaki Institute for Integrative Bioscience, respectively.
The Administration Bureau turned into Okazaki Adminis-

tration Office of NINS.

Nov., 2005

Division of Neurobiology and Behavioral Genetics was reformed to the Center for Genetic Analysis of Behavior.

Apr., 2007

Prof. OKADA Y. was elected the Director-General of the Institute.

The following were added:

- Department of Molecular Physiology
  - Division of Nano-Structure Physiology
- Department of Cell Physiology
  - Division of Cell Signaling
- Department of Information Physiology
  - Division of Developmental Neurophysiology

Apr., 2008

Division of Active Transport in Department of Cell Physiology was renamed to Division of Neural Systematics.

The following were abolished:

- Division of Learning and Memory Research
- Center for Brain Experiment

The following were added:

- Center for Multidisciplinary Brain Research
- Supportive Center for Brain Research
- Center for Communication Networks

Apr., 2009

Division of Intracellular Metabolism was abolished.

Apr., 2011

The following was added:

- Section of Health and Safety Management

Apr., 2013

Prof. IMOTO K. was elected the Director-General of the Institute.

Oct., 2013

Research Enhancement Strategy Office was established.

Jan., 2014

The following were added:

- Department of Information Physiology
  - Division of Cardiocirculatory Signaling

Center for Multidisciplinary Brain Research

- Research Strategy for Brain Sciences Office

Apr., 2014

Division of Developmental Neurophysiology in Department of Information Physiology was renamed to Division of Visual Information Processing.

The following were abolished:

- Department of Molecular Physiology
  - Division of Nano-Structure Physiology
- Department of Cell physiology
  - Division of Correlative Physiology
- Center for Communication Networks
  - Section of Communications and Public Liaison

Apr., 2016

The following were abolished :

- Department of Molecular Physiology
- Department of Cell Physiology
- Department of Information Physiology
- Department of Integrative Physiology
- Department of Cerebral Research
- Department of Developmental Physiology
- Center for Multidisciplinary Brain Research
- Division of Computational Neuroscience
- Division of Adaptation Development

The following were renamed :

- Division of Cerebral Structure to Division of Cell Structure
- Division of Sensori-Motor Integration to Division of Integrative Physiology
- Division of Homeostatic Development to Division of Homeostatic Development

The following were added :

- Department of Molecular and Cellular Physiology
  - Division of Biophysics and Neurobiology
  - Division of Neurobiology and Bioinformatics
  - Division of Membrane Physiology
  - Division of Neural Systematics
  - Division of Neural Development and Regeneration
- Department of Homeostatic Regulation
  - Division of Cell Structure
  - Division of Cell Signaling
  - Division of Cardiocirculatory Signaling
  - Division of Endocrinology and Metabolism
- Department of Fundamental Neuroscience
  - Division of Neural Signaling
  - Division of Cerebral Circuitry
  - Division of Homeostatic Development
  - Division of Visual information processing
- Department of System Neuroscience
  - Division of Sensory and Cognitive Information
  - Division of Behavioral Development
  - Division of System Neurophysiology

Division of Integrative Physiology
Division of Cerebral Integration
Center for Research Collaboration
Section of Collaboration Promotion
Section of Advanced Research Support
Section of Visiting Collaboration Research Project
Section of International Collaborative Research Project

Regarding Supportive Center for Brain Research, Section of Viral Vector Development and Section of Primate Model Development have reorganized to Center for Genetic Analysis of Behavior and Center for Research Collaboration, respectively. Section of Primate Model Development has been renamed to NBR Project.
Section of Evaluation and Collaboration in Center for Communication Networks has also been renamed to Section of Research Archives.

Mar., 2018
The following was abolished :
Okazaki Institute for Integrative Bioscience

Oct., 2018
The following were abolished:
Department of Molecular and Cellular Physiology
Division of Neural Systematics
Department of Fundamental Neuroscience
Division of Cardiocirculatory Signaling
The following was added:
Department of System Neuroscience
Division of Neural Dynamics

Apr., 2019
Prof. NABEKURA J. was elected the Director-General of the Institute.
The following were abolished:
Department of Molecular and Cellular Physiology
Division of Neurobiology and Bioinformatics
Department of System Neuroscience
Division of Sensory and Cognitive Information

The following was added:
Department of Homeostatic Regulation
Division of Ultrastructural Research
Center for Experimental Animals has also been renamed Center for Animal Resources and Collaborative Study

Oct., 2019
The following was abolished:
Department of System Neuroscience
Division of Integrative Physiology
The following was added:
Department of Fundamental Neuroscience
Division of Biophotonics

Apr., 2021
The following was abolished:
Department of Fundamental Neuroscience
Division of Cerebral Circuitry
The following were added:
Department of Molecular & Cellular Physiology
Division of Structural Biology
Supportive Center for Brain Research
Section of Cellular Electrophysiology

Section of Behavioral Patterns and Section of Metabolic Physiology in Center for Genetic Analysis of Behavior were merged and Section of Multilayer Physiology was established.

Sep., 2021
The following were added:
Department of Fundamental Neuroscience
Division of Multicellular Circuit Dynamics
Department of System Neuroscience
Division of Sensory and Cognitive Brain Mapping

Nov., 2021
The following was added:
Department of Homeostatic Regulation
Division of Molecular Neuroimmunology

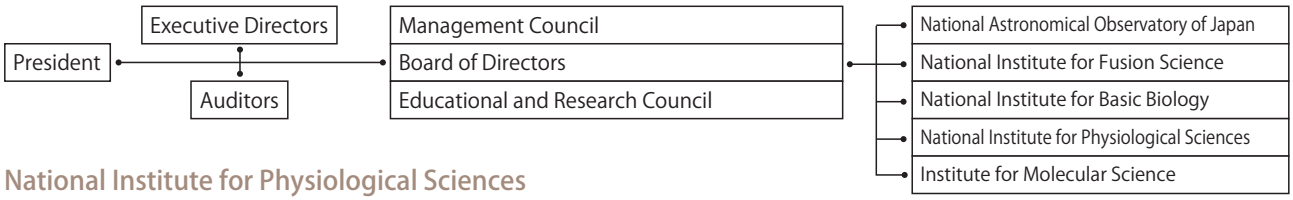
Oct., 2022
The following was abolished:
Center for Research Collaboration
Section of Visiting Collaborative Research Project
The following was added:
Center for Research Collaboration
Section of Advanced Project Promotion

Apr., 2023
The following were abolished:
Department of System Neuroscience
Division of System Neurophysiology
Division of Cerebral Integration

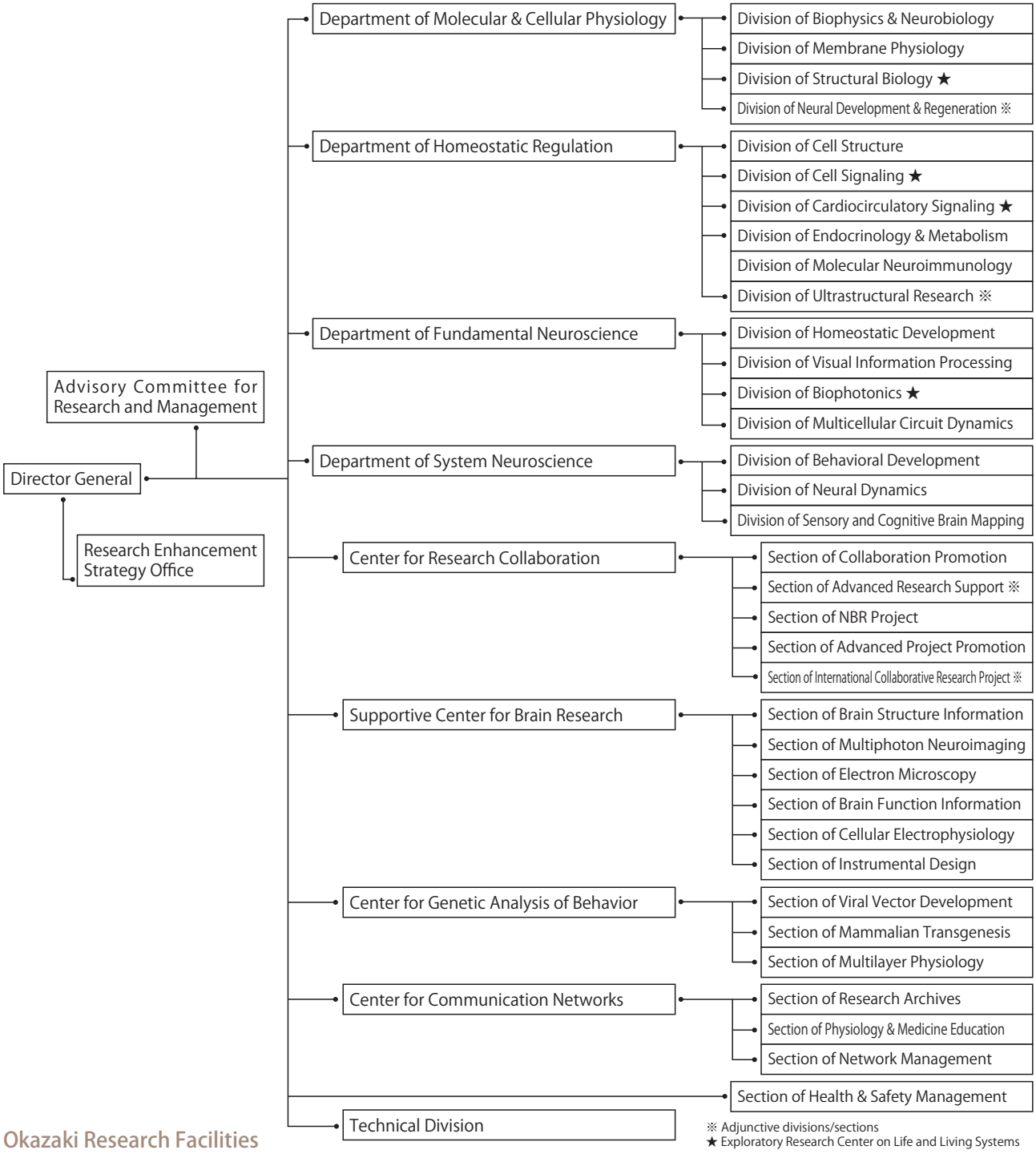
Asterisk (*) denotes adjunct division.

Organization of the Institute

National Institutes of Natural Sciences

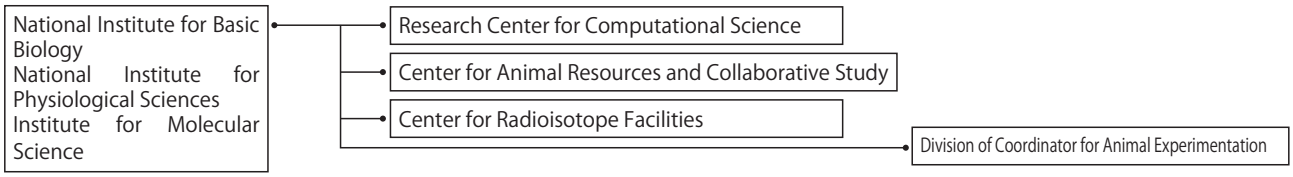


National Institute for Physiological Sciences



※ Adjunctive divisions/sections
★ Exploratory Research Center on Life and Living Systems

Okazaki Research Facilities



Advisory Committee for Research and Management

Chairman ◎ , Vice-Chairman ○

Advisory Committee for Research and Management shall advise the Director-General of the Institute, upon his request, on important matters in management of the Institute.

（Outside）

AKAHANE, Satomi	Professor, Department of Physiology, Faculty of Medicine, Toho University
HANADA, Reiko	Professor, Oita University Faculty of Medicine
HIDA, Hideki	Professor, Graduate School of Medical Sciences, Nagoya City University
KUBA, Hiroshi	Professor, Nagoya University Graduate School of Medicine
MATSUDA, Tetsuya	Professor, Tamagawa University Brain Science Institute
MIYATA, Mariko	Professor, Tokyo Women's Medical University School of Medicine
NAKABEPPU, Yusaku	Director, Japan Society For The Promotion of Science San Francisco Office
○NAWA, Hiroyuki	Professor, School of Medicine, Wakayama Medical University
ONO, Kyoichi	Executive Director / Vice-president, Akita University
TANAKA, Masaki	Professor, Hokkaido University Graduate School of Medicine

（Inside）

FURUSE, Mikio	Professor, NIPS
ISODA, Masaki	Professor, NIPS
KITAJO, Keiichi	Professor, NIPS
KUBO, Yoshihiro	Professor, NIPS
MINOKOSHI, Yasuhiko	Professor, NIPS
NEMOTO, Tomomi	Professor, NIPS
NISHIJIMA, Kazutoshi	Professor, NIPS
TOMINAGA, Makoto	Professor, NIPS
◎YOSHIMURA,Yumiko	Professor, NIPS

Director General/Vice Director General/Chief Researcher

Director General NABEKURA, Junichi

Vice Director General KUBO, Yoshihiro

Chief Chairperson ISODA, Masaki

Chief Researcher / Chairperson for Cooperative Studies YOSHIMURA,Yumiko

Chief Researcher / Chairperson for Animal Experiment Management NISHIJIMA, Kazutoshi

Chief Researcher /Chairperson for Safety and Research Ethics Problems TOMINAGA, Makoto

Chief Researcher / Chairperson for Public Affairs and Information Management KITAJO, Keiichi

Chief Researcher / Chairperson for Educational Problem FURUSE, Mikio

Chief Researcher / Chairperson for Special Project YOSHIMURA,Yumiko

Emeritus Professors

OOMURA, Yutaka
WATANABE, Akira
MORI, Shigemi
KANEKO, Akimichi
MIZUNO, Noboru
NAGAYAMA, Kuniaki
OKADA, Yasunobu
OHMORI, Harunori
KOMATSU, Hidehiko
IMOTO, Keiji
KAKIGI, Ryusuke
KAWAGUCHI, Yasuo
SADATO, Norihiro
NAMBU, Atsushi

Deceased Emeritus Professors

IRISAWA, Hiroshi
UCHIZONO, Koji
EBASHI, Setsuro
KATSUKI, Yasuji
KUNO, Motoy
HAMA, Kiyoshi
TSUKAHARA, Nakaakira
YANAIHARA, Noboru
WATARI, Hiroshi
SASAKI, Kazuo
IKENAKA, Kazuhiro
YAMAGISHI, Shunichi
OBATA, Kunihiko

DeceasedEmeritus Technical Staff

OHIRA, Hitoo

Division of Biophysics and Neurobiology

KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

TATEYAMA, Michihiro
Associate Professor
Pharmacology
Physiology

SHIMOMURA, Takushi
Assistant Professor
Molecular Physiology
Biophysics

Functioning mechanisms and dynamic structure- function relationship of ion channels, receptors and G proteins

Ion channels, receptors and G proteins play critical roles for the excitability and its regulation of neurons. We focus on these molecules which enable brain function. From the biophysical point of view, we study structure-function relationships, regulation mechanisms and dynamic structural rearrangements of ion channels and receptors. We also study the functional significance of specific features of ion channels and receptors in the brain function by making gene manipulated mice and by studying their abnormalities in the synaptic transmission and whole animal behavior.

Our experiments start with constructions of mutants, molecular chimeras and fluorescent tagged molecules of ion channels and receptors. We express them in heterologous expression systems such as Xenopus oocytes or HEK293 cells. We then analyze the functional features and dynamic structural rearrangements by electrophysiological method such as two electrode voltage clamp and patch clamp. We also use optophysiologial methods such as Ca^{2+} imaging, FRET analysis under total internal reflection microscope, subunit counting by single molecule imaging, and voltage clamp fluorometry using fluorescent unnatural amino acid.

Major target molecules are Two pore Na^{+} channel (TPC), Two pore K^{+} channel, G protein coupled inward rectifier K^{+} channel (GIRK), ATP receptor channel P2X2, Sigma-1 receptor and various G protein coupled receptors including an orphan receptor Prrt3. We also work, as cooperative research projects, on TRP channels, Opsin, as well as various ion channel toxins.

One of the characteristic features of our experimental approaches is that we utilize in vitro expression systems such as Xenopus oocytes which enable clarification of the observation targets, high through-put recordings and precise biophysical analyses by the two-electrode voltage clamp method. Another is that we perform simultaneous recordings of electrophysiology and optophysiology to approach the dynamic aspects of the function and structural rearrangements, which is beneficial towards the understanding of the functioning images. Taking advantages of these facilities and methodologies, we would like to promote our research as well as cooperative research projects further.

* Shimomura T, Hirazawa K, Kubo Y (2023) Proc Natl Acad Sci USA120, e2209569120.
* Chen IS, Eldstrom J, Fedida D, Kubo Y (2022) J Physiol 600: 603-622.
* Andriani R, Kubo Y (2021) Elife 10: e65822.
* Hirazawa K, Tateyama M, Kubo Y, Shimomura T (2021) J Biol Chem 297: 101425.
* Shimomura T, Kubo Y (2019) J Gen Physiol. 151: 986-1006.
* Tateyama M, Kubo Y (2018) PLoS One 13: e0204447.

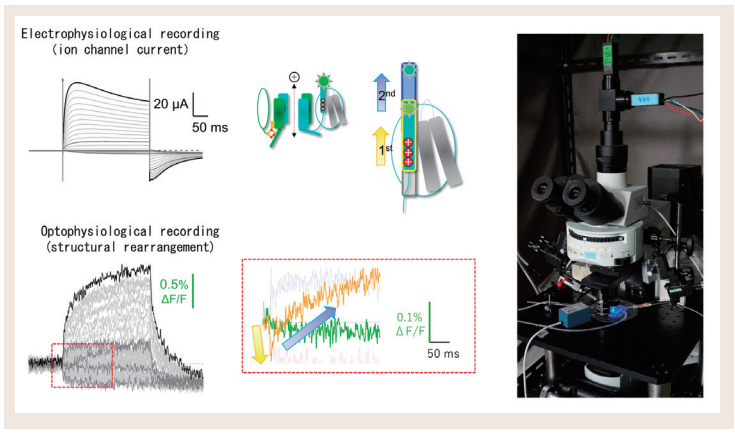
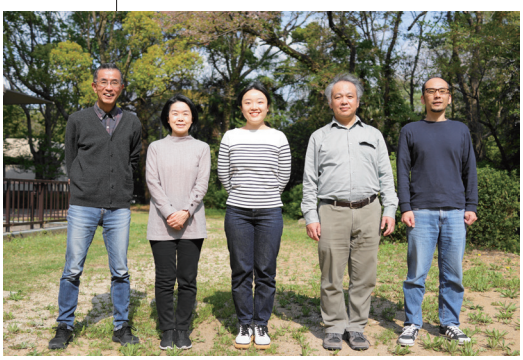


Fig. 1. Analyses of the function and dynamic structural rearrangements of TPC3 channel by simultaneous recordings of electrophysiology and optophysiology under voltage clamp using Xenopus oocyte expression systems. (Shimomura T, Hirazawa K, Kubo Y (2023) Proc Natl Acad Sci USA)



Division of Membrane Physiology

FUKATA, Masaki
Professor
Neuroscience
Biochemistry
Cell Biology

FUKATA, Yuko
Associate Professor
Neuroscience
Biochemistry
Cell Biology

YOKOI, Norihiko
Assistant Professor
Neuroscience
Biochemistry
Bioinorganic Chemistry
Structural Biology

Mechanisms for synaptic transmission and synaptic disorders

We will elucidate the core regulatory mechanisms for synaptic transmission and finally address the fundamental question, "How does our brain physiologically function and how is the system disrupted in brain diseases?". We have focused on the regulatory mechanisms for AMPA-type glutamate receptor (AMPAR) as AMPAR plays a central role in learning and memory formation. Based on our specific and quantitative biochemical methods, we discovered AMPAR regulatory proteins: the DHHC palmitoylating enzymes, ABHD17 depalmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1/ADAM22. So far, we have elucidated the physiological functions of these AMPAR regulatory proteins and the implication in the pathogenesis of brain diseases such as epilepsy and limbic encephalitis, by developing new methods to screen the palmitoyl enzyme-substrate pairs, to quantify the palmitoylation stoichiometry and to specifically visualize the palmitoylated protein, and by integrating many methods such as super-resolution imaging, mouse genetics, and electrophysiology. We will elucidate the molecular basis in which these AMPAR regulatory proteins regulate synaptic plasticity and cognitive functions of mouse and human brains using the following our developed or cutting-edge approaches and resources.

1）Analyses of in vivo protein-protein interactions
2）Screening of palmitoylating enzyme library
3）Profiling of protein palmitoylation stoichiometries
4）Observation of synapses with super-resolution microscopy
5）Generation of disease model mice by the Crispr/Cas9 method and analysis of the molecular pathology.

* van der Knoop et al., Brain **145**, 2301 (2022)
* Yokoi N et al., Cell Rep. **37**, 110107 (2021)
* Fukata Y et al., Proc. Natl. Acad. Sci. USA. **118**, e2022580118 (2021)
* Yamagata A, Miyazaki Y et al., Nat. Commun. 1546 (2018)
* Fukata Y and Fukata M, Nat. Rev. Neurosci. **11**, 161 (2010)

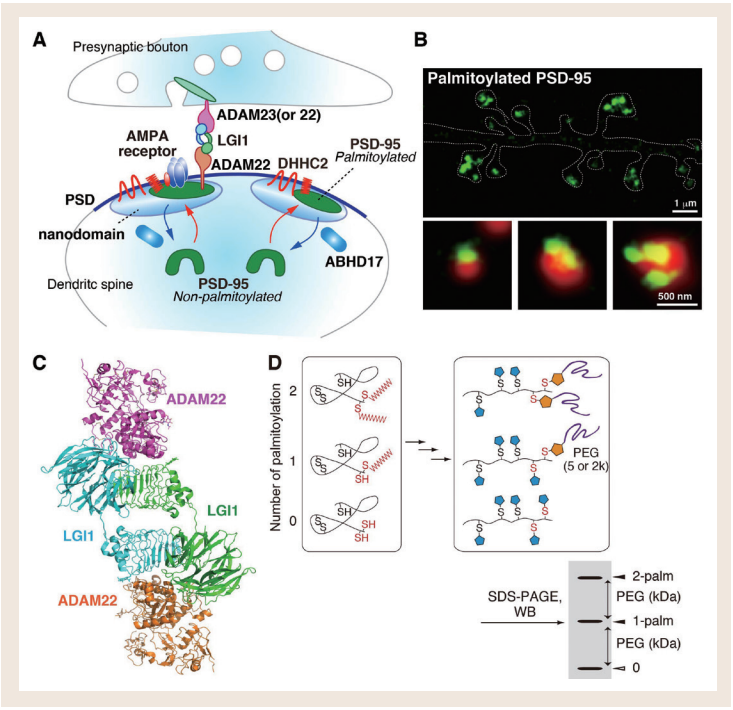


Figure (A) Unique AMPA receptor regulatory proteins: DHHC palmitoylating enzymes, ABHD17 depalmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1 and ADAM22. A synaptic DHHC protein locally regulates the formation and reorganization of nanodomains. (B) Discovery of novel postsynaptic nanodomains by palmitoylated PSD-95-specific probe and super-resolution microscopy. (C) X-ray crystal structure of the LGI1-ADAM22 dimer-of-dimer complex. (D) The acyl-PEGyl exchange gel shift (APEGS) method to quantify the palmitoylation stoichiometry.

Division of Structural Biology

Material-Life Boundary Research Group, Exploratory Research Center on Life and Living Systems

MURATA, Kazuyoshi
Project Professor
Structural biology
Electron Microscopy

SONG, Chihong
Project Assistant Professor
Cell Biology
Structural Biology

Raymond Burton-Smith
Project Assistant Professor
Biochemistry
Electron microscopy

Structural biology by cryo-electron microscopy

Living organisms are formed by biomolecules like proteins and are maintained by their chemical reactions. In our laboratory, we are studying the structures of these biomolecules using cryo-electron microscopy (cryo-EM) to elucidate these molecular mechanisms.

Cryo-EM is a method for directly observing a biological sample with an electron microscope by rapidly freezing and keeping it at a low temperature. This makes it possible to analyze the structure of biomolecules that are close to the living state at the atomic level.

The main research instruments are a 300kV Cold-FEG cryo-EM with the original bottom mount energy filter (TITAN Krios G4), a 200 kV cryo-EM equipped with an electron direct detection camera and in-column energy filter (JEM2200FS), and a cryo-FIB SEM (Aquilos2)(Fig. 1). The 3D structures of biomolecules are then reconstructed by single particle analysis or electron tomography (ET) with GP-GPU computers.

Figure 2 shows a recent example of cryo-EM result, which is the structure of a giant virus, Tokyovirus (Chihara et al. 2022). It revealed how such large virus capsids are stably formed and maintained.

We welcome young researchers and graduate students who are interested in such structural biology research.

* Chihara et al., Sci Rep 12(1), 21428 (2022)
* Miyazaki et al., J Virol 96(9), e0029822 (2022)
* Watanabe et al., J Virol 96(7), e0185321 (2021)
* Burton-Smith & Murata, Microscopy 70(6), 477 (2021)

Fig.1 300kV cryo-EM, TITAN Krios G4 (right), 200kV cryo-EM, JEM2200FS (middle), and cryo-FIB SEM (right).

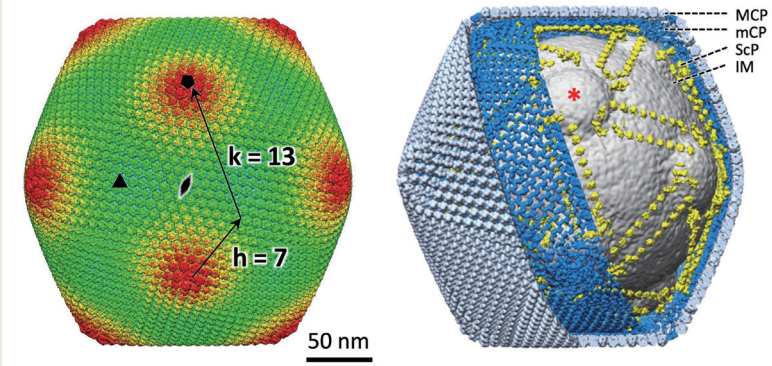


Fig. 2 Cryo-EM study of the large capsid structure of a giant virus, tokyovirus. The capsid surface is covered with the array of major capsid protein (MCP) (left), and beneath this, the minor capsid protein (mCP) and scaffold protein (ScP) enclose the central virus DNA with a nuclear membrane (right).

Division of Neural Development & Regeneration

SAWAMOTO, Kazunobu
Adjunct Professor
Neuroscience
Development and
Regenerative Biology

Elucidating the Mechanisms and Significance of Neurogenesis in the Postnatal Brain

Elucidation of the intrinsic regenerative mechanisms of the brain and development of manipulation techniques

It is becoming clear that not only in the embryonic brain, but also in the postnatal brain, neural stem cells exist in limited areas and continuously produce new neurons and glial cells, which are involved in brain development and homeostasis. It has also become clear that when the brain is injured, cell proliferation in neurogenic regions increases and neurons lost due to brain injury can be regenerated. In collaboration with other research divisions of NIPS, our group has been elucidating the mechanisms of neuronal migration and regeneration, as well as synaptic pruning by microglial cells. In this research division, we aim to elucidate the mechanisms and significance of neurogenesis in the postnatal brain using normal animals and animal models of brain injury, and to use the findings to develop new therapeutic strategies.

* Y. Ohno et al., Amphiphilic peptide-tagged N-cadherin forms radial glial-like fibers that enhance neuronal migration in injured brain and promote sensorimotor recovery. Biomaterials. 294, 122003, (2023)
* C. Kurematsu et al., Synaptic pruning of murine adult-born neurons by microglia depends on photophatidylserine.J Exp Med 219: e20202304 (2022)
* C. Nakajima et al., Postnatal neuronal migration in health and disease. Curr Opin Neurobiol 66: 1-9 (2021)
* M. Akter et al., Dynamic changes in the neurogenic potential in the ventricular-subventricular zone of common marmoset during postanal brain development. Cerebral Cortex 30: 4092-4109 (2020)
* M. Matsumoto et al., Dynamic changes in ultrastructure of the primary cilium in migrating neuroblasts in the postnatal brain. J Neurosci 39: 9967-9988 (2019)

Fig. 1. The fine morphology of newborn neurons migrating in the adult mouse brain was observed by serial block surface scanning electron microscopy (SBF-SEM) at the National Institute of Physiological Sciences (NIPS). SBF-SEM analysis reveals the whole image of newborn neurons as well as their organelles such as basal bodies (green), primary cilia (pink), Golgi apparatus (orange), and mitochondria (blue).

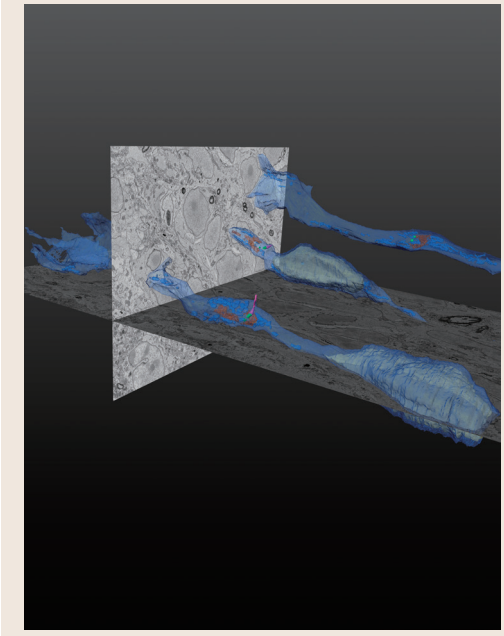


Fig. 2. Glial cells phagocytosing synapses were observed by SBF-SEM at the NIPS. Microglial prosess (green) phagocytose neuronal spines (blue) (Kurematsu et al., 2022).

Division of Cell Structure

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Cell Biology

IZUMI, Yasushi
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OTANI, Tetsuhisa
Assistant Professor
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OHASHI, Masato
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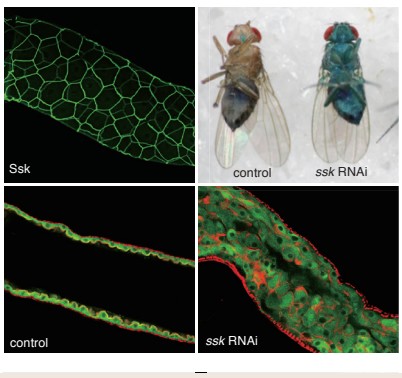
Biochemistry
Developmental Biology

Molecular basis of cell-cell junctions involved in epithelial barrier function

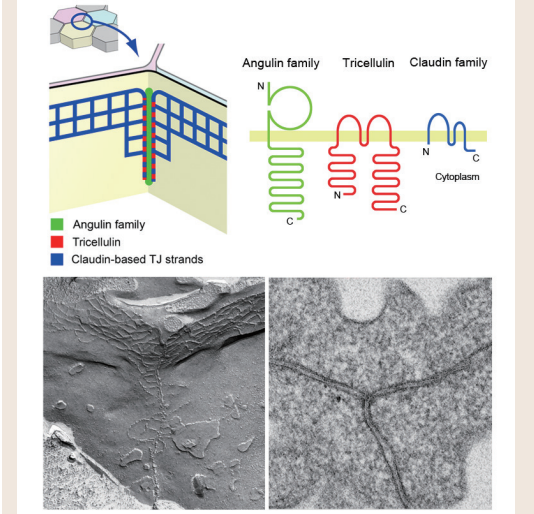
The Epithelium separates body compartments as a barrier and selectively transports various substances, thereby contributing to various functions of organs and homeostasis. Our laboratory aims to clarify the molecular bases of specialized cell structures responsible for these basic roles of the epithelium. We focus on the cell-cell junctions involved in the regulation of paracellular transport (occluding junctions), including the tight junction and its related structures, and examine their molecular architectures, functions, and dynamic behavior. One of the characteristic features of our research is that we identify structural or regulatory proteins of occluding junctions and characterize them. We take combined approaches of molecular cell biology, physiology, and morphology, including immunoelectron and freeze-fracture electron microscopy, by using cultured epithelial cells and model organisms, including mice and fruit flies. Genome editing technology has made it possible to experiment with systematic loss of function of relevant protein molecules in cultured epithelial cells, and various new findings are being obtained. The following are ongoing projects.

1. Roles of tight junction in epithelial homeostasis.
2. Molecular dissection of tricellular tight junctions and elucidation of their physiological functions.
3. Physiological functions of tight junctions and the related junctional structures in vivo.
4. Roles of septate junctions in intestinal barrier function and regulation of s tem cell proliferation in fruit fly.
5. Regulatory mechanisms of epithelial morphogenesis by membrane traffic

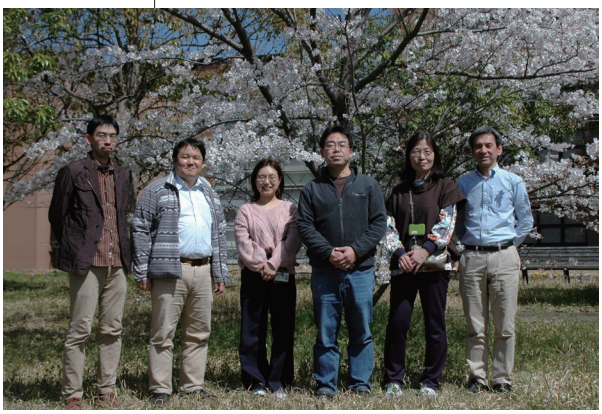
* Otani et al., J Cell Biol 218, 3372 (2019)
* Izumi et al., J Cell Sci 134: jcs257022 (2021)
* Sugawara et al., J Cell Biol 220: e202005062 (2021)



Roles of smooth septate junctions in the Drosophila midgut. When the expression of a smooth septate junction-associated membrane protein Ssk is suppressed in the adult Drosophila gut, the intestinal barrier function is impaired, leading to the leakage of blue dye from the intestinal lumen to the body cavity with overproliferation of enterocytes.



Molecular architecture and morphology of tricellular tight junctions. A. A freeze-fracture electron micrograph of tricellular tight junctions in mouse intestinal epithelial cells. B. A model of the molecular organization of tricellular tight junctions. C. An ultra-thin section electron micrograph of tricellular tight junctions in cultured epithelial cells. D. Localization of angulin-1/LSR (green) and occludin (red) in a frozen section of the mouse epididymis by immunofluorescence staining.



Division of Cell Signaling

Thermal Biology Group, Exploratory Research Center on Life and Living Systems

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SOKABE, Takaaki
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Sensory Biology

KASHIO, Makiko
Project Associate Professor
Molecular and Cellular Physiology

MARUYAMA, Kenta
Project Associate Professor
Senso-immunology
Geriatrics

SAITO, Shigeru
Assistant Professor
Evolutionary Physiology
Molecular Evolution

SATO, Shoma
Project Assistant Professor
Neurogenetics
Behavioral genetics

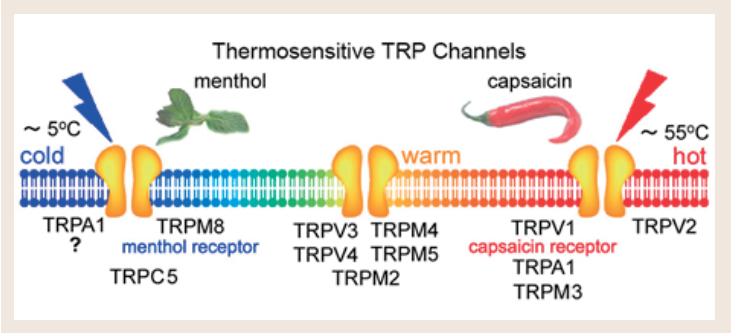
Molecular Mechanisms of thermosensation and nociception

We mainly investigate molecular mechanisms of thermosensation and nociception by focusing on so called 'thermosensitive TRP channels'. Among the huge TRP ion channel superfamily proteins, there are eleven thermosensitive TRP channels in mammals (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM4, TRPM5, TRPM8, TRPA1, TRPC5) whose temperature thresholds for activation range from cold to hot. Because temperatures below 15℃ and over 43℃ are known to cause pain sensation in our body, some of the thermosensitive TRP channels whose temperature thresholds are in the range can be viewed as nociceptive receptors. Some of the thermosensitive TRP channels are expressed in the organs or cells which are normally not exposed to the dynamic temperature changes. We found that they contribute to the various cell functions under the body temperature conditions in the normal to febrile range. Molecular and cell biological, biochemical, developmental and electrophysiological (patch-clamp and calcium-imaging methods) techniques are utilized to clarify the molecular mechanisms of thermosensation and nociception. In order to understand functions of thermosensitive TRP channels in vivo, we are also doing behavioral analyses using mice lacking the thermosensitive TRP channels. In the evolutionary process, organisms are thought to have adapted the changes in ambient temperature by altering the expression and functions of the thermosensitive TRP channels. Accordingly, we are characterizing the thermosensitive TRP channels from various species, which would help us to understand the mechanisms of thermosensation.

We are also investigating thermosensation in *Drosophila* (fruit flies) through behavioral analyses utilizing plenty of genetical tools. In addition, since TRP channels are nociceptors, we are developing novel insecticides/repellents that could be used to control insect pests.

* Endocannabinoids produced in photoreceptor cells in response to light activate *Drosophila* TRP channels. Sci. Signal. 15 (755): eabl6179, 2022.
* Evolutionary tuning of TRPA1 underlies the variation in heat avoidance behaviors among frog species inhabiting diverse thermal niches. Mol. Biol. Evol. 39(9): msac180, 2022.
* Protein kinase C-mediated phosphorylation of transient receptor potential melastatin type 2 Thr738 counteracts the effect of cytosolic Ca^{2+} and elevates the temperature threshold. J Physiol. 600(19):4287-4302, 2022.
* TRPV3-ANO1 interaction positively regulates wound healing in keratinocytes. Comms. Biol. 6: 88, 2023.

Eleven thermosensitive TRP channels



Division of Cardiocirculatory Signaling

Cardiocirculatory Dynamism Research Group, Exploratory Research Center on Life and Living Systems

NISHIDA, Motohiro
Professor
Cardiovascular Physiology

NISHIMURA, Akiyuki
Project Associate Professor
Biochemistry

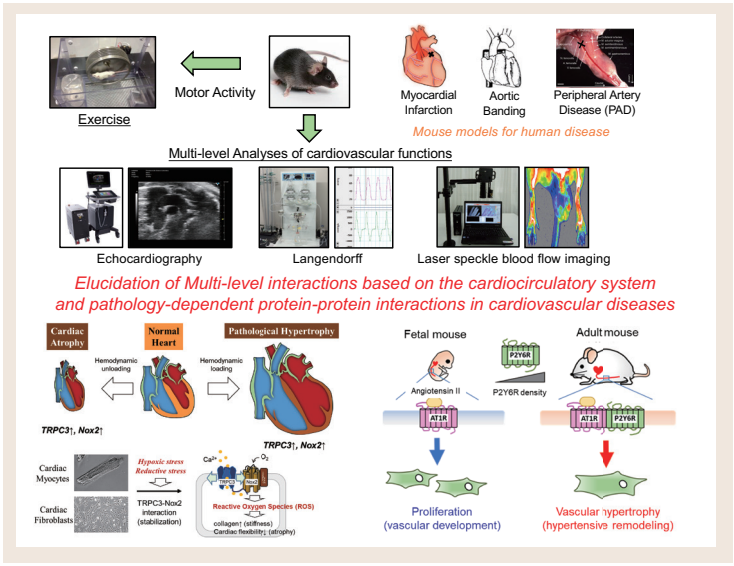
Elucidation of biological functions using multilevel techniques to evaluate cardiovascular functions and its clinical application

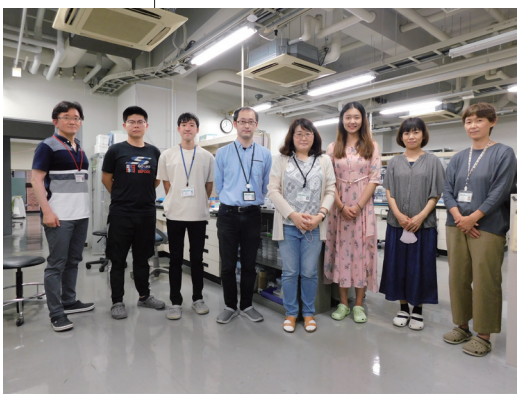
Our cardiocirculatory function is mainly controlled by muscular organs composed of striated muscles (heart and skeletal muscles) and smooth muscle (blood vessels). Our group aims to elucidate the molecular mechanisms underlying transition of the muscles from adaptation to maladaptation against various stress (hemodynamic load and environmental stress) using multi-level techniques to evaluate cardiovascular functions (in vivo and in vitro), and work toward practical application (e.g., drug discovery and fostering). In particular, we are focusing on mitochondria, energy-producing organs, and investigating the mechanism of muscle repair and regeneration from the viewpoint of mitochondrial quality control. We aim to develop a novel therapeutic strategy for refractory diseases.

Disruption of redox (reduction/oxidation) dynamics is closely related to the onset of various diseases including cardiocirculatory diseases. We are focusing on highly reactive sulfur metabolites (supersulfides) and conducting sulfur redox biology for cardiovascular homeostasis and diseases. In addition, we address the inclusive research to elucidate the mechanism underlying maintenance and transfiguration of cardiocirculatory homeostasis via multi-organ interactions by combining non-invasive measuring methodologies of motor functions and those cardiovascular functions. Our laboratory has various techniques and equipment to drive the above researches.

* X. Tang et al. Mar. Drugs. 21. 52 (2023)
* S. Oda et al. Nat. Commun. 13. 6374 (2022)
* K. Nishiyama et al. Science Signal. 15. abj0644 (2022)
* K. Shimoda et al. Sci. Rep. 10. 13926 (2020)
* A. Nishimura et al. Science Signal. 12. eaaw1920 (2019)
* A Nishimura et al., Science. Signal. 11, eaat5185 (2018)

Figure. Measuring systems for cardiovascular functions and summary of our research using these systems





Division of Endocrinology and Metabolism

MINOKOSHI, Yasuhiko
Professor
Endocrinology and Metabolism

NAKAJIMA, Ken-ichiro
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Neuroscience
Food Science

KONDOH, Kunio
Assistant Professor
Neuroscience

KIKUCHI, Akihiro
Project Assistant Professor
Biochemistry
Molecular Biology
Structural Life Sciences
Endocrinology and Metabolism

Molecular mechanism for the hypothalamic regulation of whole body energy metabolism
Hypothalamic modulation of taste and nutrient perception

The animal body has an integrated-regulatory system for "homeostasis" that maintains a normal, constant internal state by responding to changes in both the external and internal environments. Within the central nervous system, the hypothalamus is a crucial center that regulates the homeostatic activities by integrating autonomic nervous system, endocrine system and immune function. This division is investigating the role of hypothalamus in body energy balance and central regulation of taste and nutrient perception in mammals. The main subjects of our current research are as follows:

(1) Molecular mechanism of the hypothalamic regulation of food intake, glucose and lipid metabolism and taste sensations.
(2) Signaling pathway for metabolic action of leptin, adipokines and myokines.
(3) Physiological and pathophysiological roles of AMPK in whole body metabolism.
(4) Development of novel analytical method for glucose and lipid metabolism.
(5) Neuronal circuits that regulate hunger-induced taste modification.

* Y. Minokoshi, et al., Nature 415, 339, 2002.
* Y. Minokoshi, et al., Nature 428, 569, 2004.
* T. Shiuchi, et al., Cell Metab 10, 466, 2009.
* S. Okamoto, et al., Cell Reports 22, 706, 2018.
* O. Fu, et al., Cell Reports 27, 1650, 2019.
* O. Fu, et al., Nat Commun 10, 4560, 2019.

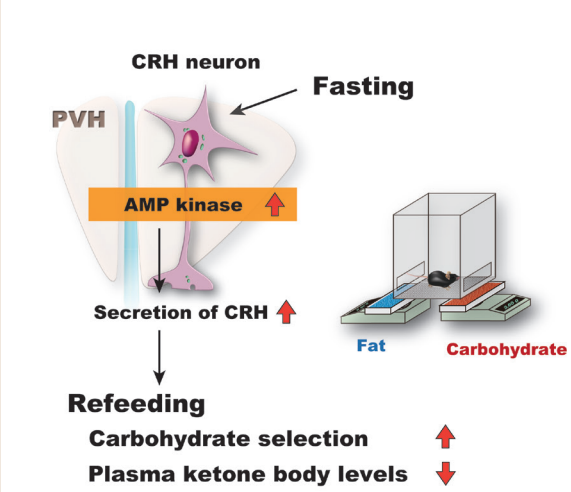

Fig. 1 Discovery of a specific neuron that induces selection of carbohydrate over fat. AMP kinase-regualted CRH neurons in the PVH are necessary and sufficient to induce selection of carbohydrate over fat after fasting.

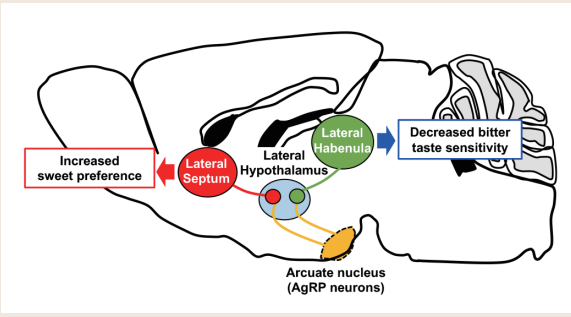

Fig. 2 Neuronal circuits that regulate hunger-induced taste modification.
Hypothalamic AgRP neurons regulate appetitive and aversive taste preferences via two distinct neuronal pathways.

Division of Molecular Neuroimmunology

MURAKAMI, Masaaki
Professor
Immunology
Neuroimmunology
Experimental pathology
Inflammatology

HASEBE, Rie
Project Associate Professor
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Immunology
Molecular Biology
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Molecular Biology
Neuropathophysiology
Virology
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Discovery of new gateway reflexes

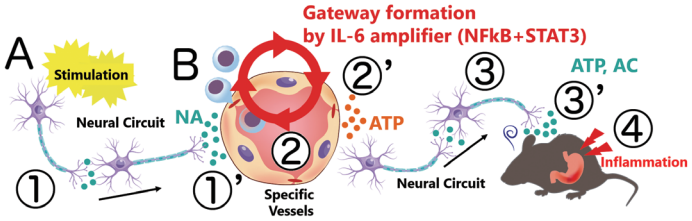
Detailed investigation of reported Gateway Reflexes

Genetic and environmental factors are involved in the development of autoimmune diseases. The genetic analysis of rare inherited autoimmune diseases directly showed the genes responsible for their development. Recently, a genome-wide association study (GWAS) to detect whole genome single nucleotide polymorphisms (SNPs) in patients with autoimmune diseases was performed using next-generation sequencing and reported many disease-associate genes. In addition, some environmental factors, such as ageing, infection and stress, are likely to worsen many of these diseases. We have conducted several studies focused on the cytokine IL-6 and CD4+ T cells. Among them, in 2008, we discovered the "IL-6 amplifier", which is a hyper-induction machinery for inflammation and presented on non-immune cells, such as endothelial cells, fibroblastic cells, and exocrine cells. Many disease-associate genes are involved in the activation of the IL-6 amplifier via the NFkB signaling pathway, including NEDD4 and GTF2I. Moreover, we discovered a novel neuro-immune interaction, named the "Gateway Reflex". In the Gateway Reflex, the activation of specific neural circuits triggered by several environmental factors leads to the secretion of noradrenaline at specific blood vessels to form gateways for autoreactive CD4+ T cells to enter the tissue, leading to the development of tissue-specific autoimmune diseases. In total, we have reported six Gateway Reflexes, in which a distinctive external stimulus (gravity, pain, stress, light, intra-articular inflammation, and artificial neuronal stimulation) induces the formation of the gateways to develop the tissue-specific inflammatory disease (Table below). In the Division of Molecular Neuroimmunology, we have studied these two novel concepts for the development of tissue-specific inflammation in collaboration with the Murakami laboratories at Hokkaido University and the National Institutes for Quantum Science and Technology. Regarding the Gateway Reflexes, we will clarify the responsible molecular and cellular mechanisms through (1) the discovery of novel Gateway Reflexes, (2) detailed analysis of the associated neural circuits, (3) analysis of the molecular basis of the gateway formation, and (4) analysis of the antigen specificity of autoreactive CD4+ T cells during the gateway formation.

* H. Ogura *et al*., Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity* **29**, 628-636 (2008).
* Y. Arima *et al*., Regional neural activation defines a gateway for autoreactive T cells to cross the blood-brain barrier. *Cell* **148**, 447-457 (2012).
* Y. Arima *et al*., Brain micro-inflammation at specific vessels dysregulates organ-homeostasis via the activation of a new neural circuit. *eLife* **6**, (2017).
* M. Murakami, D. Kamimura, T. Hirano, Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines. *Immunity* **50**, 812-831 (2019).
* R. Hasebe et al., ATP spreads inflammation to other limbs through crosstalk between sensory neurons and interneurons. *The Journal of experimental medicine* **219**, (2022).

IL-6 amplifier and Gateway Reflex

A. Stimulation	B. Immune cells	① Neural Circuits	①' Neuro transmitter	② Gateway Sites	②' Neuro transmitter	③ Neural Circuits	③' Neuro transmitter	② or ④ pathology	papers
1 Gravity	MOG-Th17	Sensory (Soleus Mus) -L5 Sympathetic G	Noradrenarine (NA)	L5 dorsal vessels				MS model	Cell (2012)
2 Electric	MOG-Th17	Sensory(quadriceps) -L3 Sympathetic G	NA	L3 dorsal vessels				MS model	Cell (2012)
3 Pain	Monocytes+MOG-Th1/Th17	Sensory-ACC-Sympathetic	NA	Spinal cord ventral vessels				Relapse of MS model	eLife (2015)
4 Light	IRBP-Th1/Th17	Optic nerves	NA	Retina vessels				Uveitis model	Sci Rep (2019)
5 Inflammation	various			Synovial fibroblasts	ATP	Sensory -Inter-N -Sensory (Antidromic)	ATP	RA model	JEM (2022)
6 Stress	MOG-Th1/Th17	PVN -Sympathetic	NA	Brain vessels	ATP	Nonsymp -DMH/AHP -DMX -Vagus-N	Acetylcholine (AC)	Progressive MS model	eLife (2017)



Division of Ultrastructural Research

OHNO, Nobuhiko
Adjunct Professor
Anatomy
Neuroscience
Cell biology

Ultrastructural analyses with electron microscopic 3D reconstruction
Regulatory mechanisms and roles of mitochondrial dynamics in myelin diseases

Our goal is to understand structural changes in biological phenomena including development, functional maintenance and pathophysiology of the nervous system, and elucidate their molecular mechanisms and roles. We utilize various imaging approaches including 3D ultrastructural analyses with serial block-face scanning electron microscopy (SBEM, SBF-SEM) and animal models, and also engage in development of new technologies and many collaborative projects.

We are interested in intercellular associations of the nervous system. Among them, we would like to clarify the structural and functional changes and their molecular background in myelination and myelin diseases. One of our focuses is on mitochondrial dynamics, which are involved in pathophysiology of various diseases. We are trying to clarify the association of mitochondria and myelin diseases, and develop approaches for their regulation.

* Nakamura et al. Elife. 12:e83108 (2023)
* Yamazaki et al. Neurochem Int. 164:105505 (2023)
* Osanai et al. Front Cell Dev Biol. 10:1030486 (2022)
* Osanai et al. Neurochem Res. 47:2815 (2022)
* Tanaka et al. Glia. 69:2488 (2021)

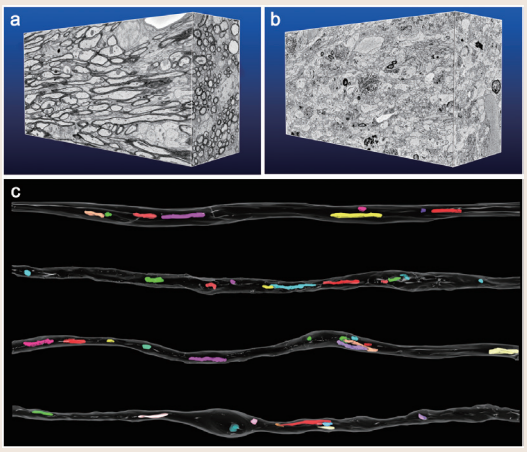


Figure 1. Reconstruction of serial electron microscopic images from corpus callosum of control (a) and demyelination model (b) mice, and 3D reconstruction of axonal mitochondria (c). Modified from Ohno et al. (2014).

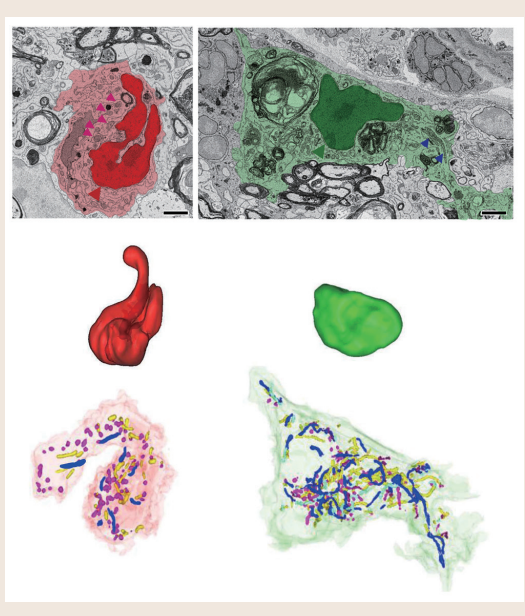


Figure 2. Colored electron microscopic images (upper row) and 3D reconstruction of nuclei (middle row) and mitochondria (lower row) of monocyte- (red) and microglia-derived (green) macrophages in a mouse spinal cord of a demyelination model. Modified from Katoh et al. (2017).

Division of Homeostatic Development

NABEKURA, Junichi
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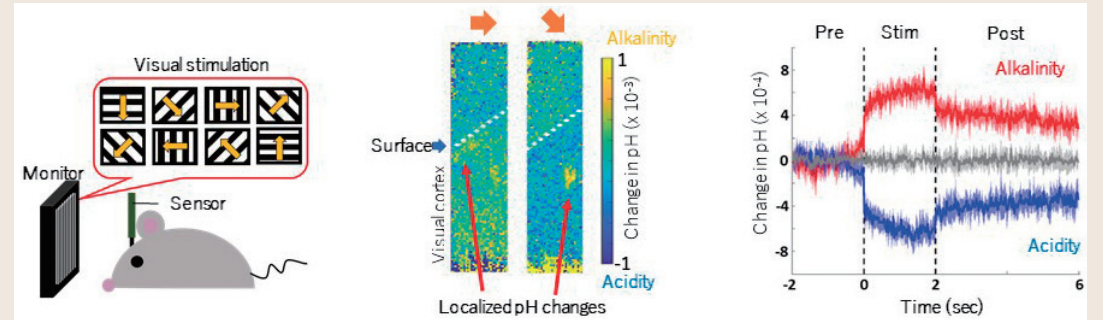
Neuroscience

NARUSHIMA, Madoka
Associate Professor
Neuroscience

AGETSUMA, Masakazu
Associate Professor
System Neurophysiology
Molecular ethology

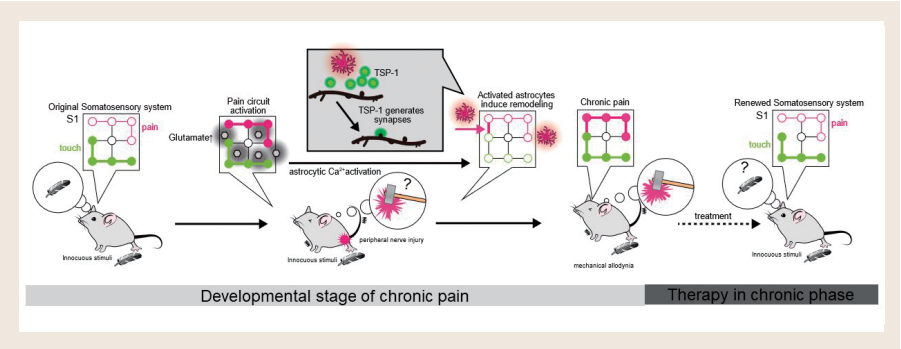
Remodeling of Neuronal Circuits in Development and Recovery, — *In vivo* Imaging and Electrophysiological Study —

Remodeling of neuronal circuits takes place during development, learning, and recovery after brain damage. The main goal of our research is to understand the regulation of neural circuits remodeling. In detail, we are focusing on glial contribution to the function of neuronal circuits. Glia is a key factor to regulate neural circuits through their physiological function. We are trying to determine their contribution to the neural circuits in physiological and pathological conditions by visualizing fine structure, controlling activity, and recording specific synaptic transmissions in living animals using multi-photon microscopy. We are also focusing on experience-dependent remodeling in sensory neural circuits during development. We use behavioral analysis, in vivo imaging, and in vitro electrophysiology to clarify the correlation between the development of behavioral patterns and synaptic plasticity as its basis.



CMOS-based ion image sensor revealed neuronal activity-dependent pH changes in the living brain

* CMOS-based bio-image sensor spatially resolves neural activity-dependent proton dynamics in the living brain. Horiuchi H, Agetsuma M, Ishida J, Nakamura Y, Cheung DL, Nanasaki S, Kimura Y, Iwata T, Takahashi K, Sawada K, Nabekura J. Nat Commun. 11(1):712, 2020.
* Controlled activation of cortical astrocytes modulates neuropathic pai-like behaviour. Takeda,I, Yoshihara K, Cheung D, Konbayashi T, Agetsuma M, Tusda M, Eto K, Koizumi S, Wake H, Moorhouse AJ, Nabekura J. Nat Commun, 13(1):4100, 2022.



Pain circuit reorganization with activated astrocytes as a therapeutic approach

Innovative technology development across fields

The progress of technology has brought about a breakthrough in life science. We recently revealed neural activity-dependent pH changes in the living brain with single-cell level resolution using a CMOS image sensor which we had newly developed. The propagation of pH change from the hippocampus before electrical epileptic activity was detected. We started the collaboration with clinics and company to develop the new tools to predict the epileptic seizures in the human patients.

Division of Visual Information Processing

YOSHIMURA, Yumiko
Professor
Neurophysiology

YONEDA, Taisuke
Assistant Professor
Neuroscience

Analysis of mechanisms underlying information processing and activity-dependent functional developments in the neocortex

Sensory experience during postnatal development is required for the maturation and refinement of neuronal circuits in the sensory cortex. This leads to the development of cortical functions suitable for the living environment. To elucidate the mechanisms underlying information processing in the sensory cortex and the experience-dependent regulation of that processing, we are studying the relationship between visual functions and the signaling properties of neural circuits using rat and mouse visual cortex. To this end, we are analyzing the visual responses of cortical neurons using multi-channel electrodes or calcium imaging with 2-photon microscopy. Also, we are studying neural circuit properties with a combination of laser scanning photostimulation and whole-cell patch-clamp recording methods in slice preparations; and neural connections morphologically using modern virus tracers. The following is a list of our main projects currently ongoing.

1. Synaptic plasticity and visual response plasticity in animals at different developmental stages and in animals subjected to the manipulation of visual experience during postnatal development
2. Developmental mechanisms of visual responsiveness, plasticity, and synaptic connections in each neuron subtypes
3. Cell-lineage dependent establishment of neuronal connections and visual responsiveness

We are also conducting collaborative research and looking for graduate students interested in the developmental mechanisms of brain functions.

* Yoneda T, Hayashi K, Yoshimura Y (2023) Experience-dependent functional plasticity and visual response selectivity of surviving subplate neurons in the mouse visual cortex. PNAS. 120(9):e2217011120
* Kimura R, Yoshimura Y (2021) The contribution of low contrast-preferring neurons to information representation in the primary visual cortex after learning. Science Adv. 7 (48)

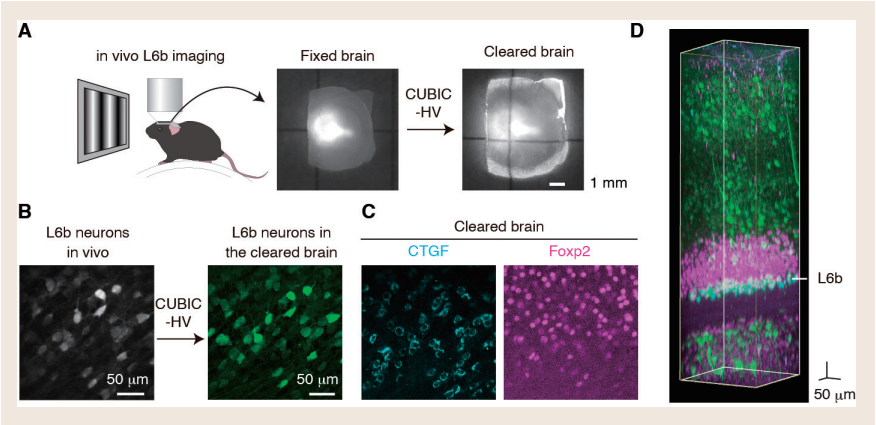


Figure Analysis of visual response plasticity based on cortical neuron subtypes
(A) Visual responses were recorded from layer 6b of the primary visual cortex of living mice with two-photon imaging, followed by tissue clearing. (B) Layer 6b neurons from in vivo two-photon imaging (left) and the same areas from a cleared brain (right). (C) Most of the recorded L6b neurons expressed CTGF which is a subplate neuron marker. Foxp2 is a marker of cortico-thalamic neurons. (D) An example of a volumetric image of cleared brain.

Division of Biophotonics

Biophotonics Research Group, Exploratory Research Center on Life and Living Systems

NEMOTO, Tomomi
Professor
Biophysics
Cell physiology

ENOKI, Ryosuke
Associate Professor
Neurophysiology
Chronobiology

OTOMO, Kohei
Associate Professor
Spectroscopy
Physical Pharmacy

ISHII, Hirokazu
Assistant Professor
Developmental biology
Biophysics

TSUTSUMI, Motosuke
Project Assistant Professor
Biophysics
Structural Biology

Quantitative analysis and elucidation of underlying mechanism of physiological functions by innovative bioimaging utilizing cutting-edge technologies of photonics

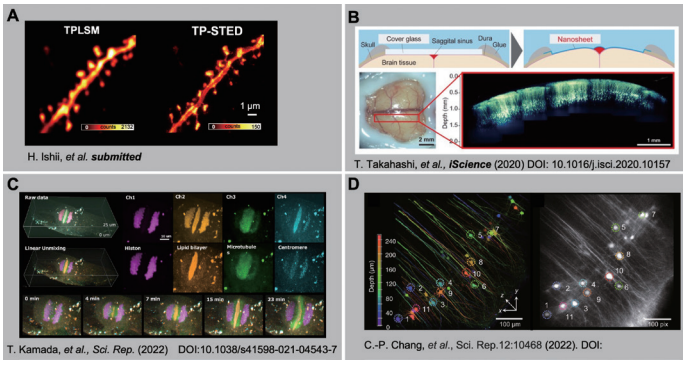
We have advanced innovative bio-imaging methods by utilizing such advanced optical technologies as lasers and nanomaterial chemistry. In particular, we aim to develop less-invasive "*in vivo*" observation and manipulation for living organisms and tissues by utilizing multiphoton excitation and nonlinear optical processes by facilitating our original world-leading ultra-deep, super-resolution, and ultra-high-speed imaging methods. These technologies will establish a quantitative visualization analysis method for physiological functions and elucidate the emergence of neural functions by analyzing neural circuits and activities, including biological rhythms and their molecular basis.

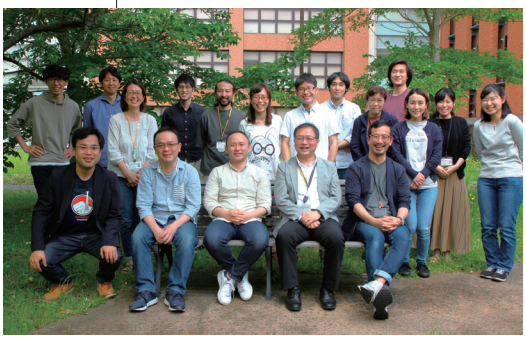
We recently developed multiphoton microscopy to realize cross-sectional fluorescence imaging at the deepest layer in the world with infra-red ultra-short pulse laser adaptive optics. As a result, we visualized neurons in the hippocampus's dentate gyrus at 1.6 mm depth from the brain surface under anesthesia. Noticeably, we observed the activity of hippocampal CA1 neurons at a video rate. Utilizing long-term imaging technology for living cell functions, we promote research on the generation and function of ultradian and circadian rhythms. On the other hand, we are also pursuing super-resolution microscopy by utilizing new laser technologies to enable ultra-micromorphology for molecular dynamics in living cells. In local neural circuits, endocrine or exocrine glands, and model animals and plants, fast three-dimensional "in vivo" imaging reveals the underlying principles of the emergence of physiological functions. These methodologies also explore the molecular basis of the pathogenic mechanism of diseases.

These methods collaborate widely with various laboratories covering life sciences and applied physics, material science, medicine, and pharmaceutical sciences in this research department. By advancing imaging methodology that visualizes physiological phenomena *in vivo*, or "as they are," and pursuing neural cell physiology, we will weave a new tapestry of interdisciplinary areas. We are looking for graduate students or young researchers who can share our passion for pioneering new academic fields. We are looking for graduate students or young researchers who share our passion for pioneering new academic fields.

* H. Ishii et al., submitted
* T. Takahashi, et al., iScience, 23(10), 101579, (2020)
* T. Kamada, et al., Sci. Rep., 23(10), 101579, (2022)
* C.-P. Chang,et al., Sci. Rep.12:10468 (2022)

Fig. (A) Super-resolution imaging with two-photon STED microscopy. (B) Wide-field in vivo imaging using nano-sheets. (C) Multicolor imaging of cell division using a multi-beam-scanning two-photon confocal microscopy. (D) High-speed volume imaging using light-needles.





Division of Multicellular Circuit Dynamics

WAKE, Hiroaki
Professor
Neuroscience
Neurophysiology
Neuroanatomy

Analysis of physiological changes in multicellular circuit dynamics responsible for higher brain

1. Aim of Research

The Division Multicellular Circuit Dynamics aims to elucidate the circuitry mechanism of neuron and glia cells in central nervous system. For this purpose, 1. We focus on the glial physiological functions that affect on the neuronal circuits and ultimately on the behavior output. 2. We focus on the functional connectivity of the local multicellular circuits and quantify the connectivity by our developed holographic microscope to modulate the circuits. Please see below for the detail.

(1) Project to reveal physiological functions of glial cells

(a) Microglia : We previously showed that microglia directly contact on synapse to monitor their functions using two photon microscopes (Wake et al., 2009). Our recent research showed that microglia contact on synapse via P2Y12 signaling to modulate their function and thus to regulate the synchronization of neuronal circuits (Akiyoshi et al., 2018, Badimon et al., 2020). In addition, we focused on blood brain barrier (BBB) permeability with systemic inflammation. Microglia migrate on blood vessels with the induction of systemic inflammation and express Cldn5 to form tight junction with endothelial cells to protect their permeability. However, with the progression of inflammation, microglia start to express CD68 to phagocyte astrocyte endfeet and thus increase the BBB permeability (Haruwaka et al., 2019). In addition, somatosensory sensation is enhanced after visual deprivation (cross-modal plasticity), and we found that the neural circuits connecting the somatosensory cortex to the higher visual cortex are important for cross-modal plasticity. We also found that microglia play an important role in the circuit rewiring (Hashimoto et al., 2023).

(b) Oligodendrocyte : Activity-dependent myelination contributes to synchrony of neuronal activity and motor learning using two-photon microscopy and electrophysiological techniques (Sugio et al., submitted).

(2) Development of holographic microscope

To manipulate neuronal and glial circuits with higher temporal and spatial resolution, we developed holographic microscope. Using this system, we measured the local circuit connectivity by stimulating single cell with simultaneous imaging of neuronal populational activity and studied the connectivity change in pain model (Okada et al., 2021). Combined with data on the plasticity of different senses, we are trying to introduce artificial sensation (Tanisumi et al., in preparation).

* Hashimoto et al., Cell Rep. (2023)
* Okada et al., Sci Adv. (2021)
* Badimon et al., Nature (2020)
* Haruwaka et al., Nat Commun. (2019)
* Akiyoshi et al., eNeuro (2018)
* Wake et al., J Neurosci. (2009)

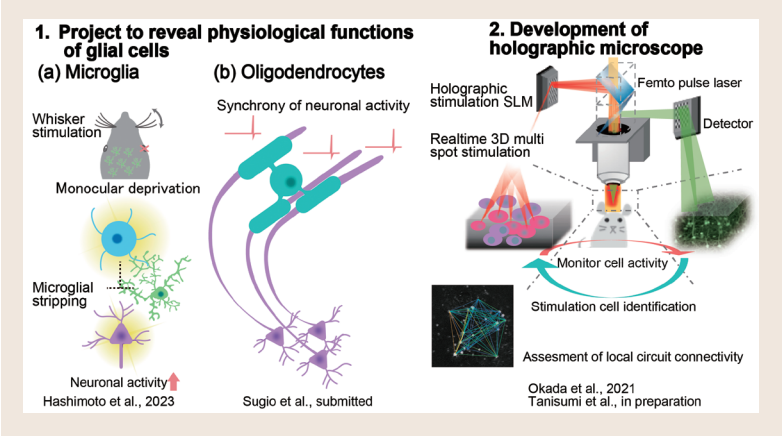
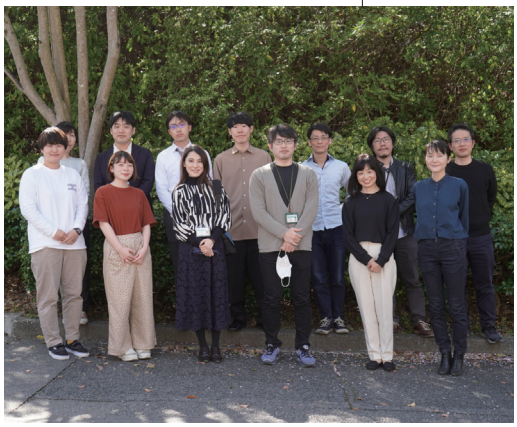


Figure 1 (a) Monocular deprivation induces microglial stripping of inhibitory synapses. This promotes neuronal activation of the secondary visual cortex (V2L) during whisker stimulation. (b) Oligodendrocyte induces synchrony of neuronal activity.

Figure 2 Holographic stimulation assess the functional connectivity of local neural circuits.



Division of Behavioral Development

ISODA, Masaki
Professor
Neurophysiology

GO, Yasuhiro
Professor
Comparative Genomics
Neurogenomics

TOMATSU, Saeka
Project Associate Professor
Cognitive Neuroscience
Neurophysiology

NINOMIYA, Taihei
Assistant Professor
Neuroanatomy
Neurophysiology

NORITAKE, Atsushi
Assistant Professor
Neurophysiology
Cognitive Neuroscience

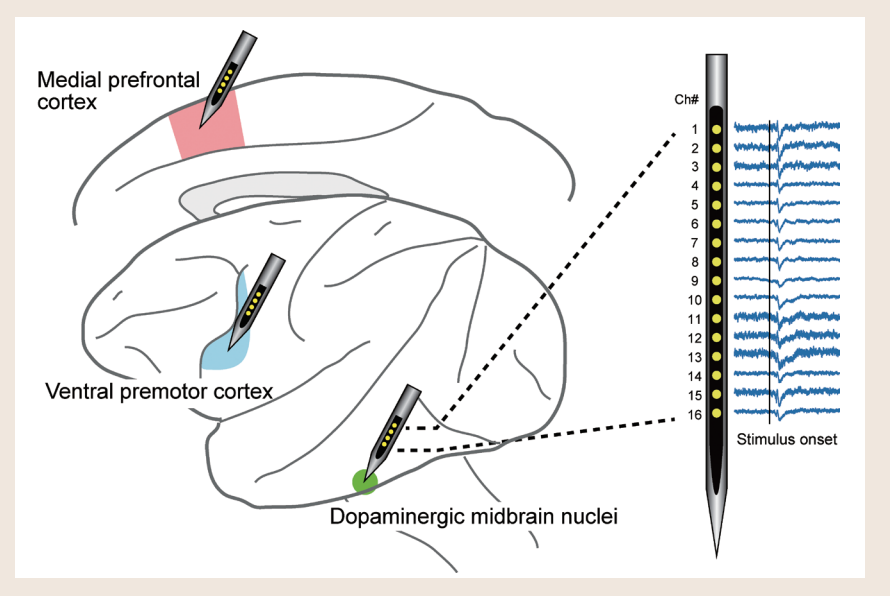
UEMATSU, Akiko
Project Assistant Professor
Neurophysiology

KANEKO, Takaaki
Project Assistant Professor
Neurophysiology
Cognitive Neuroscience

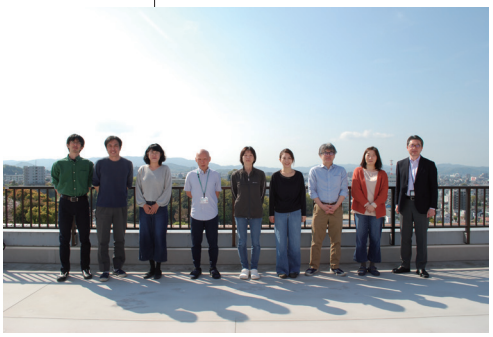
System-level understanding of social cognitive functions

There is increasing attention to social neuroscience, a discipline dedicated to clarifying the neural basis of social cognitive functions. In social neuroscience, studies on human subjects are surely indispensable, as they can tell us about our social mind most directly. Yet research using nonhuman primates is of equal importance for understanding social brain functions at the cellular and network levels. Nonhuman primates are phylogenetically close to humans, they have brain structure and function similar to humans, and they offer unique opportunities to directly record or manipulate neural activity. Our laboratory develops novel, behavioral tasks using two monkeys facing each other and carries out electrophysiological recordings of single-neuron activities and local field potentials across networks of brain regions to achieve a system-level understanding of social cognition, such as decision making on the basis of behavioral information regarding the self and others. We also perform pathway-selective blockade of neural activity using viral vectors to establish a causal relationship between a target neural pathway and a particular social cognitive function. Furthermore, we perform cognitive genomics studies in macaques with mutations in genes associated with human psychiatric and neurodevelopmental disorders, thereby clarifying the genetic basis of social cognitive functions.

* Ninomiya T et al. (2021) PNAS 118: e2109653118
* Isoda M (2021) Annu Rev Neurosci 44: 295-313
* Ninomiya T et al. (2020) Nat Commun 11: 5233
* Noritake A et al. (2020) PNAS 117: 5516-5524
* Noritake A et al. (2018) Nat Neurosci 21: 1452-1462
* Yoshida K et al. (2016) Sci Adv 2: e1600558
* Yoshida K et al. (2012) Nat Neurosci 15: 1307-1312
* Yoshida K et al. (2011) Curr Biol 21: 249-253



Multi-site, multi-electrode neural recordings for clarifying the neural basis of social cognitive functions



Division of Neural Dynamics

KITAJO, Keiichi
Professor
Computational Neuroscience
Cognitive Neuroscience

UEHARA, Kazumasa
Associate Professor
Neurophysiology
Neuroscience

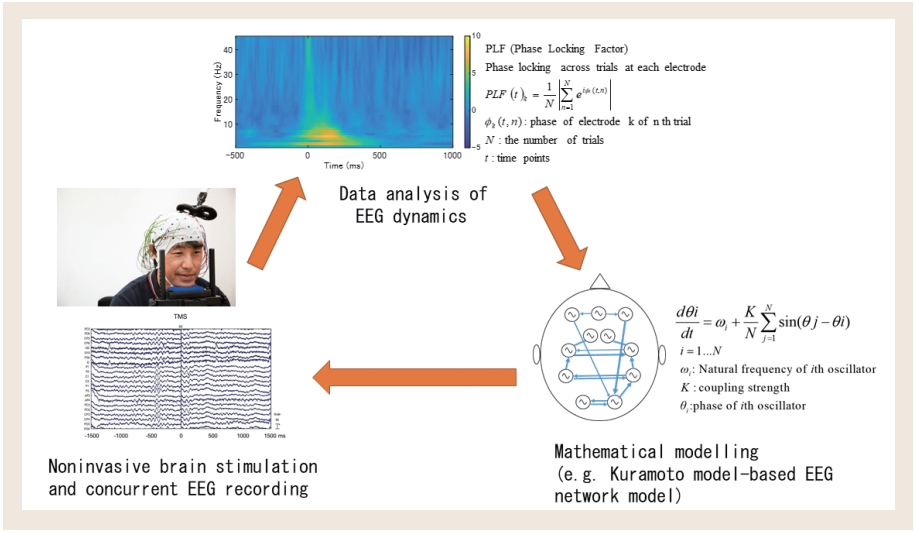
OKAZAKI, Yuka
Assistant Professor
Cognitive Neuroscience

NAKAMURA, Shinya
Project Assistant Professor
Systems Neuroscience

Unravelling the functional roles of neural dynamics

The brain can be considered a complex dynamical system, composed of a number of connected nonlinear elements such as neurons and glial cells. Its activity exhibits a wide range of nonlinear dynamics. For instance, depending on the brain state, the human brain exhibits transient oscillations and synchronization at various frequency bands. We investigate functional roles of nonlinear neural dynamics such as oscillation, synchrony, metastability, and noise-induced phenomena in perception, cognition, motor, and social functions from a computational neuroscience perspective. We measure and analyze scalp electroencephalographic (EEG) signals in humans while human participants are engaged in cognitive tasks, at rest, or during noninvasive brain stimulation such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). We also analyze electrocorticographic (ECoG), magnetoencephalographic (MEG), and functional magnetic resonance imaging (fMRI) data in humans, as well as imaging and electrophysiological data in distinct modalities in animals. We promote computational studies through data analysis and mathematical modeling based on nonlinear dynamical systems theory, information theory, signal processing theory, complex network analysis, and statistical machine learning theory. We also collaborate with researchers to analyze clinical data for stroke and epilepsy patients, as well as persons with developmental disabilities. Our goal is to understand clinical symptoms in terms of altered neural dynamics and explore potential applications for brain-machine interfaces. Moreover, we investigate the relationships between neural dynamics and modulating factors such as autonomic nervous activity and excitation/inhibition balance in neural circuits to understand the functional roles of neural dynamics from an integrative perspective.

* Yokoyama H, Kitajo K (2022) Detecting changes in dynamical structures in synchronous neural oscillations using probabilistic inference. NeuroImage, 252, 119052, doi: 10.1016/j.neuroimage.2022
* Onojima T, Kitajo K (2021) A state-informed stimulation approach with real-time estimation of the instantaneous phase of neural oscillations by a Kalman filter. Journal of Neural Engineering, 18, 066001, doi: 10.1088/1741-2552/ac2f7b
* Okazaki YO, Nakagawa Y, Mizuno Y, Hanakawa T, Kitajo K (2021) Frequency- and area-specific phase entrainment of intrinsic cortical oscillations by repetitive transcranial magnetic stimulation. Frontiers in Human Neuroscience, 15: 608947
* Kawano T, Hattori N, Uno Y, Hatakenaka M, Yagura H, Fujimoto H, Nagasako M, Mochizuki H, Kitajo K, Miyai I (2021) Association between aphasia severity and post-stroke brain network alterations assessed using the electroencephalographic phase synchrony index. Scientific Reports, 11, 112469, doi: 10.1038/s41598-021-91978-7
* Okazaki YO, Mizuno Y, T. Kitajo K (2020) Probing dynamical cortical gating of attention with concurrent TMS-EEG. Scientific Reports, 10, 4959, 1-10.



To understand the functional roles of neural dynamics in humans, we use the TMS-EEG concurrent recording paradigm to measure neural activity. Next, we analyze the EEG data and apply mathematical modeling techniques to gain insights into the neural dynamics.

Division of Sensory and Cognitive Brain Mapping

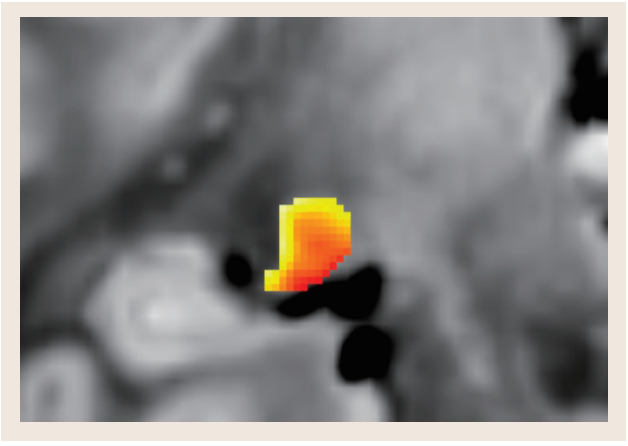
TAKEMURA, Hiromasa
Professor
Neuroimaging
Neuroscience
Vision Science

Structural and functional brain mapping

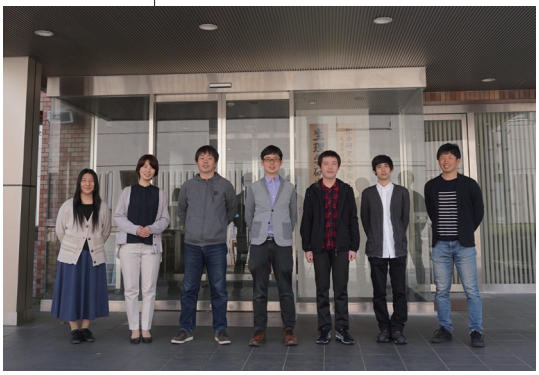
Human brain processes various information derived from the environment to support our daily life. Human brain comprises several distinct structural properties, including cortical layers, subcortical nuclei and white matter tracts connecting brain areas. However, it is not yet fully understood how our brain function emerges from these structures. In other words, how the "software" (function) of the brain can be established based upon "hardware" (structure)? We investigate structure-function relationship in brains to address this question.

Specifically, we combine structural and functional neuroimaging method using magnetic resonance imaging facilities in the institute to understand how brain functions are related to brain structure. We also perform psychophysical studies to investigate mechanisms on visual information processing in humans. In addition, throughout collaborations with other groups, we also investigate how functional and structural MRI measurements are related to visual, motor, and language functions as well as clinical disorders such as retinal diseases.

* Oishi H et al. (2023) NeuroImage 265, 119777.
* Miyata T et al. (2022) J Neurosci 42(35), 6761-6769.
* Takemura H et al. (2020) eLife, 9, e55444.
* Takemura H et al. (2019) NeuroImage Clin, 23, 101826,
* Takemura H et al. (2017) Cereb Cortex, 27(6), 3346-3359.



Microstructure of human thalamic nucleus (lateral geniculate nucleus) measured by MRI (Oishi et al., 2023).



Center for Research Collaboration

Outline

KUBO, Yoshihiro
Professor
Director

This center named "Center for Collaborative Research" was established in April 2016. It consists of 5 sections of Collaboration Promotion, Advanced Research Support, National Bio-Resource (NBR) Project, Section of Advanced Project Promotion and International Collaborative Research Project.

(1) As a mission of the inter- university research institute, NIPS promotes and conducts collaborative researches. The "Collaboration Promotion" section is in charge of facilitation of joint researches utilizing the facilities of NIPS. It responds to inquiries about available research facilities and laboratories suitable to achieve research aims, and also coordinates the joint research. Thus, it serves as a sort of "concierge" of joint research with NIPS. It also calls for requests of facilities and experimental techniques which researchers wish to have in NIPS. To advertise the collaborative research activity of NIPS, we organized NIPS research meeting(s) in universities outside of NIPS every year after 2016. In FY2023, NIPS will organize one research meeting outside of NIPS.

(2) NIPS, in cooperation with NIBB, engaged in "Supporting Platform for Advanced Bio-Imaging" project supported by JSPS KAKENHI from FY2016 to 2021. From FY2022 to 2027, NIPS, in cooperation with NIBB, will be in charge of the next round of "Supporting Platform for Advanced Bio-Imaging" project supported by JSPS KAKENHI. In this framework, the "Advanced Research Support" section serves to promote support for advanced imaging techniques using optical microscope, electron microscope and fMRI. The 2nd activity of this section is to support "The Next Generation Brain Research" project. It is to organize a symposium of wide-ranged brain science researchers including the ones belonging to MEXT Transformative Research Areas. The 3rd one is to support, as an administration office of the core organization, the activity of "Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)" project, a large-scale national project of the Japan Agency for Medical Research and Development (AMED).

(3) NIPS has been in charge of supply of monkeys for brain science experiments, as a part of National Bio-Resource Project. The "Primate Model Development" section in the "Supportive Center for Brain Research" was moved to the "Center for Collaborative Research" as a new section named "National Bio-Resource (NBR) Project", clarifying the responsible section for the project. In FY 2017, the primary responsible role of NBR Project was transferred from NIPS to the Primate Research Center ((2022 ～) Center for the Evolutionary Origins of Human Behavior) in Kyoto University. NIPS will continue to cooperatively contribute to the activity of NBR Project.

(4) "Section of Advanced Project Promotion" section was newly launched in FY2022, by reorganizing the previous "Visiting Collaborative Research Project" section. In this section, Prof Nabekura, Director-General of NIPS, will serve as P.I. and promote the exploration of cutting-edge research.

(5) The "International Collaborative Research Project" section is a laboratory run by a visiting professor from abroad who stays for a significantly long time in NIPS. The laboratory is run up to for 3 years. From FY2023, Dr. Andrew Moorhouse (University of New South Wales Sydney, Australia) newly joins and will serve as a P.I. for 3 years to promote research on the brain function at the circuit level.

In summary, the "Center for Collaborative Research" plays critical roles in the promotion of various collaborative research activities, including inter-university research, advanced bio-imaging support, supply of monkeys for experiments, and various research collaborations.

▶ Section of Collaboration Promotion

KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

NISHIO, Akiko
Project Assistant Professor
Neurophysiology
Cognitive Neuroscience

National Institute for Physiological Sciences (NIPS) is an inter-university research institute, which organizes some of the latest large experimental equipment and devices that are difficult for other universities or research institutes to purchase, maintain, manage, or operate, such as serial block-face scanning electron microscope (SBF-SEM) , multiphoton excitation microscopes, dual functional magnetic resonance imaging (dual fMRI) , 7-tesla ultra-high magnetic field MRI machines and cryo-electron microscope with the aim of providing facilities and technical support for researchers on a nationwide basis. NIPS also actively develops, produces, and provides high quality viral vectors and gene modified animals for researchers in neuroscience and other research field with technical support, as a center for the production of those resources that are difficult for individual research laboratories to create.

Section of Collaboration Promotion has been organized as a consultation counter to help researchers belonging to other universities or research institutes throughout Japan smoothly launch joint research projects in NIPS. Its aim is to support researchers who maintain passive attitudes toward such projects for various reasons, including unestablished research networks or lack of knowledge about methods to embody their ideas as studies. In addition to these, NIPS also offers research techniques and device utilizations to corporate researchers who aim to develop new technologies or products.

One of the most important purposes of us is to promote liaison between researchers in diverse research fields and NIPS. It comprehensively performs activities to support joint research and enhance its recognition, such as setting up exhibition booths to introduce joint research in NIPS at meetings of related academic societies and NIPS research meetings held outside NIPS.

▶ Section of Advanced Research Support

WAKE, Hiroaki
Professor
Neuroscience
Neurophysiology
Neuroanatomy

TAKADA, Masahiko
Adjunct Professor
Neuroanatomy

MARUYAMA, Megumi
Project Associate Professor
Neurophysiology
Environmental Physiology

AKTER, Nargis
Project Assistant Professor
Neurophysiology

Advanced Bioimaging Support (ABiS)

Section of Advanced Research Support is operating the administrative office of the Advanced Bioimaging Support (ABiS), which is newly launched in 2022 as a project of FY2022-2027 Grant-in-Aid for Transformative Research Areas — Platforms for Advanced Technologies and Research Resources.

ABiS is a framework for supporting cutting-edge imaging techniques (observation of samples and data analysis) using various types of microscopy and MRI, where the National Institute for Physiological Sciences (NIPS) and the National Institute for Basic Biology (NIBB) work as the core organizations. Through the collaborative research that these institutes promote, ABiS is forming a network with domestic partner organizations to provide custom-made support for bioimaging techniques.

In succession with the community unity fostered in the previous program conducted between FY2016-2021, ABiS will support the promotion of life science research in Japan by providing innovative imaging technologies.

JISEDAI-NOU Project

Section of Advanced Research Support has also operated the administrative office of the JISEDAI-NOU Project since FY2016. This project, which is led by members of the brain science–related Grant-in-Aid for Scientific Research on Innovative Areas and Transformative Research Areas (A), promotes efforts that support the brain science community, including planning symposia with a focus on cultivating young researchers, disseminating related information via a mailing list, and operating a website. It will contribute to the promotion of brain research by taking advantage of the established community that developed over the course of the Comprehensive Brain Science Network project (FY2010–2015, Grant-in-Aid for Scientific Research on Innovative Areas).

Brain/MINDS Beyond

From November 2018, the National Institute for Physiological Sciences (NIPS) has been adopted as the core organization of the newly launched AMED program, the Strategic International Brain Science Research Promotion Program (Brain/MINDS Beyond). This program aims at contributing to the flight of the brain research globally by enhancing collaboration with the domestic projects of other countries across the world. This office, serving as the core organization and operation secretariat, coordinates the domestic efforts for the international promotion of brain science research. It also works in close coordination with other programs by the AMED, the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS).

ISODA, Masaki
Professor
Neurophysiology

NAMBU, Atsushi
(Emeritus Professor)
Project Research Staff
Neurophysiology

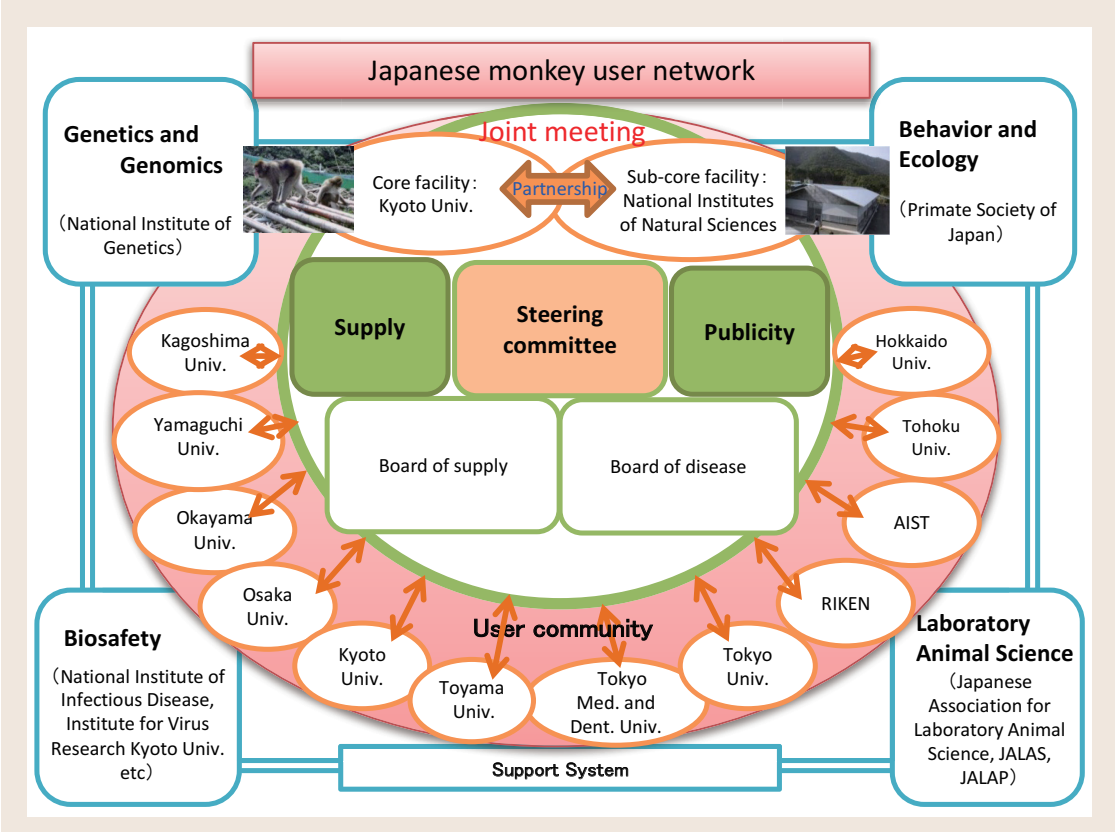
The promotion of National Bio-Resource Project "Japanese monkey"
The improvement of monkey quality

This laboratory has been organized since 2002 for acceleration of National Bio-Resource Project (NBRP) “Japanese monkey”. National Institute for Physiological Sciences (sub-core facility) and Kyoto University (core facility) together keep promoting the project.

NBRP “Japanese monkey” was established as a stable breeding of and supply system for Japanese macaques for laboratory use. We have performed the projects with emphasis on the followings: (1) establishment of the breeding system, (2) provision of monkeys for researchers in Japan, (3) collection of data characteristic of the Japanese macaque, and (4) integrative administration of NBRP "Japanese monkey".

The Japanese macaques have high cognitive abilities and hand dexterity. Therefore, this animal species has been used for research into higher brain functions and various neurological diseases. We have administered this resource project while coordinating with researchers. We have collected data about Japanese macaques for the improvement of monkey quality.

＊ 中村克樹，他，ナショナルバイオリソースプロジェクト「ニホンザル」の現状と課題 . 霊長類研究 33 巻 (2017)
＊ T. Isa et al., Japanese Macaques as laboratory Animals. Exp. Anim. 58 (5), 451-457 (2009)



▶ Section of Advanced Project Promotion

NABEKURA, Junichi
Director General
Neuroscience

The aim of this research unit is to intensively explore new research areas and develop advanced research technologies under the leadership of the director-general. It has been established according to the opinion of the National Institute for Physiological Sciences Steering Committee in 2022.

▶ Section of International Collaborative Research Project

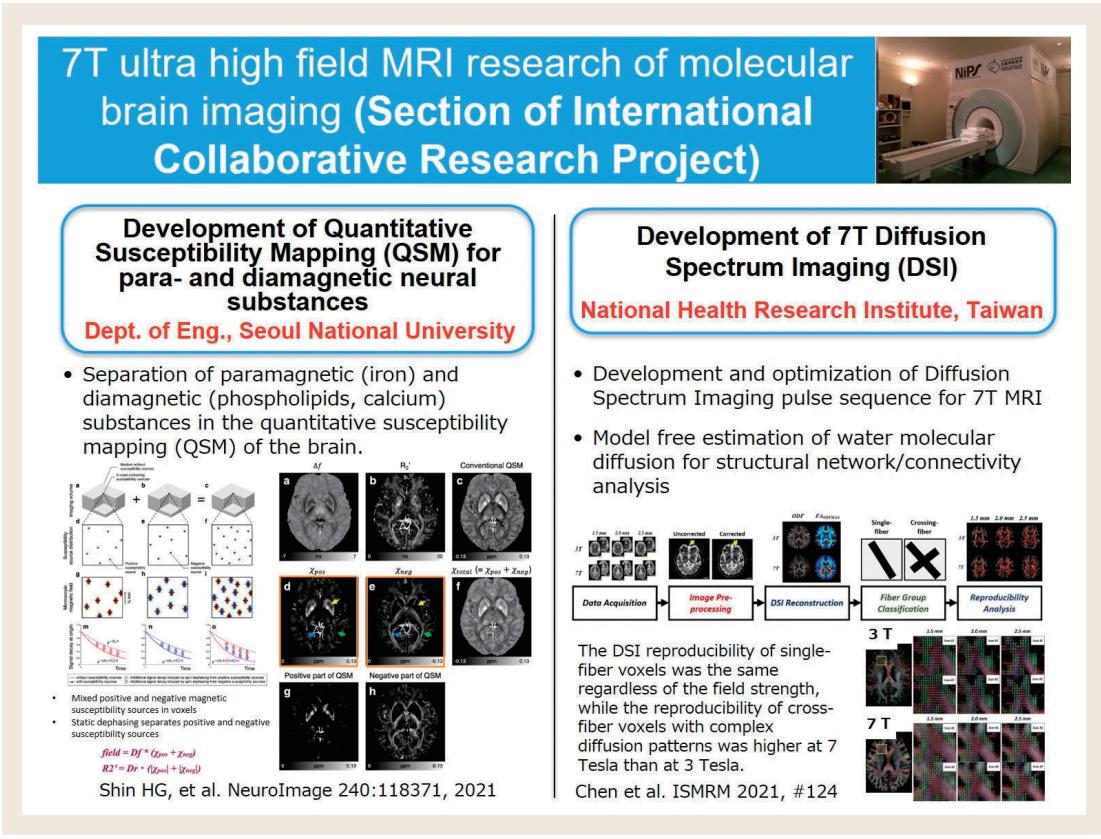
MOORHOUSE, Andrew
Visiting Professor
Neuroscience

WAKE, Hiroaki
Professor
Neuroscience
Neurophysiology
Neuroanatomy

Introduction of the Section of International Collaborative Research Project

In FY2014, NIPS established the Section of International Collaborative Research Project. In FY2017, NIPS invited Dr. Denis Le Bihan to join as a Principal Investigator (P.I.) of the section. He is a leading authority on Magnetic Resonance Imaging (MRI) and is well-known as an inventor of the revolutionary imaging method called diffusion-weighted imaging. Dr. Le Bihan was also a founding director of NeuroSpin, which belongs to the Life Science Bureau, a basic research division of France's Commissariat à l'énergie atomique et aux énergies alternatives (CEA). The institute conducts brain research using MRI at a very high level of technological sophistication and is also leading the development of the world's highest-performance MRI instrument, the Human-oriented 11.7 Tesla Device. Dr. Le Bihan served as P.I. of the Section of International Collaborative Research Project in NIPS for 6 years till FY2022, and engaged in research on the development of imaging technology using 7Tesla-MRI and its application to brain science, in collaboration with the Division of Cerebral Integration in NIPS (Professor Norihiro Sadato). Two international projects with Seoul National University (South Korea) and National Health Research Institutes (Taipei) were also performed (Fig. 1).

From FY2023, NIPS newly invites Dr. Andrew Moorhouse (University of New South Wales Sydney, Australia) as an adjunct foreign professor. Dr. Moorhouse serves as P.I. of this section and promote research on the brain function based on the circuit, in collaboration with Division of Multicellular Circuit Dynamics (Professor Hiroaki Wake).



Supportive Center for Brain Research

ISODA, Masaki
Professor
Director

Outline

The Center for Brain Experiment was reorganized into the Supportive Center for Brain Research in April 2008 to expand its role of supporting brain science research at the NIPS. The new center was initially comprised of six sections: Sections of Brain Structure Information, Brain Function Information, Multiphoton Neuroimaging, Electron Microscopy, Instrument Design, and Ine Marine Laboratory. In 2010, the Ine Marine Laboratory completed its mission and was closed. In 2012, two sections - the Section of Viral Vector Development and the Section of Primate Model Development - were newly opened. The mission of the former was to develop and distribute viral vectors, and the mission of the latter was to breed and supply Japanese macaques, both to researchers for brain research purposes. In April 2016, the Section of Viral Vector Development was relocated to the Center for Genetic Analysis of Behavior. At the same time, the name of the Section of Primate Model Development was changed to the NBR Project and relocated to the Center for Research Collaboration. In April 2021, the Section of Cellular Electrophysiology was created.

Brain science is one of the hottest research fields worldwide, of course including Japan, and recent progress in this field is amazing and surprisingly rapid. The NIPS is now widely recognized as an important hub for brain science research in Japan, and most NIPS researchers are engaged in some way in the relevant field. The mission of the Supportive Center for Brain Research is not only to support intramural studies at the NIPS, but also to play a role in promoting fruitful collaborations in the neuroscience community both in Japan and abroad through joint researches.

▶ Section of Multiphoton Neuroimaging

MURAKOSHI, Hideji
Associate Professor
Biophysics
Neuroscience

Imaging activation of signaling molecules in living cells by 2-photon fluorescence lifetime imaging microscopy

Our state of the art two-photon fluorescence lifetime imaging microscopes allows us to image protein activity and protein-protein interaction in living cells in deep tissue such as brain slice and brain of living mouse. We accept the collaborative research using the fluorescence lifetime imaging microscope for imaging the activity and interaction of various signaling proteins. We also accept students to pursue the PhD degree, especially, the students who are interested in molecular imaging.

In addition to the cutting-edge microscope techniques, we try to develop novel fluorescent proteins and light-controllable signaling proteins. By far, we succeeded in visualizing the activities of signaling proteins in dendritic spine of hippocampal neuron by using two-photon microscopy by combining the photo-activatable probes, new fluorescent proteins, electrophysiology. These techniques will enable us to reveal the system of neural networks and underlying molecular mechanisms in a living mouse neuron.

Our mission is to reveal "missing-links" underlying between molecular functions and physiological functions in a living body. We believe that the development & application of optical imaging methods will reveal the biological system at the cellular level.

* Ueda et al. Cell Reports 2022
* Shibata et al. Nature Communications 2021
* Saneyoshi et al. Neuron 2019
* Chen Xi et al. eLife 2018
* Murakoshi et al. Neuron 2017
* Hedrick et al. Nature 2016
* Murakoshi et al. Nature 2011

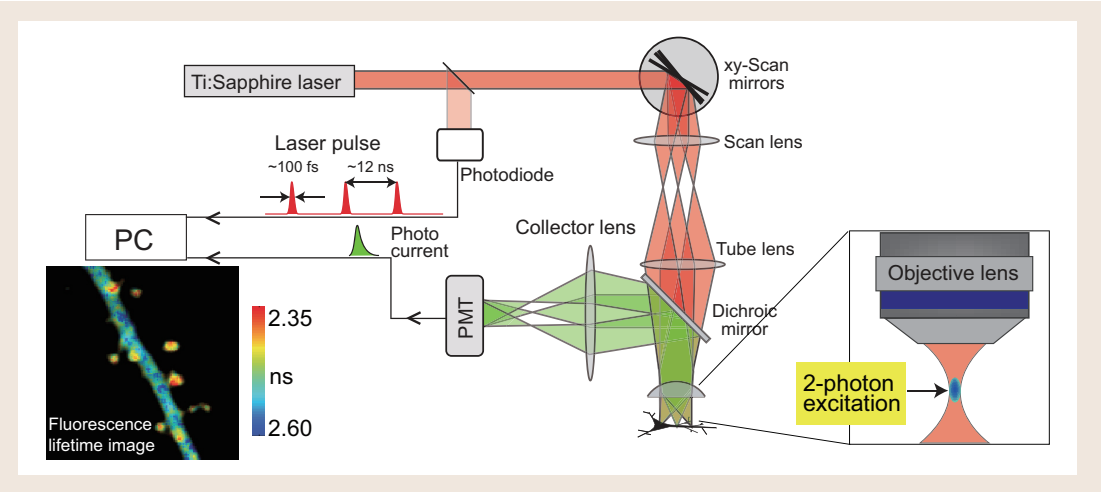


Figure 1. Two-photon excitation is the phenomenon that two photons of half energy than needed for one photon excitation can excite a fluorescent molecule. The advantages of 2-photon excitation are 1) Because infrared light is used for excitation, it minimizes excitation-light scattering in the tissue 2) Because 2-photon excitation happens only at the focal point of an objective lens, the background signal is strongly suppressed. These effects enable us to image cells and subcellular structures in deep tissue with high spatial resolution. Recently, the combination of 2-photon excitation and fluorescence lifetime imaging method enabled us to image the protein-protein interaction or structural change of protein in deep tissue such as brain slice. The fluorescence lifetime is measured by counting the arrival time of signal photon at the detector upon a laser pulse. After making histogram of lifetimes at each pixel by repeating this measurement, the pixel-by-pixel lifetime image is constructed in a pseudocolor format.

▶ Section of Electron Microscopy

FURUSE, Mikio
Professor
Cell Biology

MURATA, Kazuyoshi
Project Professor
Structural biology
Electron Microscopy

KUBOTA, Yoshiyuki
Associate Professor
Neuroanatomy
Neuroscience

ISHIHARA, Yoshihisa
Project Assistant Professor
(Grant Project)
Neuroanatomy
Neuroscience

Support for electron microscopy

Ultrastructures of tissues, cells and macromolecules are observed using transmission or scanning electron microscopes (JEOL JEM1010, Hitachi HT-7700, Zeiss Σ IGMA). The facility also provides instruments for their specimen preparations, i.e. ultra-microtome (Leica UC7), high-pressure freezing device (BAL-TEC HPM010), and freeze fracture and replica machine (BAL-TEC BAF060), vacuum evaporator (JEOL JEE-400), etc. For digital image analysis, image processing software and volume rendering software (FEI Amira) are available. Serial block-face SEMs (Gatan 3view/Zeiss Σ IGMA/VP & MARLIN; Fig. 1) and Array tomography SEM system (Zeiss ATLAS5) have opened since 2013 (Fig. 1), which reveal 3D structures of biological thick specimens. The SBF-SEMs, especially, are used for many collaborative projects.

Functional architecture of cortical microcircuit

How the cerebral cortex processes complex information is still unknown. Our laboratory is elucidating the fundamental rules that govern cortical microcircuits, such as cell diversity and functional connectivity, using modern physiological, anatomical and molecular methods. We focus on the primary and secondary motor cortices and use a wide variety of experimental techniques such as in vivo imaging, immunohistochemistry, correlated light and electron microscopy, and a large-volume electron micrographic data analysis. We are also interested in learning and memory and associated rewiring in cortical microcircuits. We analyze neocortical local circuits and brain system circuits to understand the functional role of each neuron type and layered structure in cortex, and various functions of projections from the motor cortex to the sensory cortex, hippocampus, thalamus, basal ganglia, cerebellum.

* Kubota et al. Nature Communications, 9: 437 (2018)
* Sohn et al. Science Advances, 8 (39):eabm0531 (2022)

Fig. 1 Serial block-face SEM (SBF-SEM) Gatan 3view - Zeiss S Σ IGMA/VP

Fig. 2 Transmission electron microscope (TEM) JEOL JEM1010 equipped with 2kx2k CCD camera

▶ Section of Brain Function Information

FUKUNAGA, Masaki
Project Professor
Magnetic Resonance
Neuroimaging
Neuroscience

SADATO, Norihiro
Professor
Functional Neuroimaging
Neuroscience

INUI, Koji
Adjunct Professor
Neurophysiology
Psychiatry

YAMAJI, Kazutsuna
Adjunct Professor
Information Science

GODA, Naokazu
Assistant Professor
Neuroscience
Neuroimaging
Psychophysics

YAMAMOTO, Tetuya
Project Assistant Professor
(Grant Project)
Neuroimaging
Visual Neuroscience
Visual Psychology

Studies on the structure-function relationship of the brain using noninvasive neuroimaging techniques

The Section of Brain Function Information aims to support collaborative studies using high-field magnetic resonance imaging (3T and 7T) and promote research on the structure-function relationship of the human and nonhuman primate brains. We actively promote collaborative studies ranging from basic research and development of MRI to clinical applications as well as studies on establishing standards for MRI procedures, including safety, applications, and quantitative imaging analyses. We are also developing an algorithm to quantitatively and statistically handle brain image data generated by MRI. In addition to collaborative research, training junior researchers in MRI applications and basic neuroscience research is promoted.

* Schijven D, Postema MC, Fukunaga M et al. Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium. Proc Natl Acad Sci U S A. 120:e2213880120 (2023)
* Nakamura NH, Fukunaga M, Yamamoto T et al., Respiration-timing-dependent changes in activation of neural substrates during cognitive processes. Cereb Cortex Commun 3:tgac038 (2022)
* Goda N, Hasegawa T, Koketsu D et al., Cerebro-cerebellar interactions in nonhuman primates examined by optogenetic functional magnetic resonance imaging. Cereb Cortex Commun 3:tgac022 (2022)
* Maruyama S, Fukunaga M, Sugawara SK et al., Cognitive control affects motor learning through local variations in GABA within the primary motor cortex. Sci Rep 11:18566 (2021)
* Yamamoto T, Fukunaga M, Sugawara SK et al., Quantitative evaluations of geometrical distortion corrections in cortical surface‐based analysis of high‐resolution functional mri data at 7T. J Magn Reson Imaging. 53:1220 (2021)
* Fukunaga M, Li TQ, van Gelderen P et al., Layer-specific variation of iron content in cerebral cortex as a source of MRI contrast. Proc Natl Acad Sci U S A. 107:3834 (2010)

▶ Section of Cellular Electrophysiology

YOSHIMURA, Yumiko
Professor
Neurophysiology

SATAKE, Shin'Ichiro
Assistant Professor
Neurophysiology

OTSUKA, Takeshi
Assistant Professor
Neuroscience

Advancing Research Collaboration by Supporting Electrophysiological Studies

Electrophysiological techniques are useful for studying the activity of cells, tissues, and organs (such as the brain and heart) with a high temporal resolution. This section aims to promote a better understanding of the cellular and molecular mechanisms underlying body and brain functions by collaborating with other research groups and supporting their electrophysiological studies. Ongoing projects are listed below.

1) Neural information processing at the tripartite synapse

Tripartite (three-part) synapses are characterized by physical connections and functional interactions between pre- and postsynaptic neurons and the surrounding glial processes. We focus on the role of neurotransmitter transporters in the integration of neuronal information at the tripartite synapse. We also analyze genetically engineered animals to understand the pathophysiology of neurological disorders, including rapid-onset dystonia with parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and CAPOS syndrome. In addition to classical techniques such as electrophysiology, immunohistochemistry, and pharmacology, our laboratory has recently introduced photo-releasable caged compounds.

2) Regulation of neural network activity

Neurons form complex networks between them and send information to multiple brain areas. We are investigating how neural network activity related motor function is regulated in the cortex and the basal ganglia system (Fig. 1). We approach these questions using electrophysiology, computer simulation, and behavior analysis. We also analyze how neurotransmitters including dopamine regulate intrinsic membrane properties of cells and reward related behaviors as a research collaboration.

* T. Otsuka, Y. Kawaguchi, *Commun. Biol.* 4, 495 (2021).
* S. Satake, S. Konishi, *Eur. J. Neurosci.* 54, 7048-7062 (2021).
* S. Satake, T. Inoue, K. Imoto, *Cerebellum* 15, 201-207 (2016).
* T. Otsuka, Y. Kawaguchi, *J. Neurpophysiol.* 110, 795-806 (2013).

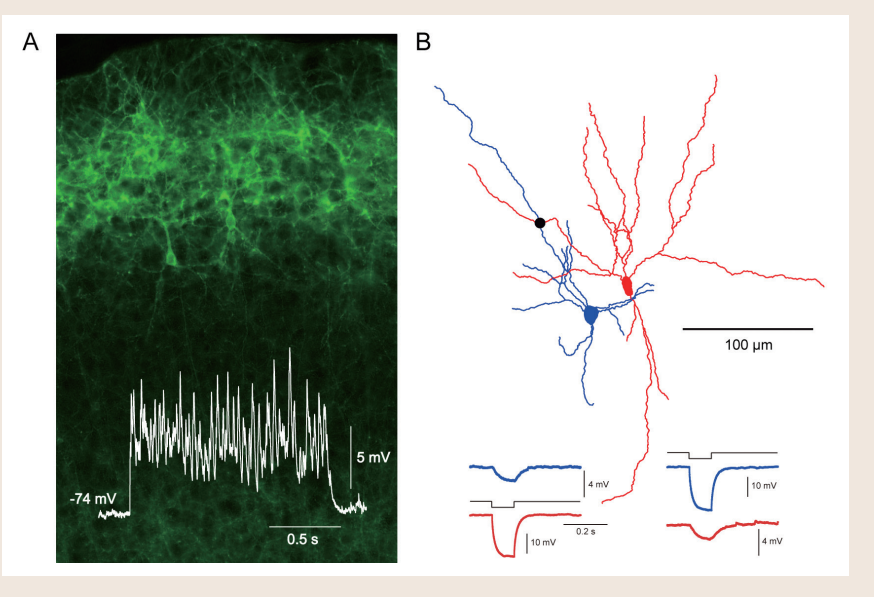


Fig. 1. (A) Network activity evoked by optogenetic stimulation. ChR2-Venus was selectively expressed in cortical L2/3 pyramidal cells. During light stimulation, membrane potential oscillation was induced in L5 pyramidal cell. (B) Reconstraction of cortical FS interneurons. Electrically connected FS cells, confirmed by negative current injection to one of two cells, were simultaneously recorded. ● indicates electrical connection site.

Center for Genetic Analysis of Behavior

TOMINAGA, Makoto
Professor
Director

Outline

Center for Genetic Analysis of Behavior produces gene-modified rat/mouse using TALEN and CRISPER/Cas9, etc. The center also provides virus vectors for cell type-specific gene modification. The center has facilities to monitor behavior, neuronal activity and metabolism in those gene-modified rat/mouse, which are open for the collaboratory use from researchers of all over the world.

This center consists of the following 3 sections.

- Section of Viral Vector Development
- Section of Mammalian Transgenesis
- Section of Multilayer Physiology

▶ Section of Viral Vector Development

KOBAYASHI, Kenta
Associate Professor
Molecular Neurobiology

Collaboration by providing viral vectors
Functional analysis of specific neural pathways by using viral vectors
Development of the viral vector system useful for analysis of brain functions

A viral vector, which is available to various animal models, is an excellent genetic tool, and at present, it becomes one of most important experimental technologies to analyze brain functions. We set up a system to produce a large amount of high quality viral vectors, AAV and lentiviral vectors. In response to requests, we provide these viral vectors and promote the collaboration.

Brain functions are controlled by complex neural circuits. To understand brain functions, it is necessary to clarify the function of specific neural pathways forming complex circuits. We have succeeded in developing the novel gene transfer system, a dual viral vector system using highly efficient retrograde gene transfer viral vectors, enabling the functional analysis of specific neural pathways (Fig. 1). By using this system, we analyze the function of specific neural pathways forming the cortico-basal ganglia loop. In addition, we have succeeded in developing a novel retrograde gene transfer system based on the AAV vector.

* H. Sano et al., J. Neurosci. Methods. 345, 108887 (2020)
* K. Kobayashi et al., J. Neural. Transm. (Vienna). 125, 67 (2018)
* K. Kobayashi et al., Front. Neuroanat. 11, 65 (2017)
* K. Kobayashi et al., Neurosci. Lett. 630, 45 (2016)
* K. Kobayashi et al., Methods. Mol. Biol. 1382, 175 (2016)

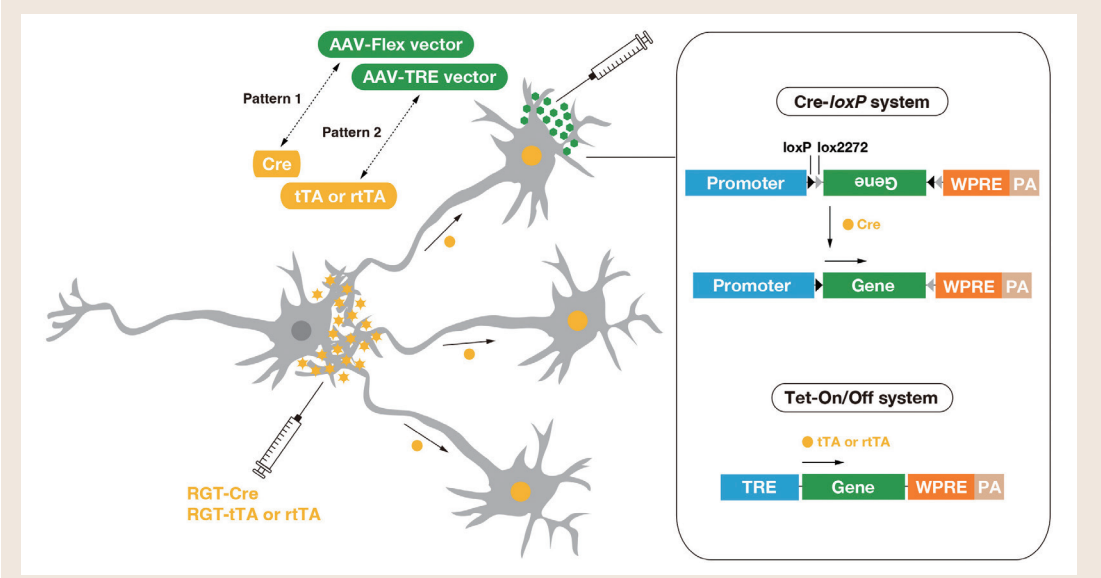


Figure 1. Gene transfer into specific neural pathways using viral vectors. Conditional gene expression in specific neural pathways becomes possible by using a dual viral vector system combining retrograde gene transfer (RGT) viral vectors and AAV vectors. These useful viral vectors are available to collaborators.

▶ Section of Mammalian Transgenesis

HIRABAYASHI, Masumi
Associate Professor
Laboratory Animal Science

KOBAYASHI, Toshihiro
Associate Professor
Stem Cell Biology
Embryology

Development of Advanced Reproductive / Transgenic Technologies in Laboratory Animals

Genetically modified animals such as transgenic and knockout animals are essential tools for current life science research. In particular, recent progress on gene editing technologies including CRISPR/Cas9 system has enabled us to generate desired such animals more efficiently and rapidly. Our facility, Section of Mammalian Transgenesis, routinely generates a variety of genetically modified mice and rats according to requests from internal and external laboratories. In addition, we have developed novel reproductive and developmental technologies using early rodent embryos and the stem cells. One of our current projects is an application of our techniques to regenerative medicine. Recently, as a collaborative research, we have established "blastocyst complementation" method which can create a specific organ from pluripotent stem cells in organ-deficient animals. Through developing new technologies and generating model animals in various mammalian species, we aim to understand the underlying mechanisms on stem cell self-renewal/differentiation, early embryo development and organogenesis, which would contribute to future regenerative medicine as well as life science research.

∗ M. Oikawa *et al*., Science 376, 176 (2022).
∗ M. Oikawa *et al*., Mol Reprod Dev. 89, 129 (2022).
∗ T. Kobayashi *et al*., Cell Rep. 37, 109812 (2021).
∗ T. Kobayashi *et al*., Nat Commun. 12, 1328 (2021).
∗ T. Kobayashi *et al*., Development 147, e183798 (2020).

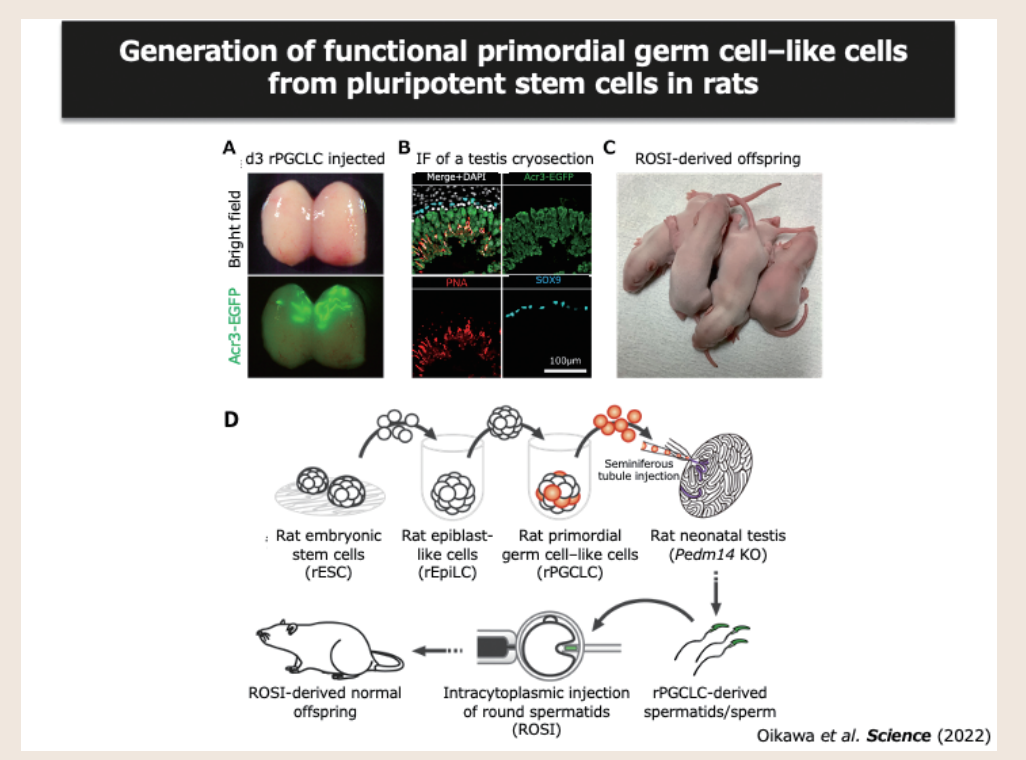


Fig 1. Functional validation of rPGCLCs. A) *Prdm14* KO rat testis at 10 weeks after transplantation of day 3 male N3T/AG-rPGCLCs, visualized by bright-field (top) and fluorescence imaging (bottom). B) Immunofluorescence (IF) of a cryosection showing testis 10 weeks after transplantation of N3T/AG-rPGCLCs. C) Offspring from rPGCLC-derived spermatids generated by ROSI. D) Scheme of generation of functional primordial germ cell–like cells from pluripotent stem cells in rats.

▶ Section of Multilayer Physiology

NISHIJIMA, Kazutoshi
Professor
Laboratory Animal Science
Reproductive Technology
Metabolism

CHIKEN, Satomi
Assistant Professor
Neurophysiology
Neurobiology

HATANAKA, Nobuhiko
Assistant Professor
Neurophysiology
Neuroanatomy

In vivo analysis of neuronal, metabolic activity and behavioral pattern in mice and rats

This section analyzes the *in vivo* neuronal and metabolic activity, and behavioral patterns in mice and rats which have been modified by their related genes and by exposure to various environmental conditions.

This section performs the following examinations:

- Single unit recording from motor related brain regions in an awake state（Figure 1）.
- Regional neural activity detected as intrinsic signals with taking the advantage of light fluorescent dynamics of flavin or hemoglobin.
- Energy intake and expenditure in free-moving animals.
- Body temperature, heart rate and blood pressure in free-moving animals.
- Measurement of non-invasive echo-graphic imaging of tissue structure-function relationships (liver, kidney and blood vessels), 4-dimensional changes in cardiac functions, and capillary blood flow (brain and umbilical cord) using anesthetized mice.
- Mouse temperature preference assay with thermal gradient ring.
- Behavioral analysis for the evaluation of emotion, learning and memory: Open field, Light-dark transition, Elevated plus maze, Forced swimming, Rota-rod, Passive avoidance, Fear conditioning, Morris water maze, Barnes maze, Y maze, 3-chamber social interaction, etc. (Figure 2).

* Hasegawa et al. Nat Commun 13: 2233 (2022)
* Chiken et al. Cereb Cortex 31: 5363-5380 (2021)
* Dwi Wahyu I et al. J Neurosci 41: 2668-2683 (2021)
* Polyakova et al. J Neurosci 40: 7451-7463 (2020)
* Watanabe et al. Nat Commun 11: 3253 (2020)

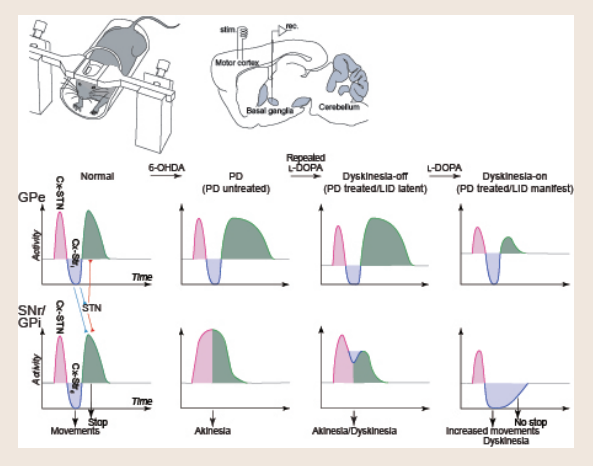


Figure 1. To elucidate pathophysiology of L-DOPA-induced dyskinesia, neuronal activity of basal ganglia neurons in response to electrical stimulation of the motor cortex was analyzed.

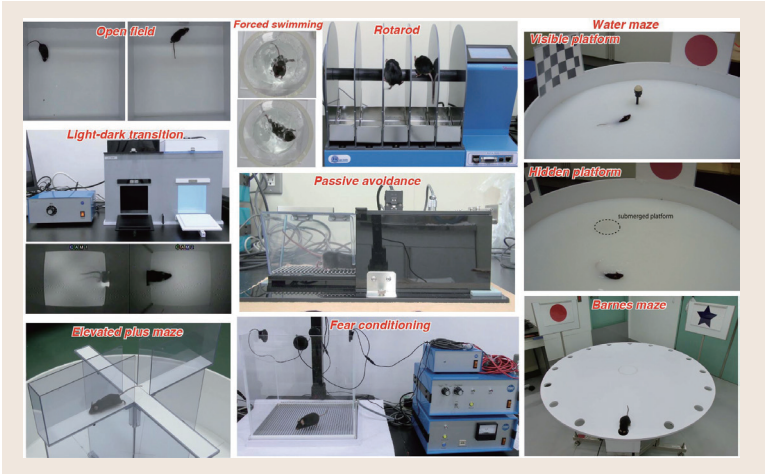


Figure 2. We perform a number of behavioral analyses in mice to explore physiological functions of specific genes and molecules.

Center for Communication Networks

KITAJO, Keiichi
Professor
Director

Outline

The center provides information of NIPS programs and activities to the public, scientific community, medical profession, and media through WEB, publication, conferences and symposium. Science education activities and Institutional review processes are also coordinated. The center maintains infrastructures of LAN as well as WEB-based services.

▶ Section of Research Archives

The Institute has made the self-evaluation and peer review every year since 1993. In addition, the Institute started editing a volume of annual plans and annual reports every year since 2004. The section was opened in 2007 to perform more efficient evaluation processes. For efficient accumulation of historical events in the institute, this section also takes care of archiving the documents that describe the activities of the Institute. The section was reorganized to be responsible for collecting and archiving various kinds of documents in 2016. The collection includes the database of documents related to the foundation of the Institute, which was completed owing to the great contribution of the late Professor Emeritus Shunichi Yamagishi. It also includes the text version of "Oral History" stated by the late Professor Yamagishi. At the 100th annual meeting of the physiological Society of Japan in 2022, the history of MIPS was introduced, and its materials were provided.

▶ Section of Physiology and Medicine Education

'step-by-step studies of brain science'

TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

An e-Learning subject 'step-by-step studies of brain science' is provided especially to the students who learn neuroscience for the first time. Students take the e-Learning-based exams in the end of each semester. Upon taking 'step-by-step studies of brain science', students are supposed to learn basic brain science completely.

▶ Section of Network Management

Computer services and network supports are now indispensable for research activity. In this section, we manage the "Computer System for Data Analysis in Physiology", which is a software sharing system for Numeric Computation, data analysis, visualization, mathematics, statistics and electronic design. We support high-speed and reliable network for intra-/internet services such as E-mail communication, Web services, and peripheral devices for in-house information network. Technological developments for the best use of these facilities are also underway (Fig. 1)

Ensuring information security is also an important part of our work. We have revised our information security policy in line with our research and are making efforts to maintain the security level by raising awareness among users. In addition, we also cooperate with CSIRT to prevent security incidents, take countermeasures, monitor them, and respond to them when and after they occur.

Fig.1. Computer System for Data Analysis in Physiology & Network Servers

Section of Health and Safety Management

TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

Outline

NIPS is sincerely trying to promote the security and health of researchers and workers, particularly considering the environments of laboratories and offices. Recently, NIPS has had to focus on resolving some serious problems, for example, storing several drugs such as narcotics properly, and safely maintaining several machines such as those using lasers. To avoid accidents caused by such drugs and machines, NIPS is conducting a regular annual medical examination for all researchers and workers. Considering how important this problem is, the Section of Health and Safety Management was founded in 2011 under the direct management of the Director-General. This section is mainly conducting the following four activities:

1. Work to prevent accidents and health problems of workers at NIPS.
2. Education related to safety and hygiene for workers.
3. Regular medical examinations.
4. Investigation of problems causing labor accidents in order to prevent them.

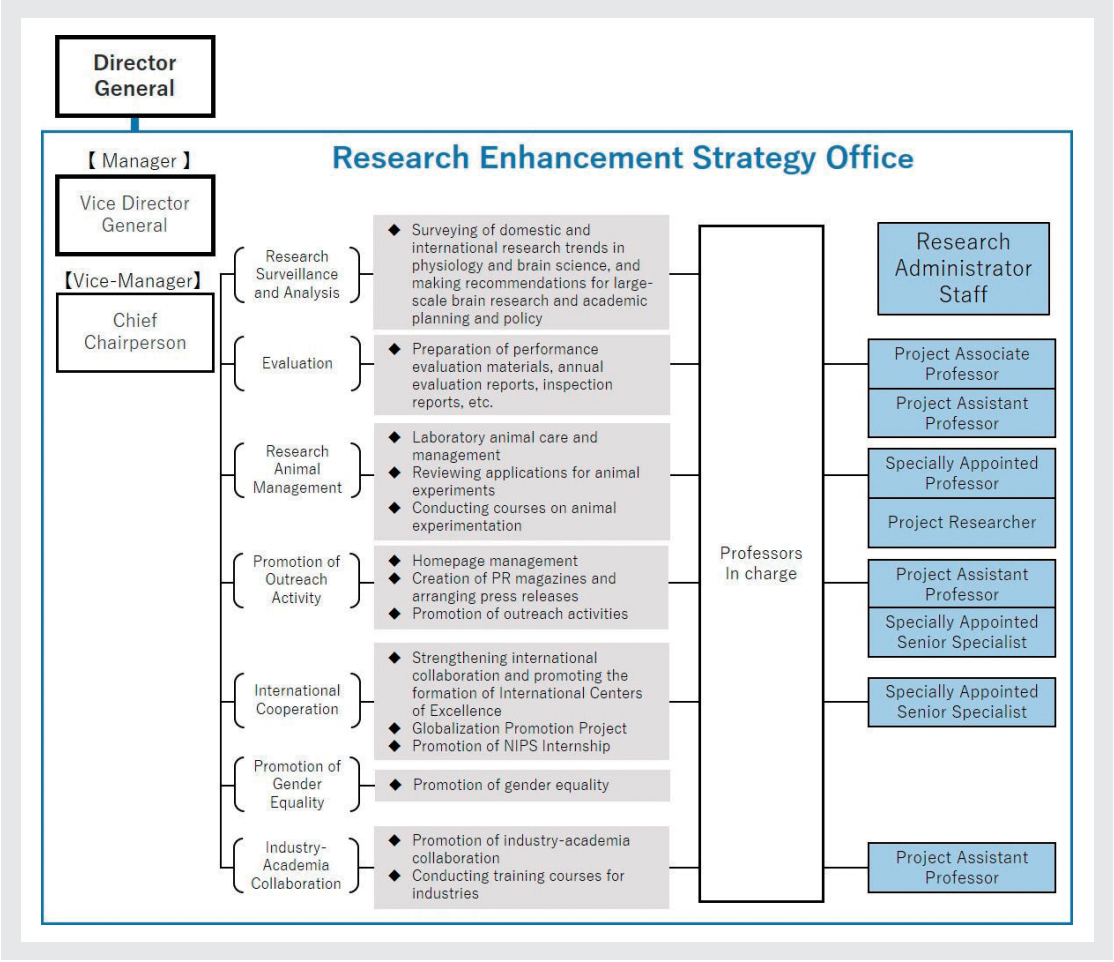
Monthly meetings are held to smoothly conduct the regulatory procedures. In addition, this section has been involved in the activities for infection prevention of corona virus from 2020.

Research Enhancement Strategy Office

Research Enhancement Promotion Project

National Institutes of Natural Sciences (NINS) has been selected as one of 20 Universities and 3 Inter-University Research Institutes in the Program for Promoting the Enhancements of Research Universities funded by Monbukagakushou (MEXT), which started from September 2013. Research Enhancement Promotion Headquarters and Research Enhancement Strategy Office of this program have been settled at NINS and each 5 Research Institutes, including NIPS, respectively. At NIPS, Research Enhancement Strategy Office (manager: Vice Director General of NIPS) has been composed of by 7 units, 1) Research Surveillance and Analysis, 2) Evaluation, 3) Research Animal Management, 4) Promotion of Outreach Activity, 5)International Cooperation, 6) Promotion of Gender Equality, and 7) Industry-Academia Collaboration. Specially Appointed Professor, Project Associate and Assistant Professors are assigned to Research Surveillance and Analysis Unit, Evaluation Unit, Research Animal Management Unit, Promotion of Outreach Activity Unit and Industry-Academia Collaboration Unit. Each unit promotes its activity to facilitate own research and research collaboration to achieve NIPS mission.

The Program for Promoting the Enhancements of Research Universities funded by MEXT was over by the end of FY2022. From FY2023, NIPS needs to cover the expenses to employ URA staffs by the internal budget. Although NIPS is in a difficult financial condition, NIPS plans to maintain employment of URA staffs which is indispensable for the promotion of the enhancement of research activities.



KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

ISODA, Masaki
Professor
Neurophysiology

NISHIJIMA, Kazutoshi
Professor
Laboratory Animal Science
Reproductive Technology
Metabolism

YOSHIMURA, Yumiko
Professor
Neurophysiology

KITAJO, Keiichi
Professor
Computational Neuroscience
Cognitive Neuroscience

URANO, Toru
Specially Appointed Professor
Laboratory Animal Science
Bacterial Infectious Disease

MARUYAMA, Megumi
Project Associate Professor
Neurophysiology
Environmental Physiology

NISHIO, Akiko
Project Assistant Professor
Neurophysiology
Cognitive Neuroscience

AKTER, Nargis
Project Assistant Professor
Neurophysiology

HONDA, Yukiko
Project Assistant Professor
Neurophysiology

Technical Division

Outline

The Technical Division is an organization of technical staffs to support research activities in National Institute for Physiological Sciences（NIPS）. This organization is under the direction of the Director-General of NIPS. It is organized in a management system with Head, Assistant Head, Section Chief, Unit Chief, Assistant Unit Chief and Staff.

The division is composed of the technicians, who are covering a wide diversity of fields, such as electric circuitry, mechanical machine tooling, computing, gene engineering, biochemical analysis, cell culture, microscope, raising and reproduction of gene-implanted animals and so on.

The division is divided into two sections, one is for Departments and the other is for Research Centers. The personnel belonging to the Departments support mainly the researchers in the Departments. Those belonging to the Research Center or Laboratory are maintaining and controlling common research equipment for use in joint research projects by scientists of inside and outside of the institute.

In addition to these technical supports, the division is conducting common operations（maintenance and control of equipment, machinery and other installations, and management of research meeting and supply shops）.

Beside the division conducts self-study activities by organizing technical research meeting and by publishing technical reports, in order to improve the technical abilities of individual members. A technical committee is organized to allow the institute to obtain new technologies vital to the research and to dissolve technically challenging subjects.

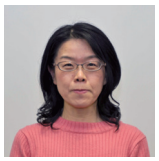
Every year, "Operation Report Meeting" is held to promote the mutual understandings of technical operations and to exchange general information in the division.

The Annual Meeting of Technical Research is held for the purpose of exchanging technological information among technicians working in all universities and research institutes in the country. In the meeting, discussions are made through oral presentations, panel exhibitions and lectures with technical practice.

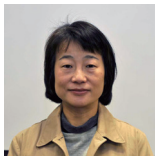
These study activities and technical research meetings conducted at the division are summarized and published in "Annual Report of Technical Division" and in "Annual Report of Technical Research Meeting."

Head :
YOSHIMURA, Nobuaki
Section Chief :
(Concurrent Post)
Research Centers Technical Section

Assistant Head :
TOGAWA, Morio
Departments Technical Section



Unit Chief :
YAMAMOTO, Tomomi
Molecular & Cellular Physiology Technical Unit



Unit Chief :
FUKUTA, Naomi
Homeostatic Regulation Technical Unit

Unit Chief :
TAKAGI, Masahiro
Fundamental Neuroscience Technical Unit

Unit Chief :
SATO, Shigeki
System Neuroscience Technical Unit

Unit Chief :
YOSHITOMO, Miki
Center for Research Collaboration Technical Unit

Unit Chief :
ISHIHARA, Hiromi
Supportive Center for Brain Research Technical Unit Ⅰ

Unit Chief :
TAKAHASHI, Naoki
Supportive Center for Brain Research Technical Unit Ⅱ

Unit Chief :
SANBO, Makoto
Center for Genetic Analysis of Behavior Technical Unit

Unit Chief :
MURATA, Yasuhisa
Center for Communication Networks Technical Unit

Unit Chief :
HIROE, Takeshi
Center for Experimental Animals Technical Unit

Unit Chief :
MORI, Masahiro
Research Infrastructure Technical Unit

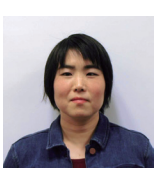
Assistant Unit Chief :
HIRAYAMA, Yuya
Homeostatic Regulation Technical Unit

Assistant Unit Chief :
YOKOI, Isao
System Neuroscience Technical Unit

Assistant Unit Chief :
KAMIYA, Emi
Center for Experimental Animals Technical Unit

Assistant Unit Chief :
KUBOTA, Mitsuko
Center for Experimental Animals Technical Unit

Assistant Unit Chief :
TAKAHASHI, Nobuaki
Center for Experimental Animals Technical Unit

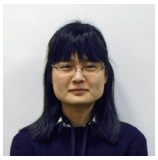


Assistant Unit Chief :
YAMANAKA, Midori
Center for Experimental Animals Technical Unit

Staff :
INAHASHI, Hiroki
Molecular & Cellular Physiology Technical Unit

Staff :
KANO, Yuichiro
Homeostatic Regulation Technical Unit

Staff :
WATAKABE, Yuki
Fundamental Neuroscience Technical Unit



Staff :
INAGAKI, Mariko
Center for Communication Networks Technical Unit

Exploratory Research Center on Life and Living Systems

Okazaki Institute for Integrative Bioscience ended in FY 2017.

A new research center "Exploratory Research Center on Life and Living Systems (ExCELLS)" was launched in FY 2018.

ExCELLS consists of 23 research groups, and the following 5 research groups also belong to the National Institute for Physiological Sciences.

- Thermal Biology Group　Division of Cell Signaling (See P. 14)
- Cardiocirculatory Dynamism Research Group　Division of Cardiocirculatory Signaling (See P. 15)
- Biophotonics Research Group　Division of Biophotonics (See P. 21)
- Material-Life Boundary Research Group　Division of Structural Biology (See P. 11)
- Cognitive Genomics Research Group

Center for Animal Resources and Collaborative Study

NISHIJIMA, Kazutoshi
Professor (Director)
Laboratory Animal Science
Reproductive Technology
Metabolism

URANO, Toru
Specially Appointed Professor
Laboratory Animal Science
Bacterial Infectious Disease

The Center for Animal Resources and Collaborative Study is one of the top-class experimental animal centers in Japan. The center was reorganized from the Center for Experimental Animals in FY2019 to further enhance collaborative study based on animal research as a common facility of the interuniversity institutes. In the terrestrial and aquatic animal sections, multiple species including mouse, rat, marmoset, Japanese macaque, fish, and amphibians are maintained and supplied for experimentation.

To enhance and support collaborative animal researches involving domestic and foreign researchers, the principal responsibilities of the center include (1) the appropriate breeding of rodents and other experimental animals, (2) embryo transfer and cryopreservation for genetically modified mouse lines, (3) development and refinement of diagnostic testing methods, microbial containment, and disease prevention strategies, (4) provision of information related to the techniques of animal experimentation as well as promotion of education and awareness with regard to ethical considerations and regulations related to the study of experimental animals. The new building in "Myodaiji" area, which is equipped with the state-of-the art system including individually ventilated cages rack and experimental rooms for collaboration studies, was completed in September, 2020. We are capable of supplying high quality animal care and resources to researchers to reach the best research achievements.

Division of Coordinator for Animal Experimentation

NISHIJIMA, Kazutoshi
Professor
Laboratory Animal Science
Reproductive Technology
Metabolism

The Division was established in 2008 to support the Institutional Animal Care and Use Committee (IACUC) covered with 3 Institutes in Okazaki (Current with National Institutes of Natural Sciences).

The important role of animal-based research in the life science, especially physiological science field has been extensively increasing in the world. On the other hand, it is needed to clarify the social transparency, ethics and animal welfare in the animal experiments based on several rules including 'Law for the humane treatment and management of animals', 'Standard relating to the Care and Management of laboratory animals and relief of pain', 'Fundamental guideline for proper conduct of animal experiment and related activities in academic research institutions under the jurisdiction of MECSST' and domestic Standard. Accordingly, this Division is responsible for the following activities.

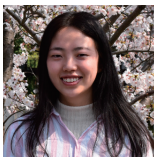
1. Education and training of the researchers
2. Review of the animal experiment plans
3. Self-evaluation and self-assessment of animal experiments
4. Information disclosure regarding animal-based research

We are also doing enlightenment activities in our own homepage.

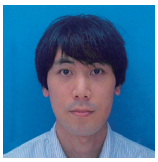
NIPS Research Fellow

The NIPS Research Fellows are young researchers with advanced research capabilities through operational expense subsidies for a certain period in order to have them be engaged in specific joint research projects, and to develop and promote research activities.

LIU, Chang
Division of Biophysics & Neurobiology
Molecular Physiology
Biophysics



LEI, Jing
Division of Cell Signaling
Molecular and Cellular Physiology



ATAKA, Mitsutoshi
Division of Biophotonics
Neurophysiology

LUO, Junxiang
Division of Sensory and Cognitive Brain Mapping
Neuroimaging
Neuroscience
Vision Science

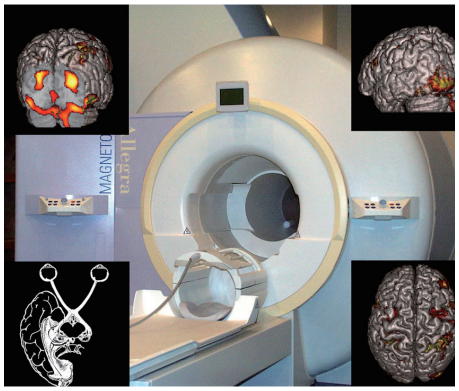
MIYATA, Toshikazu
Division of Sensory and Cognitive Brain Mapping
Neuroimaging
Neuroscience

Large facilities and equipments for cooperative studies

Outline

As a mission to be the inter-university research institute, NIPS conducts joint studies with researchers from domestic or foreign universities and other research institutes. NIPS provides specialized equipment, large-scale equipment, and research facilities, and develops new equipment for morphological and functional 4D imaging ｓ of various organs such as the brain.

▶ Magnetic Resonance Imaging System (MRI: 3 tesla, 7 tesla)

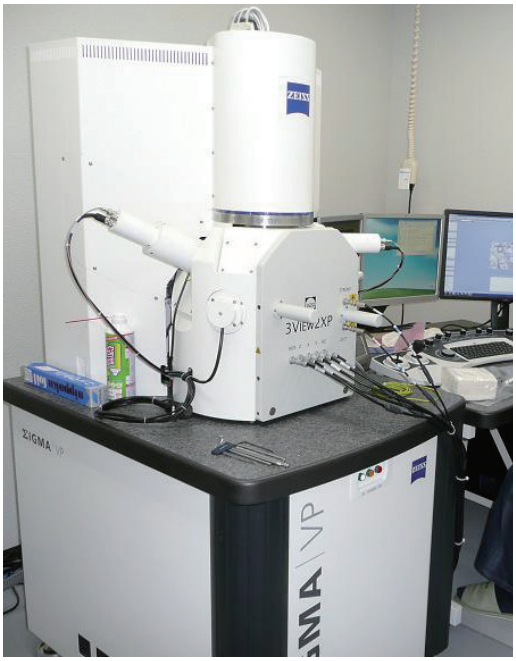


MRI is an imaging technique that utilizes the nuclear magnetic resonance of the hydrogen atom. Not only to image the anatomical details of the brain, but MRI also allows exploring the neural substrates of human cognitive function by the visualization of the task-related changes in regional cerebral blood flow（functional MRI）. For over a decade, we have been working on a 3T MRI to investigate the higher brain function of a human (The first 3T machine installed in 2000 was shut down in 2018). To simultaneously measure the neural activities of two participants during their social interaction, we have recently installed a dual-functional MRI system with two 3T MRIs. Furthermore, an ultra-high field (7T) MRI system has been installed.　In 2016 and 2017, cooperative study projects using a 7T machine were performed for the purpose of technical assessment and development. As we have confirmed stable operation in 2018, it is now fully provided for cooperative studies.

▶ Electron Cryomicroscopy

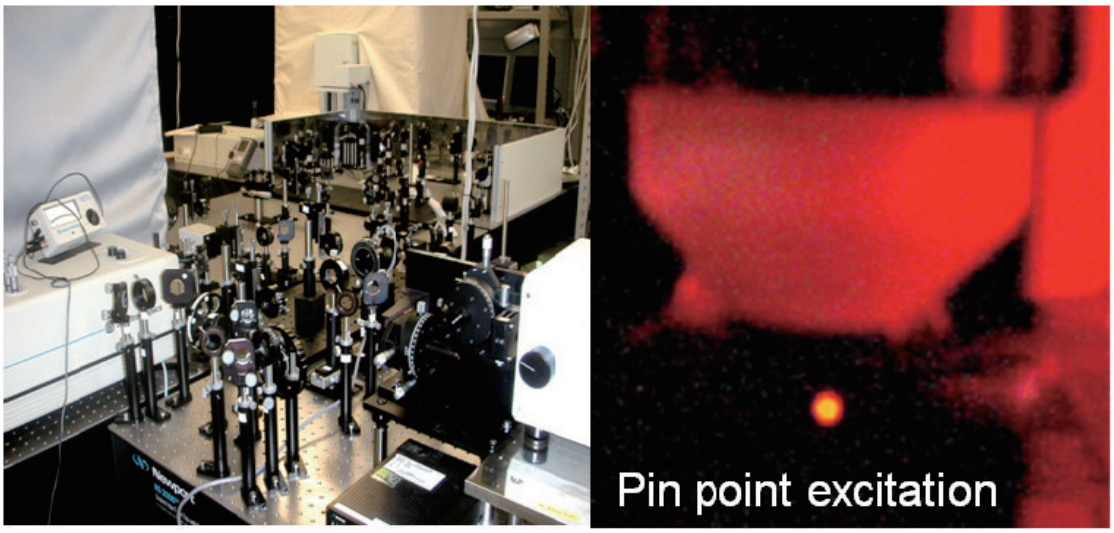
Electron cryomicroscope is an electron microscope developed for observing close-to-life state biological samples with a combination of rapid freezing and ice embedding sample preparation methods. Biological specimens up to 200 nm thicknesses can be observed with high-resolution and high-contrast. Ultrastructure analyses of protein molecules, viruses, bacteria, cultured cells, and frozen tissue sections are performed with this novel microscopic system.

▶ Serial Block-Face Scanning Electron Microscope (SBF-SEM)



Serial block-face scanning electron microscope (SBF-SEM) is an advanced 3-D nano-imaging equipment. Two different types of SBF-SEM are available; high-resolution and wide-area types. Resin-embedded biological specimens are sliced by a diamond knife equipped inside the chamber, and the block-face images are acquired by scanning electron microscopy (SEM). 3-D structures of the specimens are finally reconstructed from the acquired serial block-face images. 3-D structures of large biological specimens like brain tissue can be visualized at the resolution of several nanometers.

▶ Multiphoton excitation microscopy



Multi-photon excitation is a method to visualize living tissue by exciting the fluorescence molecules with the tightly focused near-infrared femtosecond pulse laser. Since the longer wavelength is used for multi-photon excitation, it has a superior deeper tissue penetration and reduced phototoxicity compared with single-photon excitation. Our 2-photon microscopes have the top-level specification for deep tissue imaging and can be applied to the imaging of neurons and glial cells in deep tissues such as the mouse brain. Recently, we also developed a 2-photon fluorescence imaging microscope that can be applied to image protein-protein interaction and the protein activity.

▶ Analytical equipment for in vivo neuronal, metabolic, and physiological parameters in mice and rats

We analyze the following physiological parameters in mice:

1) Energy intake and expenditure in free-moving animals, 2) Body temperature, heart rate, and blood pressure in free-moving animals, 3) Non-invasive 4-dimensional cardiac function and capillary blood flow imaging using anesthetized mice, 4) Mouse temperature preference assays using a thermal gradient ring, 5) Evaluation of behaviors related to emotions, learning, and memories, 6) Multicellular activity measurement and manipulation in vivo, and 7) Functional analysis of neuroimmune interactions in mouse models of diseases.

[Major apparatuses] Device for simultaneously measuring energy metabolism and activity of small animals using mass spectrometry, Brain wave-measuring apparatus, Electromyograph, Telemetry automatic measurement system for chronic experiments, Olympus FV100, 4D ultrasound imaging device VEVO3100, Isolated heart perfusion system, Thermal Gradient Ring, Open field test analyzer, Light/dark transition test device, Barnes circular maze test device, Elevated plus-maze test analyzer, Forced swimming test analyzer, Rotarod test analyzer, Passive avoidance test analyzer, Fear conditioning test analyzer, Morris water maze pool, Nikon A1MP+Holographic microscope, and X-ray irradiation device.

Facilities Shared by the Two Institutes

Outline

National Institute for Physiological Sciences and National Institute for Basic Biology are sharing facilities which are innovative for conducting biological researches, but rather expensive to be supported only by one institution.

▶ Section of Electron Microscopy

See P. 34

▶ Instrument Design Room

Custom-designed equipments, which are not commercially available, can be constructed in this room. The machine shop is equipped with various types of machines such as milling machines and drill presses. A small laser cutting machine also work, and laboratory equipment can be manufactured. The electronic shop is equipped with various types of test instruments used for construction and measurement calibration of electronic devices.

Machine shop equipments (Instrument Design Room)

▶ Trans-Omics Facility

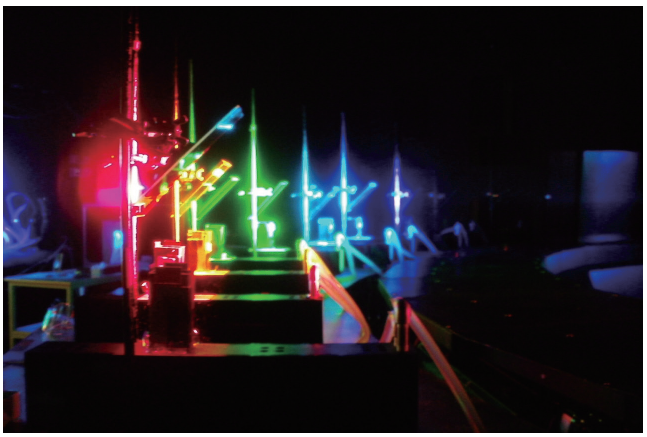
The Trans-Omics Facility is a division of NIBB Trans-Scale Biology Center and organized jointly by NIBB and NIPS for promoting DNA and protein studies. The facility maintains a wide array of core research equipments, from standard machinery like ultracentrifuges to cutting edge tools such as next generation DNA sequencers, which amount to 70 different kinds of instruments. Our current focus is supporting functional genomics works that utilize mass spectrometers and DNA sequencers.

Next generation DNA sequencers (Trans-Omics Facility)

▶ Optics and Imaging Facility

The Optics and Imaging Facility (former Spectrography and Bioimaging Facility) manages the optical equipment, such as optical microscopes, including confocal laser microscopes and two-photon microscopes, and the Okazaki Large Spectrograph. We also hold technical seminars and training sessions about microscopes and bioimaging to provide useful information to our users.

Okazaki Large Spectrograph (Optics and Imaging Facility)



Joint Researches

Outline

The National Institute for Physiological Sciences (NIPS), an inter-university research institute, carries out general collaborative research, planned collaborative research that focuses on the most critical theme, and cooperative research using large facilities.

As the following table shows, many collaborative studies are conducted each year and have produced promising results. In 2023, the institute plans to carry out 132 general and planned collaborative projects and 36 cooperative studies by functional imaging.

Another of the principal pillars of corporative studies at NIPS is the NIPS research meeting. Unlike normal academic meetings, here, most of these meetings include oral presentations, giving plenty of time for Q&A. The small number of participants also allows detailed discussions to take place. Twenty meetings are planned for this year. The number of NIPS research meetings greatly outnumbers those hosted by the other two research institutes in Okazaki, and in fact, they have become a highly important base organization. In the past, the meetings have helped establish new scientific research-funded study groups, and have even established activities such as academic conferences. The NIPS International Workshop has been running since 2008. Research meetings are inviting overseas researchers, who present their work in English, have shown positive potential for the future of science. In 2022, one International Workshop was conducted.

1. General collaborative project

The general collaborative projects and planned collaborative projects involve studies carried out by researchers from outside universities or research institutes, and professors or associate professors from within NIPS. About a total of 30 to 40 projects have been selected in the past, but in 2021, 127 projects had been selected as part of a move to raise the number of cooperative studies.

2. Planned collaborative project

Planned collaborative project themes are selected by NIPS, which are based on requests from researchers. Until 2007, there were two themes, “Physiological and neuroscientific studies into genetically modified model animals” and “Biomolecular sensors and physiological function.” Additional themes were added in 2008, with “Functional and morphological analyses of cells and tissues by multi-photon microscopy” and “Medical and biological applications of phase-contrast cryo-electron microscopy” (name changed to “Medical and biological applications of cutting-edge electron microscopy” in 2011), and in 2009 with “Behavioral analysis of mouse and rat”. Also, “Analysis of metabolic physiology for mouse and rat” began in 2011, while “Transfection study with primates,” “Analysis of fluctuations in function research in life science,” and “Multidisciplinary study of neural information” began in 2012. Also, “Transfection study with viral vector neurological system" was started in 2013. Furthermore, “Purification of supra-molecular complexes and analyses of their constituents by mass spectrometry” was started in 2016, and “Analyses of dynamic aspects of the function and structure of membrane proteins” in 2017, “Multi-dimensional fluorescence imaging analysis with a multi-point scanning microscope” and “Elucidation of the pathology of mental/neurological disease by analysis of neural activity dynamics” in 2021. All these themes cover the most talked about scientific topics today, and are areas where NIPS is considered to be a frontrunner in Japan. We expect to receive many new proposals. Two projects, ”Analysis of fluctuations in function research in life science” and “Multidisciplinary study of neural information” were closed in 2015, due to the finish of the related NINS projects. “Behavioral analysis of mouse and rat” was closed due to the shutdown of the Section for Behavior Patterns. In 2016, NIPS performed only the collaborative experiments carried over from the prior year. “Analyses of dynamic aspects of the function and structure of membrane proteins” was closed in 2022.

In regards to the proposed agenda, long discussions had been carried out at both faculty meetings and work meetings in 2012. The agreed requirements are as follows.

1) Proposals should clearly state the aim and experimental design of the research project and should be completed within five years. However, depending on the state of the research, an extension period may be granted after the initial five years.
2) Proposals should specifically state the research area of interest. Broad themes will not be accepted.
3) There will be a limit to the number of proposals accepted. Each general collaborative research area category and research facility will accept five projects each at most, in principle.

The details of the planned collaborative research are as follows.

In accordance with the renovation and reorganization of the Animal Resource Center, starting in FY2022, the following items have been transferred to the Center's planned joint research projects.

(1) Production of advanced animal models (until FY2021, this project has been conducted as “1) Physiological and neuroscientific analysis of genetically modified model animals”, a joint research

project planned by the National Institute for Physiological Sciences).
(2) Analysis of metabolic physiology for mice and rats.

Planned collaborative projects (Animal Resource Center)

"Production of advanced animal models"

Since genetically modified model animals are extremely effective for gene function analysis at the individual level, they are widely used in the field of life sciences. The recent engineering required to create such model animals has taken huge leaps forward; e.g., a new genome-editing tool (CRISPR/Cas9 system) can relatively easily cut arbitrary sequences on the genome. Section of Mammalian Transgenesis at the Center for Genetic Analysis of Behavior in Animal Resource Center has established the latest technology such as the CRISPR/Cas9 system capable of providing an endogenous genetic modification to mice and rats. Our staff familiar with not only physiology and brain science but also reproductive biotechnology, have greatly contributed to researchers all across the country by providing technology to create genetically modified model animals. We can support cooperative studies by providing the technologies to develop adoptive models such as transgenic or knock-out mice and rats. We will continue to work on the requested creation of genetically modified model animals by applying the new genome-editing tools. Fourteen projects are now scheduled for 2023.

"Analysis of metabolic physiology for mice and rats"

The Section of Metabolic Physiology was set up in 2010, and the planned collaborative research project, "Metabolic physiology analysis of mice and rats," had started in 2011. In FY2021, it was integrated with the Section of Behavioral Pattern Analysis and moved to the Section of Multilayer Physiology of the Center for Genetic Analysis of Behavior. Since then, researchers from within and outside NIPS have been looking at the following topics concerning genetically modified animals.

(A) Evaluation of behaviors related to emotions, learning, and memories, and analyses of neural and muscular activities
(B) Energy intake and expenditure in free-moving animals
(C) Body temperature, heart rate, and blood pressure in free-moving animals
(D) Non-invasive 4D cardiac function and capillary blood flow imaging using anesthetized mice
(E) Mouse temperature preference assays with a thermal gradient ring
(F) Multicellular activity measurement and manipulation in vivo
(G) Functional analysis of neuroimmune interactions in mouse models of diseases

Note that (B) through (D) were conducted until FY2021 as part of the National Institute for Physiological Sciences Project "(2) Analysis of metabolic physiology for mice and rats."

Seventeen projects are now scheduled in 2023.

"Ultrastructure analysis of biological specimens by cutting-edge electron microscopy"

One cryo-electron microscope (cryo-TEM) and two serial block-face scanning electron microscopes (SBF-SEMs) are mainly used for this joint research program. Cryo-TEM shows the best performance when combined with a rapid-freezing sample preparation method. Under this condition, it is possible to study three-dimensional structures of unstained biological specimens, including isolated proteins, viruses, bacteria, cultured cells, and tissues, to more or less their true state with higher resolution. On the other hand, SBF-SEMs are used for the studies of ultrastructural analysis of thick biological specimens, like brain tissue. The specimens embedded in the plastic resin are sliced by a diamond knife and imaged by SEM continuously. Finally, the three-dimensional ultrastructure of the specimens is rebuilt at dozens of nanometer resolutions. The program support studies by using these states of the art electron microscopes. Fifteen projects are now scheduled in 2023.

"Functional and morphological analyses of cells and tissues by multi-photon excitation microscopy"

A two-photon excitation fluorescence microscope is a less invasive method for studying the microscopic structure and functions of cells in deep tissues of biological organisms. Currently, our institute has three upright two-photon excitation microscopes, and these allow us to observe the structure in the depth of one millimeter with a spatial resolution of a micrometer. Since the maintenance of a two-photon microscope is complicated, NIPS is the only institute that can provide the opportunity for collaborative research with a high-quality experience. Furthermore, we recently build the two-photon fluorescence lifetime microscope system which enables us to observe the intermolecular interactions and the activity of signaling protein in a living cell in the deep tissue. We are also working on single-molecule imaging using quantum dots in a combination of a fluorescence microscope. Using these "cutting-edge methods," we have conducted collaborative research. Recent successes are particularly in vivo Ca2+ imaging, and long-term imaging of neurons in living mice. One planned collaborative project is scheduled in 2023.

"Development and supply of viral vectors and gene-transfer to primates"

Advances in technology to control molecular functions or change neural activity by inserting certain genes into primate brains using virus vectors can lead to major possibilities. Getting to do such research, however, requires a long list of equipment and facilities

to enable researchers to develop do things such as develop vectors, or insert vectors. A planned collaborative research project "Transfection study with primates" was launched in 2012 so that researchers could share their resources, and work together to unravel mysteries about higher brain functions and pathological conditions. In 2013, five projects were carried out, and five projects were carried out in 2014.

The key point of the experiments is the development of suitable viral vectors. Also, viral vectors are useful, not only for primates but also for other animals. Thus, a planned collaborative project "Gene transfer into the nervous system using viral vectors" was started in 2013. In Section of Viral Vector Development, we promote collaboration with many laboratories by providing various serotypes of AAV vectors, conventional lentiviral vectors, and highly efficient retrograde gene transfer vectors. Moreover, we proceed with the collaboration to exploit the more advantageous viral vectors. Up to 2014, we provided more than 100 viral vectors for other laboratories and performed two planned collaborative research in 2013, and 4 in 2014. At present, very intriguing research results are being obtained. In 2015, the two projects were merged as "Development and supply of viral vectors and gene-transfer to primates." The three examples of the achievements are as follows. 1) Virus vectors helped to identify system circuits that compensated motor functions after spinal cord injury in macaque monkeys. 2) Virus vectors revealed the property of subnetwork composed of excitatory and inhibitory neurons in layer 5 of the rat frontal cortex. 3) Virus vectors identified a specific subset of neurons commanding the dietary preference for carbohydrate over fat in mice. Thirteen projects are now scheduled in 2023.

"Purification of supramolecular complexes and analyses of their constituents by mass spectrometry"

To understand the function of proteins in vivo, it is necessary to identify the constituents of supramolecular complexes precisely. Therefore, there are gradually increasing needs for the support to perform purification of protein complexes from tissues and cells, and to identify constituents of the complex and the target antigens in auto-immune diseases by mass spectrometry. This project was newly started in 2016 to respond to the needs. Two projects are now scheduled in 2023.

"Multidimensional fluorescence imaging analysis by multipoint scanning microscopy"

We conduct joint-use research based on our originally developed multipoint scanning confocal and two-photon microscopy method. In particular, quantitative visualization analysis of cellular physiological functions, including biological rhythms, will be performed by high-speed 3D, ultra-long term, multi-color, and super-resolution observation. Two projects are scheduled in 2023.

"Elucidation of the pathology of mental/neurological disease by analysis of neural activity dynamics"

To study the relationship between human and animal neural activity dynamics and the pathology of various mental and neurological diseases by combining unit recording, local field potentials (LFPs), electrocorticography (ECoG), scalp electroencephalography (scalp EEG), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) are utilized in a multi-layered manner. In particular, we analyze neural activity dynamics such as vibration, synchronization, and fluctuation. Eight projects are now scheduled in 2023.

3. NIPS research meeting

In 2022, due to COVID-19, almost all meetings were run on the hybrid-form. In 2023, 20 meetings are scheduled to be held.

The discussions often lead to new collaborative research project ideas both within and outside the institute or even new research funding. For example, the Glial Young Researcher Meeting in 1994 – 1996 had led to the priority area (B) "Glial cell role in the neural transmission regulation mechanism" discovery, and later on, the became the priority area "Glial Neural Network." Another example would be the Biomolecular sensor-related NIPS research meeting held in 2008, which lead to the Grant-in-Aid for scientific research on the priority area "Cell Sensor." The establishment of two priority areas in 2015, "Thermal biology" and "Oscillology" was also triggered by the activity of the NIPS research meeting. Also, synapse research meetings and research meetings on pain have all helped progress in research communities across Japan, and have led to the establishment of new fields.

In 2016, one NIPS research meeting was held at Kyushu University. Traditionally, NIPS research meetings had been held in the Okazaki area. We aimed to contribute to the physiological research communities located in the Kyushu area, and to the functional enhancement of the universities there. As this trial-run meeting won popularity, we conducted one in Tohoku and another in the Tokyo area in 2017, and in Nagoya and Tokyo in 2018, and one in Osaka in 2019. In 2021, one hybrid meeting was held in the Sendai area due to the COVID-19 extension. One meeting was held in the Nagano area in 2022.

More recently, there have been some debates going on about whether it was useful or not to hold research meetings on the same topic every year.

As a result, the meeting application guidelines were revised and put into use from 2013. The revised guidelines are as follows.

1) Research meetings: This research debate meeting will aim to create a new research field or develop new technology, and will only involve up to 100 participants, one of which must be a Professor or Associate Professor from NIPS. NIPS will provide some financial support to pay for travel expenses.

2) Meeting Duration: Up to three days.
3) Meeting Venue: Meetings will take place within the Okazaki area, where the National Institutes for Natural Sciences is based. The Okazaki Conference Center is available for use, and reservations can be made by contacting the International Research Support division (TEL: 0564-55-7138).
4) Research report: The organizer is required to submit a report to the Institute head within 30 days after the meeting has ended.
5) Other: Researching meeting themes may only be repeated for three consecutive years. If you wish to continue research meetings on a theme for more than three years, please submit an agenda that has included new points of discussion.

4. NIPS International Workshop

To promote the international efforts at NIPS, the NIPS International Workshop was launched in 2008. The workshop invites renowned scientists from around the world, and a wide range of participants from around the country. All presentations and discussions are held in English. In 2015, one International Workshop was held. The themes were TRPs and SOCs --Unconventional Ca^{2+} Physiology--". In 2016, two NIPS international workshops were conducted, "Towards elucidation of memory engram," and "The 4th International Symposium on Salivary Glands in Honor of Niels Stensen". In 2017 and 2018, no International Workshop was conducted. In 2019, two workshops were held. In 2020, one workshop was scheduled in Kyushu but conducted on the WEB because of COVID-19. In 2022, one workshop "Multi-disciplinary approach to understand neuronal network architecture to control motor actions" was carried out.

5. Cooperative study by functional imaging (combined study of 2011's cooperative study by functional magnetic resonance imaging and cooperative study by Magneto-encephalography)

Until 2011, NIPS had been conducting two individual cooperative studies on its large-scale functional imaging machines, the magnetic resonance imaging machine, and the magnetoencephalography machine. However, as it became apparent that many researchers used both machines, it would be more efficient for everyone if the two studies were combined into one in 2012.

Magnetic resonance imaging involves two research themes, "non-destructive three-dimensional observation of living organisms" and "structure and energy state observation of organic activity, including brain activators." Currently, the institute has a 3 Tesla machine in 2000, which is twice as powerful as the standard 1.5 Tesla machine, and has a considerable advantage when measuring cerebral blood flow in brain activator tests. Another characteristic is that it is capable of running primate brain activation tests. On top of this, it systematically processes all experimental designs, image data, and statistical image analysis, making it more than just a high-resolution image machine, but something that produces high-quality data that researchers need. In 2010, the two machines were interlocked, becoming a dual system capable of analyzing brain function related to social communication. A new 7 Tesla magnetic resonance imaging machine for a human was introduced in 2014, and the operation was started in 2015. In 2017, two cooperative study projects using 7T machine were performed for the purpose of technical assessment and development, and five were conducted in 2018. As we have confirmed the stable operation, it is now fully provided for cooperative studies. In 2023, 36 studies are scheduled.

In 1991, the first 37 channel magnetoencephalography (MEG) machine in Japan was installed at NIPS and has since been a pioneer for MEG studies, even getting recognition from the international community. At the same time, researchers from universities and institutes without a MEG machine took part in collaborative studies with NIPS, many of who discovered fascinating results. In 2002, a new whole-head type MEG machine was installed, allowing clinical test measurements impossible at other universities to be made at NIPS. After 20 years of installation, it was discontinued at the end of March 2022.

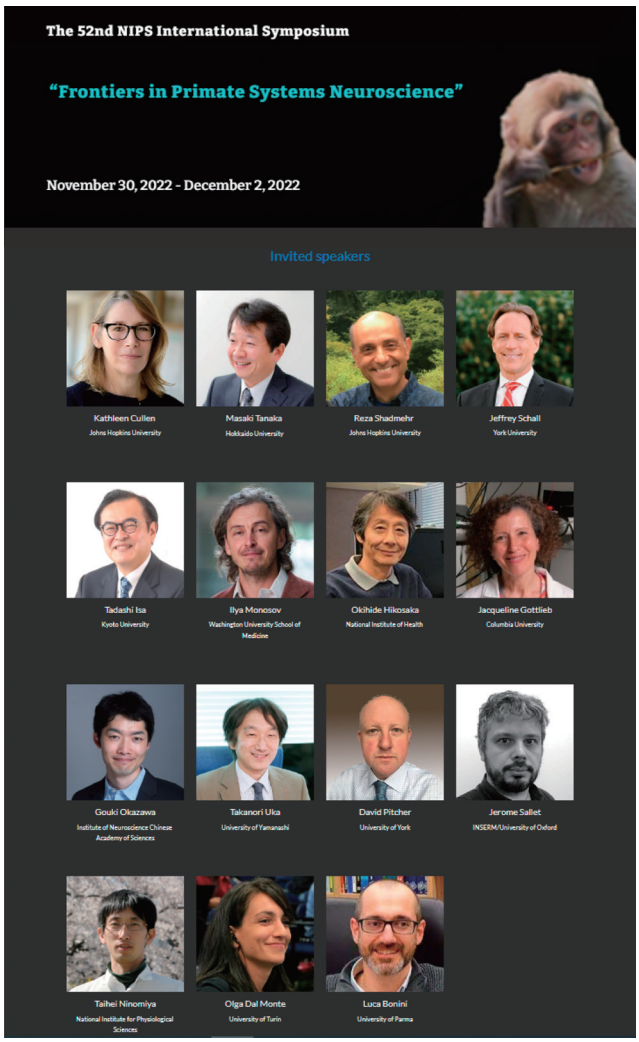
The 52nd NIPS International Symposium

The 52nd international symposium “Frontiers in Primate Systems Neuroscience”

The 52nd international symposium “Frontiers in Primate Systems Neuroscience” was held online from November 30 to December 2, 2022, which focused on research into higher brain function using nonhuman primates as an experimental animal model. The symposium organizer was Professor Isoda of the Division of Behavioral Development, and the staff of the division was in charge of the administrative management. There were 15 speakers, 11 of whom were invited from overseas institutions (5 from the U.S., 1 from Canada, 1 from the U.K., 1 from France, 2 from Italy, and 1 from China). A total of 136 people attended, 39 of whom were overseas researchers.

Three main themes were set out this time, all of which attract increasing attention in the community: (1) sensory integration and action, (2) motivation, learning, and decision-making, and (3) social cognition. The program was organized so that the contents of each talk were serially linked in each session. The lineup was well-balanced, ranging from young PIs to distinguished PIs. All the talks were given a 10-minute Q&A period. Each session was chaired by two researchers from the Division of Behavioral Development.

Throughout the symposium, active discussions with insightful questions continued uninterruptedly. Although the symposium was held online, the venue was a great success. The symposium was significant in that it provided (1) a bird's-eye view of the results of cutting-edge research using nonhuman primate models, (2) a concrete image of future research directions in the relevant field, (3) a search for new collaboration opportunities, and (4) motivation for young researchers. Although the time difference between regions is an issue when holding an online meeting, the advantages have also become evident, that is, being able to accomplish a full-scale international scientific meeting with very little expense and a small administrative structure. The organization of international symposiums on timely themes is one of the most important missions for the National Institute for Physiological Sciences as an inter-university research institute.



NIPS International Workshop

11.5.1 “Function and dysfunction of cortico-basal ganglia circuits”

The above-mentioned NIPS International Workshop (Organizer: Associate Professor Yoshihisa Tachibana, Kobe University Graduate School of Medicine; Co-organizer: Professor Atsushi Nambu) was held for three days from March 17 through Mar 19, 2023, in a hybrid style using both on-site and Zoom. The aim of the meeting was to elucidate the neural basis of our diverse behaviors, and we invited outstanding neuroscientists from Japan and abroad to share their cutting-edge knowledge on systems neuroscience research, mainly through oral presentations. Three speakers, Prof. Peter Strick and Prof. Thomas Wichmann from the U.S. and Prof. Thomas Boraud from France, participated in the workshop, and Prof. Jose Obeso from Spain joined online. In addition, 16 domestic speakers gave lectures (30 minutes each) and Prof. Atsushi Nambu gave a retirement memorial lecture (1 hour). Twelve posters were also presented by young researchers. The total number of participants reached 119 (9 non-Japanese).

The meeting featured a variety of presentations from motor control function to cognitive/limbic functions by cortico-basal ganglia neural circuits, the pathophysiology of basal ganglia disorders such as Parkinson's disease, and the development of new technologies to elucidate these brain functions. It should be noted that the wide range of participants, from world-leading researchers in their 70s to graduate students in their 20s, made it possible for young researchers to learn directly from senior researchers about the historical changes in systems neuroscience. At the same time, we were able to have a free and lively discussion in the information exchange session, which was very enjoyable and warm. While there have been many online research meetings in the past few years due to the COVID-19 pandemic, this meeting gave us a very good opportunity to share our enthusiasm for our research. It is hoped that this meeting will lead to more opportunities for joint research and further development of research on cortico-basal ganglia neural circuits.

The Graduate University for Advanced Studies (SOKENDAI)

In recent years, it has become necessary to train creative and highly skilled and creative scientists to support the promotion of creative research and pioneer in leading scientific areas, which is a strong demand in our country.

According to the increasing internationalization of academic research, it is also necessary to take enormous efforts to train international-minded researchers with broad perspectives, particularly for interdisciplinary research in multiple fields.

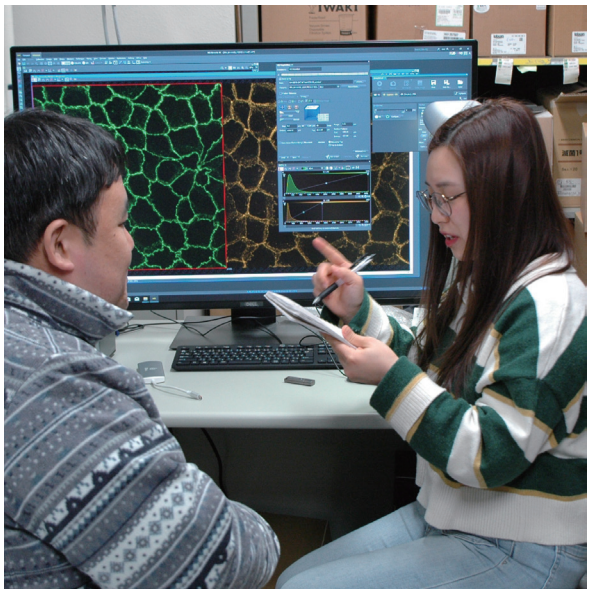
The Graduate University for Advanced Studies, SOKENDAI was established in 1988 with the aim of nurturing creative researchers with broad perspectives who can take the lead in responding to the latest streams of academic research. For this purpose, SOKENDAI provides advanced and internationally open graduate school education, utilizing its excellent research functions in close cooperation with the interuniversity research institutes. Among 6 schools of SOKENDAI, School of Life Science contained three departments; Department of Genetics (based on National Institute of Genetics), Department of Basic Biology (based on National Institute for Basic Biology), and Department of Physiological Sciences (based on National Institute for Physiological Sciences). Since April 2023, SOKENDAI has removed the boundary of previous graduate schools and transitioned to a new organization with one department that contains 20 programs corresponding to previous departments.

The outline of Physiological Sciences Program.

Physiological Sciences Program is nurturing researchers who will conduct integrative research on the underlying mechanisms of the functions of the human body. Physiological sciences, while sharing the basis with biological sciences, not only play a central role in integrating various fields of basic medicine but also maintain a close relationship with various fields of clinical medicine. Based on the original philosophy of physiological science, this course provides education and research guidance so that students can pursue the function of the body from multiple perspectives, from the molecular level (the basic structure) to the individual level (the system), and to give them a broad perspective on medicine and life sciences in general.

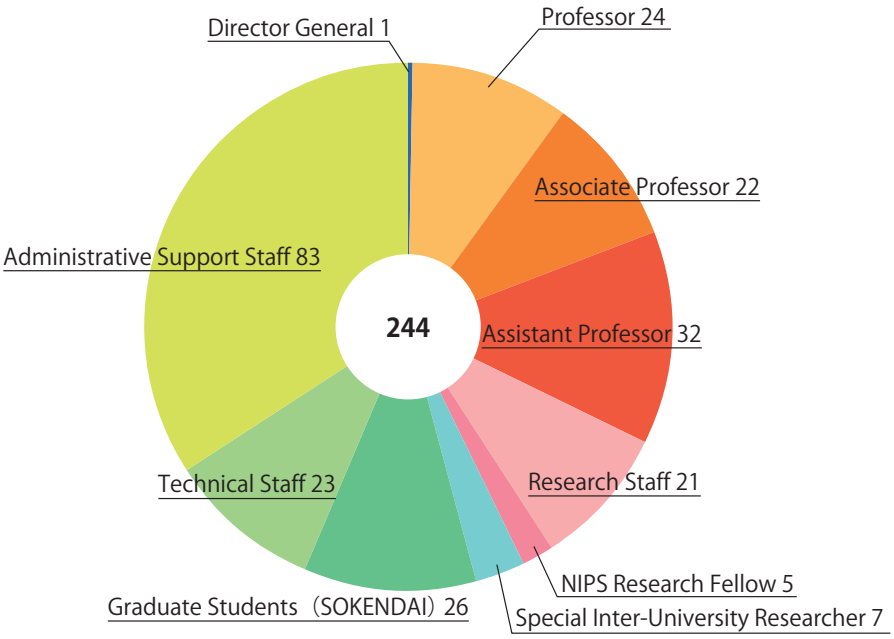
Number of graduate students enrolled by year

fiscal year	2017	2018	2019	2020	2021	2022
Number of enrolled students (international students)	25(6)	31(12)	30(14)	37(11)	39(13)	37(11)
Number of students admitted	4	10	6	14	8	5



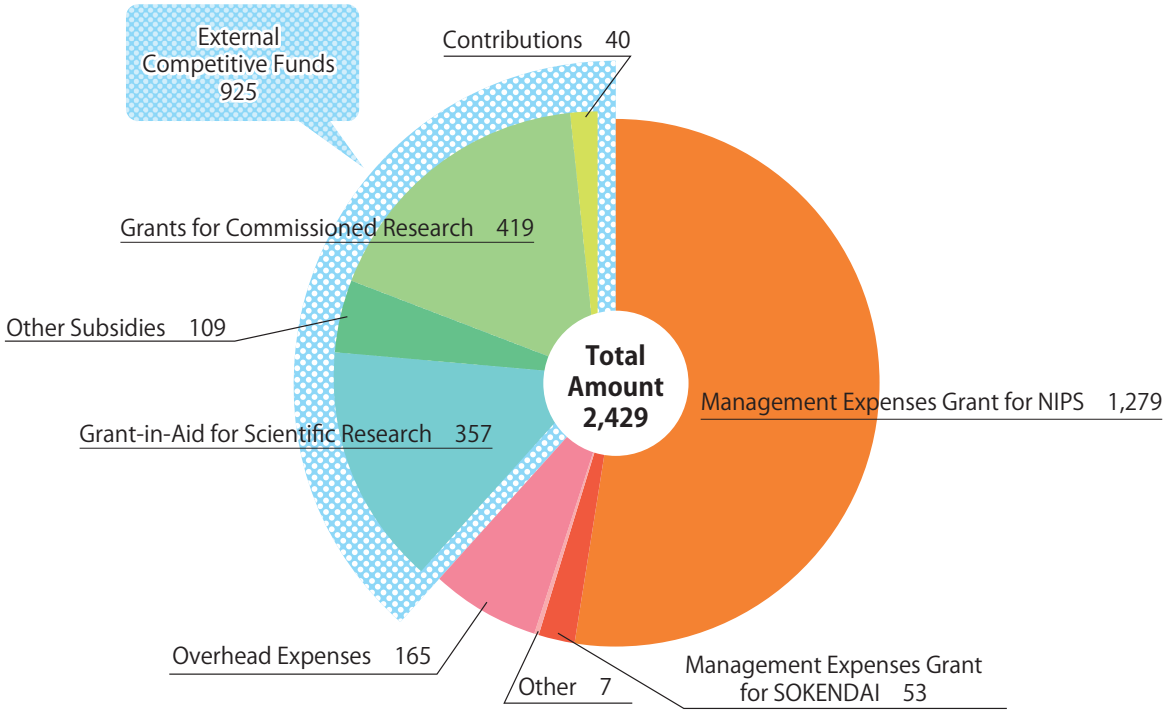
Current State

Staffs



Budget

numbers are in million yen/As of May, 2022



The budget consists of grants from the government (Management Expenses Grants・SOKENDAI Research Grants) as well as many competitive funds (Grants-in-Aid for Scientific Research, Funds for Contract Research etc.) which are awarded by competitive selection process.

International Exchanges

NIPS is an internationally recognized research institution and active international exchanges are performed. NIPS has the positions of foreign research staff, and world top-class researchers have engaged in research collaboration so far using this framework. Besides the research collaboration, visiting professors contribute to education of young researchers. In FY2014, NIPS started the Section of International Collaborative Research Project, which is run for 3 years by an adjunctive foreign professor as a Principal Investigator (P.I.). From FY2017 to FY2022, Professor Denis Le Bihan (a former Director of Neurospin, France) ran a lab for two terms as a P.I., and achieved distinguished research using 7T MRI. From FY2023, Dr. Andrew Moorhouse in University of New South Wales Sydney (Australia) is to serve as an adjunctive foreign professor and run a lab as a P.I., focusing on the brain function from the circuit level. Also, many foreign students enter Physiological Sciences Course of SOKENDAI as graduate students and engage in research actively.

One of the main international exchange activities at NIPS is the annual international symposium. A NIPS professor serves as an organizer, and leading researchers from abroad and Japan are invited. In FY2022, the 52th NIPS International Symposium entitled "Frontiers in Primate Systems Neuroscience" was held online (Organizer: Professor Masaki Isoda). In addition, the international workshop, which is an international version of NIPS research meetings, was launched in FY2008, and that entitled "Function and dysfunction of cortico-basal ganglia circuits" was held in FY2022 (Organizer: Professor Atsushi Nambu).

NIPS has an academic contract or a memorandum of understanding for academic interaction (MOU) with foreign institutions as follows, and is actively conducting joint academic activities including collaborative researches. The institutions are Korea University, College of Medicine and Yonsei University, College of Medicine and Dentistry (Korea); Tübingen University, Werner Reichardt Center for Integrative Neuroscience (Germany); Chulalongkorn University Faculty of Pharmaceutical Sciences (Thailand); University of New South Wales, Faculty of Medicine (Australia); Neurospin (France); and McGill University (Canada). In FY2022, a joint symposium with Tübingen University, Werner Reichardt Center for Integrative Neuroscience (Germany) and other institutions was held on site in Germany (Fig. 1). Also, a joint symposium with Korea University, College of Medicine and Yonsei University, College of Medicine and Dentistry was held on site at NIPS (Fig.2). In FY2023, it is planned to sign MOU with the whole Chulalongkorn University.

Besides these, many international research collaborations of high quality are performed at the individual researchers' level, supported by the budget of NIPS as well as NINS and also research grant from outside.

Fig. 1　A joint symposium with Tübingen University, Werner Reichardt Center for Integrative Neuroscience

Fig. 2　A joint symposium with Korea University and Yonsei University

Common Facilities in Okazaki

▶ Okazaki Library and Information Center

The Library collects, arranges and preserves journals and books of the three Institutes, and provides them for common use for the Institutes staff and their guests.
<main function>

1. 24hours use by The IDENTIFICATION CARD
2. Information retrieval service
（Web of Science, SCOPUS, etc）
3. Books Loan service
4. Interlibrary Loan・Photocopy Request

▶ Okazaki Conference Center

Okazaki Conference Center was founded on February, 1996 to promote international and domestic conference program of research and education.

Ohsumi Conference Hall（capacity of 208）
Conference Room B（capacity of 112）
Conference Room C（2 rooms, capacity of 50 each）

Ohsumi Conference Hall

▶ Accommodation

The lodging houses（Mishima Lodge and Myodaiji Lodge）are provided for guests, both foreign and domestic, for the common use of the three Institutes（NIPS, NIBB and IMS）.

Myodaiji Lodge

The lodging capacities are as follows :

	Single Room	Twin Room	Family Room
Mishima Lodge	60	14	12
Myodaiji Lodge	14	—	3

▶ The Sakura Nursery School

The Sakura nursery school is the institutional child care facility established for supporting both research and child-rearing. The school accept a child from the 57th day of after the birth, and is supporting a researcher's smooth return to research activity.

Age: From the 57th day of after the birth to 3 years old

Capacity: 18 persons

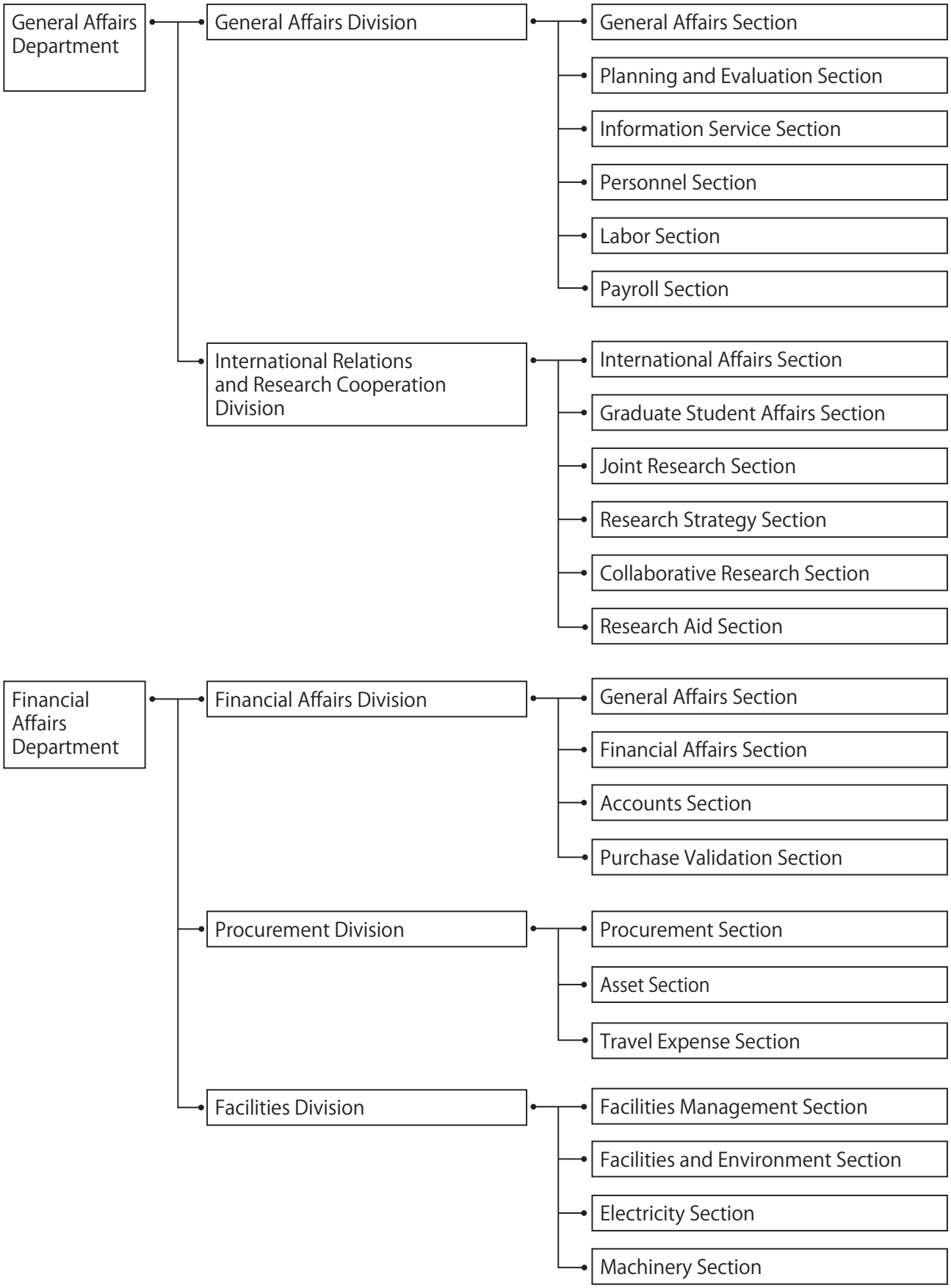
Use candidate: The officers, researchers, visiting researchers, graduate students at Three Okazaki Institutes (including ExCELLS)

Opening day: From Monday to Friday

Opening time: From 8:00 to 19:00（maximum extension 20:00）

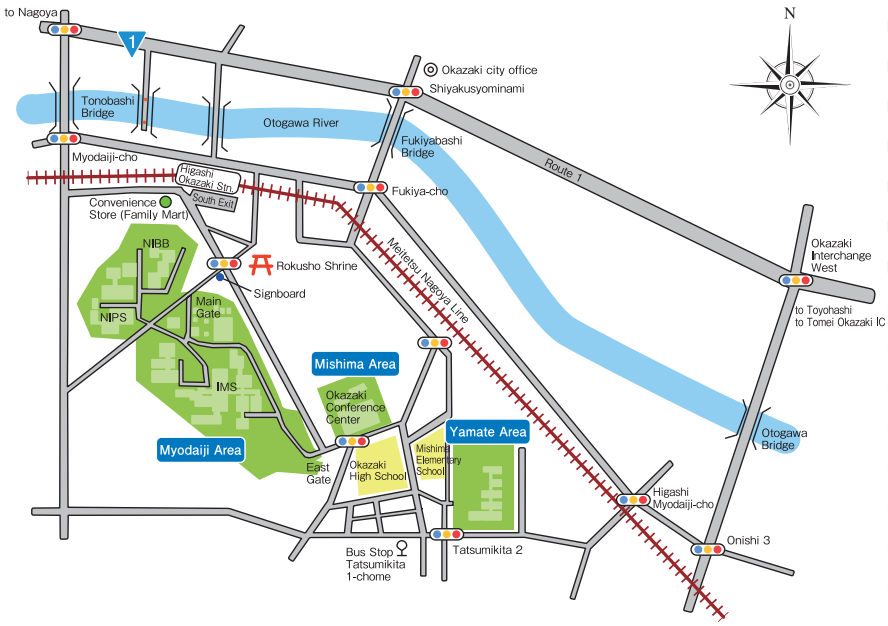
Childcare form: Regular childcare, temporary childcare

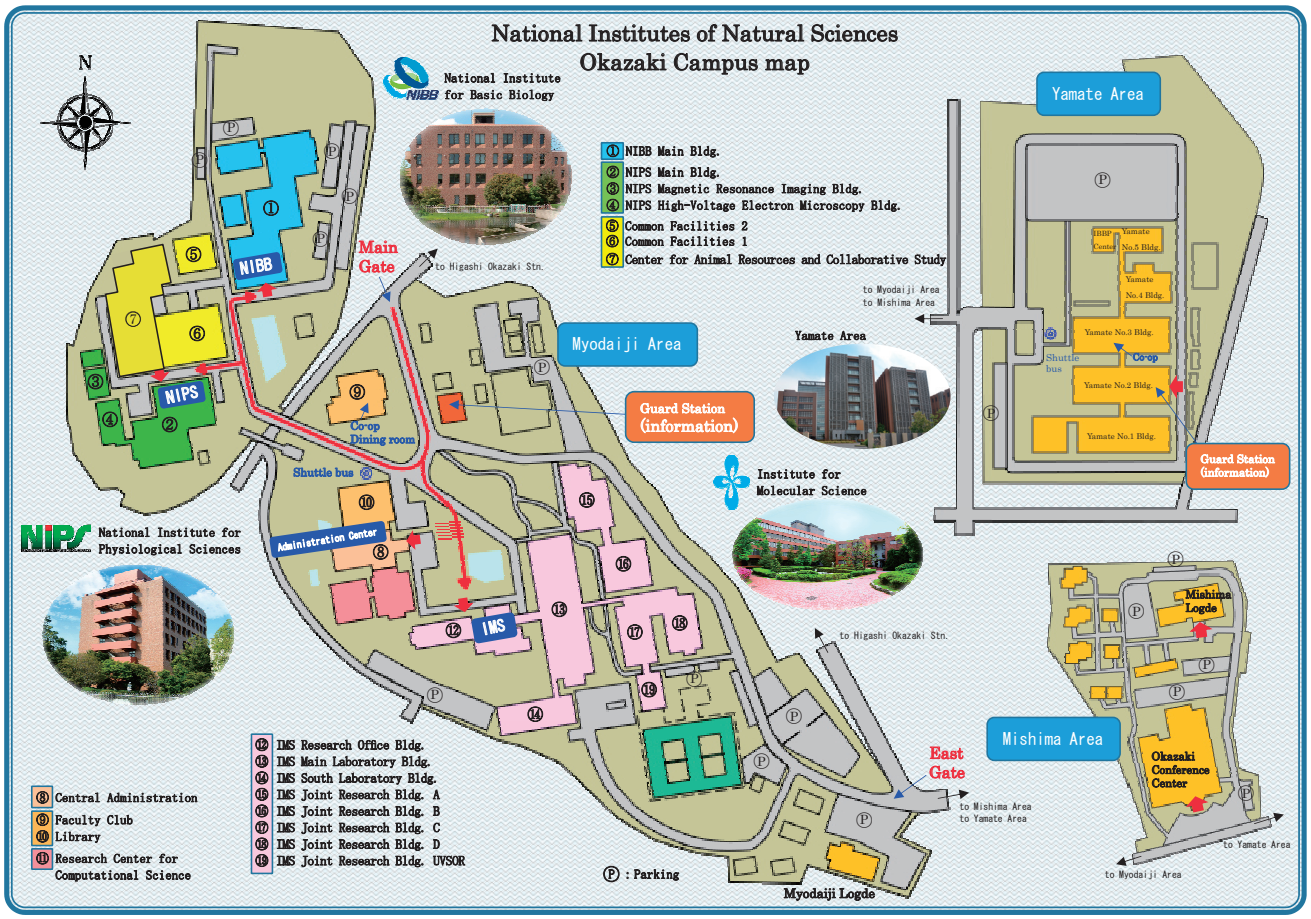
Okazaki Administration Center



Campus Map

According to area	Use classification
Myodaiji Area	National Institute for Physiological Sciences / National Institute for Basic Biology / Institute for Molecular Science / Okazaki Administration Office / Staff hall / Lodging for staff / Myodaiji Lodge
Mishima Area	Okazaki Conference Center / Mishima Lodge
Tatsumi Area	Lodging for staff
Yamate Area	Exploratory Research Center on Life and Living Systems, and others





Location

From Central Japan International Airport

By train

Take the Meitetsu train from Central Japan International Airport to Higashi Okazaki Station. NIPS is a 7-minute walk up the hill on the south side of the station.

From New Tokyo International Airport (Narita Airport)

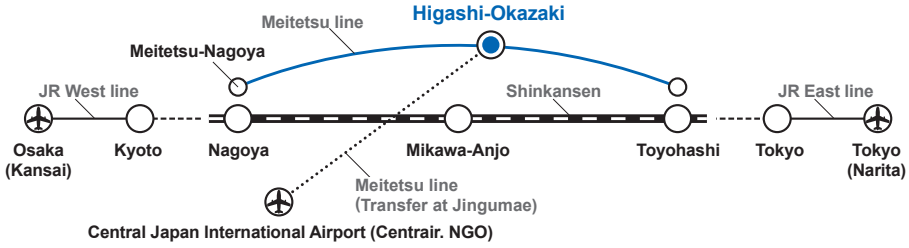
A) By plane (*Recommended)

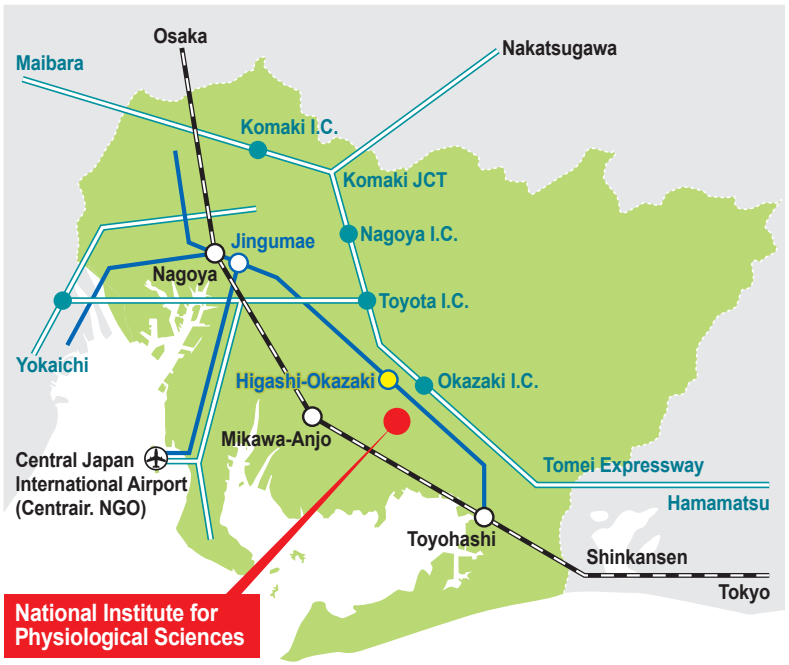
Transfer to Central Japan International Airport

B) By train

Take the JR Narita Express airport shuttle train from Narita to Tokyo Station (approximately 60 minutes) and change trains to the Tokaido shinkansen (bullet train).

At Toyohashi JR Station (approximately 80 minutes from Tokyo), change trains to the Meitetsu Line's Limited Express train bound for Gifu. Get off at Higashi Okazaki Station (approximately 20 minutes from Toyohashi). Turn left (south) at the ticket gate and exit the station. NIPS is a 7-minute walk up the hill.





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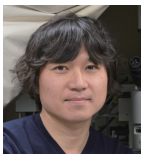

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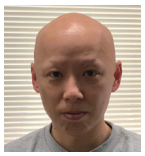

KANEKO, Takaaki
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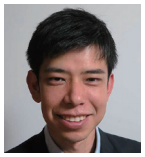

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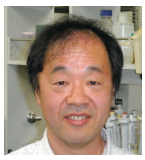

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NAMBU, Atsushi
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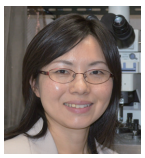

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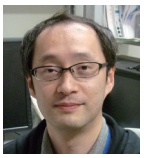

NISHIMURA, Akiyuki
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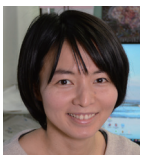

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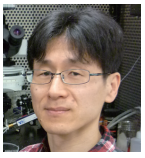

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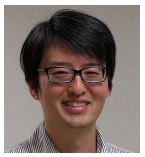

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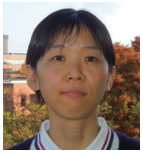

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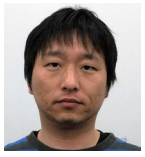

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