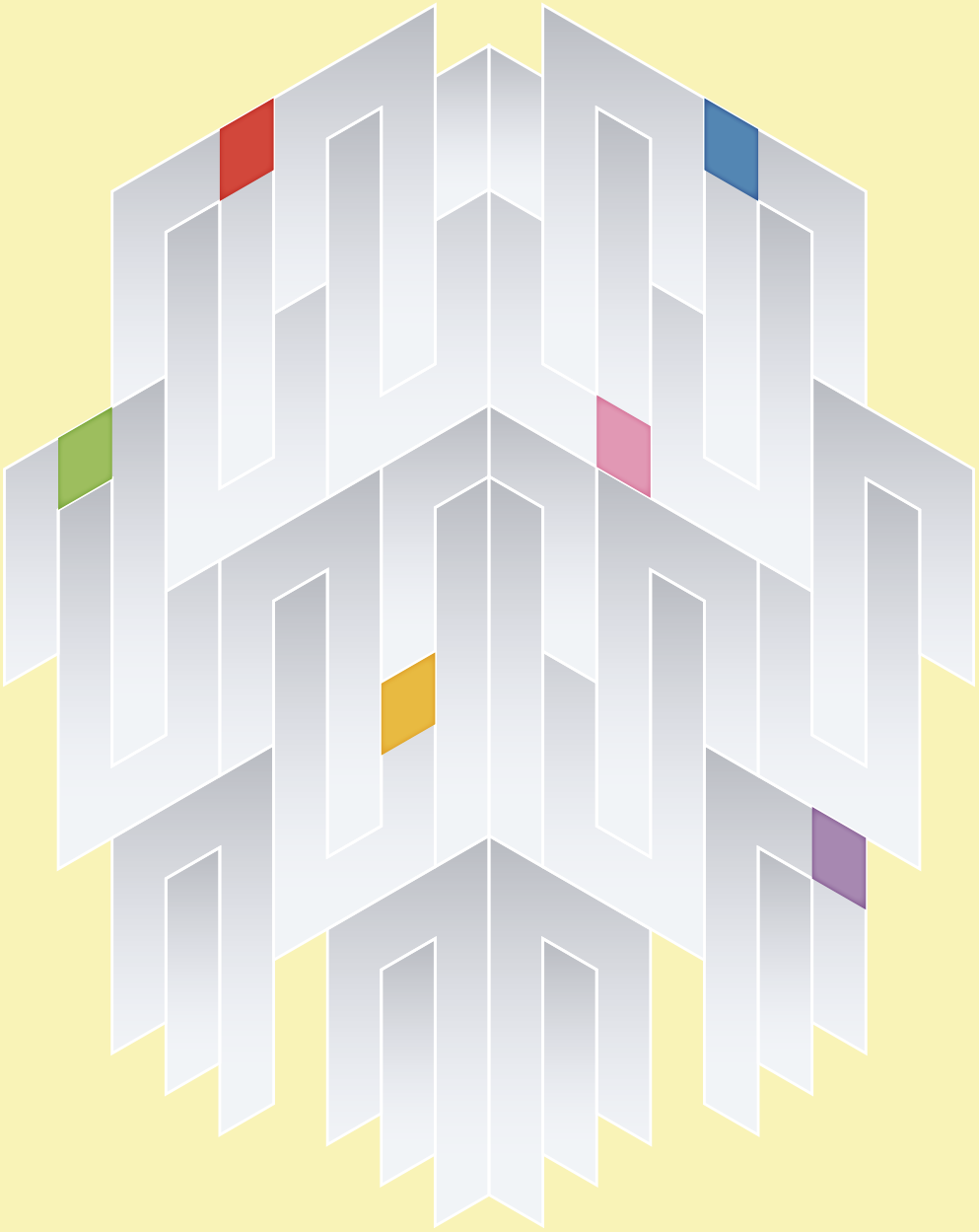


BRAIN RESEARCH INSTITUTE NIIGATA UNIVERSITY 2018

新潟大學腦研究所

Message from the Director

Hiroyuki Nawa
Director, Brain Research Institute, Niigata University

Brain Research Institute (BRI) has its roots in the Niigata Neurological Research Society of Niigata University in the early Showa era. Its deep interest and foresight in the field of the human brain led to establishing Niigata University Brain Research Laboratory in 1956, which was later replaced by the establishment of the Research Facility of Neurosurgery at the School of Medicine. The foundation of the laboratory was largely thanks to the work of Dr. Mizuho Nakata and his colleagues. Dr. Komei Ueki obtained staffing support from the School of Medicine and the facility became Brain Research Institute in 1967, the first affiliated research institute of a national university in Japan on the human brain and related fields. Ever since its foundation, the institute has been integrating basic research and clinical practice. Having placed two clinical departments (Neurosurgery and Neurology) as its core, BRI has focused on research concerning human brain disease including neurodegenerative disease. Including both basic neuroscience research branches and clinical departments of the University Hospital, BRI enables creating a seamless research environment.

In 2002, the Center for Integrated Human Brain Science was established as a COE (Center of Excellence) project by the Ministry of Education, Culture, Science, Sports and Technology (MEXT), focusing on advanced imaging diagnostics and their application. Department of Neuropathology subsequently acquired MEXT's certificate for a 21st century COE. BRI became one of MEXT's Joint Usage/Research Centers in 2009 and conducted collaborative research projects with a total of 300 research institutes across Japan during the designated period, which resulted in renewing MEXT certification. From April 2016, BRI will enhance global partnerships as the collaborative research center for brain diseases utilizing neuropathological resources. BRI is currently undergoing institutional reform. Having had a retired professor, the institute has appointed a young faculty, reorganized the departments and hired project-based faculty members. We expect this will bring new energy to the institute.

While advanced medical technology greatly helps to overcome cancer and heart disease, the increasing number of intractable neurological disease patients (e.g. Alzheimer's and Parkinson's diseases) is a significant issue in our society. BRI's responsibility is therefore to address brain diseases to provide a cure for such diseases to introduce the treatment to our patients and families as soon as possible.

In order to maintain its reputation as a leading research institute on the brain, BRI continues to grow and evolve to reflect the changing times. The institute's comprehensive approach includes, but is not limited to, imparting knowledge, boosting globalization, training young researchers, making a generation shift, developing links both with the School of Medicine and University Hospital, and reforming the internal structure. Despite the current fiscal pressures that we face, we are bidding for external funds and steadily engaging in enhancing our research capacity, self-development and contributions to medical care. We appreciate your continued support and cooperation.

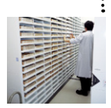
History

1957
Research Facility of Neurosurgery at School of Medicine, the origin of Brain Research Institute is founded.

1967
Research Facility of Neurosurgery, School of Medicine is transformed into Brain Research Institute. Faculty of Morphology is renamed Faculty of Neuropathology.

1971
Brain Disorder Specimen Center is set up.

1976
New Research Building opens. (3,467m²)
New Brain Disorder Specimen Center opens. (531m²)



1977
Research Building extension is completed: 1,018m² of animal testing laboratory and other laboratories are added.

1986
Reorganization results in BRI's new structure of 3 big branches: Basic Neuroscience Branch (Depts. of Molecular Neurobiology, Cellular Neurobiology, Neurophysiology, and Developmental Neurobiology), Pathological Neuroscience Branch (Depts. of Pathology and Molecular Neuropathology), and Clinical Neuroscience Branch (Depts. of Neurosurgery and Neurology). Brain Disorder Specimen Center is renamed Brain Disorder Analysis Center.

1995

1996
Ultra-high Magnetic Field MRI Research Building opens. (251m²)

2002
Brain Disorder Analysis Center is transformed into 2 Centers: Center of Integrated Human Brain Science and Center for Bioresource-based Researches. The latter merges with Genetic Research Facility of Niigata University and Animal Testing Facility, School of Medicine.

2003

Center for Integrated Human Brain Science (CIHBS) Building opens. (3,969m²)

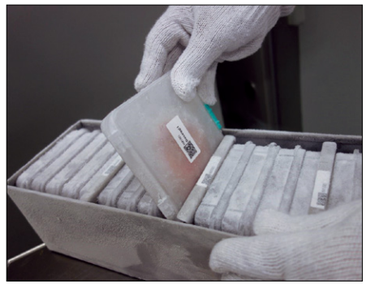
2006
Reformed Center for Bioresource-based Researches consists of 2 Branches: Bioresource Science Branch and Brain Science Branch. Dept. of Project Programs is added to Brain Science Branch. Depts. of Molecular Neuropathology (Pathological Neuroscience Branch) and Bioinformatics (CIHBS) are transformed into Depts. of Digital Pathology and Digital Medicine respectively. CIHBS PET Building opens. (416m²)

2008
Center for Bioresource-based Researches extension is completed. (200m²)
BRI is certified as a Joint Usage/Research Center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). ("the Advanced Collaborative Research Center for Brain Diseases Utilizing Neuropathological Specimens", start date: April 1, 2010)

2016
BRI renews MEXT's certification on the Joint Usage/Research Center, which is renamed "Collaborative Research Center for Brain Diseases Utilizing Neuropathological Resources".

MEXT Joint Usage / Research Center

The Collaborative Research Center for Brain Diseases Utilizing Neuropathological Resources

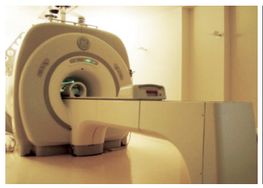


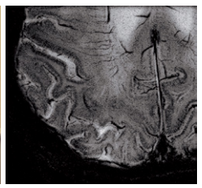
BRI was certified as a joint usage/research center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in 2010. Our extensive collection of brain disease materials and expertise have been open to the neuroscientists' community in Japan. BRI's diverse joint researches in neuropathology and related fields have brought out a great deal of achievement in relation to unravelling the pathological mechanism of brain disease. Given the MEXT's recognition for such achievements, BRI has renewed the certification of a joint usage/research center in FY 2016.
BRI has the world-class collections of neuropathological specimens and advanced imaging analysis technique. BRI is committed to tackling tasks such as neuropathological analysis on brain disorders like Alzheimer's disease, development of early diagnostic technique, and translational research on the treatment for reducing disease progression.
By utilizing the specimens of human brain disease and the animal model resources along with the underpinning of translational research for clinical application, BRI's collaboration with researchers across the world offers a prospect of reducing the burden of intractable neurological disease. Expected outcomes include the followings: to shed light on the disease pathology, to establish early imaging diagnostics, and to discover new treatment that slows disease progression.

Major Research Projects

Drug discovery for Alzheimer's disease
(MEXT Joint Usage / Research Center reinforcement project)

20 years of research efforts at Center for Integrated Human Brain Science has successfully developed non-invasive imaging method for preclinical diagnosis of Alzheimer's disease (AD), and has also demonstrated that disturbance in aquaporin-4 (AQP4) functionality, which hinders proper clearance of β-amyloid, plays a significant role in the pathogenesis of AD. The project aims to apply such a developed diagnostic technique in preventing AD: together with establishing an early diagnostic method for AD using magnetic resonance imaging (MRI) and positron emission tomography (PET), the project will target discovery of the new drug designed to modulate AQP4 function and prevent impairment in clearance of β-amyloid.





Clinical research promotion project for neurological disease by establishing the system neuropathology: Establishing a platform for clinical research utilizing neuropathological resources **(MEXT education and research activities project)**

In therapeutic research of brain disease, the diagnostics bound by the traditional theory of localization of brain function appears no longer sufficient. In order to overcome brain disease, there has been an increasing demand for a new academic discipline, which allows us to understand brain disease in accordance with the functional connectivity of each part of the brain. Niigata University launched a project aimed at setting a new pathological assessment method, naming such neuropathology as "System Pathology for Neurological Disorders." Conducting interventional trials based on the knowledge will pave a way to overcome brain disease. Connecting the collective expertise in brain at BRI, a number of research projects on neurology at School of Medicine and the medical care system at University Hospital together, the project aims to ensure a seamless environment that will readily translate basic scientific findings into therapeutic interventions for patients. The project seeks to launch a clinical research center, which will serve for translational research on brain disease.

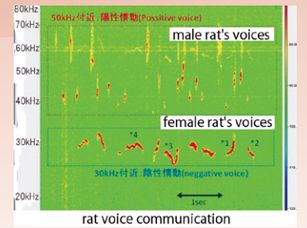
Organization

As of October 2018

Basic Neuroscience Branch	Dept. of Molecular Neurobiology	Prof.	Hiroyuki Nawa
		Assoc. Prof.	Nobuyuki Takei
		Assist. Prof.	Hisaaki Namba
		Assist. Prof.	Yuriko Iwakura
	Dept. of Cellular Neuropathology	Prof.	Takayasu Mikuni
		Assist. Prof.	Hitoshi Uchida
	Dept. of Neurophysiology	Prof.	Katsuei Shibuki
		Assoc. Prof.	Ryuichi Hishida
		Assist. Prof.	Hiroaki Tsukano
		Assist. Prof.	Kohei Yoshitake
Pathological Neuroscience Branch	Dept. of Pathology	Prof.	Akiyoshi Kakita
		Assoc. Prof.	Yasuko Toyoshima
		Assist. Prof.	Hiroshi Shimizu
		Assist. Prof.	Mari Tada
		Assist. Prof.	Hiroki Kitaura
	Dept. of Digital Pathology		
	Dept. of Molecular Pathology	Prof.	Koichi Wakabayashi
		Assoc. Prof.	Fumiaki Mori
Clinical Neuroscience Branch	Dept. of Neurosurgery	Prof.	Yukihiko Fujii
		Assoc. Prof.	Makoto Oishi
		Assist. Prof.	Tetsuya Hiraishi
		Assist. Prof.	Manabu Natsumeda
	Dept. of Neurology	Prof.	Osamu Onodera
		Lecturer	Masato Kanazawa
		Assist. Prof.	Takuya Konno
Center for Integrated Human Brain Science	Dept. of Integrated Neuroscience	Assoc. Prof.	Hitoshi Matsuzawa
		Assist. Prof.	Kosuke Itoh
	Dept. of Biological Magnetic Resonance	Prof.	Hironaka Igarashi
		Assoc. Prof.	Kiyotaka Suzuki
		Assist. Prof.	Masaki Watanabe
		Assist. Prof.	Yukimi Nakamura
	Dept. of Functional Neurology & Neurosurgery	Assoc. Prof.	Yuji Suzuki
		Assoc. Prof.	Ken-ichi Yamada
		Assist. Prof.	Satoshi Ueki
	Dept. of Digital Medicine		
Center for Bioresouce-based Researches	Bioresource Science Branch	Dept. of Molecular Genetics	Prof. Takeshi Ikeuchi; Assoc. Prof. Akinori Miyashita; Assist. Prof. Kensaku Kasuga
		Dept. of Bioinformatics	Prof. Takeshi Ikeuchi
		Dept. of Comparative & Experimental Medicine	Prof. Toshikuni Sasaoka; Assist. Prof. Nobuyoshi Fujisawa; Assist. Prof. Nanaho Fukuda; Assist. Prof. Kanako Oda
		Dept. of Animal Model Development	Prof. Toshikuni Sasaoka; Assoc. Prof. Manabu Abe; Assist. Prof. Ena Nakatsukasa
	Brain Science Branch	Dept. of Pathology Neuroscience	Prof. Akiyoshi Kakita; Assist. Prof. Rie Saito
		Dept. of Molecular Neuroscience	Prof. Osamu Onodera; Assist. Prof. Tomohiko Ishihara
		Dept. of System Pathology for Neurological Disorders	Tenure-track Prof. Kazuki Tainaka; Tenure-track Prof. Masaki Ueno
		Dept. of Translational Research	Assoc. Prof. Kouichirou Okamoto
Center for Transdisciplinary Research		Dept. of Neuroscience of Disease	Tenure-track Assoc. Prof. Hideaki Matsui; Tenure-track Assist. Prof. Atsushi Sugie

Prof.
Hiroyuki Nawa

Dept. of Molecular Neurobiology

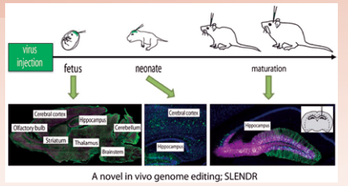


rat voice communication

Neurons and glial cells communicate to each other not only via neurotransmitters but also using various bioactive proteins, namely neurotrophic factors and cytokines. Our long-term objective is to elucidate the molecular and pathologic mechanisms of how these bioactive proteins regulate brain development or perturb neural functions. Our efforts have been paid to the following projects: (1) the specificity and functionality of the intracellular signaling driven by these bioactive proteins (BDNF, mTOR, S6 kinase, AMPK), (2) the cytokine-dependent regulation of monoaminergic development and function (GDNF, EGF, NRG1, EGFR, ErbB4), and (3) the molecular and system neuropathology of schizophrenia and its animal modeling (hallucination, auditory-evoked potential, social withdrawal). Currently we are addressing these questions employing all types of biological approaches including molecular genetic, biochemical, cell biological, electrophysiological, pharmacological, and behavioral tools and techniques. We hope these studies will lead to the understanding of how these bioactive factors control the onset and progression of developmental brain diseases such as schizophrenia, autism, which might hint at developing new drugs.

Prof.
Takayasu Mikuni

Dept. of Cellular Neuropathology

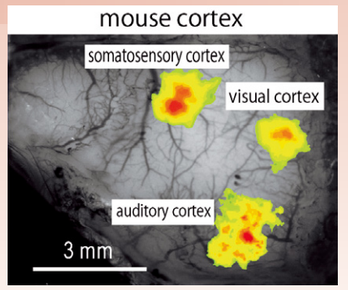


A novel in vivo genome editing; SLENDR

Our goal is to understand the physiology and pathophysiology of the brain at the cellular and molecular levels. We established "SLENDR", a technique based on in vivo genome editing, to image endogenous proteins with high specificity, resolution and contrast in single cells in mammalian brain tissue (Cell, 2016). In addition, we recently developed "vSLENDR", a genome editing method to target virtually any cell-types, areas and ages across the brain, widely expanding the applicability of genome engineering technologies in the broad field of neuroscience (Neuron, 2017). Using "SLENDR" and "vSLENDR", we will explore the cellular and molecular mechanism underlying long-lasting memory, and further investigate how the mechanism is impaired in memory disorders to provide new therapeutic strategies.

Prof.
Katsuei Shibuki

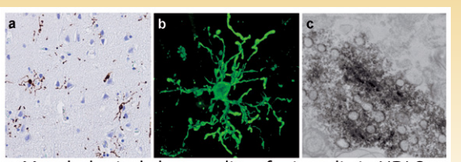
Dept. of Neurophysiology



The skull of mice is thin and transparent. Therefore, cortical activities are easily visualized using endogenous flavoprotein fluorescence signals reflecting the activity-dependent changes in oxidative metabolism in mice. We are investigating cortical activities in the auditory, visual and somatosensory cortices using this technique. However, there are higher association cortices between these primary sensory areas, and their functions are largely unknown in mice. In general, neurons in the association cortices respond to various stimuli, and therefore, may be involved in association (integration) of information. Another point is that some neural activities in the association cortices can be maintained after stimulus offset, suggesting that they are related to certain types of short-term memory. Integration of information and short-term memory are important elements of consciousness, so that the associative cortices are likely related to consciousness. Generally speaking, consciousness research is not easy in the framework of falsifiable scientific studies in mice. Fortunately, we have found a particular strain of mice that exhibit specific and simultaneous impairment of sensory integration and short-term memory. Using these mice, we are now challenging to investigate the neural mechanisms of consciousness in the framework of falsifiable scientific studies.

Prof.
Akiyoshi Kakita

Dept. of Pathology / Dept. of Pathology Neuroscience

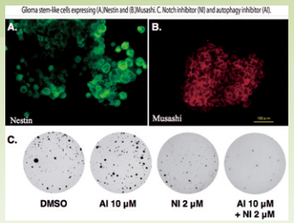


Morphological abnormality of microglia in HDLS

Mission: To expand our understanding of human diseases of the nervous system, by clinical service, education, and research.
Clinical pathology: Over 400 surgical cases and 40 to 50 autopsy cases annually, from the Departments of Neurosurgery and Neurology, as well as from various other institutes in Japan.
Research: Clinical, translational, and basic science of human disorders of the nervous system, including neurodegenerative, developmental, infections, cerebrovascular, and immune-mediated diseases.
Education: Teach medial and graduate students, residents, and fellows.

Dept. of Neurosurgery

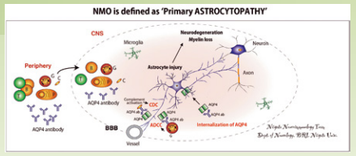
Prof.
Yukihiko Fujii



Department of Neurosurgery, University of Niigata was founded by Professor Mizuho Nakata, "the father of Neurosurgery in Japan", in 1953, becoming the first independent Department of Neurosurgery in Japan. Since then, the department has led the field of preclinical research and surgery for brain tumors, cerebral vascular disease, brain trauma, and functional surgery. Also, the department is unique in that it is affiliated with the Brain Research Institute, enabling collaboration with many basic neuroscience laboratories within the Institute. Answering clinical questions through basic research and using the results to improve clinical medicine, is precisely what Professor Nakata envisioned when he founded the Brain Research Institute. It is our obligation to carry on this spirit, and all staff is dedicated in discovering new insight into neurosurgical practice. The main research areas we are currently investigating include: (1) developing new treatment methods including manipulation autophagy and targeting of glioma stem cells to eradicate the deadly disease malignant glioma, (2) developing assistive surgical technology to enable accurate simulation for complex neurosurgery cases and education of young neurosurgeons, (3) collaboration with Nishi-Niigata Chuo National Hospital to elucidate the complex pathophysiology of epilepsy.

Dept. of Neurology / Dept. of Molecular Neuroscience

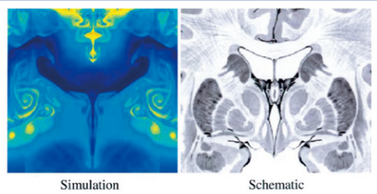
Prof.
Osamu Onodera



The Niigata University Brain Research Institute possesses not only a basic neuroscience branch but also a clinical neuroscience branch: Departments of Neurology and Neurosurgery. Thus, the aim of our Institute is to overcome brain diseases. We study a wide variety of brain diseases by using genetic, biochemical, cell biological, histological, and imaging approaches, in collaboration with other departments in the Institute.
In the past 50 years, we have produced favorable results of clinical and basic research. In the beginning, we revealed Niigata Minamata and SMON diseases, which are caused by toxic reagents, making us to have profound connections with society. Up to now, we established entities of novel brain diseases and elucidated their etiologies and disease mechanisms by genetic, biochemical, and histological approaches.
We have also educated a large number of neurologists. Careful observation of patients by the excellent neurologists brought us fruitful success in a new discovery. Our research is attributable to the support of patients and clinicians, and we will keep tight connection with them.
Neurologists need comprehensive knowledge of medicine and a wide range of social skills including communication, leadership, and problem-solving skills. We actively train young doctors to acquire the knowledge and skills to become a specialist in various fields from a cutting-edge basic neuroscience to practical neurology. We are professional for brain diseases and will ensure the best possible support for our patients.

Dept. of Biological Magnetic Resonance

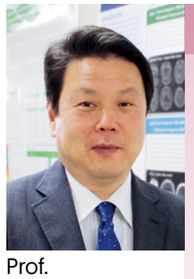
Prof.
Hironaka Igarashi



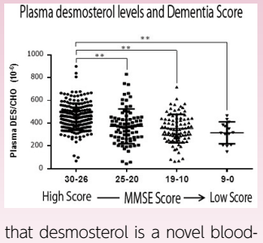
Simulation of brain morphology
The results of numerical simulation with thermal convection as a dominant equation.

Continuous technological development represents an indispensable component of the recent remarkable advancements in the state of our knowledge of human brain function. Magnetic resonance is a field which provides a number of versatile non-invasive methodologies applicable to the analysis of human specific brain function. The Department of Biological Magnetic Resonance focuses on the research, development and education of magnetic resonance technologies as well as the research and education of human brain function based on integrated knowledge of advanced engineering and non-linear computational analysis.

Dept. of Molecular Genetics / Dept. of Bioinformatics



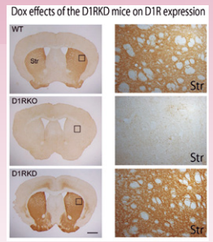
Prof.
Takeshi Ikeuchi



During the last decade, there has been significant progress in understanding the pathophysiology of dementia. Although several candidate disease-modifying drugs against dementia including Alzheimer's disease have been developed, clinical trials using these disease-modifying drugs have been failed to show the clinical efficacy. Considering that degenerative dementia develops the symptoms after long asymptomatic silent phase over decade, we need to establish biomarkers that enable the very early detection of the pathological process occurring in the brain. The aim of our research is the development and clinical application of cerebrospinal fluid (CSF) biomarkers for degenerative dementia. In addition to CSF biomarkers, we have explored blood-based biomarkers for Alzheimer's disease that is less invasive and simple to perform in clinical practice. We recently reported that desmosterol is a novel blood-based biomarker candidate for Alzheimer's disease. The other goal of our group is to elucidate the susceptible genes for dementia by comprehensive genome-wide analysis using next generation sequencer. In order to facilitate biomarker and genetics researches, we have established research consortium to collect large number of biofluid samples and genomic DNAs from patients with dementia by the collaboration with many clinical sites across Japan. Thus, we are working to translate research advances into improved diagnosis and therapeutics for patients with dementia and to find a way to cure and possibly prevent dementia.

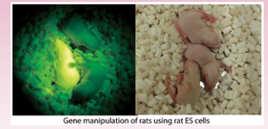
Dept. of Comparative & Experimental Medicine

Prof.
Toshikuni Sasaoka



Dopamine is considered to be closely related to controlling of motor function, learning and memory and motivation. Our research interest is focusing on understanding of the mechanism of motor control and developing of a novel therapeutic strategy regarding the motor symptoms of Parkinson's disease, one of the major neurological disorder. We develop various model animals such as the genetically modified mice of dopamine receptor and related molecules and examine them by biochemical analysis of gene expression, behavioral analysis of motor and cognitive function and electrophysiological analysis of neuronal activity.
Another mission of our group is management of the animal facility of Niigata University and improvement of environment of animal experiments using mice, rats, rabbits, guinea pigs, dogs, pigs, Japanese monkeys, marmosets and Japanese medaka. We perform research support activity using the reproductive and developmental engineering technologies such as in vitro fertilization, cryopreservation of embryos/sperms and provide services of production of genetically modified mice by the rapidly evolving genome editing technique. We ensure the microbiologically-controlled environment as the SPF (specific pathogen free) grade and contribute to facilitating progress of research by efficient production of animals using techniques described above.

Dept. of Animal Model Development

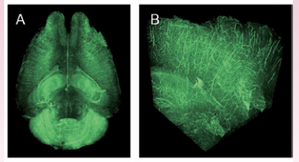


Gene manipulation of rats using rat ES cells

Our research efforts are focused on understanding of molecular mechanisms of higher brain functions such as learning and memory. Making good use of current methods in molecular biology and developmental engineering, we are now engaged in the following projects: 1) functional assay of neurotransmitter receptors and related molecules with gene-targeting techniques, 2) generation and analysis of animal models for human nervous diseases, 3) establishment of germ line-competent embryonic stem cells derived from rat embryos, and 4) development of basic methods for generation of gene-modified animals using gene-editing technology.

Dept. of System Pathology for Neurological Disorders

Tenure-track Prof.
Kazuki Tainaka

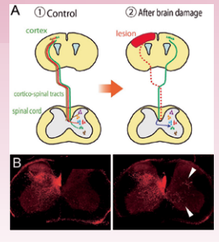


Whole 3D brain imaging by light-sheet microscopy

Current biopsy and histology have long relied on thin-sectioned 2D images with several chemical staining methods and specific immunohistochemistry. Facile 3D visualization of human brain tissue with single-cell resolution would provide a novel concept of the neuropathological diagnosis and contribute our understanding of pathological mechanisms based on comprehensive and quantitative analysis of individual biomarker. In this laboratory, we aim at establishing a novel 3D neuropathology by developing a highly efficient clearing protocol for human brain tissue and combining with a rapid 3D imaging using light-sheet fluorescence microscopy.

Dept. of System Pathology for Neurological Disorders

Tenure-track Prof.
Masaki Ueno



Central nervous system injuries due to stroke or trauma disrupt neural circuits and result in severe deficits of functions. The brain and spinal cord have very limited capacity to reconstruct the circuit once it is damaged, and therefore none of effective therapeutic methods have been developed so far. We previously demonstrated that spared motor and autonomic circuits are dynamically reorganized after injuries and influence the recovery process of functions. These results suggest that controlling the rewiring of the circuit would lead to make proper neuronal connections that achieve functional recovery. The goal of our study is to understand the process of rewiring and its underlying molecular mechanisms and neural functions. Toward this aim, we are analyzing neural systems of both normal and injured brain and spinal cord, using cutting-edge techniques including, mouse genetics, viral tracers, optogenetics, chemogenetics, and 3D behavior analysis. We believe that this study paves the way to develop novel strategies to regenerate circuits and restore neural functions.

Global Partnerships

Global partnerships can bring together complementary strengths and deepen the impact of joint research. BRI is committed to forming such partnerships and will further develop existing partnerships. The institute regularly welcomes scientific visitors from around the world and signs MOUs and agreements with overseas research institutions. BRI also annually hosts international symposia, which feature fascinating lectures by distinguished scientists from across the world.

Medical Practice and Education

BRI's mission is to advance scientific research on the nervous system of the brain. BRI has a historical background that has developed through the clinical care of neurosurgical cases in the School of Medicine. BRI offering an integrated approach to its research, along with clinical and educational activities, is therefore a great strength. The research at BRI covers a wide spectrum from Basic Neuroscience to Clinical Neuroscience related research to human brain disease. Pathological Neuroscience that bridges these two areas and the integrated research of these three areas brings greater progress, making BRI one of the most desirable institutes for research on brain disease in Japan. In order to continue to engage in cutting-edge research, BRI is dedicated to training competent researchers. BRI is also dedicated to research in the clinical area to advance medicine.




World Brain Awareness Week:
Let's examine the human brain and mind

Brain Awareness Week is the global campaign to increase public awareness of the progress and benefits of brain research. Once a year, BRI stages an event to stimulate student interest and understanding of neuroscience. The event includes lab tours and lectures.


Brain Seminar

Every summer, BRI offers a three-day seminar for young researchers across Japan to learn and explore topics at the forefront of neuroscience. Participants learn cutting-edge knowledge on specific topics from both BRI and external scientific experts at the forefront of neuroscience research through lectures and discussions. The seminar also features an on-site training course that provides an opportunity to participate in current experiments.


Science Education

Partnering with the local Super Science High Schools specified by MEXT, BRI provides opportunities including study tours at the institute and lectures that BRI scientists travel to the schools to give. BRI is working to nurture the next generation of global researchers by introducing the attractive world of neuroscience.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Published October 2018