

PROJECT FOR PSYCHIATRIC AND NEUROLOGICAL DISORDERS

Strategic Research Program for Brain Sciences (SRPBS)

Brain Mapping by Integrated Neurotechnologies for
Disease Studies (Brain/MINDS)

Research and Development Grants for Longevity Science

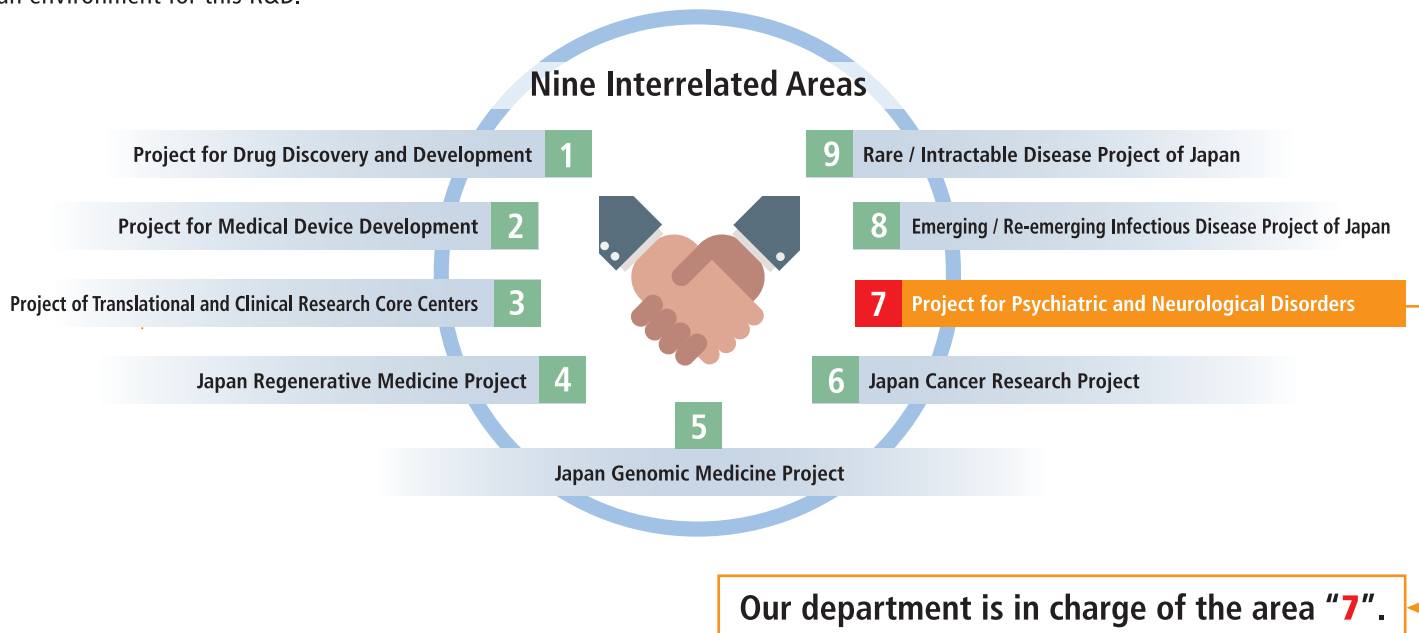
Research and Development Grants for Dementia

Research and Development Grants for Comprehensive
Research for Persons with Disabilities



About Programs

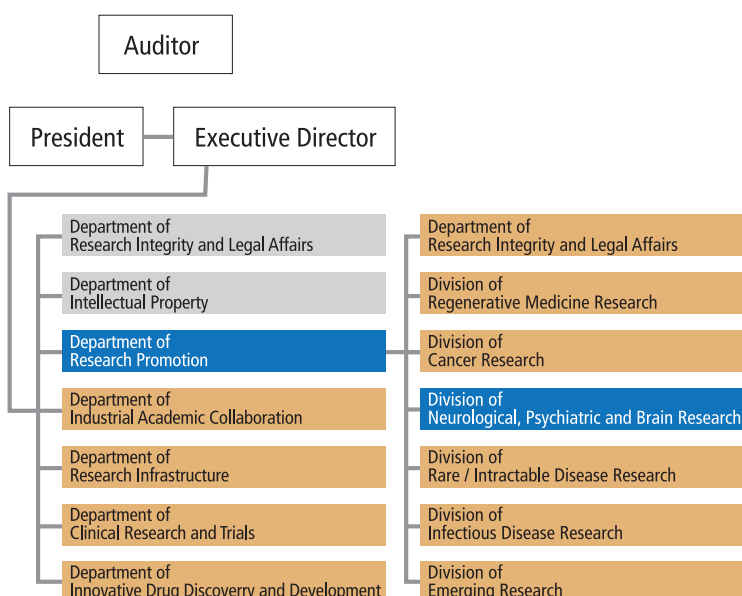
Based on the Plan for Promotion of Medical Research and Development prescribed by the government of Japan, the Japan Agency for Medical Research and Development (AMED) promotes integrated R&D in the field of medicine, from basic research to clinical trials, focusing on nine interrelated areas including regenerative medicine and oncology. In addition to ensuring that outcomes are linked through to practical application, it undertakes projects with the aim of comprehensively and effectively establishing and maintaining an environment for this R&D.



Management and Evaluation Framework

AMED assigns program directors (PD), program supervisors (PS), and program officers (PO) who have top-class academic backgrounds and R&D achievements in the appropriate field of research, and are knowledgeable concerning the evaluation of R&D topics and operation of R&D projects. PDs, PSs, and POs work together to gain an understanding of research topics in all interrelated areas. They provide sophisticated expert coordination for program operation in the interrelated areas for which they are responsible and promote cooperation between interrelated areas. They also evaluate and discover excellent R&D proposals, and provide integrated management of the program so that basic research outcomes are linked through to clinical research and practical application.

About our Department



Project for Psychiatric and Neurological Disorders
Program Director

Shigeo OKABE

Professor, The University of Tokyo

Project for Psychiatric and Neurological Disorders accelerates endeavors aiming at overcoming dementia, depression, and other brain disorders. Our goal is to establish innovative strategies for diagnosis, prevention, and treatment of brain disorders through strong promotion of researches on neural circuits and brain functions related to pathophysiology of brain.

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Strategic Research Program for Brain Sciences (SRPBS)

Program Supervisor

Ritsumeikan University

Masayoshi MISHINA



Riken

Tadafumi KATO

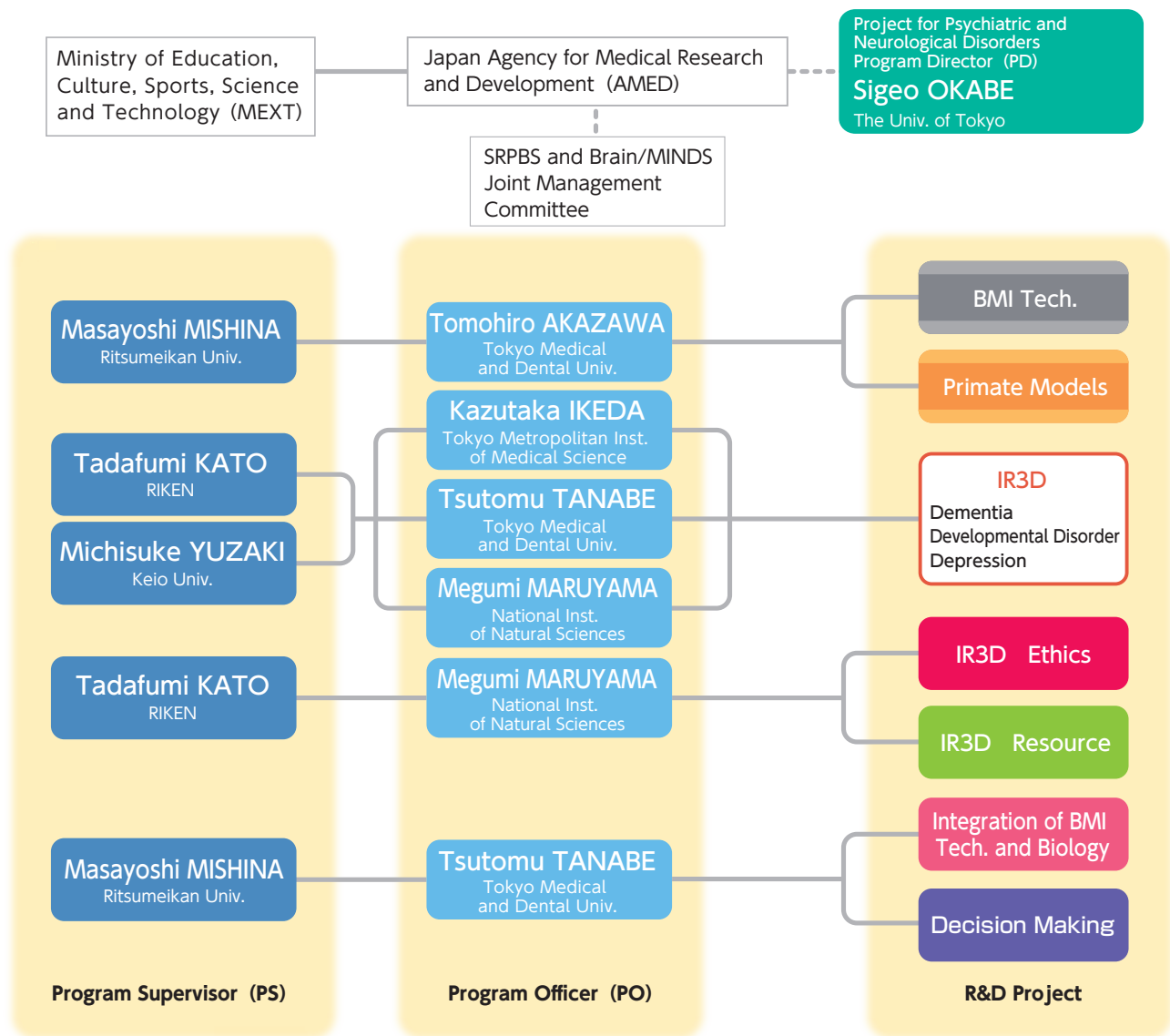


Keio University

Michisuke YUZAKI



Organizatrion



BMI Technologies

Development of BMI Technologies for Clinical Application

BMI Technologies

The mission of the Base is to promote researches that will lead to the development of innovative preventive, diagnostic and therapeutic strategies for independence support and conquest of mental and neurological disorders. The project is run through a close collaboration among the 3 groups, "The Compensatory BMI Group" that is developing minimally invasive implantable BMI, "The Restorative BMI Group" that aims at developing innovative rehabilitation technologies and "The Mental and Neurological Diseases Treatment Group" that consists of "The DecNef Group" that is developing DecNef technologies to treat mental disorders, and "The Primate rTMS Group" that aims at elucidating the effects of rTMS and establishing neuromodulation methods. The Base is striving for research and development with the aims of transmitting world's cutting-edge scientific achievements visible to the public.

Development of innovative BMI rehabilitation device and method based on brain systems theory and its clinical application - with emphasis on hemiparetic stroke

2013-2017 **Meigen LIU**

Keio University
Professor

We are developing innovative and clinically applicable BMI rehabilitation technologies to restore post stroke reaching and gait disturbances. Keio University (project management and building of clinical bases), National Center of Neurology and Psychiatry (multidimensional visualization of brain plasticity), Tokyo Institute of Technology (development of decoding technologies) and Advanced Telecommunications Research Institute International (development of upper and lower extremities exoskeletal robots) collaborate closely to promote the two projects: In the "upper extremity project", we will develop innovative BMI rehabilitation strategies that enable neural-pathway-selective rehabilitation. In the "gait restoration project", we will establish a comprehensive gait restoration strategy by combining robotic assistance triggered by brain activities, spinal stimulation and hybrid orthosis.



Development and control of upper- and lower-limb exoskeleton robots for BMI Rehabilitation

2013-2017 **Jun MORIMOTO**

ATR
Head of Department

We develop upper- and lower-limb exoskeleton robots for assisting human movements. We support BMI rehabilitation through our exoskeleton robot control strategy based on our originally designed safe and compliant actuation system. We design an upper-limb exoskeleton robot to assist shoulder joint movements as well as a balance control system for a lower-limb assistive robot to support recovery of walking function.



Multi-modal imaging of neuroplasticity underpinning functional recovery enhanced by BMI

2012-2017

Takashi HANAKAWA

National Center of Neurology and Psychiatry
Director

Brain machine interface (BMI) combined with rehabilitation draws attention as a measure to restore functions after stroke. The visualization of neuroplasticity through multi-dimensional imaging will help understand the underlying mechanism of BMI-rehabilitation and develop monitoring systems of its efficacy.



Development of decoding method using musculoskeletal model

2013-2017

Yasuharu KOIKE

Tokyo Institute of Technology
Professor

In this project, we aim for developing decoding method to detect the motion from brain signals and for making robot controlled by the decoded signals. Those techniques will be applied to the rehabilitation.



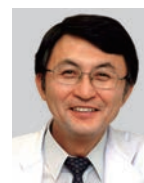
Brain-machine interfaces for restoration of motor and communication

2013-2017

Toshiki YOSHIMINE

Osaka University
Specially-appointed Professor

This project is to develop a brain-machine interface (BMI) to support motor and communication function in severely-disabled people such as with advanced stage of ALS. In this system, the implanted device amplifies and transmits the electrocorticographic signals (ECoGs) recorded on the surface of the brain to the external receiver. The signals are decoded by a computer so that he or she can operate the robots or communication devices just by thinking.



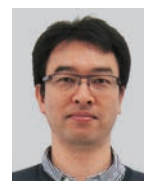
Bidirectional restoration of somatosensory and motor function using brain-machine interface

2013-2017

Yukio NISHIMURA

Kyoto University
Associate Professor

Precise control of the upper limb relies on both descending motor commands and ascending somatosensory feedback about limb position and force production. Spinal cord injury often damages these pathways, although leaving neural circuits locate above and below the lesion remain intact while crippling its function. This study aims to restore both lost motor and somatosensory function in monkeys with neuronal damage by re-wiring preserved neural structures via bidirectional brain-machine interface: simultaneous electrical stimulation to nerves innervating the muscles controlled by motor cortical activity and electrical stimulation to the somatosensory cortex controlled by upper limb movements.



Development and application of multi-channel BMI measurement system and decoding technology

2013-2017 **Takafumi SUZUKI** National Institute of Information and Communications Technology
Senior Researcher

Our objectives are research and development of an implantable BMI system aiming at clinical application of BMI based on electrocorticogram (which is measured directly on the surface of the brain). More specifically, our targets are development of basal technologies such as neural electrode array, LSI for neural signal processing, wireless communication, and decoding. And then we evaluate the safety and the effectiveness of the integrated systems. We execute the tasks collaborating with Osaka University, the University of Electro-Communications and National Institute of Natural Sciences.



Development of intelligent electric assistance device for BMI control

2013-2017 **Hiroshi YOKOI** The University of Electro-Communications
Professor

We develop robotic prosthetic arms and non-invasive BMIs for clinical applications.

In cooperation with Osaka University and the National Institutes of Natural Sciences, we develop intelligent robotic prosthetic arms for subtle holding of objects with various grasping postures.

In collaboration with Osaka University and the National Rehabilitation Center for Persons with Disabilities, we construct neuro-feedback (Nef) systems with real-time magnetoencephalogram (MEG) measurement, which is a non-invasive BMI technique, and develop BMI controlled devices as the peripheral technologies.



Application of DecNef for development of diagnostic and cure system for mental disorders and construction of clinical application bases

2013-2017 **Mitsuo KAWATO** ATR
Director, ATR Fellow

Our aim is to clarify the principles and thus improve the performance of the DecNef (Decoded Neurofeedback) method, which effectively includes the patterns of brain activity by using a mathematical/statistical technique. We are building a clinical base for DecNef work in Tokyo. Furthermore, we are developing biomarkers of multiple psychiatric disorders based on data measured at multiple sites. We promote the quantification of drug efficacy by using a multi-dimensional evaluation method, based on biomarkers of multiple psychiatric disorders, and the development of DecNef treatments based on a multi-dimensional evaluation method.



Development of new treatments of intractable pain with convenient rTMS device and DecNef method

2013-2017 **Youichi SAITOH** Osaka University
Professor

- 1) The data of rs-fcMRI of post-stroke pain revealed increased functional connectivities within Default mode network.
- 2) With the same imaging parameters of study group, the data of rs-fcMRI of intractable pain have been accumulated to obtain the biomarker.
- 3) We developed the DecNef using magnetoencephalography (MEG). The MEG-DecNef was applied for the phantom limb pain patients. We succeeded to decrease their pain by controlling their neural information of the phantom movements.
- 4) Convenient rTMS machine for clinical trial is developed. Investigator initiated clinical trial (phase III) will start in end of December 2015.



Development of biomarker and neuromodulation techniques for neuropsychiatric disorders based on BMI technologies

2013-2017 **Hidehiko TAKAHASHI** Kyoto University
Associate Professor

Diagnosis and treatment evaluation of neuropsychiatric disorders depend on superficial behavioral observation and self-report, and are not supported by biological foundations. For a more precise diagnosis, the development of biomarkers based on biologic data is necessary. We will aim to develop the biomarkers of schizophrenia from multidimensional brain information, mainly based on resting state functional MRI. We will use not only supervised machine learning but also non-supervised machine learning to explore subtypes of schizophrenia. After the biomarkers established by a cross-sectional study, we will conduct longitudinal studies to investigate the effects of conventional treatments, such as pharmacotherapy and electroconvulsive therapy, on these biomarkers. At the final state of this project, we will try to develop novel neuromodulation methods for treating neuropsychiatric disorders. Utilizing real-time fMRI and decoded neurofeedback, we will aim to change the brain activity patterns (biomarkers) of schizophrenia and mood disorder patients to resemble healthy patterns.



Development of innovative diagnostic and intervention methods for developmental disorders and construction of clinical research center for BMI in psychiatry

2013-2017 **Nobumasa KATO** Showa University
Director

The mission of our research is to develop MRI-based BMI research for adult high-functioning autism spectrum disorder (ASD). More specifically, we are committed to the following projects: 1. Development of biomarker for ASD by data-driven analysis of resting-state functional connectivity MRI data. 2. Development of neurofeedback methods with the aim of advancing brain functions of ASD. 3. Establishing research environment for fMRI-based neurofeedback in Tokyo area.



Revealing the neural basis of plasticity induction by DecNef

2013-2017 **Masamichi SAKAGAMI** Tamagawa University
Professor

It is necessary to reveal the neural basis of DecNef to establish its safety and efficacy and to improve its performance. In Tamagawa University, we implanted ECoG electrodes on monkeys' prefrontal cortices to record local field potentials, which are the source of the BOLD signal, and to develop an animal model for DecNef. Furthermore, we will analyze the plastic change of neural activity in the prefrontal network in aim to understand the neural basis of DecNef.



Development of novel repetitive transcranial magnetic stimulation parameters from motor control and decision-making via dopaminergic and acetylcholinergic systems of monkeys

2013-2017 **Yasushi KOBAYASHI** Osaka University
Associate Professor

Midbrain dopamine (DA) and brainstem acetylcholine (ACh) are implicated in the regulation of movement, decision-making and learning and play an important role in neurological disorders (Parkinson's disease, etc.). In view of the recent up-growing interest of non-invasive brain stimulation as potential tool for treatment of neurological disorders, it would be key to investigate dynamical interactions among the cerebral cortex, DA and ACh. We will investigate how modulation of the focal cortical area (prefrontal and motor area) influences monkey's performance and behavior on cognitive tasks (eye movement and forelimb reaching tasks) and activity of DA and ACh neurons by using repetitive transcranial magnetic stimulation (rTMS). From this animal study, we will develop ideal rTMS treatment parameters for patients with neurological disorders.



Investigating the mechanisms of the effect of transcranial magnetic stimulation (TMS) on motivation, arousal, learning, and decision making by the monitoring of the neural activity in the prefrontal cortex

2013-2017 **Ken-Ichiro TSUTSUI** Tohoku University
Associate Professor

Transcranial magnetic stimulation (TMS) is a non-invasive method to manipulate the brain activity, and is expected as a new treatment for various neural and mental disorders. In this project, we aim to investigate the basic mechanisms how TMS induces change in the brain activity, and provide information necessary for the optimization of its use in clinical practice, through neural measurements in animal experiments.



Development of a methodological framework for a neuroimaging-based biomarker of neuropsychiatric disorders and its clinical application including the decoded neurofeedback (DecNef)

2013-2017 **Tsuyoshi ARAKI** The University of Tokyo
Associate Professor

Based on a large sample of neuroimaging and clinical data, we aim to establish a methodological framework that enables optimal extraction of disorder-specific features of the brain and thereby to develop an algorithm (biomarker) that facilitates objective identification of neuropsychiatric conditions and therapeutic application of decoded neurofeedback (DecNef). We will also establish an animal (rat) model of DecNef to optimize its implementation protocol and to evaluate the effects of psychotropic drugs to its efficacy.



Establishment of depression biomarker and its application to neurofeedback

2013-2017 **Yasumasa OKAMOTO** Hiroshima University
Associate Professor

The mission of Hiroshima University Research Team is developing depression specific biomarkers using resting state functional connectivity MRI to be utilized at different facilities, applying them to Decoded Neurofeedback by NIRS-EEG, relatively simple brain function measurement device, and eventually undertaking the development of a new treatment for depression. We also expect our study in depression specific biomarkers will lead to development of cross-disorder biomarkers.



Biological BMI

Biological BMI: A new strategy to enhance the effect of BMI-based treatment

In this two-year project, we are aiming to develop a cutting-edge biological approach to facilitate and amplify the effect of engineering based BMI-based treatment. By combining transcranial ultrasound and magnetic stimulation as well as high resolution brain imaging technique, we will develop a new method to access the central nervous system and navigate its plasticity.

Non-invasive stimulation and drug delivery to focal, deep brain structures by transcranial focused ultrasonic stimulation (tFUS)

2016-2017 **Kazuhiko SEKI** National Center of Neurology and Psychiatry
Director

Purpose of this project is to develop a less-invasive method to stimulate focal, deep brain area and deliver various drug to them by using transcranial focused ultrasound stimulation (tFUS). A interdisciplinary team from Biology (Seki), Engineering (Takagi), Medicine (Azuma), and Pharmacy (Maruyama) is pursuing to establish this cutting-edge treatment using animal experiments.



Development of combination therapy consisting of BMI technology and biological compounds to promote restoration of the injured central nervous system

2016-2017 **Toshihide YAMASHITA** Osaka University
Professor

We aim to elucidate the mechanism of compensatory neural network formation and functional recovery during acute to chronic phases following the injuries in the central nervous system, and then will develop the strategy comprising of multiple therapeutic methods to promote functional recovery after neuronal injury and degeneration. In addition, we will find out the biomarkers to appropriately estimate functional recovery after them.



Primate Models

Construction of System for Spread of Primate Model Animals

Primate Models

Higher cognitive function such as speech, thinking, memory and learning are important abilities to live as human being. When these competencies are missing, psycho-neurologic disease will be onset. Non-human primates play important roles to uncover the mechanisms how the high cognitions are realized. In this program, we will establish new infrastructure for studying higher cognitive function using genetically modified marmoset models and uncover the mechanisms of high cognitions.

Construction of system for spread of primate model animals

2013-2017 **Erika SASAKI**

Central Institute for Experimental Animals Director /
Keio University Professor

Central Institute for Experimental Animals is the Core Institute of Strategic Research Program for Brain Science, "Maintenance of Systems for Creation and Spread of Primate Model Animals". We are tightly collaborating with the Partner Institutes to aim the spread of genetically modified marmoset models for brain science. Central Institute for Experimental Animals will develop non-invasive reproductive-developmental biological technics and target gene knock-in technology for expanding usefulness of genetically modified marmoset to widely spread as brain science models.



Development of gene targeting technology and establishment of genome information infrastructure in common marmoset

2013-2017 **Seiji SHIOZAWA**

Keio University
Lecturer

Our project consists of three components.

- 1) Development of gene targeting technology for knock-out and knock-in marmosets.
- 2) Evaluation of mutant α -synuclein and TDP-43 transgenic marmosets as preclinical models for Parkinson's disease and ALS, respectively.
- 3) Increase the utility of marmoset as an experimental primate by establishing their genome information infrastructure of the common marmoset.



Generation of transgenic common marmosets that are beneficial for neuroscience researches

2013-2017 **Masanori MATSUZAKI**

The University of Tokyo
Professor

Tet-on and Tet-off system can be used to amplify the expression of exogenously introduced genes, which would make them useful in models of neurological disorders. In this assignment, the main aim is to show that the expression of Channelrhodopsin-2 (ChR2) and genetically-encoded calcium indicators can be controlled in Tet-on and Tet-off transgenic marmosets. We will also increase the number of animal lines of Tet-on and Tet-off transgenic marmosets and then, establish a breeding colony for their broad diffusion among neuroscientists.



Comprehensive analysis of cytochrome P450 in common marmosets

2013-2017 **Hiroshi YAMAZAKI**

Showa Pharmaceutical University
Professor

The common marmoset (*Callithrix jacchus*) is a non-human primate that could prove useful as human pharmacokinetic and biomedical research models. The cytochromes P450 (P450s) are a superfamily of enzymes that have critical roles in drug metabolism and disposition via monooxygenation of a broad range of xenobiotics; however, information on some marmoset P450s is currently limited. Therefore, identification and quantitative analysis of those of P450s need to be carried out in detail before the marmoset can be used as an animal model in drug development.



Enhancement and development of the reproductive biotechnology technics for the effective production of genetically modified marmosets

2013-2017 **Yusuke SOTOMARU**

Hiroshima University
Professor

We carry out improvement and development of the reproductive biotechnology technics, aiming at the establishment of the effective production system of useful experimental marmosets including genetically modified individuals. We are improving basic reproductive biotechnology technics such as ovarian stimulation, IVC of oocytes and fertilized egg, IVF/ICSI, cryopreservation of embryos/gametes, and trying to produce genetically identical marmosets by embryonic and somatic/ES cell cloning techniques and embryo splitting.



IR3D -Dementia

IR3D -Dementia

The total number of demented individuals in Japan exceeds 4 million, and the total economic burden amounts to 14.5 trillion yen, urging us to develop prevention and therapeutic methodologies against dementia. The Dementia Research Team aims to merge cutting-edge basic neuroscience with clinical research, and elucidate the molecular pathophysiology of dementia and develop diagnostic and therapeutic methods, e.g., analysing metabolic and inflammatory stress, Abeta degradation in Alzheimer's disease, developing novel immunotherapies, diagnostic and therapeutic drugs against dementia with Lewy bodies and molecular targeted therapies in FTLD, thereby finding cure for dementia by 2025.

Project Leader

Comprehensive development of therapeutic strategies for Alzheimer's disease based on novel amyloid hypothesis.

2016-2020 **Takeshi IWATSUBO** The University of Tokyo Professor

Through the re-definition of novel amyloid hypothesis for the pathogenetic mechanism of Alzheimer's disease (AD) involving the up- and downstream of amyloid β ($A\beta$), we aim to develop novel therapeutic and diagnostic strategies against the earliest stage of AD. Iwatsubo group develops strategies for prevention and treatment of AD based on analyses of metabolic and inflammatory stress including diabetes. Tagawa group develops an antibody therapy for AD against HMGB1, a damage-associated molecular pattern. Okochi group establishes plasma APL1 β , an $A\beta$ -related protein, as an AD biomarker. Each group study collaborates closely toward the development of novel therapeutic and diagnostic strategies based on the merge of basic and clinical neurosciences.



Development of a new disease-modifying therapy and early diagnostic method of Alzheimer's disease based on a cause of amyloid deposition observed in sporadic type.

2016-2020 **Nobuhisa IWATA** Nagasaki University Professor

Down-regulation of major $A\beta$ -degrading enzyme neprilysin in the brains is one of causes of amyloid deposition of sporadic Alzheimer's disease. In this research project, we develop a lead compound to up-regulate neprilysin activity as a disease-modifying drug of Alzheimer's disease, and carry out a translational research. We also develop a plasma or cerebrospinal fluid biomarker to monitor a change in neprilysin activity in the brain as an early diagnostic method of Alzheimer's disease.



Biomarker for Alzheimer's disease in plasma and $A\beta$ dynamic analysis in the brain

2016-2020 **Nobuto KAKUDA** Doshisha University Assistant Professor

$A\beta$ species in plasma will be one of biomarker for early Alzheimer's disease stage. In this study, I will develop measurement methods and measure them. And I will follow $A\beta$ deposition mechanism and γ -secretase activity in AD model mice.



Novel mechanisms for degradation of α -synuclein

2016-2020 **Tomohiro KABUTA** National Center of Neurology and Psychiatry Section Chief

Accumulation of α -synuclein proteins in neurons is closely involved in the pathogenesis of dementia with Lewy bodies. Therefore, understanding of intracellular system for degradation of α -synuclein is important for the development of therapy of α -synucleinopathy. We have found a novel protein that regulates intracellular degradation of α -synuclein. The aim of this study is to clarify novel mechanisms underlying degradation of α -synuclein. This study may provide an intellectual basis for the development of therapy of α -synucleinopathy.



Development of innovative research on tauopathy diagnosis and therapeutics

2016-2020 **Shigeomi SHIMIZU** Tokyo Medical and Dental University Professor

The aim of this project is to unveil the pathological mechanism of Alzheimer's disease and non-Alzheimer's disease tauopathies from the aspect of tau degradation. We develop small compound chemicals against tauopathies and imaging PET ligands capable of visualizing the tau degradation. We also apply these knowledge to other misfolding diseases.



Development of molecular-targeted therapy and biomarker for disease-modifying therapy in FTLD

2016-2020 **Gen SOBUE** Nagoya University Designated Professor

FTLD is one of the three major neurodegenerative dementia. The etiology of the disease remains unclear and there is no effective therapeutics for the disease so far. In this project we will develop the novel ASO therapy targeting tau isoform and TDP-43 expression which are involved in the pathogenesis of FTLD. Moreover, we will also conduct to develop the integrated imaging biomarkers which provide the very early diagnosis including prodromal stage, prognosis, and the assessment of drugs effects on disease progression based on the novel molecular and anatomical findings in FTLD pathology and FTLD model animals.



Development of preventive therapies for Alzheimer's disease by targeting endogenous molecules showing unsuspected disease-modifying activities

2016-2020 **Masaki NISHIMURA** Shiga University of Medical Science
Professor

Age-related decline in expression levels of brain secretory proteins ILEI and p3-Alc β is considered as a risk factor for Alzheimer's disease, and these molecules may be promising targets for disease-modifying therapy. The aim of this project is to develop preventive treatments for Alzheimer's disease by targeting neuronal ILEI and p3-Alc β activities to reduce production and neurotoxicity of A β peptides.



Research on the regulatory mechanism of dementia-related seeds transmission and propagation and development of therapeutic basis

2016-2020 **Nobuyuki NUKINA** Doshisha University
Professor

Abnormal accumulation and aggregation of proteins, such as tau and synuclein are main pathological features of dementia-related neurodegenerative disorders. Recently, the hypothesis that those proteins are transmitted and propagated like prion is proposed. In this project, we will elucidate the regulatory mechanism of transmission and propagation, and the structural specificity of those abnormal proteins to each disease and brain lesions. We will further develop the diagnostic and therapeutic basis for those diseases.



Novel approaches for treatment of dementia by improving sleep quality

2016-2020 **Yu HAYASHI** The University of Tokyo
Associate Professor

In dementia, sleep disorders comprise a major peripheral symptom. Sleep disorders threaten the lifestyle of the patient's family or care personnel. Moreover, sleep disorders may contribute to the progression of dementia itself. In this study, we address the underlying mechanism of sleep disorders in dementia, and aim to develop effective treatments. Furthermore, we attempt to prevent the progression of dementia by improving the quality of sleep.



Developments of early diagnostic method and disease modifying therapeutics for dementia with Lewy bodies

2016-2020 **Kohji FUKUNAGA** Tohoku University
Professor

Dementia with Lewy bodies (DLB) including Parkinson's disease is caused by neurodegeneration with spreading of abnormal α -synuclein aggregation. Early diagnosis and therapeutics inhibiting α -synuclein aggregation allow for important early treatment and improvement of quality of life. We discovered that fatty acid binding proteins (FABPs) promote α -synuclein aggregation. In the present study, we establish the clinical benefit of FABPs for diagnostic biomarkers and develop the disease-modifying therapeutics and imaging probes using FABP ligands.



Exploring therapeutic candidates for Alzheimer's disease through targeting neuroinflammation.

2016-2020 **Koji YAMANAKA** Nagoya University
Professor

Neuroinflammation, consisted of the neurotoxic and protective reactions of microglia phagocytosing amyloid β of Alzheimer's disease brain, is recognized as one of the key factors for pathomechanism of dementia. In this program, we aim to explore the therapeutic candidates for Alzheimer's disease through targeting neuroinflammation.



Developing imaging agents of molecules for diagnosis and treatment of Alzheimer's disease (AD), and an analysis of pathophysiological mechanisms in AD by developing blood-brain barrier transitable ABO antibodies

2016-2020 **Takanori YOKOTA** Tokyo Medical and Dental University
Chief Professor

Our study is focusing on amyloid- β oligomer (ABO) of Alzheimer's disease, and we will use anti-ABO antibodies the phase 1 clinical trial of which for prevention of AD has already been progressing in the United States. We will newly develop a carrier with Glucose transporter-1 (GLUT1) ligands packaging the antibodies, or directly fuse the antibodies to GLUT1 ligands, which will be able to penetrate blood-brain barrier (BBB). Then we also develop new PET/MRI contrast agents for ABO using our newly created antibodies, which can be used for the diagnosis of early AD, analysis of ABO pathophysiology, and of treatment effects for preventing AD.



IR3D

-Developmental Disorders and Schizophrenia

IR3D -Developmental Disorders and Schizophrenia

The common goal of our research projects is to develop novel diagnosis strategies and treatments by uncovering the pathophysiology of psychiatric disorders considered to be having their pathophysiology in neurodevelopmental processes including autism spectrum disorder and schizophrenia. To archive the goal, researchers from various fields will be collaborating in animal researches and human clinical studies at genes, cells, neural circuits, system, behavior and clinical symptom levels. Clinical studies also include some exploratory clinical trials and multi-site independent clinical trials.

Project Leader

Development of an innovative treatment of autism spectrum disorder utilizing oxytocin, development of a novel technology enabling prediction of individual differences in response to treatment, and identification of a novel therapeutic agent based on uncovering mechanisms of ASD pathophysiology and therapeutic effects on it

2016-2020 **Hidegori YAMASUE** Hamamatsu University School of Medicine Professor

Regarding development of an innovative treatment of autism spectrum disorder, we will conduct clinical trials of a novel therapeutics to be approved by Japanese FDA. Regarding development of a novel technology enabling prediction of individual differences in response to treatment and uncovering mechanisms of ASD pathophysiology and therapeutic effects on it, we will conduct an integrative analyses of behavioral, neural, and molecular level data collected from participants of the trials. Then, the data will be analyzed to develop novel methods assessing social communication and its deficits and drug response objectively and quantitatively. In addition, animal studies will be conducted to uncover the mechanisms of therapeutic effects and ASD-like behaviors.



Innovations of diagnostic methods and therapeutics for schizophrenia and developmental disability.

2016-2020 **Masanari ITOKAWA** Tokyo Metropolitan Institute of Medical Science Director, Center for Medical Cooperation

We will detect the pathophysiology by using a large functional change caused by rare variant to innovate the diagnostic methods and therapeutics for schizophrenia and developmental disability.

We will clarify the mechanism of development of the diseases by analyses of mouse model using rare variations and will find the association between rare variants and the illnesses by investigation of functional neural networks and behavioral analyses.



Development of diagnostics and therapeutics against schizophrenia and autism spectrum disorder based on genomic analysis

2016-2020 **Norio OZAKI** Nagoya University Professor

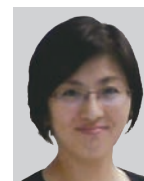
We identify rare genomic variants (copy number variants and single nucleotide variants) associated with risk for schizophrenia or autism spectrum disorder using genomic analysis. Based on the findings, we develop and analyze animal and cell models (iPS cells derived from patients) for the two disorders. Finally we are going to elucidate molecular pathogenesis, develop biomarkers and novel therapeutics for these conditions.



Elucidating the molecular and cellular basis of psychiatric disorders based on abnormal calcium signaling

2016-2020 **Sayaka TAKEMOTO-KIMURA** Nagoya University Professor

In this project, we will focus on a group of psychiatric disorder-related genes that are responsible for neuronal calcium signaling, as indicated by human genetic studies. We will examine the effect of gene mutations on the molecular function and develop a genetically-modified disease animal model. Utilizing the disease animal model, we will conduct a multi-discipline analysis to understand the molecular and cellular pathogenesis underlying psychiatric disorders based on abnormal calcium signaling.



Understanding schizophrenia pathology, diagnosis and treatment through engagement of the brain nuclear receptor regulatory system

2016-2020 **Motoko MAEKAWA** RIKEN Brain Science Institute Research Scientist

I will investigate schizophrenia pathology focusing on the nuclear receptor system and develop novel diagnostic and therapeutic tools using ligands and biomarkers for nuclear receptors. Integration of these approaches will contribute to helping schizophrenia patients.



Harnessing cellular metabolism and dynamics to understand the mechanisms and steer the development of novel therapies for autism and schizophrenia

2016-2020 **Takeo YOSHIKAWA** RIKEN Brain Science Institute Laboratory Head

To address the major challenges in psychiatric medicine, including the lack of approved drugs for autism and the urgent need for better treatments for schizophrenia, we will harness the principles of cellular metabolism and dynamics to decipher underlying disease mechanisms and provide innovative therapeutic approaches.



IR3D

-Developmental Disorders and Schizophrenia

IR3D -Developmental Disorders and Schizophrenia

We are examining environmental factors, genomes, neuroimaging and biomarkers in blood associated with etiology of mood disorders in human, and will elucidate the neural circuit and molecular pathophysiology related to depressive symptoms. Furthermore, we will identify the etiological mechanisms of depression by conducting the molecular pathophysiological and behavioral analyses using animal models. Based on these results obtained, we will finally attempt to develop techniques for stratification of depression and novel diagnoses by machine learning technique, to establish methods of prevention based on lifestyle, and to develop new treatments such as neurofeedback treatment and new medications for mood disorders.

Project Leader

Stratification based on the pathophysiology of depression and the development of innovative diagnosis and therapy of modulating neural circuit

2016-2020 **Shigeto YAMAWAKI** Hiroshima University Professor

We are comprehensively examining the neural circuit, molecular pathophysiology and clinical data in patients with depression, and will establish the technique for the stratification and diagnosis of depression. We are also developing neurofeedback treatment of directly modulating abnormal neural circuit and a new drug treatment based on "Drug re-profiling studies". Furthermore, we are studying the biological etiology of being the basis for diagnosis or treatment of depression.



Development of novel treatment and diagnosis for mood disorder based upon gene-environment interaction

2016-2020 **Nakao IWATA** Fujita Health University School of Medicine Professor

Mechanism of mood disorders (bipolar disorder and major depressive disorder) remains unknown, however, several hypotheses have been proposed so far. In this project, focusing on the abnormal lipid metabolic state, we examine whether (1) abnormal state of lipid pathway is associated with or has causal relationship to bipolar disorder and (2) the intervention of omega-3 polyunsaturated fatty acid (PUFA) is potent therapeutic option. In addition, we examine the pathophysiology of major depressive disorder by gene-environment interaction study and aim to detect novel susceptibility genes for this condition.



Identification of genetically defined subsets of bipolar disorder by trio sequencing

2016-2020 **Atsushi TAKATA** RIKEN/Yokohama City University Senior Visiting Scientist/Assistant Professor

In this project, we comprehensively analyze de novo mutations and inheritance patterns of rare variants by performing exome and genome sequencing of bipolar patients and their unaffected parents. Through these analyses, we aim to identify genes/mutations associated with bipolar disorder (BD) with a strong effect size, which could genetically define a subset of BD, and to uncover molecular pathways contributing to pathogenesis of BD.



Cross-sectional study of psychiatric disorders with the PET probe for AMPA receptors

2016-2020 **Takuya TAKAHASHI** Yokohama City University Professor

A number of patients suffer from psychiatric disorders. In order to establish effective treatments for psychiatric disorders, we need to elucidate molecular mechanisms underlying them. However, the molecular basis of psychiatric disorders are still poorly understood. AMPA receptors are major neurotransmitter receptors in the brain. We developed novel PET (positron emission tomography) probe to visualize AMPA receptors in living human brain. We will cross-sectionally investigate psychiatric disorders with this novel PET probe for AMPA receptors. Our study can establish novel concept of psychiatric disorders and lead to innovative treatment of psychiatric disorders.



Development of personalized medicine for depression based on the pathogenesises related to nutrition, life style and inflammation

2016-2020 **Hiroaki TOMITA** Tohoku University Professor

This project aims to elucidate the pathogenesises of depression and postpartum depression, related to nutrition, life style and inflammation, and develop personalized medicine for the pathological conditions, by conducting integrative studies utilizing resources from large scale genome cohorts conducted by Tohoku University Tohoku Medical Megabank Organization, biomarker study settings utilizing cerebrospinal fluid, plasma and intestinal flora samples from depressed patients conducted by the group in the National Center for Neurology and Psychiatry, and mouse models of depression-related pathology developed by the group in Fujita Health University.



Development of diagnostic and therapeutic methods for depressive symptom based on mesocorticolimbic system

2016-2020 **Kenji HASHIMOTO** Chiba University Professor

The purpose of this project is to develop the diagnostic and therapeutic methods for depressive symptom based on mesocorticolimbic system. The NMDA receptor antagonist ketamine shows a rapid antidepressant effect in treatment-resistant patients with depression. We will identify the molecular mechanisms of R-ketamine without side effects, and we will perform clinical trial of R-ketamine. Furthermore, we would like to transfer R-ketamine to pharmaceutical industry.



IR3D

-Resource/Ethics

IR3D -Resource/Ethics

- Resource
The Japan Brain Bank Network promotes your biological research with brain resources.
- Ethics
Support for researchers, ethics education, and research on research ethics will promote a social consensus on neuroscience.

Project Leader

Establishment of Japan brain bank net

2016-2020 **Yuko SAITO** National Center Hospital of Neurology and Psychiatry
Medical director

Postmortem brain resource is essential for the study of intractable neurological and psychiatric disorders. In this project, we have established the Japan Brain Bank Net (JBBN), which forms a collaborative network of major brain banks in this country. This all Japan system guarantees appropriate amount of resource of common disease to researchers, such as Alzheimer' disease, Parkinson disease and Schizophrenia. This project also helps effort of each member to build up the resource of rare neurodegenerative or psychiatric disorders like corticobasal degeneration or bipolar disorders. The aim of this project is to establish the infrastructure to reach the goal of final cure of these disorders.



Resolving ethical, social legal issues in neroscience

2016-2020 **Yoshiyuki TAKIMOTO** The University of Tokyo
Associate Professor

Our agenda is to provide ethical support for researchers involved in neuroscience research. Next, we hope to establish clinical research subjects protection through the comprehensive efforts of academic research groups addressing the Ethical, Legal, and Social Implications (ELSI) of brain science including the field of neuropsychiatric disorders.



Decision Making

Decision Making

Special feature of the primates including humans is their capability of making flexible decision and behavior selection by detecting subtle fluctuations in the rapidly changing environment. In this project, we aim at clarifying the neural circuit mechanisms of flexible behavior selection of primates, either instinctive, reward-based, cognitive or social, by developing and fully applying the innovative technologies such as 2-photon imaging and viral vector-mediated circuit manipulation techniques.

Project Leader

Integrative studies on neural circuit basis of flexible decision making in humans and nonhuman primates

2016-2020 **Tadashi ISA** Kyoto University Professor

In this research project, we aim at clarifying the neural basis of flexible decision making. For this purpose, we record multiple unit activity and try manipulation of circuit functions in nonhuman primates, and perform noninvasive recording of large-scaled network activity by functional MRI and manipulation of the activity by transcranial magnetic stimulation in humans while the subjects are performing the task that requires flexible decision. Then, we analyze the big data obtained in these experiments and try to decode the mode of decision making by machine learning algorithm to causally demonstrate the contribution of the neural activity to decision behavior.



Towards a system-level understanding of social decision-making and behavioral control

2016-2020 **Masaki ISODA** National Institute for Physiological Sciences Professor

This study aims to promote a system-level understanding of social cognitive function, in particular decision-making and behavioral control in social contexts. For this purpose, we use macaque monkeys as an experimental model, as they are inherently social animals and the functional structure of their brain is most similar to that of humans. This study is expected to clarify the global-network mechanism and genetic basis of social cognitive function through the development of better-controlled laboratory tasks.



Understanding the mechanism of common marmosets' neural circuit responsible for their basic social behaviors

2016-2020 **Kumi KURODA** RIKEN Team Leader

In mice, it has been shown that four kinds of innate social behaviors (mating, parenting, offence, defense) are governed by forebrain subnuclei, and can be decoded by the activation pattern of these subnuclei. In this project we will try to identify the marmoset counterparts of these brain areas and primate-specific regulatory mechanisms, to ultimately decode the behavioral choice of innate social behaviors in primates.



Development of measurement of decision-making-related outputs from marmoset basal ganglia

2016-2020 **Masanori MATSUZAKI** The University of Tokyo Professor

This project aims to develop a decision-making task for a small non-human primate, common marmoset, to image the activity of frontal cortex-projecting axons from the thalamic nuclei that receive signals from the basal ganglia during the task performance, to quantify decision-making-related information represented by these thalamocortical axons at single and population levels, and to prove that this information is critical for decision making by inhibiting the neural activity in the basal ganglia. The final goal is to develop the method to clarify some aspects of the primate-specific mechanisms for decision making.



Development of functional intervention and recording techniques with a novel retrograde gene-manipulation method for the macaque prefrontal and basal ganglia networks

2016-2020 **Keiji TANAKA** RIKEN Team Leader

Cognitive control functions of the prefrontal network in decision making and behavior selection depend on functional interactions among prefrontal cortical areas. Aiming at resolving the functional interactions, we develop the techniques of projection-specific functional blockage and projection-target identification of neurons during animal's behavior, using a novel retrograde gene-manipulation method. The developed techniques will be applied to the prefrontal network of macaque monkeys performing a cognitive task which requires rule application based on internal information, to verify their efficiency.



Chemogenetic imaging: in vivo visualization of axonal DREADDs expression and control of network dynamics for decision-making

2016-2020 **Takafumi MINAMIMOTO** National Institutes for Quantum and Radiological Science and Technology Team Leader

We are aiming to develop the "Chemogenetic imaging" methods, which allow us to localize the targets for reversible pathway-specific DREADDs manipulation and to analyze the change of whole brain neural activity. We will manipulate the activity of specific pathways from subcortical structures in monkeys to associate network activity with decision-making.



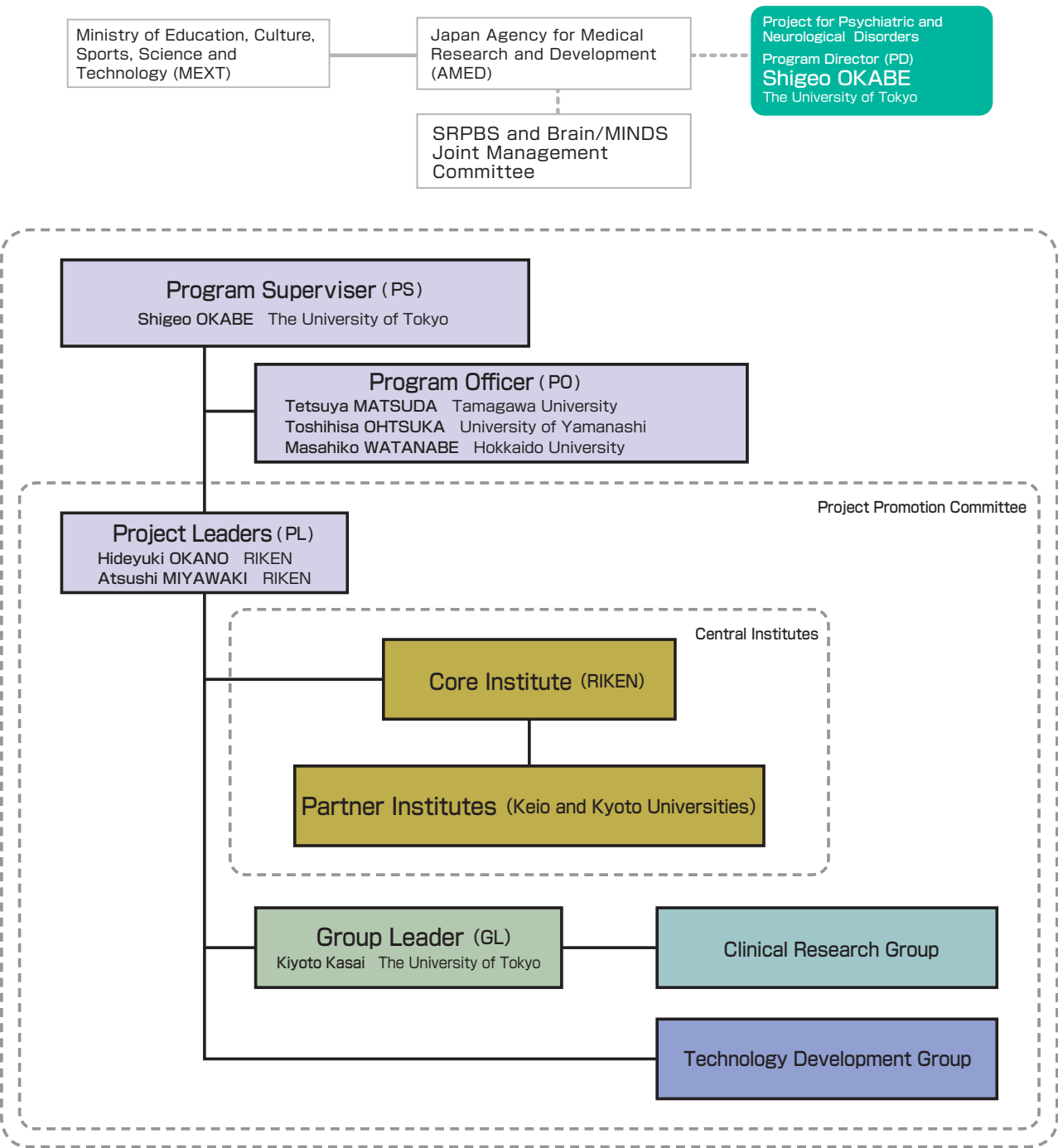
Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)

Program Supervisor
The University of Tokyo
Shigeo OKABE



Studying the neural networks controlling higher brain functions in the marmoset, to gain new insights into information processing and diseases of the human brain.

Organization



Central Institutes

Central Institutes

One of the important characteristics of Brain/MINDS is that we pay considerable efforts in mapping the brains of a small new world monkey, the common marmoset (*Callithrix jacchus*), since research on the non-human primate brain is essential for understanding the human brain and for developing knowledge-based strategies for the diagnosis and treatment of psychiatric and neurological disorders.

Brain Mapping by Integrated Neurotechnologies for Disease Studies

2014-2023 **Atsushi MIYAWAKI** RIKEN
Deputy Director

Development of novel, cutting-edge technologies that support brain mapping:

Our group is engaged in the 1) development of techniques for high-resolution, wide, deep, fast and long-time imaging of brain structures and functions, 2) development of techniques for controlling neural activity, and 3) establishment of a neuroinformatic platform for integrating heterogeneous and multi-scale data. The platform will cooperate worldwide for generating global databases.



Brain Mapping by Integrated Neurotechnologies for Disease Studies

2014-2023 **Hideyuki OKANO** RIKEN Team Leader /
Keio University Professor

Structure and functional mapping of the non-human primate brain (particularly the marmoset brain): In our group, as regards the structural (anatomical) mapping of the common marmoset, we will examine macroscale, mesoscale and microscale mappings by utilizing MRI-based diffusion tensor imaging (DTI), stereotactic tracer injections followed by light microscopic observations and a new method of serial EM. We will examine the functional mapping of the marmoset brain by resting state fMRI. As outputs of brain functions, behavioral and cognitive test batteries of common marmoset will be established.



Innovative approaches for the compilation of non-human primate brain map

2014-2018 **Shinsuke SHIBATA** Keio University
Assistant Professor

Keio University is one of the Partner Institutes in Brain/Minds project group. Tightly collaborating with the Core Institute (RIKEN) and the Partner Institute Kyoto University. Keio University is now trying to carry out the structural and functional mapping of the non-human primate brain. The cutting edge technologies for generating transgenic marmoset are applied to obtain the non-human primate disease model. MRI and electron microscopy are used for generating a structural and functional brain map.



Neural networks underlying higher brain functions in the common marmosets

2014-2018 **Katsuki NAKAMURA** Kyoto University
Professor

We analyze neural networks underlying cognitive and social behavior of marmoset monkeys, develop marmoset models for human disease/disorder with various gene transfer vectors, and develop new informatics methods for primate connectomics.



Clinical Research Group

Clinical Research Group

We aim to map control and patients-derived human brains. Three clinical research teams are organized, including Neurodegenerative Disease Research Team, Psychiatry Disease Research Team and Vascular and Neuro-rehabilitation Research Team. These clinical research teams will generate multi-center patients-derived database of MRI and other biomarkers and will make feedbacks to marmoset researches.

Reciprocal translation between the Central Institutes and our group will be examined to determine causal relationships between the structural/ functional damage of neuronal circuits and disease phenotypes and to eventually develop innovative therapeutic interventions for these diseases.

Clinical Research Organizing Team

Translation between brain maps in primates and brain circuits in patients with neuropsychiatric disorders using integrative neuroimaging data resources

2014-2018 **Kiyoto KASAI** The University of Tokyo Professor

The mission of the Clinical Research Organizing Team is (a) to coordinate multi-center collection of neuroimaging, neurophysiological, and behavioral data in patients with various neuropsychiatric disorders to identify disease-specific and -common neural circuit abnormalities that could then be translated to primate studies led by Central Institutes; (b) to innovate technologies for human neuroimaging measurements and analysis to realize precise translation between marmoset brain maps and clinical neuroimaging and neurophysiological data.



Elucidation of pathological neural network via identification of rare genomic variants associated with mental disorders

2014-2018 **Norio OZAKI** Nagoya University Professor

We have been collecting brain MRI data of patients with mental disorders and healthy subjects, in cooperation with other research facilities, to improve an auxiliary diagnosis method of mental disorders. Our goal of the current study is to develop novel accurate diagnostic techniques by using our brain imaging database integrated with genome analysis data and intermediate phenotypic data.



Elucidation of neural circuit responsible for cognition and behavior in disease pathology

2014-2018 **Ryota HASHIMOTO** Osaka University Associate Professor

In this study, it is intended to connect the neural circuits in the marmoset derived from Central Institutes and neural circuits involved in brain pathology in humans from Clinical Research Groups interactively. Based on sufficient cooperation in Clinical Research Groups, we bridge between Central Institutes in RIKEN and each Clinical Research Group and develop a physiological and cognitive behavior database.



The research on neural circuit of neuropsychiatric disorders - molecular mechanism and modeling

2014-2018 **Tetsuya SUHARA** National Institutes for Quantum and Radiological Science and Technology Director

To establish the comparative neural circuits in marmoset and human, we will analyze and compare several molecular imaging data from human and marmoset. To establish the brain molecular and network model in human, macaque and marmoset, we will accumulate functional brain imaging in those different species.



Acquisition of detailed functional and structural brain images of human healthy subjects for promotion of understanding brain circuits of the marmoset, a new animal model for neuropsychiatric diseases

2014-2018 **Kenji MATSUMOTO** Tamagawa University Professor

We aim to promote translation between maps of the marmoset brain (obtained by the Core Institute) and brain imaging data from neuropsychiatric patients (obtained by the Disease Research Teams). To do so, we will acquire detailed brain imaging data of human healthy subjects by employing high-speed/high-resolution MRI imaging techniques developed by the Core Institute on one hand, and we will record detailed auditory electrophysiological responses from macaque brains on the other hand. Furthermore, we aim to promote identifying brain circuits related to psychiatric disorders by providing a standardized intrinsic motivation task for the Disease Research Teams, and by exploring brain circuits underlying social function in healthy subjects.



Identification of disease-common neural circuit abnormalities

2014-2018 **Tetsuo KOBAYASHI** Kyoto University Professor

We develop an automated quantitative evaluation method of all nerve fiber bundles using diffusion MRIs combined with a precise parcellation map of whole brain. Subsequently, we apply the method to various neuropsychiatric disorders, such as schizophrenia and analyze disruption of white matter integrity in various disorders quantitatively. In addition, we investigate new high-speed MRI sequences and develop innovative neuroimaging techniques towards the goal to identify disease-specific and -common neural circuit abnormalities.



Clinical Research Teams

Translation between brain maps in primates and brain circuits in patients with neuropsychiatric disorders using integrative neuroimaging data resources

2014-2018

Kiyoto KASAI

The University of Tokyo
Professor

The mission of the Psychiatry Research Team is (a) to identify disease-related neural circuits by using neuroimaging, neurophysiological, and behavioral data; (b) to develop psychiatry-oriented "translatable" brain markers that can be measured using techniques common to humans and primates; (c) to characterize clinical relevance of brain circuits by circuit analysis and manipulation experiments using marmoset disease models; and finally, (d) to establish neural circuit markers useful for re-classification systems, supplementary diagnostic markers, and innovative treatment strategies in psychiatric disorders including schizophrenia, autism spectrum disorder, major depression, and bipolar disorder.



Elucidation of pathological neural network via identification of rare genomic variants associated with mental disorders

2014-2018

Norio OZAKI

Nagoya University
Professor

We have been identifying genetic mutations involved in the cross-sectional onset of bipolar disorder, schizophrenia, and autism spectrum patients. The goal of the current study is to develop useful diagnoses and therapies targeting disease-specific or disease-wide neural networks from comprehensive understanding of brain imaging database, postmortem brain analysis and model organisms, based on the genetic mutations.



Elucidation of neural circuit responsible for cognition and behavior in disease pathology

2014-2018

Ryota HASHIMOTO

Osaka University
Associate Professor

Schizophrenia shows positive symptoms (hallucinations and delusions), negative symptoms (a willingness decline and apathy) and cognitive impairment. Schizophrenia is a typical mental illness that results in a decrease of social function. Intermediate phenotypes, neurobiological traits related to risk for schizophrenia such as cognitive impairment, abnormal neuroimaging findings and neurophysiological abnormalities, are considered the key to unlock the pathological mechanism of schizophrenia. In this study, we elucidate the pathology of neural circuit using an intermediate phenotype of schizophrenia. It is an object to develop a translatable brain and behavioral indicators.



The research on neural circuit of neuropsychiatric disorders- molecular mechanism and modeling

2014-2018

Tetsuya SUHARA

National Institutes for Quantum and
Radiological Science and Technology
Director

To establish the translatable imaging biomarkers through the investigation of pathological circuits and molecules of the symptoms of neuropsychiatric disorders, we will measure the behavior, accumulate PET and MRI data of model animals.



Investigation of abnormal neural circuits in autism spectrum disorder and schizophrenia using multimodal MRI and development of translatable cross-species measures of brain functions

2014-2018

Ryuichiro HASHIMOTO

Showa University
Visiting Professor

We aim to reveal abnormal neuronal circuits/networks in adult high-functioning autism spectrum disorder (ASD) by applying multimodal MRI methods of structural MRI, diffusion tensor imaging (DTI), and functional MRI. We specifically focus on neural networks centering in the temporal lobe, and seek to develop translatable brain functional measures of auditory-voice processing by collaboration with primate research groups for macaque and marmoset.



Neural pathways for saliency detection during free-viewing

2014-2018

Masatoshi YOSHIDA

National Institute of Natural Sciences
Assistant Professor

Eye-tracking data during free-viewing of natural images from schizophrenic subjects will be analyzed by the saliency computational model. Eye-tracking data during free-viewing from macaque monkeys and marmoset monkeys will be acquired to establish translatable neural and behavioral marker for psychiatric disorders using the saliency computational model. Eye-tracking data from marmoset models for psychiatric disorders will be analyzed to develop methods for investigating the mechanisms for saliency detection in the brain network.



Elucidation of neural networks associated with mood disorders by analyzing neuroimaging

2014-2018

Yasumasa OKAMOTO

Hiroshima University
Associate Professor

The mission of Hiroshima University Research Team is, under the leadership of the Central Institutes and the Clinical Research Management Team, to study neural networks associated with mood disorders by multilaterally collecting and analyzing imaging and clinical data of patients with mood disorders (major depression and bipolar disorder) and of healthy volunteers. We will obtain the neural network dysfunction data of other psychiatric disorders as well as share the study findings with the Clinical Research Management Team. Then we aim to identify difference between neural networks of mood disorders and other psychiatric disorders, and finally map them to neural networks in marmoset elucidated by the Central Institutes.



Analysis of molecular-motor in animal models

2014-2018

Yosuke TAKEI

University of Tsukuba
Professor

It has been pointed out that neurons of schizophrenia and ASD patients have defects in synaptic plasticity in their specific brain circuits. To elucidate the molecular pathology, our group put a focus on molecular motors and related cytoskeletons, and generate and analyze various animal models from rodents to marmosets that include genetic and poly: C models.



Translational research for neuronal circuitry pathologies of Parkinson's and cerebrovascular diseases

2014-2018 **Ryosuke TAKAHASHI** Kyoto University Professor

The goal of this study is to develop the novel translatable biomarkers for presymptomatic or very early stage in Parkinson's disease (PD). In order to elucidate the mechanisms of neuronal circuitry rewiring in PD associated with the onset and progression of the symptoms and compensatory actions of the brain, we are going to establish genetic, toxic protein propagation and drug-induced rodent and marmoset models of PD, and analyze them by using in vivo time-lapse fluorescent imaging.



Identification of mechanism for motor paralysis and higher brain dysfunction after cerebrovascular disorder, and establishment the translatable biomarkers for their functional recovery using nonhuman primate model

2014-2018 **Tadashi ISA** Kyoto University Professor

First, we will identify the critical circuits and compensatory circuits for motor paralysis using both rat and macaque monkey models of cerebrovascular dysfunction. Then, we will establish the hemineglect model of macaque monkeys by lesioning the white matter connecting the frontal lobe and parieto-temporal lobes, and that of common marmoset by supplying pathway-selective blocking techniques with viral vectors to the pathways connecting the frontal lobe and parieto-temporal lobes. Using these animal models, we will establish the translatable biomarkers that reflect the functional deficit and recovery of motor paralysis and hemineglect following the cerebrovascular dysfunction.



Elucidation of injured neural networks and their compensatory mechanisms due to the acute and chronic neurological disorders

2014-2018 **Miho MURATA** National Center of Neurology and Psychiatry Director

There are two compensatory processes in neurological disorders; the compensation as the recovery process after acute injury such as cerebral vascular disorders (CVD) and the compensatory process with chronically progressive degeneration such as Parkinson's disease. To reveal the mechanisms of these phenomena, we will establish the marmoset model of CVD and compare the brain activity between before and after the CVD. To reveal very early compensatory system of Parkinson's disease, the long-term human cohort study of premotor Parkinson's disease is going on to establish the database of multi-dimensional imaging information connected to clinical information.



Development of PET probes to detect synaptic proteins

2014-2018 **Takuya TAKAHASHI** Yokohama City University Professor

We developed PET (positron emission tomography) probe recognizing AMPA receptors. We will be able to visualize AMPA receptors in living human with this technique. A number of studies with rodent have revealed that AMPA receptors play crucial roles in neuronal functions such as learning and memory. Since we do not have techniques to visualize AMPA receptors in living human, we could not categorize neuronal diseases with the distribution of AMPA receptors.



The ultrastructural identification of translatable biomarkers for the diagnosis of the early stages of Parkinson's disease and related disorders

2014-2018 **Masato KOIKE** Juntendo University Professor

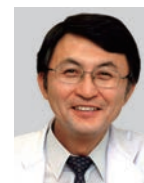
By ultrastructural analyses of the organelles, axons and synaptic terminals of the murine models of Parkinson's disease (PD) and related disorders, we are trying to identify translatable biomarkers for the earlier diagnosis of these disorders. On the basis of the results obtained from these mouse models, we are going to develop ultrastructural analytical methods that enable to identify translatable biomarkers from Marmoset monkey models of PD.



The analysis of pathological neural networks in the patients with movement disorders and animal disease models

2014-2018 **Toshiki YOSHIMINE** Osaka University Professor

The Department of Neurology develops animal models for Parkinson's disease by administration of α -synuclein aggregate or MPTP toxin. The abnormalities of neural networks in these models will be investigated, and novel therapeutic materials to correct the abnormality will be investigated. The Department of Neurosurgery is to establish new methods to analyze the functional brain connectivity in patients with Parkinson's disease as well as post stroke patients. The biomarkers common available to disclose altered brain connectivity in patients as well as animal models will be investigated.



Comprehensive researches to elucidate neuro-network dysfunctions in neurodegenerative dementia

2014-2018 **Hitoshi OKAZAWA** Tokyo Medical and Dental University Professor

In this project, we aim to reveal chronological changes of micro/macro-neurocircuit pathologies focusing on the commonality and specificity across multiple types of degenerative dementia. We elucidate morphological, functional and molecular bases of neurodegenerative dementia, and apply the knowledge to therapeutic development. This group also supports collaboration with the central institutes and with the other clinical research groups.



Identification of neuronal circuit affected in very early Alzheimer disease patients and molecular mechanism of tau pathology spreading

2014-2018 **Taisuke TOMITA** The University of Tokyo Professor

We will clarify the pathological changes in neuronal circuits caused by genetic risk factors for Alzheimer disease (AD) and molecular mechanisms of tau pathology spreading using model mouse. In addition, we will prove and compare the neuronal circuits in brains of MCI due to AD/preclinical AD with those in mouse and common marmoset models. Final aim of our research is identification of key neuronal circuit that is damaged in very early AD brains.



Developing innovative therapeutic interventions for frontotemporal lobar degeneration based on the elucidation of neural circuit disruption

2014-2018

Gen SOBUENagoya University
Designated Professor

In this project, we take charge of developing innovative therapeutic interventions for FTLD-ALS based on the elucidation of neuronal circuits breakdown. Our mission is 1) to identify the specific early macro brain network disruption in FTLD/ALS patients; 2) to establish the translatable indicator leading to the clarification of ultra-early neuronal circuit involvement and subsequent progression by establishment of TDP-43/FUS mouse models; 3) to accelerate the development of novel diagnostic tool and treatment by validating the human and mouse findings using common marmoset models.



Multiple molecular and radiological analysis of Parkinson's disease pathogenesis based on patients and animal models

2014-2018

Nobutaka HATTORIJuntendo University
Professor

We aim to identify disease-specific biomarkers for Parkinson's disease (PD), PD with dementia, and dementia with Lewy bodies based on comprehensive analyses of cranial MRI diffusion tensor imaging, plasma metabolites, and exome sequencing. Adding on that, we try to establish marmoset models with mutation in the disease susceptibility gene and analyze them.



Detection of a key neural circuit in very early stage of Alzheimer's disease

2014-2018

Hiroshi MATSUDANational Center of Neurology and Psychiatry
Director General

We are in charge of investigation of a key neural circuit for cognitive impairment in very early stage of Alzheimer's disease. We are planning to establish methods for a high-resolution brain morphometry and analysis of resting state functional MRI data in patients with mild cognitive impairment due to Alzheimer's disease (AD) and preclinical AD diagnosed by amyloid PET. Then a key neural circuit is identified by obtained structural and functional MRI combining a biomarker by numerous modality data.



Translatable imaging and mechanistic controls of a pathological cascade in age-related neurodegenerative conditions

2014-2018

Makoto HIGUCHINational Institutes for Quantum and
Radiological Science and Technology
Team Leader

The current project is committed to development of imaging techniques applicable to neurodegenerative dementias and rodent and marmoset models of these diseases, in order to clarify the molecular basis of neural circuit abnormalities. We therefore aim to establish translatable indices of brain pathologies and dysfunctions by generating neuroimaging probes for pathological protein deposits and pathogenetic modifiers. Our research also focuses on chemogenetic reporters detectable by in-vivo imaging to delineate functional connectivity in the brain through imaging-guided manipulations of specific neural circuits.



Molecular mechanisms of spreading of TDP-43 pathology

2014-2018

Masato HASEGAWATokyo Metropolitan Institute of Medical Science
Head

To investigate the molecular mechanisms of TDP-43 accumulation in cells, we will identify the regions and the sequences responsible for TDP-43 aggregation, and establish the cellular models of seeded aggregation of TDP-43. Furthermore, we will inoculate these abnormal proteins (tau, alpha-synuclein and TDP-43, etc) into brains of mice and marmosets, and analyze the spreading of the abnormal lesions by immunohistochemistry.



Technology Development Group

Group for electrode technology and data analysis

We develop thin-film arrays for electrocorticogram (ECoG), LED arrays for optogenetic stimulation, and wireless connection systems. We also develop computational techniques for integrating massive heterogeneous data into structural and functional maps.

Computational frameworks for multi-scale models using structural and functional brain map data

2014-2016 **Kenji DOYA** Okinawa Institute of Science and Technology Graduate University Professor

We will develop computational frameworks for constructing multi-scale neural models that link cellular and network dynamics to behavioral and cognitive functions by utilizing large-scale anatomical and physiological data sets. Specific targets are the following: 1) Estimation of cellular and synaptic parameters from connectome, imaging, and electrode recording data. 2) Automated reduction of conductance-based models to integrate-and-fire models, and spiking neural network models to population firing rate models. 3) Application and validation of the above methods with the data being produced by the Brain/MINDS project.



Development of the brain signal measurement system of the marmoset using the internal implanted integrated circuit internal organs flexible ultrathin membrane sensor sheet

2014-2016 **Tsuyoshi SEKITANI** Osaka University Professor

We develop implantable multichannel brain signal measurement system utilizing the state of the art technologies of "ultra-flexible, and -thin transistor integrated circuits and sensors" and "rubber-like stretchable elastic conductors and integrated circuits". Furthermore, with integrating ultra-flexible, and -thin light-emitting diodes and photo-detectors, we will adapt the system to optogenetics. Our research target is to measure wide range brain signals from small primate marmosets and contribute to unveiling the functional networks of the brain.



Group for development of optogenetic techniques and functional measurements

This group aims to develop the following methods for marmosets: multimodal multi-scale functional mapping techniques, multidimensional functional and anatomical approaches, novel two-photon microscopy, cognitive tasks, newly developed viruses, and teleopto, and the following methods and probes for rodents: to record spike activity of multiple neurons and identify their axonal projections, to simultaneously label multiple memory circuits, novel fast Ca^{2+} sensors, and innovative probes that detect long-term activity traces.

Development of optical techniques to manipulate and measure cortical circuits with higher brain functions

2014-2016 **Masanori MATSUZAKI** The University of Tokyo Professor

We intend to develop a novel two-photon microscope to measure multi-neuron activity in lateral areas of the marmoset frontal cortex to examine higher brain functions during task performance. After detecting cortical neurons and pathways that are crucial for the higher brain functions using these techniques, we will manipulate their activity by optogenetic or image-processing techniques to change brain functions and behaviors.



Bridging the gap between macroscopic and microscopic functional organization with multimodal functional mapping

2014-2016 **Kenichi OHKI** The University of Tokyo Professor

Our project aims to develop multimodal multi-scale functional mapping techniques to bridge the gap between the macroscopic functional organization obtained with functional MRI or optical imaging and the microscopic functional organization obtained with two-photon calcium imaging. More specifically, we will investigate the macroscopic and microscopic functional organization of the primary visual cortex and the higher visual areas of marmosets and integrate the multimodal multi-scale information.



Fast 3D recording of neuronal activity and long-term imaging of activity traces through development of innovative probing technologies

2014-2016 **Haruhiko BITO** The University of Tokyo Professor

Information processing in the brain is based on neuronal electrical activity (i. e. excitatory/inhibitory postsynaptic potentials and action potential firing) as well as chemical signal transduction (such as activation of enzyme cascades, transcription or gene expression). To facilitate functional brain activity mapping, we will create and ameliorate novel and fast Ca^{2+} sensors and develop fast 3D imaging technologies, while also generating innovative probes that detect long-term activity traces in active ensembles. Together, these novel probing technologies will provide the basis for better understanding information representation in the brain and interrogating the dynamics and stability of active neuronal ensembles in living animals.



High-speed three-dimensional imaging of neural activity in vivo

2014-2016 **Kazuo KITAMURA** Yamanashi University Professor

We develop highly sensitive, fast genetically-encoded calcium indicators and activity trace probes to obtain detail functional map of the brain. By using these innovative functional probes, we develop multi-color, high-speed three-dimensional imaging and monitor neural activity at single cell and single synapse resolution in awake behaving animals.



A novel multi-neuronal recording with optogenetic identification of axonal projections

2014-2016 **Yoshikazu ISOMURA** Tamagawa University Professor

We are aiming to develop the 'Multi-Linc' method, which allows us to analyze spike activity of multiple neurons whose axonal projections are identified optogenetically. We will establish a basic technology of it covering the cerebral cortex of behaving animals, and apply it to the basal ganglia to clarify a circuitry of decision-making. We will also automatize and optimize it by computer controls.



Development of innovative method for projection pathway specific gene expression to manipulate neural network

2014-2016 **Akihiro YAMANAKA** Nagoya University Professor

Recent development of new techniques to control the activity of neurons, such as optogenetics or pharmacogenetics, enable study the function of neural network in vivo. However, these require expression of gene in the targeted neurons. In this research, we will develop new techniques to support functional mapping of marmoset brain by using newly developed high efficient retrograde and anterograde trans-synaptic Cre recombinase or flippase for neural pathway specific gene expression using multi-selection system. And we will develop teleopto for marmoset to manipulate specific neurons using optogenetics.



Group for gene expression analysis and gene transfer technology

Our group for gene expression analysis and gene transfer technology aims to analyze the pattern of gene expression for neurochemical markers and changes in the expression of genes related to neurological/neuropsychiatric diseases during development of the marmosets. For efficient gene transfer into the marmoset brains, we optimize the technology of cell type-specific gene promoter and retrograde gene transfer, which is useful for pathway-specific manipulation of brain functions, and develop the knock-in approach by using genome editing technique.

Two-photon multi-color imaging of memory circuits in the fixed and transparent brain

2014-2016 **Haruo KASAI** The University of Tokyo Professor

We are developing new optogenetic probes that allow labeling and optical manipulation of dendritic spines underlying specific learning and memory tasks in mice. Subsequently, we will label axons involved in memory, and thereby identify memory circuits from the memory synapses.



Development of technologies for pathway-specific manipulation and structural analysis of neural circuits aiming at functional brain research of common marmosets

2014-2016 **Kazuto KOBAYASHI** Fukushima Medical University Professor

To complement and accelerate the Brain Mapping by Integrated Neurotechnologies for Disease Studies, this project aims to develop neuroanatomical techniques for multiple labeling and morphological visualization in marmoset brains in order to construct neurochemical maps and specify input-output properties.



Analysis of marmoset brain using multiple approaches

2014-2016 **Atsushi NAMBU** National Institute of Natural Sciences Professor

Functions of marmoset brain are analyzed using following methods: (1) Establishing marmoset chronic experiments, (2) Functional mappings by electrical stimulation and neuronal recording, (3) Anatomical study of cortico-cortical or cortico-deep structure connections, (4) Electrophysiological analyses, (5) Developing virus vectors for marmosets. These techniques and data will be shared with other groups.



Development of neuroanatomical tools for synaptic circuit analysis and manipulations of defined circuits in marmoset brains

2014-2016 **Miwako YAMASAKI** Hokkaido University Associate Professor

To complement and accelerate the Brain Mapping by Integrated Neurotechnologies for Disease Studies, this project aims to develop neuroanatomical techniques for multiple labeling and morphological visualization in marmoset brains in order to construct neurochemical maps and specify input-output properties.



Development of cell type-specific gene expression techniques in marmoset brain

2014-2016 **Hirokazu HIRAI** Gunma University Professor

Viral vectors carrying cell type-specific promoters allow us to express transgenes specifically in certain cell types in a temporally regulated manner. Compact cell type-specific promoters having robust promoter activity are indispensable for viral vector-mediated transgene expression. In this project, we develop various cell type-specific promoters optimized to the marmoset brain.



Development of innovative technologies for genetic engineering and rapid reproduction of the marmoset.

2014-2016 **Atsu AIBA** The University of Tokyo Professor

Our research project aims to establish genetic-engineering technologies which are valuable for studying higher brain functions in the marmoset. We try to generate knock-in animal resources by applying genome editing to marmoset embryos. We are also developing the cryo-preservation method of marmoset embryos for improving efficiency and ethical aspect of embryo engineering of primates.



Development of innovative technologies for genetic engineering and rapid reproduction of the marmoset.

2014-2016 **Atsuo OGURA** RIKEN Division Head

In collaboration with Prof. Atsu Aiba, University of Tokyo, we will develop reproductive engineering techniques for shortening the generation turnover of genetically modified marmoset. Spermatids (immature spermatozoa) collected from prepubertal males are used for microinjection into oocytes. Alternatively, testicular tissues obtained from neonatal males are transplanted into host mice to accelerate the spermatogenesis. Spermatids or spermatozoa thus obtained are used for microinjection. With these strategies, it is expected that males at about one-year old or younger will be fathers of the next generation.



Comprehensive measurement and analysis of spatiotemporal transcriptome and epigenome dynamics in the common marmoset brain

2014-2016 **Yasuhiro GO** National Institutes of Natural Sciences Specially Appointed Associate Professor

Spatiotemporal transcriptome gene regulations are essential for construction of brain structure and for proper function. Comprehensive analyses of the dynamics of transcriptome in the both wild and diseased animal models also lead to understand the molecular causality of the human neuropsychiatric disease. Here we examine the spatiotemporal transcriptome dynamics using the common marmoset brain to identify the spatiotemporal-specific modulating genes. Thorough this study, we aim to identify the molecular dynamics and trajectories between proper and atypical brain gene expressional networks.



Group for brain clearing, fluorescent probe and structural analysis

The aim of this group is establishing core technologies for analyzing structure and function of the primate brain. For this purpose, we are developing scalable brain clearing and imaging protocols, novel photo-functional organic molecules for super-resolution, genetically-encoded fluorescent probes, and new super-resolution microscopy and in vivo deep imaging techniques.

Developing new imaging techniques which visualize the functional map of the brain

2014-2016 **Junichi NAKAI** Saitama University Professor

The purpose of this project is to establish new techniques which visualize the functional map of the brain. Toward this goal, we are currently developing new fluorescent calcium probes which can detect neuronal activities in the brain. In combination of these fluorescent probes with the cutting-edge imaging techniques, we will be able to analyze the neural network activity in the brain at a mesoscopic level.



Development of elemental technologies for comprehensive neural circuit mapping of primate brain

2014-2016 **Hiroki UEDA** The University of Tokyo Professor

Our group aims to provide an elemental technology for circuit mapping of primate brain, by applying "CUBIC", the whole-brain analysis technology with single-cell resolution. In the first project, we are optimizing viral tracers for CUBIC application to achieve whole brain-scale neural circuit mapping. In the second project, we are improving the efficiency of tissue-clearing method in order to target the larger primate brains. These technologies will help to promote the understandings of structures and functions in primate brains.



Development of innovative photo-functional small molecule probes for advancing comprehensive understanding of brain structure and function

2014-2016 **Yasuteru URANO** The University of Tokyo Professor

Our project aims for developing novel photo-functional organic molecules, so called "fluorescence probes", which realize precise analyses of complex nerve circuit and fine synapse structure in brain. For example, highly selective and sensitive fluorescence probes capable of visualizing target nerve cells by administered to living animals or brain slices before fixation will be developed. Those for visualizing fine synapse structure based on super-resolution technique will be also developed. Thus, we aim for establishing core technologies for visualizing brain structure of a high order and for manipulating brain function.




Multi-photon super-resolution microscopy utilizing a novel semiconductor laser based light source

2014-2016

Tomomi NEMOTO

Hokkaido University
Professor

For investigating the emergence of neural circuit functions, it is a pressing necessity to establish microscopic technologies to visualize the morphology in a vaster area "in vivo" without degrading the resolution. This team aims to establish new super-resolution microcopy and "in vivo" deep imaging by developing a semi-conductor based laser light and by utilizing a novel laser light "vector beam".




Development of pulse laser light sources for multi-photon-excitation STED microscopy

2014-2016

Hiroyuki YOKOYAMA

Tohoku University
Professor

We participate in researches and developments in which Hokkaido University is the core institution. To perform the world's most advanced imaging, we are responsible for the development of required new pulse laser sources, based on the unique pulsed semiconductor laser technology, for multi-photon-excitation STED microscopy.



Completed Projects

※ The affiliation and position are at the time of project completed.

Strategic Research Program for Brain Sciences (SRPBS)

Field F 2011–2015 Integrated Research on Neuropsychiatric Disorders

Research Team for Developmental Disorders

We perform genomic analysis for neurodevelopmental disorders (autism spectrum disorder) and identify responsible genetic variants. We develop early diagnostic methods for ASD based on GazeFinder, MEG, PET and blood analysis. We confirm effectiveness of oxytocin through multicenter study.

Research aiming at reorganization of diagnostic system and development of therapy for autism spectrum disorder and schizophrenia based on pathogenesis elucidated by genome analysis: Focusing on copy number variants (CNVs) with pleiotropic effects

Norio OZAKI Nagoya University
Professor

Evolutional studies on diagnosis and treatment for autism spectrum disorder with intellectual disabilities

Haruhiro HIGASHIDA Kanazawa University
Professor

Planning and conducting the next stage clinical trial of oxytocin by considering protocol and endpoints

Hidegori YAMASUE The University of Tokyo
Associate Professor

Molecular Study of the Action Mechanism of Oxytocin in the Brain

Katsuhiko NISHIMORI Tohoku University
Professor

Development of a novel technique for early diagnosis of autism and promotion of better understanding of the pathophysiology

Norio MORI Hamamatsu University School of Medicine, Department of Psychiatry
Professor

Understanding the mechanism underlying abnormalities in serotonin transporter of the brain in autistic individuals, and the diagnostic application

Taiichi KATAYAMA United Graduate School of Child Development, Osaka University
professor

Studies on possible medication for autism spectrum disorders (ASD) and the underlying mechanisms

Makoto SATO Research Center for Child Mental Development, University of Fukui
Specially assigned Professor

Molecular basis of developmental disorders

Naomichi MATSUMOTO Yokohama City University
Professor

Understanding the molecular basis of autism associated with epilepsy

Kazuhiro YAMAKAWA RIKEN
Lab head

Research Team for Mood Disorders

The purposes of this project are identify the associated molecule in genome-wide analysis including an interaction with crucial environmental factors and to search biomarkers predicting for onset and clinical phenotypes of depression by using biological samples from mood disorder patients. We also aim to identify abnormal neural network and molecular pathophysiology of mood disorder with neuroimaging research of the patients and the molecular pathophysiological and behavioral analyses of animal models. Based on these results, we finally attempt to conduct the research leading to development of an objective diagnostic tool by machine learning technique, and an innovative treatment by using a neurofeedback method.

Understanding the neurocircuit - molecular mechanism underlying pathophysiology of depression and the development of its neuroscience-based diagnosis and treatment

Shigeto YAMAWAKI Hiroshima University
Professor

Subtype identification, classification and therapeutic planning of depression by machine learning and computational modeling

Kenji DOYA Okinawa Institute of Science and Technology
Professor

Neural circuit in depression-development of molecular mechanism based diagnosis and treatment

Tetsuya SUHARA National Institute of Radiological Sciences
Program Leader

Research on the diagnostic biomarkers and the molecular pathophysiology of depression focusing on its onset-age heterogeneity

Masato FUKUDA Gunma University
Professor

Analysis of rat with white matter lesion induced by endothelin-1 injection as late onset depression model

Nobuhito SAITO The University of Tokyo
Professor

Exploration of the biological markers for discrimination of heterogeneous pathophysiology of major depressive disorder

Hirohata YAMAGATA Yamaguchi University
lecturer

Mechanism Identification of Mood Disorder by Large Scale Gene-Environment Statistically Interaction Analysis

Nakao IWATA Fujita Health University School of Medicine
Professor

Identification of pathophysiological mechanisms of Mood Disorder by large scale genotyping and bioinformatics

Yoichiro KAMATANI RIKEN
Team leader

Integrated Approach to Treatment-Resistant Mood Disorders focusing on the Dopaminergic System

Mitsuhiro YOSHIOKA Hokkaido University
Professor

Research Team for Brain Aging

Prof. Takeda's group is developing an AD pathology-based blood biomarker which can detect change in A β 42 production, investigating lipid abnormality triggering A β 42 accumulation and performing genomic study to find new AD risk genes. Prof. Sobue's group is establishing model mouse of FTLT which mimic neurodegeneration caused by TDP-43 or FUS and trying to discover the pathology related molecules and to develop disease modifying drugs. Prof. Ihara's group is developing tau-targeting drugs to improve declined cognition using mouse and C.elegans models. They are aiming to introduce a candidate drug into clinical studies after completion of their optimization.

Development of blood biomarker of Alzheimer disease and disease modifying drugs based on the research about upstream of pathological process which occurs far before the disease onset and accumulation of pathogenic molecules.

Masatoshi TAKEDA Osaka University
Professor

Quantification of plasma surrogate marker for Alzheimer disease

Takeshi TOMONAGA Laboratory of Proteome Research, National Institutes of Biomedical Innovation, Health and Nutrition Project Leader

Development of disease-modifying drugs for Alzheimer disease through targeting the initial pathological event on neuronal membranes

Katsuhiko YANAGISAWA National Center for Geriatrics and Gerontology
Director General, Research Institute

Developing blood-diagnosis markers and drugs by utilizing revolutionizing technologies and by clarifying upstream disease-causing mechanisms that lead to decreased brain function and accumulation of abnormal proteins according to aging

Tatsuhiko TSUNODA RIKEN & Tokyo Medical and Dental University
Group Director & Professor

Development of anti-tauopathy drug

Yasuo IHARA Doshisha university, Organization for research progress and development
visiting professor

Screening chemical compound using animal model, and finding a mechanism of neuronal dysfunction

Akihiko TAKASHIMA, PhD National Center for Geriatrics and Gerontology
Director, Department of Aging Neurobiology

Development of disease-modifying therapy for FTLT based on the molecular pathogenesis

Gen SOBUE Nagoya University Graduate School of Medicine
Designated Professor

Elucidation of the pathomechanisms and development of a therapy for frontotemporal lobar degeneration (FTLD) using newly-established Drosophila models

Yoshitaka NAGAI National Center of Neurology and Psychiatry
Section Chief

Field G 2011–2015 Bioinformatics for Brain Sciences

Field G

We aim to uncover information that will allow us to understand the monoamine-mediated mechanisms that control emotions, thereby clarifying the machineries that regulate the operating principles of neural circuits and their restructuring. Three research groups investigating neural circuits, proteomics and computation work together to carry out this data-driven research.

Establishment of the research platform for the regulatory mechanisms of emotion in model animals

Hitoshi OKAMOTO RIKEN
Deputy Director

Development of Model Animals for Constructing Bioinformatics for Brain Sciences of Emotional System

Naoki MATSUO Kyoto University
Guest Research Fellow

Spatiotemporal analysis of signal transduction pathway implicated in emotional regulation

Taku NAGAI Nagoya University
Associate Professor

Structural plasticity of dendritic spine in the nucleus of accumbens

Haruo KASAI Graduate School of Medicine, The University of Tokyo
Professor

Brain Project Theme G "Analysis of monoamine neurons in the fruit fly Drosophila adult brain"

Kei ITO Institute of Molecular and Cellular Biosciences, The University of Tokyo
Associate Professor

Molecular and cellular basis for preference choice in Drosophila

Kazuo EMOTO The University of Tokyo
Professor

Temperature memory, decision making and monoamine regulations in the nematode *C. elegans* thermotaxis

Ikue MORI Nagoya University
Professor

Developments of computational methods and model animals to establish bioinformatics for brain sciences for elucidating the mechanism in emotional systems

Shin ISHII Kyoto University
professor

An informatics approach to understanding the neural mechanism of emotion regulation

Junichiro YOSHIMOTO Okinawa Institute of Science and Technology Graduate University
Visiting Researcher

Construction of a neuroinformatics database for neural basis of emotional system

Shiro USUI RIKEN
Visiting Principal Investigator

Bioethics 2011–2015

Resolving key issues in bioethics

Yoshiyuki TAKIMOTO The University of Tokyo
Associate Professor

Biological BMI 2014–2018

The mechanisms of the effect of transcranial magnetic stimulation (TMS) by monitoring the dynamics of monoamine neurotransmitters and the cortex-brain stem networks

Kae NAKAMURA Kansai Medical University
Professor

(Finished in 2015)

Research and Development Grants for Longevity Science

Program Supervisor

Yukihiko WASHIMI

Vice Director of the Hospital
National Center for Geriatrics
and Gerontology



Program Officer

Setsu IIJIMA

Rehabilitation Service Bureau Director
National Rehabilitation Center for Persons with
Disabilities

In light of the increasing aging of Japanese society and the anticipated explosion in medical and care needs from 2025 as members of the baby-boomer generation enter their late 70s, this project focuses on elderly-specific diseases and conditions with the aim of establishing multiple, comprehensive approaches to treatment, with the main goal being to contribute to the establishment of a sustainable long-term care insurance system and the promotion of collaboration between healthcare workers and care staff.

Treatment strategy construction to prevent need of nursing care by making predictive score for onset and exacerbation of osteoarthritis of the knee

2014-2016 **Shuichi MATSUDA** Kyoto University Professor

Clinical symptoms, X-rays, sonography, quantity of lower limbs muscle, bone density, an exercise function, obesity, blood pressure, diabetes, arteriosclerosis, recognition functional disorder, cerebrovascular disorder, a blood marker, genetic polymorphism, the mental health are investigated for 10,082 Nagahama city, Shiga citizens. Endpoints are determined as an onset, exacerbation of the osteoarthritis of the knee, primary nursing care requirement, and nursing care level. This project will clarify the association between various factors and knee pain, and will comprehensively examine the main effect for the endpoint, by adjusting confounding extracted risk factors, from a long-term longitudinal study.



Manual development of initial conservative treatment for osteoporotic vertebral fracture

2014-2016 **Atsushi OKAWA** Tokyo Medical and Dental University Professor

We would like to clear how we should make the appropriate treatment for new osteoporotic vertebral fracture initially. Then it will be considered in randomized clinical trials about the treatment efficacy by using elastic orthosis or rigid orthosis. We would establish the evidence and standardize the initial conservative therapy for osteoporotic vertebral fracture.



The integrated community care system for elderly with eating and nutritional problem

2014-2016 **Haruka TOHARA** Tokyo Medical and Dental University Associate Professor

The main purpose of our research team is outlined to promote the local area to provide effective support for the elderly with eating problem. We started to visualize the medical and nursing resources. Concretely, we performed mapping of the medical and nursing resources in each area and made a guidebook based on the examples of effective cooperation team as the role model. These materials are put on the web site we developed. And the address of the web site will be distributed to each local administrative, hospitals, and related facilities. Furthermore, a questionnaire for local administrative will be performed to reveal if the local regional has sufficient cooperative approach for elderly. We promote a new regional cooperation from those results.



The study of development and usefulness of an evaluation tool for the eating and nutritional support in the integrated community care system.

2014-2016 **Takeshi KIKUTANI** The Nippon Dental University Professor

The hospital inpatient with pneumonia has risk of declined eating /swallowing function and impaired nutritional status. It is important to provide consistent support for the patients in the region in order to avoid exacerbation of relapse the risk for pneumonia after discharge from hospital. In this study, we develop the evaluation and support tools for the eating and nutrition of the patients, and build a support model in the integrated community care system.



Development of regional emergency home visiting care system for persons requiring care during nighttime, weekend, and holidays

2014-2016 **Satoru YOSHIE** The University of Tokyo Hospital Project Researcher

This study aims to develop regional emergency home visiting care system for persons requiring care during nighttime, weekend, and holidays. In Japan, emergency home visiting care is usually provided by each clinic or home visiting nurse station. But these organization-based system is sometimes inefficient because every organization has to hold the emergency phone and the on-call staff. So we study how region-based emergency home visiting care system could be developed in Japan, like Netherland where the regional system called "GP ambulance" has developed.



Study on Evidence-Based Community Building Interventions for Long-term Care Prevention

2014-2016 **Naoki KONDO** The University of Yamanashi Associate Professor

Long-term care prevention activities should utilize objective community diagnosis data and make cross-stroral collaborations. Using the fields of our following-up studies, involving approximately 100,000 order participants: JAGES, we have evaluated the effects of our intervention activities of data-oriented community building activities on disability prevention.



Research and Development
Grants for Longevity Science

Research and Development
Grants for Dementia

Physical Disability Area and
Intellectual Disability Area

Sensory Disability Area

Mental Disorder Area

Neuromuscular Disease Area

Area-control trial to investigate the effectiveness of the community activities for prevention of dependence on long-term care through public collaboration

2014-2016 **Shuichi OBUCHI** Tokyo Metropolitan Institute of Gerontology
Chief Researcher

The purpose of this study is to develop an area-intervention model to promote community activities for prevention of dependence on long-term care and novel mutual support thorough public collaboration and to investigate the effectiveness by the area-control trial. Community activity increases not only "Social cohesion and trust" which means unity of community but also "Informal social control" which may isolate the requiring assistance person. We are carrying out an area-intervention in which the Informal social control is not increased by the involvement of some coordinators and conducting the large cohort survey to verify the effectiveness.



The study of development of utilization manual of municipal medical data in Japan for the evidence -based formulation of integrated community care system

2014-2016 **Toshiro KUMAKAWA** National Institute of Public Health
Senior researcher

The purpose of this study is to develop the utilization manual of municipal medical data in Japan for the evidence -based formulation of integrated community care system.

In addition we investigate the current status of social prescription and collect data for the formulation of integrated community care system in Japan.



A study of the development of strategies and community leaders training program of regional management force for the community based integrated care system construction

2014-2016 **Masahiro KAWAGOE** National Institute of Population and Social Security Research
Director

To enhance of community management skill of municipalities is important issue for construction of the community-based integrated care system. In particular, improvement in the ability to grasp the regional problems, as well as improvement in the methodology for solving the problem areas are the key points. Therefore, in this study, first, through the data analysis support in light of municipal needs, to carry out the development of a highly versatile regional diagnostic support tool. Furthermore, on the basis of the planning and conference management support, to carry out development of the manual and training program contributes to skills of municipal staff.



Preventing the worsening of care-requiring condition in femoral neck fracture patients 1 year after surgery.

2014-2016 **Ryo TANAKA** Hiroshima International University
Lecturer

The aim of this study is to identify the risk factors predicting whether long-term care will be needed 1 year after surgery in femoral neck fracture patients, and to confirm the preventive effect of rehabilitation management for the patients having risk factors to let their care-requiring condition get worse. Firstly, we develop the screening tool to predict the worsening of care-requiring condition 1 year after surgery. Next, we evaluate the effect of rehabilitation program using custom relief rollator on recovery of ADL after surgery.



Study for promotion of care prevention by community developing approach

2015-2017 **Katsunori KONDO** National Center for Geriatrics and Gerontology
Director

From 2015, targets of care prevention policies have been shifted from secondary prevention, in which only frail older people at high risk is targeted, to "care prevention by community developing approach", which led by community and any people could participate in. However, because of inexperience, many municipalities are puzzled about how to introduce and evaluate the new policies. Toward spread of effective "care prevention by community developing approach", we are aiming 1) to draw out protocols; 2) to develop evaluation methods; 3) to utilize and improve "visualizing" system for integrated community care; 4) to develop training programs.



Study to develop practical guides for physician-pharmacist collaboration

2016-2017 **Masahiro AKISHITA** The University of Tokyo
Professor

The aim of this project is to develop "Practical guides for physician-pharmacist collaboration to reduce polypharmacy in elderly patients," which is expected to play an initial role in multidisciplinary approach to optimize pharmacotherapy in the elderly. To do so and collect the information, this research team is conducting surveys on current situation and trials of physician-pharmacist collaboration. Furthermore, to improve the patients' understanding of appropriate medications, the team members consisting of physicians and pharmacists are collaborating with each other and making a pamphlet for the general public.



Study to develop novel ADL assessment scores and intervention strategies to reduce the number of disabled older people to half

2016-2018 **Hidehiko ARAI** National Center for Geriatrics and Gerontology
Deputy Director

For disability prevention and the collaboration of health care and long-term care, we intend to develop a simple ADL checklist consisting of 5 to 10 items in each ADL domain and validate the checklist in patients admitted to the convalescent rehabilitation ward. We also intend to develop a training program to correspond to each item of the ADL checklist and tried to address the effect of the training program on each ADL.



Development of methodological model to achieve 'ACTIVE community' -Approach of comprehensive frailty prevention program by aggressive leadership of senior citizen supporters-

2016-2018 **Katsuya IJIMA** The University of Tokyo
Professor

Early detection and prevention of 'multi-dimensional frailty' are essential and indispensable to develop an ACTIVE community embodying a concept of healthy life expectancy extension. Aim of our action research is to develop "approach of comprehensive frailty prevention program by aggressive leadership of senior citizen supporters" based on our previous works on frailty early detection. This challenge by construction of its methodological model certainly contribute to redesign the aging community.



The interdisciplinary care system with advanced nursing assessment for community dwelling elderly with eating or bowel trouble MA

2016-2018 **Hiromi SANADA** The University of Tokyo
Professor

Elderly people with dementia have difficulty in complaining their conditions and needs. It is important to support them to independently eat and defecate. This study aims to develop the following three technologies and programs: (1) a technology that observes eating and bowel with ultrasonography, along with a coaching program which utilizes image processing technique to facilitate this particular observation procedure; (2) the educational program for nursing care that uses the observation procedure; and (3) the interdisciplinary collaboration system using ICT among houses, nursing facilities, and hospitals. This study tests the effectiveness of these technologies and programs for prevention of aspiration pneumonia as well as improvement of chronic constipation.



The development and verification of prevention strategies of physical and cognitive frailty

2016-2018 **Hiroyuki SHIMADA** National Center for Geriatrics and Gerontology
Department Head

Physical and cognitive activities are important factors for the prevention of physical and cognitive frailty, which is a risk factor of disability, and the development of a system to promote the activities is an urgent problem in aging societies. The biggest task to enhance the preventive effect of disability is how active lifestyles are facilitated in older adults. The aim of the study is to develop a system to promote physical and cognitive activities and to determine the effects of the developed system in a randomized controlled trial.



Oral management by dental treatment and nutritional management for the support of oral feeding in elderly people with dementia.

2016-2018 **Hirohiko HIRANO** Tokyo Metropolitan Geriatric Hospital
Dentistry and Oral Surgery
Chief

The purpose of this study is to create guidelines for dental treatment in order to support oral feeding in people with dementia. Furthermore, based on the guidelines, the aim is to spread dental treatment and support of oral feeding at each care-giving site. The contents of the guidelines will be in accordance with the existing "Providing health care and long-term care services in a timely and appropriate manner as the stages of dementia progress" shows in the Japanese Dementia Strategy (New Orange Plan).



Research and Development Grants for Dementia

Program Supervisor

Yukihiko WASHIMI

Vice Director of the Hospital
National Center for Geriatrics and
Gerontology



Program Officer

Kunihiro YOSHIDA

Specialty-appointed Professor
Shinshu University

This project promotes priority research projects from the viewpoints of understanding the actual state of dementia and its prevention, diagnosis, treatment, and care.

- (1) Cohort studies to investigate the etiology of dementia and the development of methods of treatment, diagnosis, and prevention
- (2) Research on familial dementia
- (3) Research on the development of dementia drugs through drug repositioning
- (4) Research on the development of novel methods of prevention, diagnosis, and treatment for dementia patients

Identification of novel molecules and pathways of cognitive decline in a population-based omics cohort study.

2014-2016

Yasuharu TABARA

Kyoto University
Associate Professor

The aim of this study is to identify novel molecules and pathways for cognitive decline in a large-scale general population-based cohort study with a dataset including 1) comprehensive analysis of blood metabolites, peptides, and lipids, 2) genome-wide genotype data, and 3) detailed clinical information including cognitive function.



Development of plant extracts for therapeutic agents for dementia

2014-2016

Kenji KAWABATA

National Institutes of Biomedical Innovation,
Health and Nutrition
Project Leader

Dysregulation of energy metabolism between neurons and astrocytes is a cause of dementia. By monitoring the metabolic flow, we try to identify therapeutic agents for dementia from plants extracts. Human iPS-derived neuronal cells are used for the estimation of efficacy.



Cohort and comprehensive genome studies to elucidate fundamental molecular bases of Alzheimer disease

2014-2016

Shoji TSUJI

The University of Tokyo Hospital
Professor

To elucidate molecular bases of sporadic Alzheimer disease (AD), AD cohorts will be established to collect longitudinal clinical information as well as bioresources. Combined with previously collected bioresources, comprehensive genome analyses (whole exome-association studies) and affected sibpair analyses will be conducted to identify rare variants with large effect sizes for developing AD.



Randomized, multicenter, open, two-arm parallel group trial of Oral myofunctional training for Clinical evidence to dementia

2014-2016

Tomomi IDE

Kyushu University
Lecturer

The increase in aging, dementia in our country accelerates so as to never examine, and the development of an effective cure is urgent matter. We suggest from our previous clinical pilot test, oral myofunctional training may stimulate vagal nerve and is effective for dementia, resulting in useful to treat and prevent various malfunction in aged people. In this project, we perform open clinical randomized trial to establish an effectiveness and safeness of this training. Furthermore, we carry out clinical trial using image analysis to elucidate the mechanisms.



Observation cohort study on familial Alzheimer's disease

2014-2016

Hiroshi MORI

Osaka City University
Professor

An observation cohort study on familial Alzheimer's disease is attempted to establish the longitudinal profiles of MRI and PET neuroimaging and fluid biomarkers to clarify the disease progression and to provide evidence for the drug development in future. The aim is to stop the disease onset of asymptomatic children in the pedigrees.



Information therapy using inaudible high-frequency sounds for behavior and psychological symptoms (BPSD) of dementia

2014-2016

Manabu HONDA

National Center of Neurology and Psychiatry
Associate Professor Director

The current project aimed at developing novel non-pharmacological therapy for behavior and psychological symptoms of dementia (BPSD) using the effect of inaudible high-frequency sounds that activate brain regions including midbrain, hypothalamus, and prefrontal cortex. In addition, the project also investigates a scientifically valid evaluation method for BPSD using non-invasive brain imaging techniques.



Development of system for collecting and accumulating information about care for person with dementia and extracting good practices automatically using the Information and Communications Technology

2014-2016 **Hiroaki KAZUI**

Osaka University
Associate Professor

Behavioral and psychological symptoms of dementia (BPSD) threatens the livelihoods of dementia patients and their caregivers. Various care methods for BPSD are proposed in books and on websites. However, the effectiveness of these care methods have not been examined. We are developing a system for collecting and accumulating information about care methods for person with dementia with information about whether the care methods are effective or not using the Information and Communications Technology. In the system, good practices are automatically extracted from the accumulated care methods and the useful care methods are allowed public access with probabilities of effectiveness of the care methods.



Development of intervention methods for the prevention of cognitive decline through community-wide physical activity campaign

2014-2016 **Yuko OGUMA**

Keio University
Associate Professor

We carry out multi-directional, multi-level interventions to increase physical activity throughout Fujisawa city, in order to promote health. Namely, we provide information widely among citizens, provide educational opportunities to the target demographic (the elderly, 60 years old and up), promote cooperative planning to utilize local resources, and promote the formation of community to do physical activity together among the residents (community-wide physical activity campaign). We examine whether these efforts lead to increase physical activity and enhance fitness as well as to prevent cognitive decline. From the resulting knowledge we develop interventions for the prevention of dementia.



Establishment of evaluation of preclinical Alzheimer's disease by neuroimaging

2015-2019 **Hiroshi MORI**

Osaka City University
Professor

A multi-center clinical study to establish the longitudinal profiles of MRI and PET neuroimaging and fluid biomarkers to quantitate the disease progression or to predict the future progression to MCI or dementia at the very early stages of Alzheimer's disease. In parallel, clinical and cognitive data are collected, to validate the significance of biomarkers in normal elderly, preclinical AD and MCI.



Development of a battery for precise evaluation of cognitive function in hearing-impaired patients and analysis of cognitive function and symptom effected by hearing aid fitting

2016-2018 **Koichi OMORI**

Kyoto University
Professor

Elderly people are often suffering from age-related hearing loss and dementia. In the present study, we are planning to establish a new visually oriented test battery to precisely evaluate cognitive function even in patients with hearing loss. In addition, we elucidate which aspects of cognitive function are ameliorated by hearing aid fitting in aged patients with both dementia and hearing loss. Through these investigation, we aim to find out what type of patients with dementia are recommended to use hearing aid. Results of the present study will contribute to further large clinical trials assessing correlation between cognitive function and hearing impairment.



Development of a support program (PENTA program) as a multidisciplinary intervention for treatment and care of people with dementia in acute hospital settings

2016-2018 **Asao OGAWA**

National Cancer Center, Psycho Oncology Division,
Exploratory Oncology Research & Clinical Trial Center
Director

With the increasing proportion of elderly people, the prevalence of dementia with physical impairment, cognitive impairment and psychological problem at acute hospitals has increased. The purpose of this study was to develop a support program for people with dementia in acute hospital settings (PENTA program) as a multidisciplinary intervention for the treatment and care of dementia, and to establish multiple access points in the dementia care pathway in Japan.



Project on dementia clinical study support center toward clinical trials for Alzheimer's disease modifying drugs and establishment of trial ready cohort

2016-2020 **Yuichi KATO**

Osaka City University
Professor

The aim of this project is to arrange dementia clinical study support center, research infrastructure that provides support to large clinical studies on developing Alzheimer's disease modifying drugs for the treatment of early stage disease. One approach we undertake is to build a network of clinical sites that enables to promote standardization of cognitive assessments, PET, MRI imaging and biomarker analyses, to facilitate data management, and to monitor study quality. The other is to establish registry/trial ready cohort for enrollment into trials, fundamental scheme for Japanese research team to take part in global clinical trials.



Study of evidence-based intervention of care, nursing and rehabilitation to improve functions of dementia patients

2016-2018 **Takako TSUTSUI**

University of Hyogo
Professor

We examine the evidenced-based delivery methods of care, nursing and rehabilitation by analyzing relevance between the results of assessments to dementia patients and submitted contents of care procedures for them. Meanwhile, we also examine validity of the evaluation criteria for QOL of dementia patients and their family members and review how self-care of patients and informal care by family are conducted. In the end, we propose a methodology for a comprehensive training system to support dementia patients and their family members based on the research findings.



Evolving the existing CSF biomarkers for Alzheimer's disease into blood samples and brain-derived blood exosomes, and practical application of the multi-item blood-based biomarkers developed in this study for the diagnostic system of Alzheimer's disease

2016-2018 **Takahiko TOKUDA**

Kyoto Prefectural University of Medicine
Professor

To develop easy-to-use and less invasive methods for objective diagnosis of Alzheimer's disease, we establish the assays to quantify the established CSF biomarkers in blood samples (serum/plasma or brain-derived blood exosomes), and validate them by using blood samples from multiple large cohorts. The final goal is to establish the objective diagnostic system for Alzheimer's disease using the multi-item blood-based biomarkers developed in this study.



A nation-wide coordinated registry system for different stages from preclinical, MCI to dementia care

2016-2020 **Kenji TOBA**

National Center for Geriatrics and Gerontology
President

This study is to establish "Orange platform" which is a nation-wide registry and coordination system which enables clinical observation of people with dementia throughout their clinical stages. The primary goal of the registry is to develop new treatment, medications, and care techniques for dementia by utilizing the data mass accumulated in the system.

These coordination of multiple dementia-related registry consist of different stage from preclinical, MCI to dementia care. Already more than one thousand people were registered. ORANGE preclinical registry targets subjects in community-dwelling cohort, and urge them to participate in the early preclinical study. MCI registry is going to link with preclinical and care registry as well. Nation-wide major institutions related dementia are included in the registry. Several institutes can provide amyloid imaging as well as Tau imaging for additional clinical studies.



Plasma biomarker for Alzheimer's disease reflecting cerebral amyloid deposition: a multicenter study

2016-2018 **Akinori NAKAMURA**

National Center for Geriatrics and Gerontology
Section Chief

Along with the recent advances in disease-modifying clinical trials for Alzheimer's disease, needs for blood-based biomarkers, which are simple, minimally invasive and cost-effective, are intensified. Recently, we developed a novel plasma biomarker that can accurately predict brain amyloid deposition. The objective of this project is to validate its clinical usefulness and feasibility through a multicenter study in order to realize the clinical application within a few years.



Large-scale dementia cohort study for realizing healthy aging society

2016-2020 **Toshiharu NINOMIYA**

Kyushu University
Professor

This study is a collaborative prospective cohort study of approximately 10,000 elderly people from 8 newly-established community-based dementia cohort studies in Japan, in which the data is prospectively collected by using the pre-specified standardized protocol. The purpose of this study is to evaluate quantitatively environmental and genomic risk factors for dementia in Japanese and to establish effective preventive strategies for dementia, in order to realize healthy aging society.



Establishment of a research and development consortium on novel imaging diagnostics and therapeutics targeting tau pathologies

2016-2018 **Makoto HIGUCHI**

National Institutes for Quantum and
Radiological Science and Technology
Team Leader

One of the primary focuses of the current project is to construct a multi-center clinical assessment system enabling identification of genetic factors and blood biomarkers associated with tau pathologies and determination of the time point of therapeutic interventions targeting pathological tau aggregates. This system is also applied to evaluation of a new positron emission tomographic imaging agent for tau lesions and clinical trials of a repositioned drug as an anti-aggregant for tau. In the meantime, development of novel therapeutic compounds counteracting tau aggregation is conducted at a non-clinical level. The eventual goal of this project is to establish "Tau Translational Consortium" as a platform of drug discoveries through bidirectional translations between nonclinical and clinical accomplishments.



Gene Ontology-based microarray analyses of the mechanisms with which dementia progresses or regresses

2016-2017 **Sosuke YAGISHITA**

National Center of Neurology and Psychiatry
Section Chief

As dementia, including Alzheimer disease, are multifactorial diseases, it has been difficult to understand the mechanisms of dementia progression or prevention. In this study, we aimed to understand mechanisms regulating the levels of phosphorylated tau. For the purpose, we have found near-physiological conditions that increase or reduce the levels of phosphorylated tau. To elucidate what happen under the conditions, we perform Gene Ontology-based microarray analysis, followed by comparing with the accumulating "big data" in the database.



Dietary factors for Prevention and Treatment of Dementia

2016-2018 **Masahito YAMADA**

Kanazawa University
Professor

To discover dietary factors for prevention and treatment of dementia, we investigate the effects of dietary factors on amyloid β protein and α -synuclein which are associated with development of Alzheimer's disease and Lewy body disease. The investigations include (1) population-based longitudinal study, (2) *in vitro* and *in vivo* experimental study, and (3) placebo-controlled randomized control trials with dietary factors for patients with early stage Alzheimer's disease.



Research and Development Grants for Comprehensive Research for Persons with Disabilities

Program Supervisor

Kozo NAKAMURA

Professor Emeritus
The University of Tokyo



Program Officer

Yasoichi NAKAJIMA

Director-General, College
National Rehabilitation Center for
Persons with Disabilities

Satoshi KATO

Associate Professor
The University of Tokyo

Kotaro ISHIKAWA

Head Otorhinolaryngologist
National Rehabilitation Center
for Persons with Disabilities

Teruhiko HIGUCHI

President Emeritus
National Center of Neurology and
Psychiatry

Emi IKEBUCHI

Professor
Teikyo University

This project promotes research and development with the aim of providing appropriate support for rehabilitation for all forms of disability, elucidating the etiology and pathology of diseases and conditions that result in disability, and cutting-edge, practical research on aspects including methods of diagnosis, prevention, treatment, and rehabilitation.

Work of the reconfiguration and utilizing of database system of the people with severe motor and intellectual disabilities and medical and welfare policy proposals

2014-2016

Takeshi MIYANOMAE

National Hospital Organization Minami-Kyoto Hospital
Director

Database system of people with severe motor and intellectual disabilities (SMID) is operating in 73 hospitals which belong the group of National Hospital Organization in Japan. About sixty thousand data are registered in this database system for 15 years. Under Services and Supports for Persons with Disabilities Act, we face to the change of circumstance of medical and welfare and to reconstitute this database system. We promote the use and improvement of this data-base system.



A study of early interventions for Japanese children with autism: a comparison of applied behavior analysis (ABA) with eclectic methods

2014-2016

Yoko KAMIO

National Center of Neurology and Psychiatry
Director

In Japan, existing intervention services for young children with autism spectrum disorder (ASD) are generally insufficient in terms of their quantity and quality to meet the identified needs of young children with ASDs and their families. The aim of this study is to assess the outcome of interventions for young children with ASD and their families and to identify the factors associated with them. The interventions are classified into less intensive ABA and non-ABA methods. In addition, we will conduct a meta-analysis of early intervention RCTs for young children with ASD to compare the effects across intervention types, undertake a national survey of ABA-based services privately provided for children with ASD in Japan, and conduct a case-series study to explore the long-term outcome of children with ASD after ABA completion. The present study will thus determine the basic principles on which future community-based early interventions for young children with ASD should be based.



Development of the novel rehabilitation system using Near infrared spectroscopy mediated Neurofeedback for patients with neurological disorders

2013-2016

Hideki MOCHIZUKI

Osaka University
Professor

Neurofeedback is the less-invasive neuromodulation technique in which subject can voluntarily regulate brain activity using real-time feedback of the brain activity. We are developing the novel near infrared spectroscopy mediated neurofeedback-based rehabilitation system in combination with the rehabilitative training, and investigating the clinical efficacy of this system for gait and balance impairment in patients with neurological disorders.



A study on the effective use and construct of disability statistics

2014-2016

Tsutomu IWAYA

National Rehabilitation Center for Persons
with Disabilities
Advisor

The Purpose of this study is to identify the meaning and system to utilize disability statistics. Firstly detailed statistic is made on "Survey on difficulties in daily living" by Ministry of Health, Labor and Welfare in to consider the plan of next survey. Secondly, systems to utilize survey results and service data is searched nationally and internationally.



Construction of information infrastructures for creating assistive technology innovation.

2014-2016

Seishi KATO

National Rehabilitation Center for Persons
with Disabilities
Advisor

Assistive technology is useful for promoting social participation of persons with disabilities and aged persons and for improving their QOL. This project aims to construct information infrastructures that facilitate assistive technology innovation, including (1) database useful for research and development of assistive technology and for promoting its use, (2) information infrastructure prepared by cooperating with persons with disabilities, (3) a base for human resource development for promoting assistive technology innovation.



Research and Development
Grants for Longevity Science

Research and Development
Grants for Dementia

Physical Disability Area and
Intellectual Disability Area

Sensory Disability Area

Mental Disorder Area

Neuromuscular Disease Area

The development of body temperature management system for spinal cord injury patients.

2015-2016 **Toru OGATA**

National Rehabilitation Center for Persons with Disabilities
Director

For persons who have impairment in controlling body temperature, high temperature is a threatening factor for their daily life and social participation. In this study, we attempt to develop a system containing body temperature monitoring and a cooling device, which is based on thermal cycling and conduction. The developed system would be tested by wheelchair users in the field as a verification test.



Innovation of new communication interface device for disabled people with advanced stage of neuromuscular diseases such as ALS etc.

2015-2016

Takashi NAKAJIMA

Niigata National Hospital, NHO
Deputy director

Disabled people with advanced stage of neuromuscular disease such as ALS etc. are not able to convert their intention to movement and fail to communicate. These patients can operate ordinary communication PC system with detection and real time analysis of characteristic motor unit potentials from patient's skin using non-invasive Cybernic interface developed newly in this research project.



Development of Gesture Interface for Persons with Severe Motor Dysfunction (cerebral palsy and traumatic brain injury)

2015-2017

Kazuyuki ITOH

Research Institute, National Rehabilitation Center for Persons with Disabilities
Director

We have researched and developed about the gesture interfaces for persons with motor dysfunction ((cerebral palsy and traumatic brain injury) that could not use normal interface switches.



Verification of the effects of existing robotic devices for rehabilitation used in clinical practice

2016-2018

Toyoko ASAMI

Saga University Hospital
Clinical Professor

This study aims to develop and standardize the evaluation criteria for robot rehabilitation. We verified the effects and evaluate the safety of the robotic devices for rehabilitation already used in clinical practice in order to provide evidence certifying the effectiveness at the functional level. And we created a database of effectiveness and safety in order to lead to the creation of guidelines and principles for robot rehabilitation in the future.



Research for practical use of Brain-Machine Interface (BMI) -based assistive technology for persons with disabilities.

2016-2018

Takenobu INOUE

National Rehabilitation Center for Persons with Disabilities
Director

We have developed Brain-Machine Interface (BMI) -based assistive technology for persons with disabilities. The in-house BMI-based environmental control systems have been successfully operated by persons with amyotrophic lateral sclerosis (ALS) in the longitudinal evaluation. In this study, we continue the evaluation and further develop the systems based on feedback from the users. We also investigate the manner to introduce the systems to the users.



Clinical trial for testing the effects of noisy galvanic vestibular stimulation for improving body balance in patients with bilateral vestibulopathy and development of the device to deliver noisy galvanic vestibular stimulation at home

2016-2018

Shinichi IWASAKI

University of Tokyo Hospital
Associate professor

To provide a new treatment for improving body balance in patients with bilateral vestibulopathy, for which there have been no effective treatments, we develop a new treatment device utilizing noisy galvanic vestibular stimulation (noisy GVS). In this study, we conduct a clinical trial to verify 1) noisy GVS for a long period can improve body balance in patients with bilateral vestibulopathy, and 2) the ameliorating effects of noisy GVS continue after the cessation of the stimulus. We also improve the device of the GVS stimulator for the patients to use it easily at home.



Development of strategy for supporting high physical activity of people with disabilities

2016-2018

Toru OGATA

National Rehabilitation Center for Persons with Disabilities
Director

For people with disabilities who use wheel chairs in daily life, high activity such as sports requires a specific care. In this project, we attempt to develop a guide book for increasing fitness and conditioning for sports activity. As basic component, we focus on body composition measurement and seating pressure measurement. We also choose wheel chair marathon and Boccia as models for condition management.



Self-body sensations and related brain functions of users wearing a robotic power assist suit

MA

2016-2018

Takako YOSHIDA

Tokyo Institute of Technology
Associate Professor

We'll develop an fMRI-safe, magnetic-safe, reasonable, and lightweighted wearable robotic power assist suit. This will enable us to scan the robot users' brain activation. This type of the brain activation study can be a basis for performing a scientific and quantitative assessment on the users' experience and sensations, e.g., the power suit can be a part of their own body, and also lead to the development of assessment methods to determine the temporal changes in human self-body sensations by the robotic rehabilitation and sport training.



Medical Arts (MA) are the technologies or systems for effectiveness, safety and efficiency of medicine.

Development of social system for health promotion of people with disabilities in middle-age

2016-2018

Toru OGATA

National Rehabilitation Center for Persons with Disabilities
Director

In aged-society, the life span of people with disabilities is also elongated, which bring a series of health problems such as obesity, hypertension and diabetes. In this project, we attempt to survey the condition of obesity and weakness among people with disabilities. We develop a practical protocol which enable evaluation and intervention (based on exercise and nutritional care) for each disabled condition. We also propose a social model to run the protocol.



Sensory Disability Area

Study on the development of hearing function evaluating system and of auditory cognitive training for presbycusis

2014-2016

Tatsuya YAMASOBA

The University of Tokyo
Professor

Subjects with presbycusis typically complain "I hear the sound, but have difficulty in understanding the meaning especially under noise. Perception due to presbycusis is greatly influenced not only by a threshold increase due mainly to peripheral auditory disorder but also by the impairment in center hearing processing. Nonetheless, no examinations to evaluate the central auditory disorder or rehabilitation methods to train center auditory processing have been established. Because of these backgrounds, we attempt to establish precisely evaluating system of hearing function that reflects everyday life and to develop auditory training to reinforce the central hearing function.



A long-term follow-up study of Auditory Neuropathy Spectrum Disorders in New born hearing screening

2014-2016

Kimitaka KAGA

National Tokyo Medical Center
Emeritus Director

Auditory neuropathy spectrum disorders (ANSD) is one of congenital hearing disorders defined as DPOAE (+) and ABR (-) by newborn hearing screening but is not only one disorder. Our aim of this study is to reveal what kind disorders is included among ANSD after development and growth in infants and are investigate possibility of cochlear implantation.



Technological development on early identification, diagnosis, treatments, orthoptics, rehabilitation for vision-threaten diseases during childhood and young ages.

2014-2016

Noriyuki AZUMA

National Center for Child Health and Development
Director, Professor

Ocular diseases that threaten vision during childhood and young ages mostly begin at an early age less than one year, early identification of which usually is difficult. To obtain good visual outcomes and social reintegration, we develop technology on early identification, diagnosis, treatments, orthoptics, rehabilitation for vision-threaten diseases during childhood and young ages.



To develop a new method for investigation of fetal Rubella virus infection from preserved umbilical cord with congenital hearing loss.

2014-2016 **Noriko MORIMOTO** National Center for Child Health and Development
Chief

Congenital hearing loss appeared to be caused by fetus Rubella virus infection even if the latent virus infection. However, there are no retrospective investigation of the child whose hearing loss is caused prenatal rubella virus infection. We are succeeded to detect Rubella virus from preserved umbilical cord. To develop this technique give us useful information how rubella virus infection affects the etiology of congenital / progressive hearing loss, therefore provide the information of several aspects of congenital rubella syndrome.



Development of a medical management system for congenital hearing loss patients based on their individual etiology.

2016-2018 **Shin-ichi USAMI** Shinshu University School of Medicine
Professor

Congenital hearing loss is one of the most common sensory disorders, occurring in 1/700 to 1000 newborns. Recent advances in genetic testing, imaging and congenital CMV infection testing have enabled us to identify the cause in each patient. Based on a 3-year research project, we sought to facilitate the precise diagnosis through the use of genetic testing, imaging and congenital CMV infection testing as well as the proper medical management based on each patient's specific etiology.



research on development of Japanese tinnitus guideline

2016-2018 **Kaoru OGAWA** Keio University
Professor

Tinnitus affects approximately 10-20% of the overall population, 30% or more at the age 65 and over. The incidence will increase in the future aged society and stress society. Tinnitus is a subjective symptom as well as a pain, an objective examination method has not been established. There is no radical treatment for it. Recently, in the clinical practice of tinnitus a variety of evidences has been reported. American tinnitus guidelines has been published in 2014, however, in Japan we have different medical systems. We should prepare our own guideline. In this study, we are preparing Japanese original tinnitus guidelines to provide the standard clinical practice on tinnitus for ear nose throat (ENT) doctors.



Development of comprehensive low vision care system by inter-professional work

2016-2019 **Yoshimi SUZUKAMO** Tohoku University
Associate Professor

The aim of this study is to develop comprehensive low vision care system by inter-professional work, in order to convey pertinent information and to deliver necessary care to people with low vision. First, we will identify the achievements and problems of the visually impaired supporting project of the model city and will develop the methods for assessment/instruction for multi-disciplinary specialists and will assimilate existing systems. We will then develop, implement, evaluate and improve the new system, followed by to test the feasibility of this system in other city.



Provision of regional or in-home low vision care by scarce specialists using information and communication technology (ICT)

2016-2019 **Satoshi NAKADOMARI** Riken
Researcher

We are serving as an intermediary to connect low vision individuals with the scarce low vision specialists by establishing and evaluating a remote support system using video phone software. We aim to accumulate know-how for using such a support method as well as examine its effectiveness.



Building new intervention strategies and practice-based guidelines for management of developmental stuttering

2016-2018 **Koichi MORI** National Rehabilitation Center for Persons with Disabilities
Director

Although a majority of preschoolers with developmental stuttering recover completely, both spontaneous and intervened recovery becomes rare after reaching a school age. Early intervention is therefore desirable in spite of the early high recovery rate. The first objective of this research is to set a clinical guideline for managing preschool stuttering based on cohort and intervention studies. The second objective is to develop a new therapy approach, mainly based on cognitive behavior therapy, that rapidly enables natural and fluent speech for adolescents and adults who tend to show complicated and severe reactions to persistent stuttering.



Mental Disorder Area

Setting of guidelines on medical treatment of psychiatric disorders in children and adolescents, including neurodevelopmental disorders

2014-2016 **Kazuhiko NAKAMURA** Hirosaki University Professor

We review recent publications and guidelines on medical treatment of psychiatric disorders in children and adolescents. Then we set guidelines on medical treatment of psychiatric disorders in children and adolescents for each medication: antidepressants, mood stabilizers, antipsychotics, anxiolytics, hypnotics and psychostimulants. We also set guidelines on medical treatment of psychiatric disorders in children and adolescents for each disorder: mood disorders, schizophrenia, anxiety disorders, ASD, ADHD, Tourette's disorder, sleep disorders and PTSD. Furthermore, we consider dose adjustments, adverse effects and lowering the dosage of medicine.



Development of educational program among medical professionals for early intervention of psychiatric patients - Application of Mental Health First Aid -

2014-2016 **Takahiro A. KATO** Kyushu University Associate Professor

Mental Health First Aid (MHFA) is an 12-h educational program among general people for early intervention of psychiatric patients in community, which has been spreading world wide including Australia and USA. In this study, we will develop a short educational program among medical professionals for early intervention of psychiatric patients by application of MHFA. We hope that our developing program will contribute to early detection, intervention to psychiatric patients in clinical settings out of psychiatry.



Early intervention for people with mental disorders and establishing its system in Japan.

2014-2016 **Masafumi MIZUNO** Toho University Professor

Making up the guideline for early intervention in psychiatry, this project aims to find the effects of the duration of untreated psychosis (DUP), the clinical characteristics in the prodromal stage, help-seeking behavior patterns, and treatment strategies for the subjects with the first episode of schizophrenia. It collects information about clinical evidences of early psychosis and support system in foreign countries, and propose the optimal system design for early intervention in Japan. Additionally, this study investigates the feasibility of the cognitive behavioral treatment (CBT) for the subjects at risk mental state (ARMS) in Japanese environment of psychiatric treatment.



Research on biomarkers associated with carbonyl stress for schizophrenia

2014-2016 **Masanari ITOKAWA** Tokyo Metropolitan Institute of Medical Science Director

Our research goal is to develop the diagnosis for early stage of schizophrenia by using biomarker associated with carbonyl stress as objective index.



Development of early diagnostic method of schizophrenia by polygenic neuroimaging analysis

2014-2016 **Ryota HASHIMOTO** Osaka University Associate Professor

Psychiatrists diagnose mental disorders are by examine symptoms. As objective diagnosis is not established, the development of objective and scientific diagnostic methods is needed. Polygenic neuroimaging analysis, combination of genetic risk, structural vulnerability and resting state fMRI reflecting the current brain pathology using the data resources of brain phenotype consortium in Osaka University is employed to develop early diagnosis of schizophrenia. The achievement of this research is to contribute to the improvement of health, medical care, and welfare of misunderstanding and prejudice overcome and the people for mental illness.



Development of diagnostic blood biomarkers for major depression and bipolar disorder

2014-2016 **Kenji HASHIMOTO** Chiba University Professor

The purpose of this study is to develop blood diagnostic biomarkers for major depression and bipolar disorder using blood samples (Chiba University, NCNP, Hamamatsu Medical School, Kanazawa University, Osaka University, Kobe University).



The development of new treatment methods and identification of index variables related to behavior control under the Medical Treatment and Supervision Act

2015-2017 **Naotsugu HIRABAYASHI** National Center of Neurology and Psychiatry Head of the Department of Forensic Psychiatry

Twelve years have passed since the enforcement of the Medical Treatment and Supervision Act (MTSA) in Japan. While the law has demonstrated excellent effect of social integration, it has also revealed issues such as recidivism, suicide, and readmission. The purpose of this study is to identify the predictive index factors of treatment outcome and prognosis, and to develop effective and efficient treatment methods in order to further promote the reintegration of MTSA patients into the society.



Projecting for the prevalence and the needs for treatment on mental disorder using spatial epidemiology

2015-2017 **Hisateru TACHIMORI** National Center of Neurology and Psychiatry
Section Chief

We will develop a methodology to estimate the prevalence and the needs for treatment on mental disorder by considering future population. We will also develop a methodology to visualize the results of classification of each region based on their characteristics in psychiatric service use.



Research on peripheral biomarkers that can measure severity of psychiatric disorders

2015-2017 **Shigenobu KANBA** Kyushu University
Professor

We are trying to identify biomarkers that can reflect CNS pathology and can be measured by blood testing with the use of phenotypes and intermediate phenotypes. We have identified several biomarkers for schizophrenia, bipolar disorders, major depression and autism spectrum disorders. We are going to examine the validity of these markers in independent samples.



A study on evaluation and management for new psychoactive substances: the cross-disciplinary study between psychiatry, emergency medicine, and forensic medicine

2015-2017 **Toshihiko MATSUMOTO** National Center of Neurology and Psychiatry
Director

This study is to evaluate the medical disorders caused by new psychoactive substances in the various types of institutions including psychiatric hospitals, emergency unit, and forensic medicine institute, and to develop the guideline for managing the new psychoactive substance-related disorders.



System development to improve the medical standards of psychiatric inpatients care

2015-2017 **Yoshio YAMANOUCHI** National Center of Neurology and Psychiatry
Director

We will develop the system that performs an analysis using collecting the data from the electronic medical record about the contents of inpatients care in psychiatric hospitals. Through this system, we will create knowledge about the quality of psychiatric care.



The effective interventions for suicide attempters with psychiatric disorders after discharge from emergency departments.

2015-2017 **Mitsuhiko YAMADA** National Center of Neurology and Psychiatry
Director

Although most suicidal patients are suffering from psychiatric disorders, these patients often do not receive adequate management at emergency department and mental health services in their communities after their discharge. The aim of this study is 1) to examine the effective interventions for suicide attempters after discharge from emergency departments by systematic review, 2) to evaluate the efficacy in different psychiatric conditions, and 3) to develop educational program for caregivers.



Use of blood biomarkers for prognostic evaluation of patients with higher brain dysfunction

2015-2017 **Toru OGATA** National Rehabilitation Center for Persons
with Disabilities
Director

The precise evaluation of brain damages is critical in the treatment and support of traumatic brain injury (TBI) and subsequent higher brain dysfunctions. In this study, we attempt to use blood biomarkers for predicting functional prognosis after TBI. We select candidate biomarkers related to nerve injury and set up cohort study of TBI patients, evaluating the relationships between value of biomarkers in acute phase and functional deficit in sub-acute phase.



Treatment models for patients with comorbid mental and medical disorders

2015-2017 **Hiroto ITO** National Center of Neurology and Psychiatry
Director

To conduct an observational study on patients with type 2 diabetes and depression, and develop integrated community care models



Research on development of the assessment package and the method for sharing information available through many different fields in support for individuals with the neurodevelopmental disorders.

2015-2017 **Jun ADACHI** Hokkaido University
Professor

This research project develops an assessment package and a method for sharing information of characteristics of individuals with the neurodevelopmental disorders and issues for their support through the life-course. The assessment package and the device for sharing information are planned to be available in many different fields through the internet. A viewpoint of ICF framework is introduced to the assessment package so that a support network can be formed and a support program can be created considering the environmental factors. The aim of this project is a continuous and consistent support. After the trial period of the assessment package and the device for sharing information in local areas, a model for a nationwide workshop will be developed.



Study on the development and clinical application (support for university life and employment) of psychiatric Short Care Program based on the characteristics of people with developmental disabilities

2015-2017 **Nobumasa KATO** Showa University
Director

1) The Rehabilitation Project for People with Developmental Disabilities

We will implement our program in multiple facilities and validate the program. Then, we will introduce the validated program into various facilities on a nationwide scale, optimize the program with considering the size of programs and quality of participants, and develop the standard Short Care Program.

2) The Social Participation Program for Students with Developmental Disabilities
We will verify and modify the standard Short Care Program for university students with developmental disabilities. In the process of the program modification, we will identify those students' needs and encourage their social participation by supporting their university life and employment.



Development of treatment manual for and drug discovery research, by using iPS cells for treatment-resistant schizophrenia

2016-2016 **Masami IYO** Chiba University
Professor

We will develop the treatment manual for treatment-resistant schizophrenia in use of clozapine and methods to treat dopamine supersensitivity psychosis, such as long-acting injectable or sustained release of second generation antipsychotic drugs or modified electroconvulsive therapy. We also perform drug discovery research for treatment-resistant schizophrenia, by using iPS cells, established by blood samples of patients with treatment-resistant schizophrenia.



Societal implementation on care for suicide attempters: developing, disseminating, and systematising the effective intervention for suicide attempters

2016-2018 **Chiaki KAWANISHI** Sapporo Medical University
Professor and Director

More than 800,000 individuals commit suicide in the world. The present study aims to grow societal implementation of care for suicide attempters, the high risk group of later suicide. It tries to disseminate the ACTION-J model, the evidence-based intervention program into general hospitals and establish the consortium. The observational cohort study is conducted. Furthermore, the risk assessment on suicide behaviors, developing the educational program for medical staff, and the fidelity of the intervention program will be also investigated.



Research on Validity and Utility of [Mental and Behavioral Disorders] in ICD-11

2016-2017 **Shigenobu KANBA** Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University
Professor

A field study organized WHO has started in 13 countries to examine validity and utility of guidelines for Mental and Behavioral Disorders in ICD-11 draft. Japan participates in this project by organizing 23 sites all over Japan. Entry of patients has started. The entry is planned to finish by the middle of this year. Then the result will be published, and the draft of ICD-11 will be modified accordingly.



Development of biomarkers for depressive disorder using cerebrospinal fluid samples

2016-2018 **Hiroshi KUNUGI** National Center of Neurology and Psychiatry
Director

This study is aimed to establish biomarkers for depressive disorder by using the largest sample of cerebrospinal fluid (CSF) resource. Based on multisite research collaboration, we will collect many CSF samples from patients with depressive disorder, bipolar disorder, schizophrenia, and healthy controls. Using the collected bioresource, we will obtain evidence for the clinical use of promising biomarkers such as high fibrinogen and low ethanolamine. Furthermore, we will develop biomarker-based new treatments in preclinical studies.



Gambling Disorder: epidemiological investigation, biological evaluation and study of medical treatment, welfare and social support

2016-2018 **Yukio MATSUSHITA** National Hospital Organization Kurihama Medical and Addiction Center
Vice Director

Reality explication by an epidemiological investigation using DSM5 (Diagnostic and Statistical Manual of Mental Disorders Fifth Edition) is performed for gambling disorder in the country. By this investigation, gambling related problems are made clear. Based on this, the comprehensive support system, which consists of medical treatment, health, welfare and public administration, is discussed. And a guideline for Japanese disordered gamblers is made.



Dissemination and implementation of cognitive behavior therapy in clinical, occupational and community settings: development of training programs

2016-2018 **Atsuo NAKAGAWA** Keio University
Assistant Professor

This project aims to enhance the dissemination and implementation of efficacious cognitive behavior therapy (CBT) treatments for common mental disorders through the development of training program and written guide. In addition, we attempt to develop CBT-based training program to help more effectively solve problems for occupational and community health professionals and school teachers.



Development of objective diagnostic methods and practical treatment protocols for treatment-resistant schizophrenia

2016-2016 **Ryota HASHIMOTO** Osaka University
Associate Professor

Clozapine, the most effective antipsychotic medication for treatment-resistant schizophrenia (TRS), should be disseminated. We perform rechallenging of clozapine for clozapine-induced granulocytopenia to develop objective diagnostic methods that contribute to the treatment selection. We also explore the therapeutic response mechanisms using iPS cells from TRS patients to accelerate the development of new therapeutic drugs. The achievement of this research is to contribute to the improvement of health, medical care, and welfare of misunderstanding and prejudice overcome and the people for mental illness.



Study on the actual conditions of alcoholism and development of early intervention and recovery programs through community coordination

2016-2018 **Susumu HIGUCHI** National Hospital Organization Kurihama
Medical and Addiction Center
President

The following four tasks are addressed.

- (1) Implementation of a field survey to assess the drinking pattern and alcohol-related issues in general adults, a field survey of patients with alcohol use disorder who are attending a place of treatment or a recovery facility, and a study of the treatment gap
- (2) Development of guidelines for early detection and initiation of treatment in patients with alcohol use disorder and verification of the effectiveness of the guidelines
- (3) Development of guidelines for recovery programs to improve the therapeutic outcomes and the recovery rate in patients with alcohol use disorder and verification of the effectiveness of the guidelines
- (4) Coordination of community and general medical care, and accumulation and processing of good examples of such coordination



A co-production project to develop a practical guidance for patient-centered and life-oriented recovery of schizophrenia

2016-2018 **Masato FUKUDA** Gunma University
Professor

The aim of this study is to develop a practical guidance for schizophrenia recovery both in subjective quality of life and objective social functioning in "co-production" integrating experiences and strengths of subjects with schizophrenia and their supporters and scientific evidences of professionals. The goal of this project is value-based and life-oriented support for schizophrenia recovery.



Development of recovery college operation guidelines: Co-production and co-delivery by a multi-professional team including people with lived experiences

2016-2018 **Yuki MIYAMOTO** The University of Tokyo
Associate professor

Recovery colleges have become a central component in recovery focused mental health services in England and there is currently significant interest internationally in the operation of recovery colleges. In our study, we will develop a set of guidelines for the operation of a recovery college which is co-produced and co-delivered by multiple professionals, including people with lived experience of mental health challenges. We aim at providing information on facilitating recovery, and tips for co-production and collaboration with multi-professionals including peer support specialists.



Standardization and Dissemination of Japanese Treatment Guideline for Major depressive disorders

2016-2018 **Koichiro WATANABE** Kyorin University
Professor

Japanese treatment guideline for major depressive disorders was published in 2012 and revised in 2016. It is, however, unclear that publication of the guideline has attributed to adjust clinical psychological and pharmacological treatment for depressive patients. Further, dissemination of contexts of the guideline is essential for the adjustment since medicine based on a guideline is not common in clinical practice. Therefore, we conduct a study to estimate sequential alteration of treatment after holding educational lectures and workshops nationwide to deliver psychiatrists the knowledge and the way to use guideline Furthermore, we will revise the guideline by collecting evidences to discriminate other disorders such as diffuse lewy body disease and post maternal depression, and by developing clinical scales to evaluate QOL, social function and patients' satisfaction.



Neuromuscular Disease Area

Therapeutic development for chronic fatigue syndrome (CFS) and proposal a treatment guideline for CFS

2015-2017 **Hirohiko KURATSUNE** Kansai University of Welfare Sciences Professor

There has not been established any decisive treatment for the patients with chronic fatigue syndrome (CFS). Recent Japanese study indicated that one-quarter of CFS patients had no visible sign of recovering and that most of them required bed rest on during the day. In this study we conduct surveys on the treatments for CFS in Japan, and engage in an evaluation of effectiveness of representative treatments for CFS in Japan. We also launch the study of treatment for neuro-inflammation found in CFS. Furthermore, we draw up a treatment guideline for CFS in Japan through the evidencebased evaluation of CFS treatments across the world.



Disturbance of autonomic nervous function in the cases of intracranial hypotension

2016-2018 **Nobuo ARAKI** Saitama Medical University Professor

The effectiveness of bloodpatch against intracranial hypotension is limited; the availability has been reported as 36 to 60%. Mokri and Low reported that the substantial number of patients suffering from postural headache without CSF leak had postural tachycardia syndrome, suggesting that postural tachycardia is a differential diagnosis for intracranial hypotension. We have, however, encountered the cases of intracranial hypotension associated with postural tachycardia syndrome. Suga et al. reported that the 25% of intracranial hypotension cases accompanied postural tachycardia syndrome. We would like to investigate autonomic nervous function in the patients suffering from intracranial hypotension to clarify the contribution of postural tachycardia syndrome to the intractabilizing tendency of intracranial hypotension.



Research of cerebrospinal fluid (CSF) hypovolemia in which CSF leak could not be detected by our reported methods, and in children cases.

2016-2018 **Takamasa KAYAMA** Yamagata University Specially appointed professor

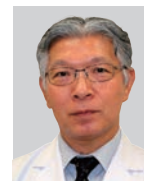
We established a diagnostic criteria of cerebrospinal fluid (CSF) leak in typical adult cases in Oct. 2011. Because the CSF leak seemed to be the most frequent cause of CSF hypovolemia, we focused our efforts on adult CSF leak as the first step. As the second step, this research aims to establish clinical entities of CSF hypovolemia in which CSF leak could not be detected by our reported criteria, and in children cases. Finally we aims to publish therapeutic guidelines for CSF hypovolemia with the approval of 9 academic societies related to this syndrome including the society of pediatrics.



Study concerning resolution of pathophysiology, development of diagnosis and treatment for cerebrospinal

2016-2018 **Masamichi SHINONAGA** International University of Health and Welfare Atami Hospital Professor in neurosurgery

Recently, many cases with childhood cerebrospinal fluid hypovolemia were reported. Children suffering from multiple symptoms caused by sports-related trauma in the school and traffic accident in school zone are not rare. Cerebrospinal fluid hypovolemia might be an important factor in these issue. But, actual condition of childhood cerebrospinal fluid hypovolemia is not clear. This disease is not well known in pediatrician. We will study symptoms, image study and treatment in many registered cases. Finally we will establish the guideline including less-invasive image study for childhood cerebrospinal fluid hypovolemia.



Analyses of clinical features and development of therapy in Tubular aggregate myopathy

2016-2018 **Satoru NOGUCHI** National Center of Neurology and Psychiatry Section Chief

We aim to establish the pathomechanism from genetic mutations in tubular aggregate myopathy and develop therapeutic applications for it. We will make several disease models of this disease group and analyze the consequent events from primary gene defects in skeletal muscles. On this project, we will also search drugs to make a functional recover of the affected muscles.



Development of Diagnostic Methods for Chronic Fatigue Syndrome by using Imaging and Novel Biomarkers

2016-2018 **Yasuyoshi WATANABE** RIKEN Center Director

Chronic fatigue syndrome (CFS) is a persistent and unexplained pathological state characterized by exertional and severely debilitating fatigue, with/without infectious or neuropsychiatric symptoms, lasting at least 6 consecutive months. The objective diagnosis of this disease has not yet been settled. In the present study, we are going to further develop PET imaging on neuroinflammation and abnormal task performance detected by magnetoencephalogram (MEG). Unique substances in exhaled gas, microsome and autoantibody analyses in the plasma, and immune abnormality will be added to convey correlation analyses with all data sets, which give us the chance to develop the methods of objective and differential diagnosis.



Completed Projects

※ The affiliation and position are at the time of project completed.

■ Research and Development Grants for Longevity Science

Studies on safety of pharmacotherapy to older adults

Masahiro AKISHITA The University of Tokyo
Professor

Study of Algorithm for Post-stroke Patients to improve oral intake Level and Nutrition Administration

Akira OGAWA Iwate Medical University
President

Effects of age on motor organs
— A comprehensive examination of sarcopenia —

Atsushi HARADA National Center for Geriatrics and Gerontology
Director of the Hospital

The study of improvement of oral function, oral health and quality of dietary habits in the elderly from community-dwelling people to those in long-term care.

Hirohiko HIRANO Tokyo Metropolitan Institute of Gerontology
Vice-Chief Researcher

Research for the prevention of knee pain, low back pain, bone fractures, and subsequent disability: The follow-up of the Longitudinal Cohorts of Motor System Organ (LOCOMO) study.

Noriko YOSHIMURA The University of Tokyo Hospital
Associate Professor

Development and Verification Trial of the in-home neurorehabilitation system for preventing and improving age-associated musculoskeletal disorders

Masahiko SUMITANI The University of Tokyo Hospital
Department Director

■ Research and Development Grants for Dementia

The comprehensive study on the assessment and management of behavioral and psychological symptoms of dementia (BPSD)

Tetsuaki ARAI University of Tsukuba
Associate professor

Development of the treatment method and the coping method based on both the prevention method and the expression mechanism of BPSD

Hiroaki KAZUI Osaka University
Associate Professor

Elucidation of risk and protective factors for dementia by the large genome epidemiological collaboration study

Yutaka KIYOHARA Kyushu University
Professor

Research on the search of promoting and suppression factors of dementia by the large-scale epidemiological studies

Hiroshi SHIMOKATA Nagoya University of Arts and Sciences
Professor

Study of Care and Nursing Skills for Dementia

Takako TSUTSUI University of Hyogo
Professor

Development of high-sensitive sensor for diagnosis of Alzheimer's disease using polyme-based photonic crystal

Tatsuro ENDO Osaka Prefecture University
Associate Professor

Safety and efficacy of rosmarinic acid in patient with Alzheimer's disease

Moeko SHINOHARA Kanazawa university
Assistant professor

The research project for establishing a large-scale cohort study of dementia in Japan

Yutaka KIYOHARA Kyushu University
Professor

Studies on the establishment of international and domestic infrastructures and network to support dementia clinical research.

Yuichi KATO Osaka City University
Professor

Organized Registration for Assessment of dementia on Nation-wide General consortium toward Effective treatment in Japan: ORANGE

Kenji TOBA National Center for Geriatrics and Gerontology
President

Research and Development Grants for Comprehensive Research for Persons with Disabilities

Physical and Intellectual Disability Area

Construction of a social technology platform for promoting appropriate use and development of assistive technologies

Motoi SUWA Research Institute of the National Rehabilitation Center for Persons with Disabilities
Adviser

Development of Public Support System of Communication Aids for Persons with Intractable Neural Disease about Speech and Language Function

Tamotsu IMURA Chubu gakuin university
Professor

The Exercise Program Aimed the Physical Fitness for People with Impairment

Yukinori SAWAE University of Tsukuba
Associated Professor

Development of Brain-Machine Interface (BMI) -based assistive technology for persons with disabilities.

Koichi MORI National Rehabilitation Center for Persons with Disabilities
Director

Sensory Disability Area

Development of an implantable bone conducting hearing device using giant magnetostrictive material to the patients with moderate to severe hearing loss

Naohito HATO Ehime University
Professor

Development and clinical application of a Next Generation DNA Sequencing (NGS) based comprehensive mutation screening for deafness genes

Shin-ichi USAMI Shinshu University
Professor

Study to elucidate the pathogenesis of age-related macular degeneration and to establish a noble preventive medicine with the use of induced pluripotent stem cells from patients

Akitaka TSUJIKAWA Kagawa University
Professor

practical judgement of a next-generation support model for persons with visual impairment

Satoshi NAKADOMARI National Rehabilitation Center for Persons with Disabilities
Director, Professor

Next generation diffusion tensor imaging (DTI) for visualizing auditory system: from basic to clinics

Masato FUJIOKA Keio University
Instructor

Development of a device for patients with bilateral vestibulopathy to improve body balance using noisy galvanic vestibular stimulation

Shinichi IWASAKI University of Tokyo Hospital
Associate Professor

Mental Disorder Area

A large-scale epidemiologic study of prevalence of mental disorders: The World Mental Health Japan Survey Second

Norito KAWAKAMI The University of Tokyo
Professor

Studies on the clinical evaluation of chronic treatment resistant insomnia and development of an alternative treatment for the disorder

Yuichi INOUE Institute of Neuropsychiatry
Visiting Researcher

The effect of cognitive behavioral therapy for families of pervasive developmental disorder patients with HIKIKOMORI: the application of the CRAFT program

Motohiro SAKAI Tokushima University
Associate Professor

Development and practical use of imaging biomarkers to diagnose and evaluate geriatric depression.

Yoshiro OKUBO Nippon Medical School
Professor

Clinical application of MRI for the diagnosis of mood disorders

Kiyoto KASAI The University of Tokyo
Professor

Blood diagnostic biomarkers for major depressive disorder using DNA methylation profiles

Tetsuro OHMORI Tokushima University
Professor

Development of diagnostic methods of bipolar disorder based on neuropathology

Tadafumi KATO RIKEN
Team Leader

Development of objective diagnosis and treatment for treatment-resistant schizophrenia

Ryota HASHIMOTO Molecular Research Center for Children's Mental Development,
United Graduate School of Child Development, Osaka University Associate Professor

Development of cerebrospinal fluid biomarkers for depressive disorder

Hiroshi KUNUGI National Center of Neurology and Psychiatry
Director

Neuromuscular Disease Area

Integrated genetic analysis dissecting human developmental disorders

Naomichi MATSUMOTO Yokohama City University Professor

Development of disease modifying drugs of neurodegenerative diseases based on the hypothesis of prion-like propagation of abnormal proteins

Masato HASEGAWA Tokyo Metropolitan Institute of Medical Science Division Head

Molecular chaperone therapy for folding disease by using new evaluation method.

Osamu ONODERA Niigata University Professor

Development of therapeutic applications for distal myopathy with rimmed vacuoles with higher efficacy

Satoru NOGUCHI National Center of Neurology and Psychiatry Section Chief

Research of a diagnostic criteria and treatments for cerebrospinal fluid hypovolemia

Takamasa KAYAMA Yamagata University Specially appointed professor

Understanding the pathophysiology of chronic fatigue syndrome (CFS) and epoch-making development of diagnosis and treatment for CFS

Hirohiko KURATSUNE Kansai University of Welfare Sciences Professor

Investigation of the molecular mechanism of central nervous system remyelination

Rieko MURAMATSU Osaka University Associate Professor

In Search of Valuable Biomarkers for Clinical Development of Duchenne Muscular Dystrophy Exon-Skipping Drugs *

Shin'ichi TAKEDA National Center of Neurology and Psychiatry Director

A natural history study of Fukuyama muscular dystrophy and the identification of disease-associated biomarkers. *

Tatsushi TODA Kobe University Professor

Development of novel therapy for progressive muscular dystrophy using G-CSF *

Keiichi FUKUDA Keio University Professor

Research on establishing clinical platforms to facilitate clinical trials for myotonic dystrophy *

Tsuyoshi MATSUMURA National Hospital Organization Toneyama National Hospital Director

Calpain-1 inhibitor treatment for Duchenne muscular dystrophy *

Masafumi MATSUO Kobegakuin University Professor

Development effective cell therapy for muscle diseases *

Akiyoshi UEZUMI Fujita Health University Professor

* These projects have been transferred to the Division of Rare / Intractable Disease Research, Department of Research Promotion at AMED since FY 2016.

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