PROJECT FOR PSYCHIATRIC AND NEUROLOGICAL DISORDERS

Strategic Research Program for Brain Sciences (SRPBS)

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

Strategic International Brain Science Research Promotion Program (Brain/MINDS Beyond)

Research and Development Grants for Longevity Science

Research and Development Grants for Dementia

Research and Development Grants for Comprehensive Research for Persons with Disabilities

Program for Establishing Public-Private Infrastructure for Verification of Innovative Measures against Dementia



Japan Agency for Medical Research and Development

Programs of Japan Agency for Medical Research and Development

Based on the plan for Promotion of Medical Research and Development prescribed by the government of Japan, the the Medical Research and Development (AMED) promotes integrated R&D in the field of medicine, from basic research to clinical trials, focusing on 10 interrelated areas including regenerative medicine and oncology. In addition to ensuring that outcomes are linked through to practical application, it undertakes projects with aim of comprehensively and effectively establishing and maintaining an environment for this R&D.



[Management and Evaluation Framework]

- PD Our PDs offer expert insight into key strategic fields of research. In addition to promoting collaboration between related fields, PDs monitor entire grant programs and make expansion and acceleration recommendations to AMED.
- PS Our PSs prossess a precise understanding of the aims and challenges related to their respective programs in order to effectively oversee operation.
- PO The role of our POs is to assist PSs, taking responsibility for day-to-day program administration.



About our Department



- Division of Regenerative Medical Research
- Division of Cancer Research - Division of Neurological, Psychiatric and Brain
- Research - Division of Rare/Intractable Disease Research
- Division of Infectious Disease Research



Project for Psychiatric and Neurological Disorders Program Director

Shigeo OKABE Professor, The University of Tokyo

The Project for Psychiatric and Neurological Disorders accelerates endeavours aiming to overcome dementia, depression, and other brain disorders. Our goal is to establish innovative strategies for diagnosis, prevention, and treatment of brain disorders through the strong promotion of research on neural circuits and brain functions related to pathophysiology of brain.

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Strategic Research Program for Brain Sciences (SRPBS)

Program Supervisor

RIKEN Deputy Director Tadafumi KATO



Program Officer Tokyo Metroplitan Inst. of Medical Science Department Chair

Kazutaka IKEDA





Kyoto University Professor Ayae KINOSHITA

Ritsumeikan University

Professor

Keio University Professor Masayoshi MISHINA Michisuke YUZAKI



Tokyo Medical and Dental University Professor

Tsutomu TANABE



Organization

Juntendo University Professor

brain science.

Nobutaka HATTORI

In this project, we aim to realize "brain science that contributes to society" by clarifying the

onset mechanisms of psychological and

neurological diseases such as developmental

disorders, depression, and dementia. We will link these for their diagnosis, treatment, and prevention. We also carry out research on the development of basic technologies to facilitate

> National Institutes of Natural Sciences Associate Professor Megumi MARUYAMA



PROJECT FOR PSYCHIATRIC AND NEUROLOGICAL DISORDERS Japan Agency for Medical Research and Development (AMED) Shigeo OKABE The University of Tokyo Program Officer (PO) Research Projects Frogram Supervisor (PS) Program Officer (PO) Research Projects Machine KATO RKEN Ayae KINOSHITA Kyoto University Inst. Or Medical Science Inst. Or Medical Science Michisuke YUZAKI Kelo University Nobutaka HATTORI Jurtendo University Dementia Developmental Disorders Dementia Developmental Disorders Tadafumi KATO RKEN Megumi MARUYAMA Autonal Institutes of Natural Sciences Ethics Machina KATO RKEN Megumi MARUYAMA Autonal Institutes of Natural Sciences Ethics Masayoshi MISHINA Risumeikan University Tsutomu TANABE Developmental Sciences Ethics		0.00	
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Developing imaging agents of molecules for diagnosis and treatment of Alzheimer's disease (AD), and an analysis of pathophysiological mechanisms in AD by developing brood-brain barrier transitable ABO antibodies

Takanori YOKOTA Tokyo Medical and Dental University Professor 2016-2020

The aim of this study is to develop a blood-brain barrier (BBB) -penetrating $A\beta$ oligomer ($A\beta$ O) antibody or an antibody fragment specific for low molecular weight soluble A β O, which will act as target molecules for a possible toxic factor of Alzheimer's disease (AD). The antibody will pass through the BBB via glucose transporter-1 (GLUT1) by conjugating GLUT1 ligand. In addition we will develop imaging technology for detection of early AD using micellar antibody carrier-conjugated MRI contrast agent, elucidate BBB penetration mechanisms, and analyze $A\beta O$ pathophysiology and its removal effect.



IR3D -Dementia

IR3D -Dementia

There are over four million people living with dementia in Japan costing the nation 14.5 trillion yen each year. Therefore, the development of new and more effective treatment and prevention methods are in high demand. The "dementia initiative" aims to integrate state-of-theart basic neuroscience and clinical research to elucidate the mechanisms by which metabolism and inflammation stress affect $A\beta$ degradation pathways in Alzheimer's disease and develop new antibody therapies. It also aims to develop new diagnostic and therapeutic tools for Lewy body dementia and frontotemporal lober degeneration. The goal is to achieve a major step toward eradicating dementia by 2025.

Comprehensive therapeutic development for Alzheimer's disease based on innovative amyloid hypothesis

2016-2020 Takeshi IWATSUBO The University of Tokyo Professor

Life style-related factors, together with aging, are critical pathogenetic factors of Alzheimer's disease (AD) and are considered as targets of its prevention. However, the mechanisms whereby these factors contribute to the acceleration of AD pathophysiology, i.e., abnormality of pathogenic proteins like amyloid β , remains unknown. In this study, we elucidate the roles of environmental factors, including metabolic stresses caused by diabetes and overnutrition, and inflammatory stresses related to glial cells, to pave the way for the development of interventions and methods for prevention and treatment of AD.

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

2016-2020

Gen SOBUE

Nagoya University Professor

Frontotemporal lobar degeneration (FTLD) is one of the three major types of neurodegenerative dementia, however, the etiology of the disease remains unclear and there are no effective therapeutics for the disease so far. We will develop a novel antisense oligonucleotide (ASO) therapy targeting tau isoform and TDP-43 expression which are involved in the pathogenesis of FTLD. In addition, we will also develop integrated imaging biomarkers to perform an early diagnosis including the prodromal stage, prognosis, and drug efficacy evaluation on disease progression based on the novel molecular and anatomical findings in FTLD pathology and FTLD model animals.



Development of early diagnosis and disease-modifying therapeutics for Lewy Body Disease

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 this study, we establish the clinical benefits of FABPs as diagnostic biomarkers and develop 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 consisting of neurotoxic and protective reactions of microglia phagocyting amyloid β in the brains of Alzheimer's disease patients, 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 by targeting neuroinflammation.



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 mechanisms 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 this knowledge to other misfolding diseases.



Novel approaches for treatment of dementia by improving sleep quality

2016-2020

University of Tsukuba 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. We also attempt to prevent the progression of dementia by improving the quality of sleep.

Yu HAYASHI



Development of biomarker for Alzheimer's disease in plasma and dynamical analysis of $A\beta$ in brain

2016-2020

Nobuto KAKUDA Doshisha University Assistant Professor

This study focuses on development of a biomarker with amyloid β protein (A β) in plasma for the pre-clinical stage of Alzheimer's disease. This biomarker would allow us to study changes that occur in the brain. This study will also develop a drug to reduce Ab production in the brain.



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 the main pathological features of dementia-related neurodegenerative disorders. Recently, a hypothesis that those proteins are transmitted and propagated like prions has been proposed. In this project, we will elucidate the regulatory mechanisms for transmission and propagation, and the structural specificity of those abnormal proteins to each disease and brain lesions. We will further develop the basis for diagnostics and therapeutics for those diseases.



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 are considered as risk factors for Alzheimer's disease and so 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.



Novel mechanisms for degradation of α -synuclein

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

Accumulation of α -synuclein proteins in neurons is involved in the pathogenesis of dementia with Lewy bodies and Parkinson disease. Therefore, understanding of intracellular system for degradation of α -synuclein is important for the development of therapy for 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 which may provide the basis for developing a therapy for α -synucleinopathy.



IR3D -Depression and Bipolar Disorder

IR3D -Depression and Bipolar Disorder

Based on environmental factors and genomic factors associated with depression and bipolar disorder, animal models are generated and behavioral analyzes are performed. These models are used to identify the molecular neuropathological basis of these disorders and to elucidate their pathophysiological mechanisms, which will be useful for the development of new therapeutic agents. In addition, data on neuroimaging and blood biomarkers are analyzed by machine learning methods, which will lead to the development of diagnostic and stratification methods. We will also study new treatment strategies such as neurofeedback treatment, and lifestyle-based intervention to prevent these disorders.

Development of inovative diagnosis and treatment for depression using neuroscientific-based stratification and neuromodulation

2016-2020 Shigeto YAMAWAKI Hiroshima University Professor

Conduct basic and clinical studies on molecular pathophysiologies and neural network abnormalities in depressed patients and their model animals to elucidate the pathogenesis of depression. In addition, stratify subtypes via machine learning and the collection of multidimensional data such as clinical information, neuroimaging image data, blood biomarker candidates, and psychological examination. For depressed patients develop neuroscience-based diagnostics, methods for predicting treatment response, and innovative treatments such as neurofeedback.

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

2016-2020

Fujita Health University Nakao IWATA Professor

Mood disorders mechanisms (bipolar disorder and major depressive disorder) remain unknown however several hypotheses have been proposed. In this project, while focusing on the abnormal lipid metabolic state, we examine (1) whether abnormal state of lipid pathway is associated with or has a causal relationship with bipolar disorder, and (2) the intervention of omega-3 polyunsaturated fatty acid (PUFA) as a potential 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.



Elucidation of the pathogenesis of depression and evelopment of technologies for personalized medicine for the disease by focusing on nutrition, lifestyle, and inflammation

Hiroaki TOMITA 2016-2020

Tohoku University

This project aims to elucidate the pathogenesis of depression and postpartum depression, related to nutrition, lifestyle and inflammation, and develop personalized medicine for pathological conditions. These will be done by conducting integrative studies utilizing resources from largescale genome cohorts conducted by Tohoku University, repositories of 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.



Depression and Bipolar Disorder

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 diagnostic and therapeutic methods for depression based on the mesocorticolimbic system. We will identify the molecular mechanisms of ketamine's antidepressant actions. The patent on R-ketamine without side effects was licenced-out to a company in USA. A clinical trial of R-ketamine in depressed patients is underway.



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 the molecular mechanisms underlying them which are currently poorly understood. AMPA receptors are major neurotransmitter receptors in the brain. We developed a novel PET (positron emission tomography) probe to visualize live AMPA receptors in the human brain. We will cross-sectionally investigate psychiatric disorders with this novel PET probe for AMPA receptors. Our study will aim to establish novel concepts of psychiatric disorders and lead to innovative treatments of psychiatric disorders.



Identification of genetically defined subsets of bipolar disorder by trio sequencing

2016-2020 Atsushi TAKATA

RIKEN Senior Visiting Scientist

In this project, we analyze de novo mutations and inheritance patterns of rare variants in bipolar disorder (BD) by performing exome and genome sequencing of BD probands and their unaffected parents. Through this we aim to 1) identify genes/mutations associated with BD with a large effect size, which could genetically define a subset of BD, 2) uncover molecular pathways underlying the pathogenesis of BD, and 3) contribute to a better understanding of the overall genetic architecture of BD.



IR3D -Developmental Disorders and Schizophrenia

IR3D -Developmental Disorders and Schizophrenia

This project aims to elucidate the pathophysiological and mechanisms of autistic spectrum disorder schizophrenia, which are assumed to be associated with impaired neurodevelopmental processes. New diagnostic methods and new treatments based on their pathology will also be developed. To achieve these goals, various clinical research, including genome analysis and iPS cell models will be undertaken. This is combined with integrated research using animal models at various levels such as cells, neural circuits, and behavior. In addition, exploratory clinical trials and research associated with a multi-center clinical trial will also be undertaken. In this project, basic researchers and clinical researchers collaborate to undertake integrated research.

Development of innovative treatment utilizing a novel and improved oxytocin spray, development of methodology to predict the therapeutic effect of oxytocin, and identification of seeds for the next generation therapeutics based on uncovery of the pathophysiology of autism spectrum disorder and the mechanisms of therapeutic effects of oxytocin

2016-2020 Hidenori YAMASUE Hamamatsu University School of Medicine Professor

To develop an innovative treatment for autism spectrum disorder (ASD), we are conducting clinical trials and associated clinical studies for approval by the Japanese FDA. To develop methodology to predict the therapeutic effect of oxytocin and uncover the pathophysiology of ASD and the mechanisms of therapeutic effects of oxytocin, we are conducting integrative analyses of behavioral, neural, and molecular data collected from the participants of



clinical trials. We aimed to develop technologies to objectively and quantitatively diagnose social communication and its dysfunction and drug response. Our animal studies are also trying to uncover the pathophysiology of ASD and the mechanisms of therapeutic effects of oxytocin by testing the efficacy of oxytocin in model mice.

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 Team Leader

To address the major challenges in psychiatric medicine, considering 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.



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

2016-2020 Norio OZAKI

Nagoya University Professor

Psychiatric disorders are diagnosed based on clinical symptoms, however their etiology and pathophysiology are largely unknown. In our study, we aim to identify rare genetic variants that are strongly associated with the risk of schizophrenia and autistic spectrum disorder and reveal their association with phenotypes. Furthermore, based on the genetic findings, we develop and analyze disease model animals and cells (patient-derived iPS cells) to clarify the molecular pathogenesis of these diseases. Based on the above results, we aim to develop new diagnostic methods and treatments.



Innovation of the methods of therapeutics and diagnosis for schizophrenia and developmental disorders by detecting a rare variant

2016-2020

Masanari ITOKAWA Tokyo Metropolitan Institute of Medical Science Vice President

We are innovating therapeutics and diagnostic methods for schizophrenia and developmental disorders by detecting pathophysiology expressed strongly due to a rare variant with a large effect size. We make model animals by using this rare variant to clarify the mechanisms developing these disorders.



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

2016-2020

Motoko MAEKAWA RIKEN Reserch 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.



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 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. Using 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.



IR3D -Resource and Ethics

IR3D -Resource and Ethics

In the resources section we will promote the Japan Brainbank Net, an all-Japan brain bank. Brain resources will be accumulated and provided to researchers to overcome neuropsychiatric disorders. In the ethics section there will be three pillars, ethics support, ethics education and ethics research. These will contribute to the promotion of brain science that harmonizes with society.

Establishment of Japan Brain Net

2016-2020 Yuko SAITO

National Center of Neurology and Psychiatry Head Physician

Based on half-brain freezing, eight major Brain Bank facilities in Japan are constructing resources by a common methodology to cooperate and provide resources for research and educational purposes. With a secretariat at the central facility, we aim to unify windows for inquiries from researchers to quickly provide high-quality resources and produce better research results. We have also made an effort to introduce value-added resources by linking with other businesses, such as Biobank, and introducing a donor registration system.

Resolving ethical, social legal issues in neuroscience

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 subject protection by addressing the ethical, legal, and social implications (ELSI) of brain science including the field of neuropsychiatric disorders.



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

The cognitive control function of the prefrontal cortex in decision making and action selection depends on the interaction between prefrontal areas. To elucidate this interaction, we are developing methods applicable to the prefrontal cortex of macaque monkeys. These are methods of projection-specific, reversible function block and of projection-target identification during recording activities from the cell. To verify their efficiency, the developed methods will be applied to projections between prefrontal areas of monkeys, while they are executing a ruleapplication task.



Development of measurment of descision-makingrelated 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. This is to quantify decision-makingrelated 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 a method to clarify aspects of the primate specific mechanisms for decision making



Circuit mechanism of selection of innate social behaviors in common marmosets

2016-2020 **Kumi KURODA**

RIKFN Team Leader

In mice, it has been shown that innate social behaviors such as parenting, fillial attachment and mating, are governed by hypothalamic 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



Chemogenetic imaging: in vivo visualization and control of neural circuit for decision-making

2016-2020

National Institutes for Quantum Takafumi MINAMIMOTO Radiological Science and Technology Group Leader

We are aiming to develop 'chemogenetic imaging' methods which enable localization of targets for reversible pathwayspecific DREADDs manipulation and analysis of changes in whole brain neural activity. We will identify the specific role of cortical-subcortical pathways in decision-making.



and

Decision Making

Decision Making

Human and nonhuman primates have the ability to adapt to complex circumstances including social relationships by flexibly switching the mode of decision making according to the evaluation of relative values. Psychiatric disorders such as neurosis and dependence can be regarded as impairments of decision making. This project will reveal the circuit mechanism of decision making using cutting-edge techniques of circuit manipulation and neuronal activity imaging, and provide basic knowledge for cognitive behavioral therapies.

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

2016-2020 Tadashi ISA

Kyoto Universtiy Professor

Our goal is to understand the neural basis of flexible decision making. We record multi-unit activities and analyze the big data to decode the mode of decision making. By machine learning algorithms we causally demonstrate the contribution of the neural activity to decision behavior. We also try to manipulate the neural circuit 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 tasks that require flexible decision making.



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

2016-2020 Masaki ISODA

National Institutes for Natural Sciences Professor

The goal of this project is to develop experimental procedures that enable a system-level understanding of social decision-making and behavioral control using macague monkeys, a social animal species whose brain structure is similar to that of humans. This project is expected to devise better controlled social tasks in laboratory environments and clarify the global-network mechanisms and the genetic basis that underlie social decision making.



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

Program Supervisor The University of Tokyo Professor Shigeo OKABE



[PROJECT FOR PSYCHIATRIC ANE

Program Officer

Tamagawa University Professor Professor

The University of Yamanashi Hokkaido University Professor Tetsuya MATSUDA Toshihisa OHTSUKA Masahiko WATANABE



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

oLOGICAL DISORDERSJ ram Director eo OKABE The University of Tokyo			
Program Supervisor Shigeo OKABE The University of Tokyo Program Officer Tetsuya MATSUDA Tamagawa University Toshihisa OHTSUKA The University of Yam Masahiko WATANABE Hokkaido University	Project Promotion Committee		
Central Institute (RIKEN)			
Project Leaders (PL Atsushi MIYAWAKI RIKE Hideyuki OKANO RIKEN	Project office		
·	The study of neurodegenerative disease marmoset models group		
	The study of wild type marmosets group		
	Clinical research group		
	Technology development group		

Central Institutes

Research on Neurodegenerative Disease Marmoset Models

Central Institutes

The main aim of this project is to develop genetically modified marmosets to elucidate the pathophysiology of human brain diseases. To achieve this we will develop technologies required for producing such animal models, construct a map of primate structure/function and make a database that holds associated data, alongside innovative analysis techniques.

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

2014-2023 Atsushi MIYAWAKI RIKEN Team Leader

We are engaged in technological innovation in optical bioimaging for studies using primate and rodent brains. Our new technologies will set a trend in visualization and manipulation of brain functions and in diagnosis of diseaserelated molecules. In particular, we develop comprehensive imaging methods that enable us to detect subtle but significant signals of neuronal activity in freely moving animals. Also, we use post-mortem patient brain samples to elucidate brain disease pathophysiology.



This project involves the production and neurodegenerative breeding of disease marmoset models using gene modification technology. We develop efficient production and breeding methods using developmental engineering technology. We will generate mainly animal models for neurodegenerative diseases, such as dementia, which we will distribute to many researchers.

Study of developing neurodegenerative model marmosets and establishment of novel reproductive methodology

2019-2023 Erika SASAKI

Central Institute for Experimental Animals Department Head

The rapid increase in the number of patients with dementia following an aging society has become a major issue. This is accompanied by social burdens such as medical expenses related to dementia, care expenses, and informal care. To develop prophylactic methods and new therapies of dementia, the identification of neural circuits involved in the onset of dementia using model animals that are phylogenetically, physiologically, and morphologically close to human are required. In this study, we will develop dementia disease non-human primate models using the common marmoset which is small, prolific and genetic modification is available.



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

2014-2023 Hideyuki OKANO RIKEN Team Leader

The Brain/MINDS project aims to provide an integrated structural map of the marmoset brain at the macro-, meso-, and microspatial scales, as a foundational template for overlaying functional mapping data derived chiefly from brain imaging technologies including fMRI, PET imaging, and calcium imaging. In addition, this project aims to provide genetically modified marmoset disease models for Rett syndrome and Parkinson's disease, which will contribute to understanding the pathogenesis of neurological and psychiatric disorders.



Research on Wild Type Marmosets

Platform for marmoset research support

2019-2023 Erika SASAKI

Central Institute for Experimental Animals Department Head

The purpose of this research is to establish a research infrastructure that allows Brain/MINDS researchers to conduct research using marmosets in a stable manner. In particular, to cope with the shortage of animals we will breed animals to provide to Brain/MINDS researchers. In addition, to improve animal quality as a research resource, such as downsizing of animals and reduction of genetic diversity, we will improve breeding and raising performances.



Research on Wild Type Marmosets

We will improve the breeding environment and mating/breeding technology to establish a method for breeding wild type marmosets suitable for brain science research. We will study the interactions of gene and environment for wild type marmosets. The results will allow them to be stably distributed to researchers to support brain science research.

Common marmosets as experimental animals suitable for brain science research: research on breeding, housing, and distributing methods

2019-2023

National Center of Neurology and Psychiatry Director

The National Center of Neurology and Psychiatry (NCNP) has one of the nation's leading marmoset colonies. The first aim of this research is to establish a stable supply system of wild-type animals to domestic researchers using this marmoset colony. The second aim is to dissect the marmoset breeding system that have been established in NCNP colony in an empirical way, from the perspective of down-sizing prevention, stress reduction, and mortality reduction, and provide a good prototype for breeding marmoset that is appropriate to use in neuroscience research in Japan.

Keiji WADA

Establishment of a method for rearing marmosets of strong physique and providing marmosets

2019-2023 Katsuki NAKAMURA Kyoto University Professor

We will investigate 1) physical environment (the cage design and structures in the cage), 2) nutritional management (diet and adding food), and 3) health management (procedure and items of the medical examination: method of anesthesia and treatment). The second aim of our project is to provide marmosets or biological samples to the researchers in the Brain/MINDS project to promote the project. The third aim of our project is to teach rearing and handling know-how to researchers and care-takers.



Studies on psychiatric disorders using mutant marmosets generated by autologous embryo transfer

2019-2023 Atsu AIBA

The University of Tokyo Professor

To elucidate the molecules and circuits responsible for psychiatric disorders and to develop strategies for treatment disorders, we will carry out the following projects. 1) Development of a protocol for autologous embryo transfer to effectively generate mutant common marmosets (Callithrix jacchus). 2) Generation of model marmosets for tuberous sclerosis complex (TSC) to study its biology. 3) Screening of the candidate genes responsible for psychiatric disorders.



Clinical Research Group

Clinical Research Group

In this project, we will elucidate the neural circuits responsible for the higher brain functions of marmosets at the neuron level to contribute to overcoming human neurological diseases. We will undertake:

- Analysis of neural circuits related to mental diseases using MRI
- · Research neurodegenerative diseases to identify biomarkers
- · Molecular biological and developmental engineering research on neurological diseases
- Research on neurodegenerative diseases by molecular imaging technology
- Functional analysis of neural circuits related human neurological disease

Study for impairment of predictive function in psychiatric disorders using a bi-directional translational approach

2019-2023 Shinsuke KOIKE The University of Tokyo Associate Professor

This research intends to conduct a cross-disease investigation for impairment of the predictive function in psychiatric disorders using a bi-directional translational approach (Patient - Human - Non-human primate - Mouse). We intend to find the translatable phenotypes for prefrontal cortex-dependent auditory predictive function and condition predictive function. We will expand the large-



scale database of the multi-center magnetic resonance imaging study in Japan and measure for people with affective disorders and autism spectrum disorder. We will find the shared and disease-specific alterations of the phenotypes and the neural and molecular basis of the impairment of the predictive function in psychiatric disorders.

Translational research for neural circuitry pathologies and biomarkers for prodromal and clinical Parkinson's disease

Ryosuke TAKAHASHI Kyoto University Professor 2019-2023

The aim of this project is to develop innovative and translatable biomarkers for the prodromal and early stages of Parkinson's disease (PD) to elucidate the latent pathology and progression before disease onset. Combining the existing longitudinal study of REM sleep behavior disorder (RBD) cohort designed as a prodromal PD cohort and a new onset PD cohort, we will explore biomarkers that can predict the conversion of RBD to PD. By using marmoset and mouse models ranging from RBD to PD which recapitulate genetic and aggregated α -synuclein propagation pathologies, we will elucidate RBD/PD circuitry pathologies and develop early therapeutic interventions.



Molecular imaging study of pathological protein aggregation and transmission and neural circuit disruptions

National Institutes for Quantum Makoto HIGUCHI Radiological Science and Technology and 2019-2023 Department Head

Diverse neurodegenerative disorders are neuropathologically characterized by accumulations of misfolded proteins in the brain, as represented by depositions of tau, α -synuclein and TDP43. These protein aggregations have been indicated to spread through neural circuits, eventually leading to a wide range of disease-specific symptoms attributable to functional alterations of these circuits. With groundbreaking and original PET probes for tau pathologies and AMPA receptors, this



translational research project reciprocally links non-clinical and clinical imaging assessments aim to clarify molecular etiologies of neurodegenerative disorders. Studies on disease models will focus on analyses of transmissions of protein aggregations. Along with this program, imaging agents for α -synuclein and TDP43 deposits will also be developed and applied to clinical assays.

Understanding the mechanism of $A\beta$ -induced aggregated tau propagation and neurocircuit degeneration in Alzheimer's disease

2019-2023

The University of Tokyo Taisuke TOMITA Professor

We will clarify the pathological relationship between amyloid- β (A β) deposition, the earliest pathological changes in Alzheimer's disease (AD), and propagation of aggregated tau that causes the neurodegeneration. We will also elucidate the earliest damaged neurocircuit in the pathological process of AD using patient samples and disease models. Our research will highlight the key neuronal circuit that is damaged by $A\beta$ -induced aggregated tau propagation and lead to an understanding of the conversion process from preclinical stage to AD.



Identification and functional analysis of neural circuit responsible for mental disorders based on genomic information of brain

2019-2023

Kazuya IWAMOTO Kumamoto University Professor

Common environmental and genetic factors are known to cause different psychotic conditions. In this project, we try to identify new brain regions affected by environmental and genetic factors using animal models, and clarify the relationship between affected regions and behavioral alterations. In addition, we analyze brain genome information in the corresponding brain regions of animal models and postmortem brains of patients.



Studies on neural circuit and molecular pathology based on human genome mutations in psychiatric disorders

2019-2023

Nagoya University Kozo KAIBUCHI Professor

We will combine behavior, morphology and dynamics of neural circuits, synaptic plasticity, and intracellular signaling analyses in psychiatric disorder model mice to elucidate the molecular and circuit pathology. Neurons and organoids derived from iPS cells established from patients with 22q11.2 deletion and tuberous sclerosis will also be characterized. The screening and verification of new mutation candidates involved in cross-disease episodes among schizophrenia, bipolar disorder, and autism spectrum disorder will be continued for additional elucidation of molecular and circuit pathology. The obtained information can be applied to the analysis of neural circuits and their functions in marmosets.



Technology **Development Group**

Technology Development Group

In this project, we develop new technologies for brain science such as new neural network manipulation technologies, physiological measurement technologies, and new behavior analysis methods. We also carry out research and developments based on new scientific principles. The final goal of this project is the development of new technologies that contribute to the elucidation of neural circuit functions in primate cerebral cortex and subcortical structures.

Multimodal multi-scale functional mapping of marmoset brain and development of functional mapping at ultra-fine scale

2017-2020 Kenichi OHKI

The University of Tokyo Professor

In the previous project in Brain/MINDS, we developed 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. We started to apply the multimodal multi-scale functional mapping techniques



to apply the multimodal multi-scale functional mapping techniques to the marmoset brain and noticed several problems specific with this. In this project, we will solve these problems (technical development 1-3) and accomplish multimodal multi-scale functional mapping of the marmoset cortex, particularly in the primary visual cortex and higher visual areas of marmosets (technical development 4-6). We will solve several questions about resting-state functional mapping 1-4). To match anatomical findings and functional mapping at an ultra-fine level, such as structural mapping by electron microscopy with the functional connectivity at synapses, we will first develop functional mapping technology at synapse level in mice (Technology Development 7, 8), with the aim of applying this to the marmoset brain (functional mapping 5).

Development of 3D imaging and analysis pipeline for marmoset brain

Hiroki UEDA 2017-2020

The University of Tokyo Professor

The aim of our project is developing technologies for efficiently mapping primate brain structure and function by applying "CUBIC," a whole brain/body 3D imaging a whole brain/body 3D imaging technology with single-cell resolution. In sub-project 1: development of a 3D observation technology for a marmoset brain and establish a clearing protocol for adult marmoset brain and then evaluate its usefulness with labeled specimens to accumulate examples of 3D imaging.



Analyze structures and functions of marmoset brains by multi-scale and multi-modal approaches

2017-2020

Atsushi NAMBU National Institutes of Natural Sciences Professor

Based on electrophysiological and neuroanatomical methods, we utilize new multi-scale and multi-modal mapping techniques and expand mapping to the prefrontal association cortex and disease states of marmoset brains, and contribute to the Brain Mapping Project of Marmoset Brains.



Production of knockout marmoset using spermatogenic cells

Takashi SHINOHARA Kyoto University Professor 2017-2020

Knockout animals can be produced using germline stem (GS) cells, cultured spermatogonia with enriched spermatogonial stem cell (SSC) activity. However, little is known about SSCs in primates. In this study, we will develop an SSC enrichment protocol and aim to establish GS cells from marmoset testis by analyzing the gene expression pattern in SSCs. We will also try to carry out gene editing using spermatogenic cells in vivo.



Analyze structures and functions of marmoset brains by multi-scale and multi-modal approaches

2017-2020 Hajime MUSHIAKE Tohoku University Professor

Based on electrophysiological and neuroimaging methods, we will develop three new multi-scale and multi-modal mapping techniques and contribute to functional mapping of the frontal association cortex and disease states of marmoset brains. 1) gAIM-MRI, 2) Ultrathin Fluorecence Endscope Imaging system (U-FEIS), 3) Multichannel recoding system for Edcope.



Super-multicolor labeling for automatic reconstruction of neuronal circuits

2017-2020 **Takeshi IMAI**

Kvushu Universitv Professor

Recent progress in connectomics has expanded throughput in image acquisition, but manual data analysis is the ratelimiting step. In this project, we aim to develop a new framework for light microscopy-based connectomics. More specifically, we will develop a super-multicolor labeling system for automatic reconstruction of neuronal circuits.



Mapping the structure and function of the cortico-basal ganglia network in marmosets by use of pathway-specific labeling and manipulation technology

2017-2020 Kazuto KOBAYASHI Fukushima Medical University Professor

A comprehensive understanding of circuit function and synaptic organization in the basal ganglia will provide a framework that can be used to develop novel treatments for neurological and psychological disorders. To address this issue, we aim to develop a detailed functional and anatomical map of the basal ganglia circuit in marmosets. By using viral vectors for highly efficient neuron-specific retrograde gene transfer, Kobayashi's group will manipulate the function of the thalamostriatal and corticostriatal pathways and elucidate their roles in motor control and cognitive functions.



AAV vector-mediated cell type-specific gene knockdown / knock-out in marmoset CNS in vivo

2017-2020 Hirokazu HIRAI

Gunma University Professor

Adeno-associated virus (AAV) vectors have been markedly developed and are now becoming essential for brain research. Our study aims to develop 1) AAV capsid permeable to the marmoset blood brain barrier and 2) methods for cell type-specific gene knock-down and knockout in marmoset brain. In addition, we distribute our original AAV vectors to and co-develop new AAV vectors together with Brain/MINDS scientists.



Development of neural circuit tracing for mapping the connectome in the common marmoset

2017-2020

Fumitaka OSAKADA Nagoya University Associate Professor

The function of the nervous system emerges from complex interactions between networks of neurons composed of multiple cell types. Understanding how these networks function both in health and disease requires revealing the connectivity between specific neuron types. The goal of our study is to develop a neural circuit tracing method combined with cell-type-specific targeting that makes it possible to map the connectome in the common marmoset brain.



Mapping the structure of the basal ganglia network in marmosets by use of pathway-specific labeling and manipulation technology

2017-2020 Miwako YAMASAKI Hokkaido University Associate Professor

We aim to develop a functional and anatomical map of the marmoset basal ganglia circuit at light and electron microscopic levels. With optimized neuroanatomical technology, including pathway tracing and cell type identification, Yamasaki's group is working on localizing glutamate and dopamine receptors in the basal ganglia circuit.



Development Group Technology

Development of innovative method for an all-optical electrophysiology to measure and manipulate neural activity

2017-2020

Masayuki SAKAMOTO The University of Tokyo Assistant Professor

We will develop an innovative all-optical electrophysiology method to record and manipulate the neural activity of multiple neurons simultaneously with cellular resolution in vivo. First, we will generate novel opsin-based genetically encoded voltage indicators which show improved brightness and voltage sensitivity by two-photon excitation in vivo. Second, we will find new optogenetic tools that are available with new voltage indicator with cross-talk-free.



Development of single neuron labeling method and three dimensional reconstruction method of ultrastructures

2017-2020 **Takahiro FURUTA** Osaka University Associate Professor

Understanding the structure of complex neural networks is one of the central themes of the Brain/MINDS project. The brain circuit consists of long fiber projections, and at the same time these fiber connections are constituted by fine synaptic structures. In our research task, we will develop innovative visualization techniques of neuronal morphology, and combine light microscopic analyses, which realize large visual field observation, with electron microscopy technologies, which provide three-dimensional ultrastructural data of brain tissue.



Zoom-in to the ultrastructure level from the whole brain level using a tissue-clearing method as the cornerstone

2017-2020 Hiroyuki HIOKI

Juntendo University Associate Professor

The tissue-clearing method ScaleS has superior retention of ultrastructure, we will use it as the main axis for establishment of the following. (1) Flexible zoom-in technology across two observation methods of the light and electron microscopy. (2) Technology to efficiently analyze at whole-brain (macro) and the ultrastructure (nano) levels. We will promote the integration of "brain structure mapping" conducted in each hierarchy.



Acoustic-optical technologies for investigating deep brain area

2019-2023 **K**

Keiichi NAKAGAWA The University of Tokyo Lecturer

To guide light to deep tissue sites in the brain, we create optical fiber or waveguide-like refractive index profiles inside brain tissues in a non-invasive manner. We will use spatiotemporal control of refractive index profiles of brain tissues by the pressure fields of nonlinear acoustic waves. We will develop novel acoustic-optical techniques based on optical and acoustical engineering technologies that enhance the performance of conventional optical stimulation and measurement methods such as optogenetics, fluorescence imaging, near-infrared spectroscopy, and whole-brain analysis with transparent brains.



Development in gene transfer techniques for primate brains by means of novel viral vector systems

2019-2023

Masahiko TAKADA Kyoto University Professor

This research project aims at establishing innovative techniques for more effective and stable pathway-selective activity manipulation/imaging and sensitive tract-tracings in primate brains by optogenetic/chemogenetic approaches with novel retrograde/anterograde viral vectors. We also aim at achieving non-invasive and brain-wide gene transfer in primates through the development of novel viral vectors and their delivery system to produce genetically modified model marmosets.



Development of a protein-based photochemical tool for all-optical neural activity measurement

2017-2020 Yuki SUDO

Okayama University Professor

The purpose of this study is to establish a technique that can measure membrane potential changes and manipulate neural activity at a single neuron level in living organisms. Here, by developing a new membrane potential sensor and combining it with optogenetics, we create an all-optical electrophysiology without electrodes. This will lead to an innovative new technology for elucidating functional networks in the brain.



Development of a method for high speed and high resolution whole-brain imaging in primates

2017-2020

Hitoshi HASHIMOTO Osaka University Professor

This study aims to contribute to the generation of brain structural and functional maps in primates. For this purpose, we are developing a high speed and high resolution wholebrain imaging method in primates with throughput increased from existing techniques. We recently developed a high-speed serial-sectioning imaging system named FAST (block-FAce Serial microscopy Tomography). In this study, we try to further increase the imaging throughput and image quality and thus increase versatility of our system in the marmoset whole-brain imaging analyses.



Development of innovative wide-view mapping of synaptic ensemble in the psychiatric model

2017-2020 Akiko HAYASHI-TAKAGI RIKEN Team Leader

We will develop functional connectomics, which involves information on what neuronal circuits are utilized and (de) potentiated during brain functions. For this purpose, we take advantage of a synaptic optoprobe, AS-PaRac1 (activated synapse targeting photoactivatable Rac1), which can specifically label recently potentiated spines. Combined with simultaneous three-color imaging of an activity-



dependent expression of the presynaptic marker (blue), postsynaptic neuronal filler (green), and AS-PaRac1 (red), we try to visualize functional connectomics. Functional connectomics will pioneer a comprehensive understanding of how the brain works and how the dysfunction of neuronal circuits are related with the pathophysiology of psychiatric disorders.

Technology Development Group

Research on high-speed super-resolution in vivo 3D imaging method by utilizing advanced laser light technology

2019-2023 **Tomomi NEMOTO** Hokkaido University Professor

The purpose of this subject is to realize biological superresolution imaging that contributes to connectomics research. By taking full advantages of novel optical laser technologies, we will develop a system that can be applied for multiple fluorescence wavelengths and realize highspeed three-dimensional image acquisition. Finally, by utilizing stimulated emission suppression to break the spatial resolution limited by classical diffraction of light and by combining it with a multiphoton excitation microscope excellent for the deep observation of the living body, we will realize super-resolution imaging of a model animal's living brain.



Elucidating circuit function via multiplexed activity trace labeling and all-optical interrogation

2019-2023 Haruhiko BITO

The University of Tokyo Professor

We previously engineered a next-generation, genetically encoded calcium indicator, XCaMPs, which can monitor neuronal activity at high speeds. We also combined the use of synthetic activity-dependent promoters, such as E-SARE, making it possible to visualize cell activity for long durations. Based on these results, we will design and develop novel technologies to simultaneously record



multiple cell types, including excitatory and inhibitory neurons. We will develop functional imaging to visualize neuronal activities of multiple cell types at high speeds in the live brains of animals while they perform behavioral tasks. In addition, we will establish technologies that enable an all-optical interrogation based on multiplexed activity trace recording.

Multiple scale functional mapping of neuronal dynamics

2019-2023 Kazuo KITAMURA University of Yamanashi Professor

Neurons receive thousands of synaptic inputs at various timings in the order of milliseconds, and convert, amplify and integrate them as chemical signals in the order of seconds to minutes, to process complex input information and maintain them as long-term memory. In this project, we develop a technique that can map intracellular signals at multiple spatiotemporal scales in live animals. For this purpose, we will develop new highly sensitive multicolor probes that can detect cellular and molecular signals in neurons, and develop new microscopy that can visualize neural signaling dynamics at multiple spatiotemporal scales simultaneously.



Development of innovative photo-activated molecules to induce de novo synaptic plasticity in vitro and in vivo

2019-2023 **Ayako WATABE**

The Jikei University Professor

Synaptic plasticity is fundamental for various adaptive brain functions, and distinct molecular mechanisms via intercellular signaling cascades have been postulated for multiple forms of plasticity. Our goal is to develop innovative tools which enable us to manipulate distinct forms of synaptic plasticity in a temporally regulated manner, and with synaptic tags to control the subcellular localization. These techniques will provide us the basis for a better understanding of how the brain works in plastic manners and how the dysregulation of plasticity leading to mental disorders.



Study of correlative microscopy on neuronal circuits and ultrastructure

2019-2023 Yusuke HIRABAYASHI The University of Tokyo Associate Professor

In this study, we will identify the synaptic targets of longrange axonal inputs by optimizing the correlated lightelectron microscopy approach. Using this optimized microscopy technique, we will correlate the activity and ultrastructural features at presynaptic boutons.



Establishment of high efficiency method for long transgene introduction based on common marmoset

Shinshu University Ikuo TOMIOKA 2019-2021 Assistant Professor

Lentiviral gene transfer is a powerful tool in the genetic modification of animal genomes and is the most efficient method for creating transgenic marmosets. However, the transgene length in lentiviral vectors is strictly limited making it impossible to produce marmoset models for most neurodegenerative diseases. Therefore, this research will establish a highly efficient method for long transgene introduction using the transposon system of common marmosets.



Efficiency improvement and standardization of cortical microcircuit analysis using 3D reconstruction of large volume EM data set

2019-2023 Yoshiyuki KUBOTA National Institutes of Natural Sciences Associate Professor

How the cerebral cortex executes complex higher brain functions by integrating inputs from the thalamus and other cortical areas is a fundamental question in neuroscience. To find the wiring rules of the cortical neural network, the use of large-volume electron micrograph (EM) data sets has emerged as a promising approach. However, a major obstacle is the inefficiency of EM imaging and subsequent



image analysis. We wish to solve these issues by introducing several technical improvements and standardization to the cortical microcircuit analysis method based on 3D reconstruction of large volume EM data sets, to bring us closer to answering the principal question in neuroscience.

Wide-field and high-resolution functional mapping of marmoset motor cortex

2019-2023 Teppei EBINA

The University of Tokyo Assistant Professor

We will develop a wide-field, high-resolution calcium imaging method to map the functional organization of marmoset motor cortex. We combine this method with previously developed two-photon imaging and optogenetic techniques to further reveal the 3D-functional organization and dynamics in the motor cortex during motor planning and execution. This project will contribute to deepening our understanding of the neural mechanisms underlying motor control in the primate neocortex.



Technology Development Group

Development of a method for linear modeling of brain-state and stimulus-related information

2019-2023 Junichi CHIKAZOE National Institutes of Natural Sciences Associate Professor

Recent studies have reported that non-invasive investigation of functional connectivity by resting state fMRI provides biomarkers for neuropsychiatric diseases. However, most available methods lack sufficient accuracy for diagnosis limiting traditional analysis methods. Here, we propose a method for quantitative estimation of neuronal network states, which dynamically change. Aiming at its clinical application, we hypothesize that spontaneous brain activity at rest reflects the computation of several parallel networks, which can be modeled by their linear combination.

2019-2023 Yosuke OKAMURA Tokai University Associate Professor

Based on material engineering, we propose coverslip-free

deep imaging by wrapping with innovative freestanding

nanosheets with a thickness of around 100 nm to push the

limits of deep brain imaging. These techniques could have a

high potential to contribute full-scale investigation of brain

limits of deep brain imaging

Development of innovative nanosheets for pushing the



Development of novel optogenetic neural circuit manipulation methods by wireless power transfer system

Kyoto University 2019-2023 Itaru IMAYOSHI Professor

The development of innovative methods that can noninvasively manipulate neural cells in the brain has been expected for circuit manipulations of the nervous system. In this research proposal, we will try to develop novel methods to selectively and efficiently manipulate neural cells by a wireless power transfer system. We will apply these light-mediated control methods to analyze neural circuit mechanisms underlying meta-learning processes.



Development of an innovative embryo manipulating system for the generation of genetically modified marmosets

2019-2023 **Toshikuni SASAOKA** Niigata University Professor

This research project will develop reliable low-priced technology and the human resources to create genetically modified marmoset. We hope to improve the access to marmosets for scientific experimentation. The project comprises three aims. The first is develop a stable method for generating mature oocyte and fertilized eggs. The second is generate model animals for brain diseases via genome editing using fertilized eggs from xenotransplanted ovaries. The third is establish naïve ES cells and generate genetically modified marmosets using the blastocyst complementation method.



Development of data-driven integrate model using Brain/MINDS database

2019-2023 Ken NAKAE

function.

Kyoto Univeristy Assistant Professor

We will develop a data assimilation method for integrating the Brain/MINDS database, which comprises structural and functional datasets from marmosets. We will apply our method to datasets from diseased marmosets and predict the source brain regions and the timing of seizures for diseases to validate our method



Advanced Multi-Linc analysis to clarify circuit mechanisms of cortical and subcortical functions

Yoshikazu ISOMURA Tokyo Medical and Dental University Professor 2019-2023

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. So far, we have established the basic technology and showed its potential usefulness in cortex and basal ganglia researches. For practical applications, we will further automatize and increase the scale by improving real-time computer controls.



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Strategic International Brain Science Research Promotion Program (Brain/MINDS Beyond)

Program Supervisor

Tamagawa University Professor Emeritus Minoru KIMURA



[PROJECT FOR PSYCHIATRIC AND NEUROLOGICAL DISORDERS]

Shigeo OKABE The University of Tokyo

Program Director



Professor

Kyushu University Professor Emeritus Toshihisa OHTSUKA Shigenobu KANBA



Tamagawa University Professor Tetsuya MATSUDA



In June 2018, "Brain/MINDS Beyond" was launched to take part in the dramatic development of brain sciences in Japan and the world through collaborations with national projects in the United States and in European countries.

A new stage of understanding of the human "mind" to be reached based on activities in specific brain molecules and neuronal circuits is expected. The results will lead to innovative development of the diagnosis and treatment of psycho-neurologic diseases.

Organization

Japan Agency for Medical Research and Development (AMED)



Program Supervisor (PS) Program Officer (PO) Program Officer (PO) Program Officer (PO)

Minoru KIMURA, Professor Emeritus, Tamagawa University Toshihisa OHTSUKA, Professor, University of Yamanashi Shigenobu KANBA, Professor Emeritus, Kyushu University Tetsuya MATSUDA, Professor, Tamagawa University



Core Organization (National Institutes of Natural Sciences)



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Core Organization

Research Group 1

Core Organization

The core organization operates the project flexibly and smoothly, accelerates the research contributing to strategic international development. The organization serves also as an international hub in Japanese brain science research. We will support international collaborations in large-scale brain science projects in Japan.

Promotion of the integrated and globally collaborative brain science research

2018-2023 Junichi NABEKURA National Institutes of Natural Sciences Director

To support all brain science research in Japan and future global collaborations we work as a response window by coordinating Japanese research activity and enhancing the collaboration with International Brain Initiative (IBI) and other countries across the world. To run the Brain/MINDS Beyond smoothly and foster the globally collaborative innovations, we are supporting the neuroethical aspects of human and non-human primate research and promoting outreach activities for the stakeholders. In a word, we are strategically backing up the research and development with an aim to increase global collaborations.



Research Group 1

We conduct comprehensive research according to the life stage (developmental stage, adulthood, and old age), such as brain images from the health stage to the disease stage. Working closely with each research project 1-1, 1-2, we aim to contribute to collaboration with the national projects in the US and Europe.

1-1: Identification of the pathogenic mechanism of mental and neurological disorders through acquisition and analysis of MRI brain images and clinical data, etc. 1-2: MRI brain image data platform

1-1

The mechanism of brain development and disorders in adolescence and young adulthood (AYA) through international MRI collaborations

2018-2023 Kiyoto KASAI

The University of Tokyo Professor

The onset of many psychiatric disorders usually occurs in adolescents and young adults (AYA). The substrates of brain maturation in the AYA generation largely remain undiscovered. In our current research project, we will acquire longitudinal MRI data of patients with schizophrenia, those with developmental disorders, and typical developing individuals using the Human



Connectome Project (HCP) protocol. In addition, we will share MRI data with our international collaborators. Through these approaches, we aim to elucidate mechanisms regarding the onset of psychiatric disorders in the AYA generation and to identify brain-circuit-based biomarkers that will be useful in diagnosis and predicting treatment outcomes.

Elucidation of neural circuits of mood disorder in adults and related disorders based on longitudinal MRI data

2018-2023 Yasumasa OKAMOTO Hiroshima University Professor

We obtain longitudinal MRI data and the associated clinical data targeting mood disorders (depression and bipolar disorders), anxiety disorders, obsessive-compulsive disorders, schizophrenia subthreshold depression and healthy individuals in adulthood. By using this data and applying AI technology to the analyses, we propose a method to distinguish between bipolar disorder and depression, a method for predicting responses to treatment (clinical course) and biotypes based on the five diseases. We also contribute to the elucidation of the pathogenic mechanism by assessing MRI images showing changes from subthreshold depression to depression.



Parkinson's disease and Alzheimer's disease Neuroimaging Initiative (PADNI) supported by MRI reference panels based on community-based cohort data

Takashi HANAKAWA National Center of Neurology and Psychiatry Department Head 2018-2023

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders involving the elderly population. In this multi-center study, we aim to collect MRI data from participants with either AD or PD, "super-healthy" elderly people defined as being at risk of AD or PD, and intermediate states such as mild cognitive impairment (MCI). Simultaneously, we will develop an MRI



reference panel representing the healthy elderly population derived from a mega-scale cohort study including 10,000 participants. By combining a cuttingedge MRI analysis of the multi-center data and the reference panel, we will clarify the similarities and differences of the neural circuits responsible for AD and PD.

1-2

Integrative MRI data platform across the lifespan and disorders toward international brain science collaborations

2018-2023

The University of Tokyo **Kiyoto KASAI** Professor

Human brain imaging data has expanded in quality and quantity because of the progress of analysis methods and measurement techniques and the development of domestic and international collaborative studies. However, a framework has not been established to easily provide large datasets to researchers. In this study, we aim to develop a framework to manage and provide datasets that enable easy analyses of existing MRI data from collaborative studies in psychiatry, as well as upcoming next-generation data from the Human Connectome Project Connectomerelated disease studies (HCP-CRDS)



Research Group 2

Research Group 2

We will carry out "an interspecies comparative study by parcellation of structure and function of human brain and non-human primate brain and homology analysis" . Through the interspecies comparative study, we try to understand human brain in a help of neurological disease model animals generated in the project of Brain/MINDS, aiming at elucidation of pathophysiology of psychological and neurological diseases.

Study of cross-species comparisons of human and nonhuman primates using high field MRI

2018-2023 Norihiro SADATO National Institutes of Natural Sciences Professor

Human neuroimaging technologies such as MRI are invaluable in order to elucidate the neural substrates of cognitive functions which are impaired by neurological or psychiatric disorders. To evaluate their functional relevance, however, it is essential to combine this with animal experiments. Here, we propose the construction of a 7TMRIbased imaging platform that enables direct comparison between the human brain and those of non-human primates.



The 7TMRI-based imaging platform will promote the understanding of the neural substrates of social cognition and the functional anatomy of basal ganglia, both of which are critical to understanding the pathophysiology of psychiatric disorders. Furthermore, the platform will elucidate the mechanism of neural plasticity at the circuit level, and this understanding is critical for rehabilitation medicine.

Primate connectomics using multimodal standardized neuroimaging

2018-2023

Takuya HAYASHI RIKEN Team Leader

How did our human brain evolve and acquire human functions? To answer this we will develop non-invasive neuroimaging techniques using data acquisition and analysis that are standardized across species. We aim to comprehensively study the brain function, architecture, and connectivity (connectome) particularly in relation to mechanisms underlining sociality and brain diseases. We will translate our findings into medical techniques.



Research Group 2

Establishing a multiscale platform for the analysis of brain circuit function by an interspecific, bidirectional approach with circuit manipulation and machine learning

2018-2023 **Toshiyuki HIRABAYASHI** National Institutes for Radiological Sciences Principal Researcher

The aim of this research is to construct an analytical platform for linking brain circuits in humans and non-human primates to understand the function and dysfunction of the human brain as a multi-scale operation from brain-wide networks to single neurons. By combining machine-learning analysis of neural images and clinical information in humans with multi-modal measurements during circuit manipulation in non-human primates, we attempt to elucidate the network/neural basis



Quantum and

of the core deficits in psychiatric/neurological disorders. In particular, we examine the causal relationships between deficits and their underlying network dysfunction, and compare those relationships between humans and non-human primates at the network level. We also investigate the physiological basis of the above network dysfunctions at the neuron level using non-human primates.

Research Group 3

Research Group 3

Research Group 3

Utilizing machine learning by AI, computational neuroscience findings, etc., we develop therapeutic protocols such as neurofeedback for human psychological and neurological diseases. In addition, we will carry out research on basic technology for the next generation AI based on models produced by brain science. Furthermore, by collaboration with the "Core Organization" and domestic and overseas institutes doing AI research, we will promote tight collaboration between brain science and AI research.

3-1

Study of diagnostic and therapeutic technology based on neuroscience and AI

2018-2023 Mitsuo KAWATO ATR Director

We will apply computational neurosciences and AI techniques to the diagnosis and treatment of neuropsychiatric disorders such as developmental disorders, mood disorders, schizophrenia, and pain. Specifically, we will contribute to the development and application of (1) biomarkers using machine learning algorithms that can learn from a small number of samples, and (2) advanced neurofeedback based on data-driven selection of intervention targets.





Research and development on next-generation AI and its key technology based on nonlinear dynamics

2018-2023 Kazuyuki AIHARA The University of Tokyo Professor

In this research project, we explore technological backgrounds of mathematical models related to information processing in the brain and next-generation AI based on such models. We review the possibility of realization of such next-generation AI technology and also the trends of state-of-the-art research. Then we will propose important tasks necessary for the realization of



next-generation AI that learns from the dynamic brain, particularly from the viewpoint of nonlinear dynamics with a focus on both functions of the normal brain and dysfunctions of the impaired brain. We will also develop basic mathematical technology for innovative brain-type algorithms and consider their applicability to robotics and mental illnesses.

Innovative Research Group

Innovative Research Group

Internationally collaborative, pioneering and multidisciplinary researches by young investigators aimed at paradigm shift by innovative ideas and technologies

Development of neuron-type specific gene manipulation techniques in primates

2018-2020 Ken-ichi INOUE

Kyoto University Assistant Professor

Nonhuman primates (NHPs) have widely and critically been utilized as animal models for understanding a variety of higher brain functions and neurological/psychiatric disorders by virtue of their behavioral actions that mimic both normal and disease states in humans. In this project, we aim at developing neuron-type specific gene manipulation techniques in NHPs. By combining state-of-theart techniques of different fields, we will be able to achieve the introduction of functional molecules into a certain neuron type for



neuron-type specific manipulation/monitoring in NHPs. We believe that the outcome of the present study will successfully promote the understanding of higher brain functions and the pathology of neurological/psychiatric disorders, and greatly contribute to create genetically manipulated primate disease models and, also, to establish gene therapy approaches especially to gene-associated diseases.

Neurofeedback-based guidance of stereotaxic plasticity for motor recovery from neurological diseases

Keio University 2018-2020 Junichi USHIBA Associate Professor

We will develop a high-density electroencephalogram based neurofeedback system (EEG-NFB) to actuate exoskeleton and neuromuscular electrical stimulation devices for driving motor recovery from neurological diseases. The system will utilize an artificial intelligence (AI) based technology that decodes brain derived sensorimotor-related information, in adaptation to disease-, lesion-, and severity-dependent brain activity variants. An AI based beamforming technique with recurrent and convolutional neural network algorithms



will be also developed to form a blood-oxygenation-level-dependent signal by nonlinear mixing of multi-channel EEG signals. For validation, a series of first-in-man studies and proof-ofconcept studies will be conducted. Through the above research and development, we will establish AI based EEG-NFB technology aiming for recovery from severe motor deficit due to neurological diseases, such as strokes, spinal cord injuries, and Parkinson's disease.

To establish synapse epitranscriptomics as a cognitive neuroepigenetic mechanism at synapses

2018-2020 Dan Ohtan WANG Kyoto University Associate Professor

A poor understanding of the mechanical and biochemical dynamic interplay between genes and experience means an effective therapy or intervention for neurodevelopmental and neuropsychiatric diseases has not been developed. Recently, our lab reported the initial draft of N6-methyladenosine (6mA) epitranscriptome at synapses (Nat Neurosci, 2018) and revealed an unexplored regulatory layer of local dynamic gene expression. We will explore the functional relevance of 6mA to brain development and cognitive function in this AMED-supported project.



Elucidation of macro neural circuit disorders in Parkinson's disease using advanced MRI techniques and artificial intelligence

2018-2020 **Koji KAMAGATA** Juntendo University Associate Professor

This project aims to elucidate macro-scale neural circuit disorders in Parkinson's disease (PD). We will use network science and artificial intelligence (AI) for the evaluation of neural circuits, extract feature quantities by analyzing large multiparametric MRI data from the whole brain, and we will develop a method to learn about the link between various clinical symptoms of PD and genetic polymorphisms. To achieve the goals of this project, we will develop an analytical method for analyzing the pathogenesis mechanism of PD and develop a pipeline that anyone can easily use for data analysis.



Analysis for pharmacological mechanism of psychoactive drugs

2018-2020 Keisuke KURODA Nagoya University Assistant Professor

Each part of the brain differs in function, cell types, and neurotransmitters. For neuropsychiatric disorders many drugs have been developed based on target molecules, however it is still unclear where they work or the mechanisms they use to tackle disease. This means this is very difficult to develop or improve such drugs. In this research, we analyze phosphorylation signals induced by



neuropsychiatric drugs in the brain comprehensively for each brain region, and use the optogenetic method to manipulate the phosphorylation signals as a disease model mouse and to mimic the effect of therapeutic drugs. Finally, we will elucidate regions of the brain where the therapeutic drugs work and the mechanisms of action that improves symptoms.

Development of standardization technique for realization of quantitative functional MRI measurement across multiple imaging sites

2018-2020

Daisuke KOKURYO Kobe University Assistant Professor

The aim of this project is to develop a MRI standardization technique for the realization of quantitative functional MRI (fMRI) measurements across multiple imaging sites. We will develop two types of phantom for correction of magnetic field heterogeneity and for calibration of the shape distortion and the signal irregularity due to the EPI sequence. A correction algorithm designed specifically for these two phantoms will be proposed. We will also establish a standard imaging protocol for the standardization of



fMRI measurements across multiple imaging sites. For realization of quantitative fMRI measurement, quantitative sequences such as ADC (apparent diffusion coefficient), CBF (cerebral blood flow) data and so on will be used and optimized. The methodology will be developed based primarily on animal fMRI and the results will be applied to human fMRI to further validate the efficiency of the calibration.

Generation of whole brain atlas for monoamines and anti-depressants localizations

2018-2020 Yuki SUGIURA

Keio University Assistant Professor

Due to recent advances in sample preparation protocols, current imaging mass spectrometry (IMS) allows for the visualization of small molecule tissue localization, including that of monoamine neurotransmitters like serotonin, dopamine, and norepinephrine. Although monoamine-producing neurons, and their projections and synapses, have been thoroughly characterized, monoamine localization within these circuits remains unclear. In this research project we will study the fluctuations in local monoamine concentration in response to physiological stimuli, drug administration,



and neurodegenerative disease progression, by analyzing in situ concentration maps afforded by coupling IMS with on-tissue derivatization protocols. Since exogenous drug pharmacokinetics can also be visualized by IMS, we will develop powerful methodologies to enable simultaneous imaging of selective serotonin reuptake inhibitors (SSRIs) and monoamines. The purpose is to reveal where SSRIs administered over the long-term accumulate and how they affect local monoamine metabolism.

Analysis of somatic mutations in bipolar disorder and methodological development of genomic neuropathology

2018-2020 Masaki NISHIOKA RikeN Researcher

Recent evidence has demonstrated accumulation of somatic mutations through human life stages. Somatic mutations are promising candidates for explaining the remaining part of the pathogenesis of mental disorders. This study aims to detect somatic mutations in bipolar disorder patients to elucidate their pathological roles with the aim of establishing a pathological method with genomic technology for brain



regions. We will use deep exome sequencing, a method in which the allele fraction of mutations is calculated by comprehensive sequencing of hundreds of DNA molecules in the exon region, and use it for the detection of somatic mutations. We will analyze relevant neural circuits and brain regions with gene expression database to elucidate neural mechanisms in bipolar disorder.

Study of daily sleepiness as an ensemble of the monoaminergic system and its disorder

University of Tsukuba 2018-2020 **Yasutaka NIWA** Assistant Professor

Previous studies (Sakurai 2007, Niwa et al. 2018) reported genetic defects to the orexinergic and the cholinergic system cause opposite abnormalities in maintaining wakefulness during the day, i.e. former causes drowsiness and the latter causes insomnia. In this project, based on the finding of these results, we hypothesis that an ensemble of the monoaminergic system, which is a major target of the orexinergic system and seems to be also regulated by the cholinergic system, is the major source for daily drowsiness. In this study, the cells we suspect are responsible for generating daily drowsiness will be genetically purified and examined for their molecular and cellular aspects.

The regulation of formation and clearance of intracellular amyloid by photooxygenation

2018-2020

The University of Tokyo Assistant Professor

The intracellular inclusion of amyloid within the cell is one of the pathological hallmarks of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Several lines of evidence suggest that the aggregation process of amyloid protein from monomer-form to amyloid is associated with the neurotoxicity and disease onset. In this study, we would like to develop a new therapeutic strategy based on regulating

Yukiko HORI



formation and clearance of the intracellular amyloid by photooxygenation, which can oxygenate amyloid selectively using photocatalysts and light irradiation. We will develop an effective photocatalyst and elucidate the effects of photooxygenation of amyloid. We would like to reveal the possibility of photooxygenation as a new therapeutic approach.

Development of a machine-learning method for extracting local functional modules from spontaneous neuronal activity in marmoset and human brains

Teppei MATSUI 2018-2020

The University of Tokyo Assistant Professor

Functional magnetic resonance imaging (fMRI) is a promising technique for developing clinical methods for diagnosing psychiatric and neurological disorders at early stages. Recently, fMRI of spontaneous brain activity (restingstate fMRI) is becoming a central tool for analyzing macroscale human brain networks. In resting-state fMRI, there still exist multiple goals for technical advancements. In



particular, a method for extracting local neocortical structures such as functional maps and local functional modules from resting-state fMRI data is of great importance. The aim of this project is to develop a new method to extract local functional modules solely from spontaneous neocortical activity using state-of-the-art machine learning techniques.

Study of toxic polypeptides related to amyotrophic lateral sclerosis

Nara Medical University Associate Professor

The goal of this project is to understand the pathophysiological mechanisms of diseases linked to toxic polypeptides translated from a hexanucleotide repeat expansion in the first intron of the C9orf72 gene. This is the most prominent form in heritable amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTD). Common among the toxic polypeptide target proteins are low-complexity (LC) domains which are necessary and sufficient for binding. The top categories of toxic polypeptide-



Research Group

Innovative

bound proteins include constituents of non-membrane invested cellular organelles, where LC domain proteins are enriched and drive liquid-liquid phase separation (LLPS). In this study, we tackle this unknown mechanism by biochemistry and proteomics combined with a structural approach and in-silico simulations. This study will offer an interpretation of the mechanisms of toxic polypeptide toxicity in a prominent form of ALS/FTD.

Research and Development Grants for Longevity Sciences

Program Supervisor

University of Tsukuba Professor Emeritus Setsu IIJIMA



Program Officer

National Center for Geriatrics and Gerontology Head Physician Manabu KOKUBO



The development of a scoring and categorization system for the risk factors associated with aspiration pneumonia in older people and the establishment of a comprehensive care strategy for preventing this disease

Kyorin University 2017-2019 Takae EBIHARA Associate Professor

The causes of aspiration pneumonia in elderly people are diverse. The purpose of this study is to clarify the relationship between life stages and the incidence of aspiration pneumonia and various aspiration pneumonia related-events, such as muscle atrophy in the respiratory and swallowing systems, malnutrition, death and other mechanisms. We propose to develop a prognostic scoring system and an algorithm to accurately diagnose which stages of life patients



are at, from signs of aspiration to end-of-life, by looking at the related events. In addition, we will apply a tailor-made approach for caring for such patients to prevent repeated onset of pneumonia and the progress to the next stages such as death. We hope the study will prove useful for comprehending the state of elderly patients and deciding their treatment and care, including nutrition.

Development of an effective screening indices that measure the degree of independence of the Japanese elderly and its verification

Noriko YOSHIMURA The University of Tokyo Professor 2017-2019

Independence assessments of elderly people are mostly determined by examining nursing care decisions, therefore may not accurately reflect actual degree of independence. In this research, we aim to highlight areas that can be looked at when conducting independence assessments. These will allow for an accurate assessment that is simple to perform and cost-effective. To achieve this, in the first year we produced a questionnaire prototype with the consent of a research group. To proceed to the next step and finalize the questionnaire we will test it in other cohorts with different backgrounds.



Dosing movement recognition using tabletop robot for medication management support

2018-2019

Aichi Prefectural University Associate Professor

In this project, point cloud processing technology has been developed so that a small table top robot with an RGB-D camera can judge whether a dose of medicine has been taken at the right time. The techniques to recognize the degree of opening of the mouth and the position of the wrists etc were developed. Movements associated with taking medicine will be recognized by inputting these feature quantities into a one-class cascade classified.

Takuo SUZUKI



The purpose of this program is to study medical and long-term care to establish societies in which people live with independence and dignity till end of their lives. For this purpose, this program promotes research to establish comprehensive treatment approaches focusing on elderly-specific diseases and conditions, to assure sustainability of the long-term care insurance system, to establish the regional comprehensive care system, and to promote cooperation between healthcare and nursing care sectors.

The development of effective infection control programs in long-term care welfare facilities for the elderly

2018-2020

Teppei SASAHARA Jichi Medical University Lecturer

Controlling infections is an important issue for facilities providing long-term care for the elderly, this is especially important in Japan with an aging population. However, little is known about the actual situation of infectious diseases in facilities for the elderly and there are very few evidencebased infection control manuals that are practically applicable. This study will investigate the current status of infections and the prevalent transmission of drug-resistant bacteria at such facilities. The goal is to develop an efficient infection control program that would serve as a model for nationwide facilities



Study of service indicators on integrated care facilities toward evidence-based management

2018-2019

Makoto KUROKI Yokohama City University Associate Professor

This study develops performance indicators from the perspective of integrated care, to use when assessing medical and nursing care. We will increase the level of knowledge of medical education, nursing, management and accounting studies into nursing care service by the following. (1) Development of an integrated outcome; (2) selection of input and process indicators related to outcome; (3) performance measurements by a third party evaluation. We aim to create a new management-style by using evidence-based management (EBMgt) through our research and development.



Compatibility among the existing ADL assessments and the development of a new ADL assessment

Aiko OSAWA 2019-2020

National Center for Geriatrics and Gerontology Head Physician

In this study, we will address the compatibility between barthel index (BI) and functional independence measure (FIM) in patients who are hospitalized in a convalescent rehabilitation ward and people in need of nursing care in the community setting. In addition, to briefly evaluate activities of daily living (ADL) in not only hospitalized patients but also people attending community-based rehabilitation programs and nursing care, we will develop a



new ADL assessment based on the ADL check list. This simple new assessment which is compatible with both BI and FIM will make ADL evaluation easier for not only rehabilitation specialists but also non-medical professionals. Our research outcomes will bridge the assessment of ADL in various clinical and community settings.

Comprehensive study for self-management group activities to prevent disability in community-dwelling older people: survey and validation study

2019-2020

Hidenori ARAI National Center for Geriatrics and Gerontology President

The disability prevention program is now regarded as an important project contributing to the realization of healthy aging by setting, as it establishes "self-management group activities". In our research, we plan to accumulate data and analyze the information so we can publish a guide for establishing and continuing self-management group activities and further verify the effect of the program to be implemented in various communities. To this end, we will conduct a mail survey for the local governments throughout the country,



and verify the characteristics of the community with a high participation rate of older people in self-management group activities. For good practice cases, we will conduct a qualitative survey to cover issues quantitative surveys cannot clarify. We will also examine the effects of providing individual exercise programs, participating in communicating activities and self-exercise, etc. on adverse health outcomes and social security expenditure during the follow-up period of 2.5 years.

Study for promotion of healthy aging by community building

2019-2020

Katsunori KONDO Chiba University Professor

The purpose of this study is to develop community building models mainly on the development of the process and effect evaluation method, and to revise the training program and teaching materials. The target is over 50 municipalities throughout Japan. FY2019 will involve project implementation support, support for creation of a participant name list and investigations to evaluate the



effect of projects. FY2020 will involve an evaluation of project participation, development of a visualization system and revision of training programs and education material. Through this research it will be possible for approaches that contribute to prevention of long-term care sought and practiced independently by residents, to be implemented and put into practice in many municipalities.

Frailty prevention promotion and healthy community development by empowering community-dwelling older adults

2019-2020

Katsuya IIJIMA The University of Tokyo Professor

This research aims to promote frailty prevention and to help develop healthy aging communities by empowering community residents. First, we will identify promoting and buffering factors of resident-driven community activities by a survey of existing resources. Second, we will clarify a methodology for empowering community residents and ensure its effects in several communities. Finally, we will create a manual for community residents and local government staff.



Exploring trajectories of disabilities in the last years of life and their determinants using insurance receipt data

2019-2021 Naoki KONDO

The University of Tokyo Associate Professor

We use the longitudinal data of elderly residents living in 40 Japanese municipalities from the Japan Gerontological Evaluation Study (JAGES) and individually-linked medical and long-term care (LTC) insurance receipt data. Using this data we will explore the transition patterns of daily functional ability. With identified patterns we will identify the social determinants and attempt to simulate changes to cost by intervention.



Research on the policy regarding home-based end-oflife care for the patients with the respiratory failure

2019-2021 Hisayuki MIURA National Center for Geriatrics and Gerontology Department Head

Improving the care of patients with respiratory failures in end-of-life stages of their lives is an urgent issue. Our research group plans to conduct research the on policies, including decision support, concerning this issue. Based on the results of a systematic review of end-of-life care for nonmalignant disease patients, we will conduct a fact-finding study on home care. We will summarize the results to recommend skills for palliative care of patients with respiratory failure. In parallel we will also create an advanced care planning program for respiratory failure. We plan to integrate the above research results for policymaking.



Decision-making process of initiation of renal replacement therapy for elderly renal failure patients and establishment of optimal palliative care

2019-2021 Nac

Naoki KASHIHARA Kawasaki Medical School Professor

The purpose of this research is to establish a decisionmaking process based on scientific evidence for introducing renal replacement therapy (RRT) to elderly patients with renal failure and palliative medicine methods. We will investigate the conditions for introducing RRT and providing a prognosis to elderly people. Furthermore, we will examine appropriate palliative care and verify its usefulness. We aim to create guidelines on the ideal palliative care and establish evidence that contributes to consensus development.



Big data based research on the typology of dying process of the elderly

2019-2020

Shinya MATSUDA University of Occupational and Environmental Health Professor

In this study, we will collect data on claims from insurers and trace claims from deceased patients. We will create a database of the illness and health service used until the death of the subject. Using this database, we will clarify the patterns leading to death using big data analysis methods such as decision tree analysis and association analysis.



Research and Development Grants for Dementia

Saitama Medical University





Program Supervisor



The Jikei University Professor Masahiro SHIGETA



Professor

The number of people with dementia is expected to increase with the aging of the population, tackling the associated problems is not only important in Japan but also globally. At present, there are no simple or noninvasive diagnostic methods for dementia and performing a differential diagnosis is difficult. Therefore, treatment and prevention methods have not been established or standardized to sufficient levels. To address this, the project will support intensive research on dementia that looks at the condition, prevention, diagnostics, treatments and care.

Establishment of evaluation of prelinical Alzheimer's disease by neuroimaging

2015-2019

Hiroyuki SHIMADA Osaka City University Professor

A multi-center clinical study will allow us to establish longitudinal profiles of magnetic resonance imaging (MRI), positron emission tomography (PET) neuroimaging, and fluid biomarkers to quantitate disease progression, or to predict the future progression to mild cognitive impairment (MCI) or dementia at the very early stages of Alzheimer's disease (AD). In parallel, clinical and cognitive data will be compiled from healthy, preclinical AD and MCI individuals, to validate the significance of biomarkers.



Japan prospective studies collaboration for aging and dementia

2016-2020

Toshiharu NINOMIYA Kyushu University Professor

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



Organized registration for the assessment of dementia on nationwide general consortium toward effective treatment in Japan

2016-2020 Kenji TOBA

National Center for Geriatrics and Gerntology Executive Adviser

The "ORANGE Registry" is a nation-wide registry and coordination system which enables clinical observation of people with dementia throughout their clinical stages. As a trial-ready cohort, over 6,000 preclinical cases and 1,200 MCI were registered. 32 institutions have joined the registry study and clinical studies on biomarkers, atrial fibrillation, healing disturbance, intestinal flora and genome analysis are ongoing.



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

2016-2020 Hiroyuki SHIMADA Osaka City University Professor

The aim of this project is to building the basis for a dementia clinical study support center and research infrastructure that provides support to large clinical studies developing Alzheimer's disease modifying drugs for the treatment in its early stage. One approach undertaken is building a network of clinical sites that promotes the standardization of cognitive assessments, PET, MRI imaging and biomarker analyses, to facilitate data management, and to monitor study quality. The other is to establish a registry/ trial ready cohort for enrolment into trials, something fundamental for Japanese research teams to take part in global clinical trials.



Development of comprehensive BPSD prevention/treatment guideline, associated with newly-developed BPSD-related scales and positive care for supporting smile life

2017-2019 **H**

Haruyasu YAMAGUCHI Tokyo Center for Dementia Care Research and Practices Director

We developed a behavioral and psychological symptoms of dementia (BPSD) notification questionnaire with 57 items version (BPSD-NQ57) to prevent BPSD and developed a new BPSD scale (BPSD+Q) to treat BPSD. Furthermore, we made a manual for preventing restraint in wards. We study cognitive-behavior therapy for dementia caregivers to reduce their stress. We study antipsychotic drug use in psychiatric wards. We study dementia care according to the dementia type, the stage and patient's age. Finally, we develop a guideline for preventing/treating BPSD.



Development of a comprehensive and practical guide to medical care and the prevention of BPSD

2017-2019 Hiroaki KAZUI

II Kochi University Professor

We are developing a practical treatment guide for the behavioral and psychological symptoms of dementia (BPSD) that is accessible via a website. The "circle of wisdom on dementia" website, translated from the Japanese *Ninchisho Chienowa*, was developed in 2016 (http://chienowa-net. com/). Visitors of the site, including patients and family members, can learn of preventive interventions for BPSD



based from when dementia is diagnosed. Non-pharmacotherapy is positioned as a preventative measure. We also clarify feelings of people with dementia when diagnosed with dementia and situations that require pharmacotherapy and hospital admission for BPSD. In addition, we collect and publish widely good management skills for BPSD which are useful in hospitals and care settings.

Development of blood-based biomarkers for differential diagnosis of Alzheimer's disease and neuropsychiatric disorders

2017-2019

 Takeshi IKEUCHI
 Niigata University

 Professor
 Professor

In this project, we attempt to establish non-invasive diagnostic tools for the differential diagnosis of patients with dementia. We focus on the development of bloodbased biomarkers such as inflammatory cytokines and brain-derived neurotrophic factors (BDNF) and validate their usefulness for differential diagnosis of cognitive disorders including Alzheimer's disease and neuropsychiatric disorders in elderly people.



Clarification of pathology by collecting multi-dimensional clinical data on dominantly inherited Alzheimer's disease

2017-2019

Osaka City University **Hiroshi MORI** Professor

The Dominantly Inherited Alzheimer Network-Japan (DIAN-J) is a clinical observational study effort focused on dominantly inherited Alzheimer's disease (DIAD). DIAD is rare but patients often suffer severely with juvenile onset. This study is a part of the DIAN, an international research led by the University of Washington School of Medicine. By sharing data globally, DIAN-J aims to clarify the pathophysiology and find solutions to treat or prevent this disease.



Investigation of prevalence and actual life situation in people living with earlyonset dementia and development of a multi-dimensional data sharing system

2017-2019

Tokyo Metropolitan Gerontoly Hospital Shuichi AWATA Team Leader

To obtain basic data for policymaking, we are investigating the prevalence and life situations of people living with earlyonset dementia in ten prefectures and two cities. In addition, to investigate in more detail patients' life situations and the longitudinal outcomes of early-onset dementia, we are examining methods for developing a multi-dimensional data sharing system.



Study on diabetes treatments to prevent the conversion of diabetes patients with MCI to Alzheimer's disease

2017-2019

Osaka University Manabu IKEDA Professor

Recent epidemiological studies have shown Alzheimer's disease (AD) onset is related to diabetes (DM) and that DM or certain DM treatments could be considered powerful risk factors for AD. This study aims to identify DM therapies to suppress the onset of AD from mild cognitive impairment (MCI) among type 2 DM patients over 65 years old. To identify the conversion mechanism we will analyze cases where DM patients also suffer from AD by performing exosome analysis.



Multidomain intervention to prevent cognitive decline in the elderly patients with type 2 diabetes -A pilot study-

2017-2019

Takashi SAKURAI National Center for Geriatrics and Gerontology Director

This is a pilot study that aims to identify whether multidomain interventions including, management of diabetes, exercise, diet, and social engagement, could delay the progression of cognitive decline in elderly patients. Target populations includes diabetic patients with high-risks for dementia, namely category II (elderly diabetic patients with mild cognitive impairment to mild dementia or impairment of activities of daily living (ADL), no impairment of basic ADL) proposed in the treatment guideline for elderly patients with diabetes mellitus 2017 by the Japan Diabetes Society/Japan Geriatrics Society (JDS/JGS) Joint Committee.



Establishment of cognitive and auditory research by gerontologically organized team

2018-2020 Naoki SAJI National Center for Geriatrics and Gerontology Vice Director

It was been reported hearing loss increases the risk of dementia, however, clarity is lacking on both the actual situation and the effectiveness of interventions with hearing aids. This research aims to elucidate the effect of correction of hearing loss on cognitive function with a particular focus on elderly patients, based on a nationwide, multi-center cohort study in Japan. The originality and merit of this research lies in the utilization of the registration and coordination system



established in the Organized Registration for the Assessment of dementia on Nation-wide General consortium toward Effective treatment in Japan (ORANGE Registry Study). The ORANGE Registry Study has a system for registering patients with pre-clinical cognitive impairment or mild cognitive impairment. It is equipped with an inter-center network that enables smooth collection of clinical information.

Developmental study of a method for stratification of dementia patients using human brain-derived exosome

2018-2021 Takashi KUDO

Osaka University Professor

Markers of cerebrospinal fluid and PET examinations have been developed as biomarkers for dementia. However, all of these tests are highly invasive and expensive, so they cannot be widely used. Therefore, we have launched a project to establish dementia biomarkers in brain-derived exosomes from peripheral plasma. This will make it possible to diagnose dementia through general blood collection. In addition, since the brain-derived exosome directly reflects the environment in brain neurons, it is possible to establish a biomarker based on the pathophysiology of dementia as "liquid biopsy"



Exploring the molecular mechanisms of dementia and identification of therapeutic targets for dementia by analyzing the human brain-derived exosomes

Yuji SAITOH 2018-2021

National Center of Neurology and Psychiatry Department Head

The number of patients with dementia and the cost of care for these patients is increasing in Japan at an alarming rate. Therefore, the establishment of a novel therapy against dementia based on the pathomechanism is a huge challenge for researchers. The aim of our project is to identify biomarkers by analyzing brain-derived exosomes, that will reflect the complicated pathomechanisms of dementia and that could be potential targets for discovering an anti-dementia drug.



Generation of disease-relevant biomarkers and therapeutic targets through investigation of neuron-derived exosomes

2018-2021

Shuko TAKEDA Osaka University Associate Professor

We propose the combination analysis of our high-quality biorepository and cutting-edge exosome analytical platform to discover novel therapeutic targets as well as biomarkers of dementia. We aim to elucidate pathomechanisms and generate therapeutic targets against dementia through the comprehensive analysis of exosomal mRNAs and pathologic proteins in neuron-derived exosomes in CSF and/or plasma.



Identification of novel pathogenesis in dementia by integrated analysis of comprehensive genomic profiling and bioinformatics approaches



Takeshi IKEUCHI Niigata University Professor

Dementia is a complex disorder in which both genetic and environmental factors are attributable to the development of the disease. In this research project, we perform whole genome/exosome sequence analysis and genome-wide association study to explore genetic risk factor (s) for Japanese patients with dementia. By taking the data-driven approach, we elucidate new pathogenesis underlying dementia.



Japan trial ready cohort for the prevention of Alzheimer's disease and dementia

2019-2023 Takeshi IWATSUBO The University of Tokyo Professor

Improving the participation of volunteers who are asymptomatic but at risk for dementia is crucial to the development of therapeutics for dementing disorders. Trial Ready Cohort (TRC) widely recruits volunteers, who are initially screened for cognitive functions through the internet. Those who are at risk are examined at study sites and eligible participants are invited to clinical trials. Close partnership with industries and societies worldwide will reduce the burden on participants and accelerate trials, expediting the approval of medications for treatment and prevention of dementia.



Molecular imaging study of pathological protein aggregation and transmission and neural circuit disruptions

2019 Makoto HIGUCHI Radiological Science and Technology Department Head

Diverse neurodegenerative disorders are neuropathologically characterized by accumulations of misfolded proteins in the brain, as represented by depositions of tau, α -synuclein and TDP43, and these protein aggregations have been indicated to spread through neural circuits, eventually leading to a wide range of disease-specific symptoms attributable to functional alterations of these circuits. With groundbreaking and original PET probes for tau pathologies and AMPA receptors, this



translational research project reciprocally linking non-clinical and clinical imaging assessments aim to clarify molecular etiologies of neurodegenerative disorders. Studies on disease models will focus on analyses of transmissions of protein aggregations. Along with this program, imaging agents for α -synuclein and TDP43 deposits will also be developed and applied to clinical assays.

Elucidation of molecular mechanism of α -synuclein propagation based on pathogenic seed structure

2019-2021

 Taisuke TOMITA
 The University of Tokyo

 Professor
 Professor

In this project, we will characterize the pathogenicity and propagation ability of α -synuclein seeds deposited in the brains of different synucleinopathies. We will clarify the intracellular milieu and structure of fibrils responsible for these differences by genome-wide screening and cryoelectron microscopy, respectively. The structure of α -synuclein fibrils will be determined with PET probe candidates to optimize the structure of the compounds. Our research will provide crucial structural and biological information for the development of therapeutics and diagnostics targeting α -synuclein aggregates.

Study on dietary factors to reduce dementia risk related to apolipoprotein E genotype and gender difference (D-AGE)

2019-2021 Masahito YAMADA Kanazawa University Professor

Apolipoprotein E (ApoE) E4 and the female gender pose a strong genetic risks for Alzheimer's disease (AD). In this study, we elucidate dietary factors to reduce AD/dementia risk related to the ApoE genotype and gender. Based on our epidemiological study, we hypothesis that vitamin C reduces AD risk of women carrying the ApoE E4. To test this, we will perform (1) a molecular epidemiological study with a community-based cohort study, and (2) an experimental study with vitamin C treatment in animal AD models with human ApoE E3 or E4.



Research and Development Grants for Persons with Disabilities

Program Supervisor

Nagano University of Health and Medicine Professor

Yasoichi NAKAJIMA



Program Officer

Teikyo Heisei University Professor Emi IKEBUCHI





Head Physician

Disabilities

National Rehabilitation Center for Persons and



Fujita Health University Professor

The University of Tokyo Associate Professor Satoshi KATO

research bases such as databases.

Juntendo University Professor Eri HIRASAWA

The total number of disabled children and adults in Japan with physical, intellectual, and mental disorders (including developmental disorders)

is over nine million, or approximately 7.5% of the population. It is

important for such people to live in peace as members of the local

community. In this project, for the people with physical and intellectual, neuromuscular, sensory, and mental disorders, we will support the development of technologies contributing to medical treatments and care, studies on the pathogenesis of diseases, and the construction of





Masazumi MIZUMA

Kisei-Kai

President

Organization





Physical Disability Area and Intellectual **Disability Area**

Development of an evaluation system using sensing technology in support for persons with severe behavioral impairment

2018-2019

Masahiko INOUE Tottori University Professor

Severe behavioral disorders in individuals with intellectual disabilities, including autism spectrum disorder (ASD), have a major barrier to social adaptation. Conventionally, in the treatment of behavioral disorders, questionnaires have been used as a therapeutic index. In this study, we aim to verify practicality by developing a measurement system of behavioral disorders. This will applying various sensors which have been evolving with progress in engineering.



User oriented product development of thermo-regulation system based on thermophysiological modeling in damaged autonomic nervous systems

2017-2019

National Rehabilitation Center for Persons with Disabilities Director

Body temperature regulation is a major issue for individuals with disabilities and improving their health. Implementing devices for assisting body temperature control requires advances in estimation, monitoring and cooling the core body temperature of individuals with disabilities. In this project, we will develop such methodologies and aim at clarifying the specification of thermoregulation system which can be used in either sports scenarios or daily life.

Toru OGATA



Development of the near-infrared spectroscopy mediated neurofeedback system for gait and balance impairment after stroke

Masahito MIHARA Kawasaki Medical School Professor 2019-2021

Gait and balance impairment post-stroke have a considerable impact on the daily activities and quality of life of stroke victims. We have developed a novel rehabilitation system adopting a neurofeedback technique using nearinfrared spectroscopy ("NIRS-Neurorehab system") to facilitate functional re-organization and functional recovery post-stroke. In this clinical trial, we aim to test the clinical efficacy and safety of the NIRS-Neurorehab system in patients with gait and balance impairment after a subcortical stroke.



A three-year study to develop a support system for the independence of parent-disabled child with adhesive relationship

2017-2019 Kaeko OGURA

Parents of children with a disability have difficulty balancing caring for their child with other responsibilities and demands. As a result, parents may experience distress, high anxiety, and family arguments. An excessively close parentchild relationship can influence many aspects of the parent's life while also being a barrier to a self-sufficient life. The central aim of this study is to develop a psychoeducational treatment for parents of children with cerebral palsy, and to test the efficacy of the treatment, targeting parent and child quality of life and distress by



National Center for Child Health and Development 2019-2021 Department Head

parents in families.

Development of a conversion table of eating assessment and working assessment questionnaire to promote the eating and working activity of physically disabled persons

Tomoki AOYAMA Kyoto University Professor 2018-2020

Food and work are the energy for life. The relationship between "work for eating" and "eat for working" is correlated bi-directionally. Our goal is to produce a widely usable questionnaire to predict a disabled person's activities at work based on their ability.



Usefulness of robotic devices and their practical use in rehabilitation

Yohei OTAKA

Fujita Health University Associate Professor

The aims of the study are to identify and summarize the present status of robotic applications in rehabilitation from both scientific and clinical viewpoints, and to propose a guideline for practical use of robotic devices. The study comprises 1) systematic reviews; 2) nationwide surveys on the practical use of robotic devices in clinical settings; and 3) proposal of a practical guideline based on the results of 1) and 2), and the consensus of an expert panel.



Development of non-contact modular gesture recognition interface for persons with sevier physical disabilities to operate ICT devices

2019-2021 Kazuyuki ITOH National Rehabilitation Center for Persons with Disabilities Section Chief

In this research, we will create an environment control system (ECS-system) able to operate ICT devices by various recognition technologies customizable for a wide variety of individuals with severe physical disabilities. By concatenating voice/gesture recognition applving technologies to the interface of the PC operation/ environment control system, users will operate ICT devices



(input to a communication aids, control of a light and TV with the wireless remote controller, make a sound for call) with slight movements or their voice. We aim to develop an intelligent ECS-system to operate certain ICT devices without the use of an ordinal mouse/keyboard devices or any other switches.

Testing the usefulness of "B-assist" : Toward a versatile BMI device for supporting patients with communication disabilities across different neuromuscular diseases

2019-2020

Kimihiro NAKAMURA National Rehabilitation Center for Persons with Disabilities Section Chief

Our neuroscience unit has developed a novel BMI system ("B-assist") for supporting motor neuron disease patients with severe communication disabilities. The present proposal aims at extending its scope of clinical application to include patients with other neuromuscular disorders and validating the usefulness of B-assist as a more versatile support device for communication disabilities. We also assess its real-life functionality extensively using objective measures (e.g. operation accuracy) and user subjective assessments, while updating both hardware and software aspects of the B-assist system.





Elucidating the influence of mechanical stress and development of therapy for muscle diseases with membrane repair defect and collapse of unnecessary protein clearance

2018-2020 Masashi AOKI

Tohoku University Professor

Skeletal muscle is an organ exposed to mechanical stress due to muscle contraction over long periods. In this study, we will focus on dysferlinopathy and inclusion body myositis. These are typical diseases that prevent mechanisms maintaining cellular homeostasis, such as cell membrane repair and clearance of unwanted proteins. The aims are to reproduce muscle degeneration and atrophy pathology by electrical muscle contraction culture with single molecule nanoimaging, and find a remedy for muscle atrophy.



Research aimed for development of immune-targeted drug in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

2018-2020

Takashi YAMAMURA National Center of Neurology and Psychiatry Director

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/ CFS) is a chronic, intractable disorder, characterized by chronic fatigue, post-exertional malaise, sleep disorders, cognitive impairment and autonomic dysfunctions, etc. Although, the cause and pathogenesis of ME/CFS remains unclear, recent research suggest the importance of neuroinflammation and immune-mediated pathogenesis. The purpose of this study is to strengthen the network among clinicians, neuroimmunologists, radiologists and rehabilitation doctors and to promote research in order to improve the clinical level of this intractable disease.



Investigation of pathophysiology of cerebrospinal fluid hypovolemia for making diagnostic criteria

2019-2021

Saitama Medical University Professor

We have conducted the autonomic nervous function test in patients with cerebrospinal fluid (CSF) hypovolemia from 2016. Among 21 cases of CSF hypovolemia, we found seven cases with postural tachycardia syndrome (POTS). We also found seven out of eight cases of POTS presented CSF hypotension and a low value of brain type transferrin. This result suggests that the production of CSF may be decreased in patients with POTS. In this new project, we would like to investigate CSF leakage, change of pulse rate of during headup tilt test, and the level of brain type transferrin in the CSF in young patients with orthostatic headache.

Nobuo ARAKI



Development of diagnostic biomarker of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

2019-2021

National Center of Neurology and Psychiatry Section Chief

Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/ CFS) are chronic intractable disorders, characterized by chronic fatigue, post-exertional malaise, sleep disorders, cognitive impairment and autonomic dysfunctions, etc. Recent findings have indicated the involvement of neuroinflammation with immune abnormalities in ME/CFS, but there are no objective diagnostic markers, which hinders the development of effective drugs for ME/CFS. The aim of this project is to develop new blood diagnostic biomarkers for ME/CFS by conducting the next-generation BCR repertoire analyses.

Wakiro SATO





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

2016-2019 Sato

Satoshi NAKADOMARI RIKEN Senior Scientist

We are serving as an intermediary to connect low vision individuals with in demand 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 and examine its effectiveness.



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



Development of the comprehensive dysphagia rehabilitation procedure

2017-2019 Yukio KATORI

Tohoku University Professor

This project is to develop a comprehensive dysphagia rehabilitation procedure with effective and good adherence. A questionnaire on impressions of current rehabilitation methods will be carried out targeting speech therapists and nurses specialized in dysphagia therapy. Rehabilitation methods found to have good impressions will be selected to develop a comprehensive dysphagia rehabilitation procedure consisting of systemic trainings and organspecific swallowing training. After approval from an ethics committee, a prospective randomized interventional study will be carried with dysphagia patients to evaluate the effectiveness of the procedure.



Neuromuscular Sensory Disability Disease Area Area

Development of disease-specific and evidence-based training program for dysphagia

2017-2019

Kyoto University Koichi OMORI Professor

The outcome of swallowing rehabilitation is not constant as swallowing training differs between each institution and therapist. In this study, we aim to provide evidence for swallowing training methods and to generalize swallowing training methods. To do this, a national survey and randomized control trials will be performed. Based on the results we will further develop a new rehabilitation program that matches each condition of a patient and make guidelines to treat dysphagia.



Survey for vision-impaired persons on employment toward establishment of the comprehensive assistant work by medical, occupational, and public health care teams

The study on the seamless coordination in low vision

2017-2019 Hiroyuki KONDO University of Occupational and Environmental Health Professor

The goal of this research is to develop a comprehensive manual for assisting vision-impaired persons (VIP) towards employment with a support team. At present, the real conditions of VIP in employment remains unknown. We will conduct several surveys using questionnaires and interviews of staff in VIP supporting organizations, including medicine (ophthalmology), occupational health, training and so on. A support manual and tool for VIP in work will be developed. The outcomes of this research will help address the issues that impede employment of VIP.

care through 'SmartSight' model program

2017-2019 Yoshimune HIRATSUKA Juntendo University Associate Professor

Smartsights are recommended for ophthalmologists to

provide patients with low vision care (LVC) facilities and

encourage awareness of LVC information. In this research,

we aim to deploy smartsights nationwide in three steps

over three years. First, we conducted a survey on patient

needs related to smartsights and analysis the current

situation concerning distant access to them. For the second and third stages an educational webpage will be created

and workshops on creating smartsights will be held.

Tetsuo HIMI



Hearing care intervention for achieving a productive aging society - with a focus on executive function and social interaction

Yasue UCHIDA 2017-2019

Aichi Medical University Associate Professor

This project will assess the effect of hearing care intervention in terms of executive function and social interactions. Assessments will be performed before and after hearing aid introduction in seven university hospital hearing-aid clinics with patients aged 60 years and over. For index parameters, we will use the digit symbol substitution test (DSST) for executive function and convoy models for social relations. The research is ongoing and we will compare data with those of an age-matched control group comprising community residents.



Survey of reading difficulties among patients with low vision and development of multiple enhancements to the reading test

A large part of patients with low vision have difficulties reading. In this project, we will conduct surveys with patients by both self-reporting QOL evaluation and performance-based MNREAD tests in the search for improvements in services based on reading evaluation. We will aim to develop a tablet-PC based reading test which can be easily administered with a multiple line of improvements including auto generated reading materials and the application of NLME for analyzing missing data.



Construction of a system for persons with visual disabilities in large-scale disaster

2018-2020 Satoshi NAKADOMARI RIKEN Senior Scientist

In preparation for future large-scale natural disasters, we will construct a support system and network for visually impaired persons. The system will be developed for when individuals go into a refuge. A remote supporting device and its manual will provided to voice guidance from based on imaging technology, which will be the central human technology. We will also establish action plans for the time of disasters by integrating the opinions from organizations supporting individuals with visual disabilities.



Construction of basic type of PDCA cycle by developmental stage of cochlear implant wearer and modeling of center institution

2017-2019

Sapporo Medical University Professor Emeritus

This project will create models for support center organizations and create models for independent support center organizations with lifelong total care functions. The aim is to solve various problems and regional disparities surrounding cochlear implant users. The project will include the development of a language development evaluation programs, language treatment program, and employment support program.



Clinical study on the usefulness of the diagnosis of chronic dizziness and guidance for vertigo

2018-2020 Izumi KOIZUKA St. Marianna University School of Medicine Professor

Chronic dizziness can be difficult to manage and if it is prolonged, will cause anxiety and pain for patients. In this study, we will examine the following for chronic dizziness patients. 1) Development of a diagnostic algorithm, 2) evaluation of the dizziness handicap inventory (DHI) by stabilometry, 3) examination of the usefulness of vestibular rehabilitation, 4) examination of the usefulness of sensory substitution using TPAD, 5) examination of the usefulness of canes, 6) evaluation of the usefulness of dizziness rehabilitation for chronic dizziness after cerebral infarction.



Clinical study toward the development of a standardized medical treatment program and a remote rehabilitation program based on the etiology of deafness

2019-2021

Shin-ichi USAMI Shinshu University Professor

In this study, we will further define the factors affecting intervention outcomes and develop a personalized medical treatment and habilitation system for children with hearing loss based on precise diagnoses. To obtain a precise diagnosis of each hearing loss patient, we will employ genetic testing, the congenital cytomegalovirus infection test and imaging analysis using thin slice CT or MRI. We also plan to collect detailed clinical information and treatment



outcomes of patients, and outcomes of interventions or rehabilitations by using the electrical registry system. In addition, we will try to develop an appropriate intervention or rehabilitation program for each patient by using the standardized test battery for accessing the development of auditory responses after intervention, and also accessing the communication language skills development.

Improvement of psychosocial function brought by exercise intervention on visually impaired persons and the development of exercise support program



When an individual is visually impaired there are five stages of the psychological reaction that follows: denial, grief, anger, depression, and acceptance. At the acceptance stage low vision care can proceed most smoothly, therefore there is a desire to intervene to help individuals reach this stage earlier. There have been many reports on the effects exercise can have on various diseases. In this study, we evaluate the effect of exercise as an intervention for patients with low vision and develop a method to adopt exercise as part of low vision care performed in ophthalmology service.



Mental Disorder Area

Development of guideline of treatment and support network and non-specialist treatment program for eating disorders

2017-2019 **Tetsuya ANDO** National Center of Neurology and Psychiatry Section Chief

The purpose of this study is to promote the collaboration of local governments and related medical institutions for eating disorders so that patients and their families can receive appropriate treatment and support at an early stage. For that purpose, specifically, 1) the problem for constructing a treatment and support network for eating disorders in the area will be clarified, 2) tools (guidelines,



manuals, materials) for collaboration within psychiatric facilities and within medical facilities (internal medicine, pediatrics, obstetrics and gynecology, emergency department and so on) will be created, 3) simple treatment programs that can be implemented even by non-specialists will be developed.

Multiplex and multilayered epilepsy care network in Japan

2017-2019 **Ki**y

Kiyohito TERADA NHO Shizuoka Institute of Epilepsy and Neurological Disorders Head Physician

Epilepsy is common with a prevalence of about 1%. Although many people with epilepsy (PWE) could be treated, some PWE cannot access the medical/social resources and take part in society. This is partially due to cooperation gaps among medical, occupational and social systems. In this study, we aim to fill in the gaps, improve the cure rate, promote social participation, and improve quality of life for PWE throughout their life cycle.



Mental health development and growth support in children and adolescents

2017-2019 **Ma**

Masafumi MIZUNO Toho University Professor

Mental health development and the growth of children is difficult to understand even for the school teachers and medical professionals. This project aims to establish methods for assessing children and adolescent mental health situations, and to develop a care network and treatment system for populations with mental health troubles or difficulties in communities.



Development of a brief intervention program to prevent the onset of alcoholism and evaluation of its effects

2017-2019

Takefumi YUZURIHA Psychiatric Medical Center Hospital Director

This study aims to materialize the goals set forth in the Basic Plan to Promote the Basic Law on Measures to Prevent Damage to Health due to Alcohol. We will (1) verify the effects of brief interventions to prevent alcoholrelated damage to health, (2) establish a regional model as an early intervention measure for preventing alcohol-related damage to health, and (3) develop a training program targeting specialized medical personnel to enable early detection and intervention. In this study, we plan to produce manuals and tools that will be used in care provided at medical institutions and health checkups performed in regional communities and at the workplace.



Development of pharmacotherapy and fMRI biomarkers for substance dependence



Methamphetamine dependence is a classified mental disorder that causes serious problems for society and affects patient quality of life. Research on pharmacotherapy for substance dependence is in the exploration phase while biomarkers required for diagnosing and curing substance dependence have not yet been developed. G-protein-activated inwardly rectifying potassium (GIRK) channels mediate signals from addictive substances. Previous studies have reported the possibility that



ifenprodil, an inhibitor of GIRK channel, is a candidate for pharmacotherapy for substance dependence. Our aim in this project is to investigate the effectiveness of ifenprodil in patients with methamphetamine dependence in a double-blind randomized placebo controlled trial and to develop biomarkers for substance dependence using functional magnetic resonance imaging.

Development of an evidence-based educational support model for families of hikikomori (a severe social withdrawal syndrome)

2017-2019

 Takahiro KATO
 Kyushu University

 Lecturer
 Lecturer

Hikikomori, a severe form of social withdrawal, is becoming a serious mental health issue. Family support/approaches are encouraged as a vital first step, however evidencebased programs haves yet to be established. Mental Health First Aid (MHFA) is one of the most well-validated educational programs encouraging lay people such as family members, to support close persons suffering from various psychiatric conditions. We will develop an educational program for family members of hikikomori sufferers mainly based on MHFA with role-play and homework.

Effects of the vocational program that combined cognitive remediation using the original software "Jcores" and supported employment for job tenure and employment rate with severe mental illness

2017-2019

Sayaka SATO National Center of Neurology and Psychiatry Section Chief

The purpose of this study is to examine the effects of a vocational program for severe mental illness that combines cognitive remediation (CR) and supported employment (SE) for job tenure and employment. This study will involve the following components: 1) revising an original computer software Jcores and its user instructions, 2) conducting a randomized controlled trial that compares CR using Jcores



+ SE group with a SE only group with vocational service non-responders, 3) conducting fidelity monitoring for minimizing validation of qualities and contents of SE in each research site. Our research team will plan the development of manuals for case formulation of individualized vocational services and its training system based on the findings of this study.

Development of objective biomarkers based on the blood metabolomic analysis for classification and treatment-adjustments for psychiatric disorders

2018-2020 **Takahiro KATO**

Kyushu University Lecturer

In the present study, we have been developing an evaluation system with blood metabolome analysis to evaluate the diagnostic classification and severity of psychiatric conditions, such as depression and suicidal ideation. We hope to develop objective blood biomarkers to estimate therapeutic responses for future precision medicine.



Stratification of major depression using biomarkers and its application for treatment planning

2018-2020

Tetsuro OHMORI Tokushima University Professor

Several biomarker candidates have been reported for depression. In this study, peripheral blood linked to antidepressant treatment response is used as a sample to measure proteins, gene mRNA expression, gene methylation modification and metabolomes. Markers are sorted into state markers, trait markers and response prediction markers that differ between good and poor treatment groups. Markers are compared with brain imaging findings to elucidate functional meaning of markers. Based on these, we try to stratify depression and apply it to the planning of treatment.



Development of identification of requiring medical intervention group and support program using the outcome of maternal prospective cohort studies

2018-2020 Norio OZAKI

Nagoya University Professor

The main cause of death for pregnant women is suicide caused by mental disorders meaning measure against mental disorders affecting perinatal women are in high demand. The purpose of this research is to clarify the risks and protective factors of postpartum depression, suicide and bonding disorder by analyzing data of prospective cohort studies of perinatal women. In addition, we will identify the intervention groups requiring medical treatment and develop a support program. Based on the results, we aim to improve the mental health of pregnant women and children, and develop countermeasures for the declining birth-rate.



Elucidation of neurophysiological basis of chronic depression and development of novel neuromodulation therapy based on its pathology

2018-2020

Masaru MIMURA Keio University Professor

A large number of patients see psychiatrists because of chronic depressive symptoms. Due to the heterogeneity and complexity of the pathophysiology of chronic depression, most of these patients do not achieve remission with currently available treatments. Since such depressive symptoms prolong over a long period of time, psychological distress is enormous. Therefore, it is crucial to elucidate and disentangle the neurobiological basis of chronic depression and to develop novel treatments targeted for their



pathophysiology. To this end, we are employing the recently developed neurophysiological modality called "concurrent TMS-EEG" that combines transcranial magnetic stimulation (TMS) and high-resolution electroencephalogram (EEG) to examine the neural basis of chronic depression. Specifically, we aim to conduct the biotyping of this distressing disorder based on the prefrontal neuroplasticity as indexed by paired associative stimulation.

The development of short-care program and the establishment of comprehensive support system for university students and withdrawals, 'Hikikomori' with developmental disabilities

2018-2020

Showa University Haruhisa OHTA Associate Professor

We have operated an out-patient clinic and rehabilitation facilities exclusively for adults with developmental disabilities for over ten years. Altogether 6,000 people have so far visited. From our experience there are more disabled university students than believed. Our research project proposes to: 1) develop a short care (three hours) rehabilitation program for university students, including withdrawals with developmental disabilities, focused on autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), 2) conduct



a general survey on the current conditions and unmet needs of students supporters with ASD and ADHD in universities, and their current employment opportunities in companies, 3) achieve multidisciplinary cooperation of day-care facilities, university health centers, professionals in support services for employment and peer-supporters among disabled and families, and then finally, 4) establish a comprehensive nationwide support system.

Development of neurofeedback for gambling disorder

2018-2020

Hidehiko TAKAHASHI Tokyo Me Tokyo Medical and Dental University

Development of an intervention method for gambling disorders based on brain science is in demand. Our objective is to develop a neurofeedback method for gambling disorders, but as a first step, it is necessary to identify brain connectivity (a biomarker) that intervenes with neurofeedback. The first two years will be devoted to the development of a biomarker for gambling disorders by resting fMRI. Using this biomarker, we will develop a neurofeedback method for gambling disorders in the final vear



The research for developing novel diagnostic and treatment methodologies in psychiatry by constructing and integrating a patient registry

2018-2020

Kazuyuki NAKAGOME National Center of Neurology and Psychiatry Hospital Director

In our research, we will construct the foundation for a registry system which combines clinical information with biological data (blood, cerebral spinal fluid, neuro-images, iPS cells, and brain tissues, etc.) by using a unique ID. The compiled information will be followed-up longitudinally. Large-scale data processing is expected to facilitate the development of personalized medicine. By cooperating with academia, industry, and the patients and families we will facilitate data selection, registry management, informed consent issues, planning principles, and regulation governing utilization of data.



Research towards development of a manual for those giving support to people with developmental disorders at times of crisis

Jiro MASUYA 2018-2020

Tokyo Medical University Associate Professor

We aim to clarify the risks for individuals with developmental disabilities in crisis situations, such as damage or crime occurrence, and what skills and knowledge are necessary for supporters to provide support for individuals in such situations. We will create a curriculum to train life support for supporters of people with developmental disabilities. They will provide support to the communities during emergencies by being able to understand the needs and characteristics of such individuals. We propose a high quality support system including a team of experts who will provide supervision.



Development and verification of practicality of Quality Indicator evaluating the quality of treatment and Intervention Techniques improving QI in the psychiatric field

2019-2021

Ryota HASHIMOTO National Center of Neurology and Psychiatry Department Head

In this research, we will develop the EGUIDE project which will spread, educate, and verify psychiatric treatment guidelines such as the Guideline for Pharmacological Therapy of Schizophrenia and the Treatment Guideline II: Major Depressive Disorder. We will design a workshop to do all over the country for psychiatrists to attend and learn about the guidelines. We will also propose a Quality Indicator (QI)



which verifies the quality of treatments. We will evaluate the effectiveness of the educational workshop for psychiatrists by QI such as clinical knowledge, clinical practice and therapeutic behavior. In this way, we aim to develop indicators of the quality of medical treatments, develop methods to improve the quality of medical treatments, and contribute to the peoples' health.

Developing implementation toolkit and objective indicators for optimal treatment with cognitive behavioral therapy

Atsuo NAKAGAWA Keio University Lecturer 2019-2021

In this research project, we will develop a cognitive behavioral therapy (CBT) treatment optimization tool that may aid physicians who are not specialized in CBT for making clinical decisions when prescribing CBT. We will also pursue objective indicators of effective CBT treatment that can be shared with patients.



Development of a smartphone cognitive behavioral therapy app to promote resilience and prevent depression among adolescents

2019-2021

Toshi FURUKAWA Kyoto University Professor

We will develop a smartphone application for cognitivebehavioral therapy (CBT) which promotes resilience and prevents development of a mental disorder between adolescence and young adulthood. The study is a full factorial trial of the five components of CBT. The primary outcome is incidence of a major depressive episode by one year. The full factorial trial will enable estimation of specific efficacy of each component of CBT.



The development and evaluation of a comprehensive treatment program for female patients with substance use disorders

2019-2021

Toshihiko MATSUMOTO National Center of Neurology and Psychiatry Department Head

The purpose of this study is to develop and evaluate a treatment program for female patients with substance use disorders. We will provide a safe and comprehensive treatment program and conduct a prospective nonrandomized controlled trial comparing 30 female patients enrolled in this trial program (intervention group) to 30 female patients taking part in other treatments or receiving the standard medical care (control croup). This study will be an important contribution to the improvement of treatment and support system for women with substance use disorders in Japan.



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Mental Disorde

Development of the clinical research system to promote translational researches in psychiatry

2019-2021

Norio OZAKI Nagoya University Professor

The level of science, technology and medical care is high in Japan, however, the return of research results to clinical practice is not well established. In this research, we investigated the actual situation of various research fields focusing on translational research in psychiatry. We collect the opinions of psychiatric patients and their family members. Based on the results, we aim to establish a system to promote psychiatric research based on the wishes of the psychiatric patients and their family members.



Elucidation of the predictive factors for active and placebo drug response on social functioning and QOL in psychiatric illnesses including developmental disorders

2019-2021

Yoshie OMACHI National Center of Neurology and Psychiatry Head Physician

The main aim of the present study is to elucidate the predictive factors for treatment response of either active or placebo drugs by integrating individual data of the clinical trials that use social functioning or QOL as assessment measures for the patients with psychiatric illnesses, including developmental disorders. Individual data will be gathered from multiple clinical trials, using social functioning and QOL as measures, to create a big data set. Data sharing policy and rules that may apply to pharmaceutical companies and academic institutes will also be established. In parallel with such processing, statistical methodology for meta-analysis of big data needs to be developed.



Establishing evidence of dose optimization of long-acting injectable secondgeneration antipsychotics in stable patients with schizophrenia to enhance social functioning through improvement of cognitive function and subjective experiences

2019-2021

Hiroyoshi TAKEUCHI Keio University Assistant Professor

Although it is necessary even for stable patients with schizophrenia to continue antipsychotics in the long run for relapse prevention, adherence to antipsychotics is poor in schizophrenia; thus, long-acting injections of antipsychotics are used. On the other hand, antipsychotics can cause cognitive dysfunction and negative subjective experiences in a dose-dependent fashion, which are related to poor



social functioning. We will conduct a multi-center randomized controlled trial to examine the effects of dose reduction of long-acting injections of secondgeneration antipsychotics on relapse, cognitive function, subjective experiences, and social functioning in stable patients with schizophrenia.

Development of early support focused on intrinsic motivation for personal recovery in individuals with psychiatric and neurodevelopmental disorders

2019-2021

Mariko TADA The University of Tokyo Assistant Professor

Focusing on just illness and disability will not allow for individuals with temporary impairments, to fully recovery, function at schools and workplaces, or live independent and meaningful lives. This study will develop a support method that that will allow adolescents and young adults with mental health issues, to achieve both clinical and personal recovery. A focus on intrinsic motivation needed to promote recovery will be a key feature of this support method.



Mental Disorder Area

Program for Establishing Public-Private Infrastructure for Verification of Innovative Measures against Dementia

Program Supervisor

The University of Tokyo Professor

Takeshi IWATSUBO

Suzuka University of Medical Science Dean Shigeki KUZUHARA

Program Officer

Osaka Kawasaki Rehabilitation University Director

Masatoshi TAKEDA



There is a compelling need for interventions that enable the slowing of cognitive decline, life support, and social inclusion of people with dementia. However, the enormous diversity of methods and criteria to evaluate the efficacy of technology, service and devices for dementia often make it difficult to judge their real value. This project aims to promote research on methods to evaluate dementia, multifactorial interventions for lifestyles, social implementation of technology, and other services and devices for dementia patients. We will also develop the infrastructure to verify effective interventions that support the life of individuals with dementia.

Development and validation of artificial intelligence to detect and classify prodromal dementia using EEG in resting state

2019-2021

Manabu IKEDA Osaka University Professor

Treatment interventions that prevent the onset of cognitive symptoms of prodromal dementia or mild cognitive impairment are in demand, thus simple and inexpensive screening techniques for detecting the stage before onset of dementia are required.



In this study, we will establish a cohort of patients with mild cognitive impairment precisely classified based on

background pathology, and develop artificial intelligence to detect and classify prodromal dementia from EEG data from the cohort. Furthermore, we will conduct prospective verification at multiple facilities and aim for social implementation of simple and inexpensive screening techniques for prodromal dementia using EEG.

Randomized control trial for dementia prevention by multimodal intervention

2019-2021

National Center for Geriatrics and Gerontology President

The prevalence of dementia increases with age, and the number of people with dementia in Japan is assumed to be approximately 5 million. Considering the rapid aging speed of our society, the development of interventions to prevent and treat dementia is an urgent issue. Here, we examine whether multifactorial interventions that combine lifestylerelated disease management, exercise and nutritional interventions, and cognitive training will suppress the progression of cognitive impairment in older people with high risk of dementia.

Hidenori ARAI



Feasibility study on group-based dyadic programs for people with MCI and dementia and their family caregivers

2019-2021 **Tami SAITO**

National Center for Geriatrics and Gerontology Department Head

ogram for Establishing Public-Privat Infrastructure for Verification of novative Measures against Dement programs for people with dementia and their family caregivers as their quality of life is at risk. This study aims to develop two group-based psychosocial programs targeting people with MCI or dementia and their family caregiver dyads and implement them using a unified study protocol. We will then examine the program feasibility by exploring how, when, and with whom those programs could meet their needs most.

It is important to develop safe and effective support



Establishment of a platform for an organized data center incorporating a sustainable study support function for clinical studies assessing non-pharmacological interventions for dementia

2019-2021

Akihiro HIRAKAWA The University of Tokyo Associate Professor

In this study, we aim to establish a data quality centralized management center that contributes to the evidence creation for non-pharmacological and psychosocial interventions for individuals with dementia and their caregivers. We develop our own electronic data capture (EDC) system for monitoring and managing the quality of data. We also organize a statistical analysis unit in the data center and prepare a statistical consulting support and statistical analysis system.



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Division of Neurological, Psychiatric and Brain Research 1-7-1, Otemachi, Chiyoda, Tokyo 100-0004, JAPAN TEL: 03-6870-2222 FAX: 03-6870-2243 Email : brain@amed.go.jp