

Brain Research Institute

NIIGATA UNIVERSITY









We've entered the age of generative AI, where the accumulation and summarization of knowledge is no longer an exclusive academic prowess or a special skill. Just as Google has revolutionarily democratized access to past knowledge, generative AI will democratize much of what was previously deemed academic. This democratization will likely lead to a significant transformation in the structure of academia, which has been built with the primary purpose of acquiring past knowledge, and in the mechanisms of professions that rely on it. Reconstructing knowledge will no longer be an exclusive task and will be open to all.

I believe this will bring about substantial changes in research as well. The significance of tasks such as literature reviews and comparisons of previous studies will likely diminish. The future is likely to see AI taking over in silico analysis using large-scale data. In such a scenario, our role will be simply to collect data. Collecting accurate data is fundamental to science, but this is not what we have aspired to be as scientists since childhood. Many of us, apart from a few scientists, may become mere data gatherers. This will demand a new employment and education system in the scientific community. However, there seems to be little sense of urgency about this in the research community. We need to urgently reassess science and research.

Scientific research is essentially the process of finding new things from nothing. The process involves struggles. Dr. Martin A. Schwartz, a professor at the University of Virginia at the time, remarked in a 2008 essay that "Science involves confronting our 'absolute stupidity'." He pointed out that research is immersion in the unknown, commenting, "We can't be sure whether we're asking the right question or doing the right experiment until we get the answer or the result." The path can be frustrating and full of errors, forcing us to face our own stupidity. He stated, however, "That kind of stupidity is an existential fact, inherent in our efforts to push our way into the unknown." He added that "One of the beautiful things about science is that it allows us to bumble along, getting it wrong time after time, and feel perfectly fine as long as we learn something each time." This statement connotes a sense of pride as a scientist.

Much of our work involves reconstructing knowledge. But in the age of generative AI, we must leave that to AI and continue to selflessly challenge ourselves to do something truly new, unknown to anyone, and yet seemingly foolish. This kind of work doesn't come with a roadmap or an exit strategy. We challenge because we don't have them. I believe that a research institute is a place where people with a spirit to keep challenging gather.

In the Age of Generative AI

A Perspective from the Director of Brain Research Institute

Osamu Onodera

Schwartz emphasized in his essay that what a scientist should do is to make a transition "from learning what other people once discovered to making your own discoveries." This essentially aligns with the old saying "standing on the shoulders of giants."

I believe that only a limited number of people who can truly practice this kind of science as a profession. And yet, we need to do science education at a research institute as well. Regarding education, Schwartz stated that "the faculty committee pushes until the student starts getting the answers wrong or gives up and says, 'I don't know'." In his view, "The point of the exam isn't to see if the student gets all the answers right. If they do, it's the faculty who failed the exam." He continued, "The point is to identify the student's weaknesses, partly to see where they need to invest some effort and partly to see whether the student's knowledge fails at a sufficiently high level that they are ready to take on a research project."

Brilliance and the spirit of challenge are traits that are difficult to coexist with. Our institute aims to nurture brilliant scientists who will continue to take on this challenge. We will continue to provide an environment in which we put generative AI to full use in order to make associations with past knowledge to reach new understandings.

In this new environment, the inquisitive mind combined with the potential of generative AI will allow us to continue to explore the unknown and constantly build new knowledge. In that process, we experience failure, learn from it, and deepen our understanding. This is what a genuine scientist is, and this is the genuine power of learning.

This new challenge brings us redefine the role of scientists and build new knowledge that will be passed on to the next generation of scientists. The new knowledge will provide the basis for them to take on another challenges.

Our mission as scientists is grounded in such approach and commitment, which will be a beacon for prospective researchers. The process allows us pursue the essence of science, search for truth, deepen our knowledge, and develop our understanding of the world. This is the role that BRI is assigned to in the age of generative AI. *Proofread by ChatGPT4.

Schwartz, M. A. "The importance of stupidity in scientific research." *J Cell Sci* 121, 1771–1771 (2008).



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

Brain Disorder Specimen Center is set up.

Heorganization results in BHI'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.

MEXT Joint Usage / Research Center

The Collaborative Research Center for Neurological and Psychiatric Disorders

BRI has been certified as a joint usage/research center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) since 2010. Its extensive collection of brain disease resources and expertise have been open to the neuroscientists' community. BRI's diverse research collaborations in neuropathology and related fields have brought out a great deal of achievement in relation to unravelling the pathological mechanism of brain disease. The institute has renewed its MEXT certification of a joint usage/research center in 2022 as "the Collaborative Research Center for Neurological and Psychiatric Disorders." BRI has the world-class collections of neuropathological specimens and advanced imaging analysis techniques. The institute 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.



MEXT Education and Research Organization Reform Project 21st Century Brodmann Areas Mapping

Integrating Molecular and Functional Information

The center for industry-academia-government collaboration and human resource development to complete a "brain map" integrating molecular and functional information in the brain that will serve as a guidepost for a dementia inclusive society

Overcoming age-related diseases of the brain, such as Alzheimer's and other types of dementia, is an urgent issue. In order to develop treatments for these diseases, it is important to establish diagnostic methods that can accurately estimate prognosis at an early stage. To do so, we need a map that can serve as a guidepost to predict the progression of the disease in the brain. This project aims to develop social implementation and human resource development in collaboration with industry, government, and academia, starting with the creation of a new human brain map that will serve as a guide to understanding the progression of brain diseases, and to give back to society through a dementia inclusive society. To achieve this aim, we are working on the establishment of cell dispersion technology from human brain tissue, clearing technology and cell labeling technology for human brain tissue, and the creation of functionrelated maps of brain regions using functional MRI.





Genetic Research Facility of Niigata University and Animal Testing Facility, School of Medicine.

CIHBS PET Building opens. (416m²)

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)

Organization

As of June 1 2023

Basic Neuroscience Branch		
Dept. of Brain Tumor Biology		
Assoc. Prof.	Nobuyuki Takei	
Assist. Prof.	Yuriko Iwakura	
Assist. Prof.	Masayasu Okada	
Dept. of Cellular Neuropathology		
Prof.	Takayasu Mikuni	
Assoc. Prof.	Motokazu Uchigashima	
Assist. Prof.	Daisuke Satoh	
Assist. Prof.	Risa Iguchi	
Dept. of System Pathology for Neurological Disorders		
Prof.	Kazuki Tainaka	
Prof.	Masaki Ueno	
Assist. Prof.	Hitoshi Uchida	
Assist. Prof.	Tokiharu Sato	
Assist. Prof.	Takahiro Inoue	
Assist. Prof.	Xinyi Liu	

Pathological Neuroscience Branch		
Dept. of Pathology		
Prof.	Akiyoshi Kakita	
Assoc. Prof.	Hiroshi Shimizu	
Assist. Prof.	Asa Nakahara	
Dept. of Molecular Pathology		
Visiting Professor	Koichi Wakabayashi	
Visiting Assoc. Prof.	Fumiaki Mori	

Clinical Neuroscience Branch

Dept. of Neurosurgery	
Prof.	Makoto Oishi
Assist. Prof.	Tetsuya Hiraishi
	Dept. of Neurology
Prof.	Osamu Onodera
Assoc. Prof.	Masato Kanazawa
Assist. Prof.	Shintaro Tsuboguchi

Center for Integrated Human Brain Science

Dept. of Integrated Neuroscience		
Assoc. Prof.	Yuji Suzuki	
Assist. Prof.	Yukimi Nakamura	
Dept. of Biological Magnetic Resonance		
Prof.	Hironaka Igarashi	
Assoc. Prof.	Kosuke Itoh	
Assist. Prof.	Masaki Watanabe	
Dept. of Functional Neurology & Neurosurgery		
Prof.	Hitoshi Shimada	
Assoc. Prof.	Yoshihiro Murakami	
Assist. Prof.	Masahiro Hatakeyama	

Center for Bioresource-based Researches		
Bioresource S	cience Branch	
Dept. of Moled	cular Genetics	
Prof.	Takeshi Ikeuchi	
Assoc. Prof.	Akinori Miyashita	
Assist. Prof.	Kensaku Kasuga	
Dept. of Comparative & Experimental Medicine		
Prof.	Toshikuni Sasaoka	
Assoc. Prof.	Nanaho Fukuda	
Assist. Prof.	Kanako Oda	
Dept. of Animal Model Development		
Prof.	Toshikuni Sasaoka	
Assoc. Prof.	Manabu Abe	
Brain Science Branch		
Dept. of Pathology Neuroscience		
Prof.	Akiyoshi Kakita	
Assoc. Prof.	Mari Tada	
Assist. Prof.	Rie Saito	
Dept. of Molecul	ar Neuroscience	
Prof.	Osamu Onodera	
Assoc. Prof.	Taisuke Kato	
Assist. Prof.	Yuka Koike	
Dept. of Neurosc	cience of Disease	
Prof.	Hideaki Matsui	
Assoc. Prof.	Ryuichi Hishida	
Assoc. Prof.	Tomoyuki Yamanaka	
Assoc. Prof.	Atsushi Sugie	
Assist. Prof.	Godfried Dougnon	
Assist. Prof.	Takayoshi Otsuka	

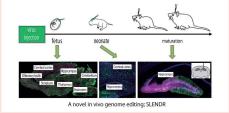
Endowed Research Branch

Advanced Treatment of Neurological Diseases Branch Specially Appointed Assoc. Prof. Tomohiko Ishihara Specially Appointed Assoc. Prof. Manabu Natsumeda

Dept. of Cellular Neuropathology



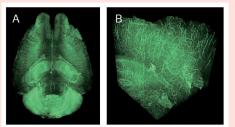
Prof. Takayasu Mikuni Our goal is to understand the physiology and pathophysiology of the brain at the cellular and molecular levels. We established "SLENDR", a technique based on in vivo genome editing, to image endogenous proteins with high specificity, resolution and contrast in single cells in mammalian 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.



Dept. of System Pathology for Neurological Disorders



Current biopsy and histology have long relied on thinsectioned 2D images with several chemical staining methods and specific immunohistochemistry. Facile 3D visualization of human brain tissue with singlecell 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.



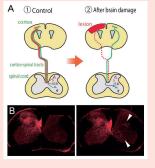
Whole 3D brain imaging by light-sheet microscopy

Dept. of System Pathology for Neurological Disorders



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.



Dept. of Pathology / Dept. of Pathology Neuroscience



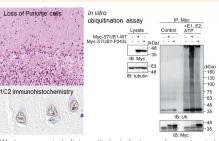
Mission

To provide the highest quality pathology services and scientific evidence focused on the advancement of developments in the field of neuropathology.

Vision

As an academic pathology department, we aim to deliver a high degree of professionalism in clinicopathological diagnostic services and neuropathology research, utilizing comprehensive and innovative approaches and building departmental competence to meet the needs of patients, institutions, and society.

Our approach will involve taking full advantage of opportunities to advance both the science and practice of neuropathology through individual and collaborative research, which hopefully will produce leading practitioners and researchers.



We have reported clinicopathologic features of an autopsied patient with Spinocerebellar ataxia (SCA) type 17-digenic TBP/ STUB1 disease (SCA17-DI), which has been recently segregated from SCA17, and demonstrated that failure of polyubiquitin chain formation is associated with the pathogenicity of the mutant STUB1.

Akiyoshi Kakita

Prof.

Dept. of Neurosurgery



Prof. Makoto Oishi

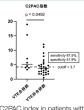
Dept. of Neurology / Dept. of Molecular Neuroscience



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 to discovering new insight into neurosurgical practice. Dr. Makoto Oishi has been appointed as the 5th professor of the Department of Neurosurgery, Niigata University since June 2023, and we will continue to proudly develop our historic department for further clinical and research development.

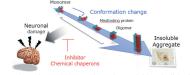
The Niigata University Brain Research Institute possesses not only a basic neuroscience branch but also a clinical neuroscience branch: Departments of Neurology and Neurosurgery. Thus, the aim of our Institute is to overcome brain diseases. We study a wide variety of brain diseases by using genetic, 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 The main research areas we are currently focusing on include: (1) establishing brain tumor cell lines and intracranial xenografts to develop the best strategies to treat each tumor, (2) diagnosing brain tumors by detecting driver mutations from cell-free DNA of cerebrospinal fluid, (3)

inventing marker to detect venous thromboembolism in glioma , (4) identifying molecular makers of human axonal regeneration and development, (5) developing assistive surgical technology to enable accurate simulation for complex neurosurgery cases and education of young neurosurgeons, (6) collaboration with Nishi-Niigata Chuo National Hospital to elucidate the complex pathophysiology of epilepsy using flavoprotein fluorescence imaging.



C2PAC index in patients with venous thromboembolism (VTE) and without VTE in patients with isocitrate dehydrogenase (IDH)wildtype gliomas.

knowledge of medicine and a wide range of social skills including communication, leadership, and problemsolving 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.

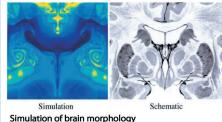


We conducted a multicenter, investigator-initiated clinical trial from 2020 to 2022 to evaluate a treatment for spinocerebellar degeneration type 6 (SCA6), an inherited disorder that commonly occurs in Japan and for which the development of an effective treatment is anticipated. The clinical trial has been successfully completed according to the planned timeline, and the results will be published in due course.

Dept. of Biological Magnetic Resonance



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.

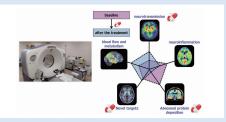


Simulation of brain morphology The results of numerical simulation with thermal convection as a dominant equation.

Dept. of Functional Neurology & Neurosurgery



Prof. Hitoshi Shimada Recent development of in vivo imaging enable us to track disruption of brain environment, such as abnormal protein deposition and neuroinflammation in addition to neuronal function. The aims of our department are to investigate the watershed between healthy brain aging and brain diseases, and to reveal pathological bases of diverse brain disorders using multimodal imaging technique including PET (positron emission tomography) and MRI (magnetic resonance imaging). We will execute the clinical imaging study contributing to finding out pathological bases of neuropsychiatric disorders, leading to the establishing novel techniques of early diagnosis, treatment and prevention, by collaborating with government, industry, and academic researchers inside and outside Brain Research Institute. As a leading laboratory in this field, we have ambitious plans to cultivate human resources capable of conducting translational study.



Dept. of Molecular Genetics

Prof

Takeshi Ikeuchi



Recent research and development of dementia has drastically changed. Therapeutic approach to dementia has shifted from symptomatic drugs to disease-modifying drug. More attention has been paid in dementia to pathophysiological diagnosis based on biomarker rather than symptom-based diagnosis. Prospering in research by virtue of paradigm shift, we have pioneered research that will bring revolution in clinical practice of dementia. Our mission has two elements; one is biomarker development, and the other is genome research of dementia. We attempt to see through pathological changes occurring in the brain affected with dementia using blood and cerebrospinal fluid samples from preclinical phase to symptomatic phase. We have established large sample collection of genomic DNA for dementia disorders. Whole genome/exosome analyses have been applied in the genome analysis of dementia to explore novel genetic factors in Japan. We have provided a clinical sequence examination for physicians across

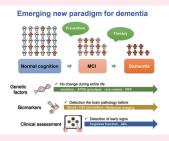
Dopamine is thought to play an important role in motor

control, memory, learning and motivation. We focus

on Parkinson's disease (PD), which is one of the most

common neurological diseases involving dopamine.

Japan for genetic diagnosis of dementia. By this effort, we will contribute to the realization of genome medicine of dementia in Japan. Even though the environmental surrounding of dementia research has been drastically moving, we keep pioneering the dementia research without forgetting our mission that we will deliver a bright future to patients with dementia.



Dept. of Comparative & Experimental Medicine / Dept. of Animal Model Development



Prof. Prof. Toshikuni Sasaoka As PD model animals, we have created genetically modified mice for dopamine receptors and their related molecules. By analyzing the animal behavior and neural circuits of these model mice, we aim to elucidate the role of dopamine signaling on motor control, learning and memory, and develop a new therapeutic approach for PD. We are also studying RNA-binding proteins that are responsible for neural circuit formation and

Our department is in charge of the management and operation of the University-wide animal experimentation facility, which provides an animal experimentation environment using mice, rats, rabbits, guinea pigs, dogs, pigs, Japanese macaques, marmosets, and killifish for advanced animal research. We also support research using reproductive technologies such as in vitro fertilization, embryo transfer, embryo and sperm functions. In addition, we are analyzing the effects of in vitro culture of early-stage mouse embryo on individual development. In collaboration with the Department of Animal Model Development, we are working on the

regeneration of defective organs by blastocyst complementation and the development of a new embryo manipulation system by using xenotransplantation of marmoset germline tissues.



cryopreservation. In addition, we create genetically engineered animals using genome editing technology. These techniques are used to maintain the animal experimentation facility in a Specific Pathogen Free (SPF) environment, and contribute to efficient research through systematic animal production.

Dept. of Neuroscience of Disease



Prof. Hideaki Matsui



Neurodegeneration such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Cerebrovascular diseases including stroke and cerebral hemorrhage, as well as Developmental disorders and Mental illnesses, present significant challenges in terms of treatment and management. Many of these disorders and disabilities have a high incidence rate and are of utmost importance both in medicine and in society.

Brain disorders may be perceived as highly complex and unique to humans. However, various organisms naturally develop brain disorders through aging or other processes similar to humans. For instance, our laboratory has revealed that African killifish exhibit a disease state reminiscent of Parkinson's disease during aging, leading to numerous insights that contribute to the understanding of novel pathological mechanisms in this disorder. Cognitive impairment in various animals is also occasionally reported in news and scientific articles. Furthermore, α -synuclein, a molecular factor implicated in Parkinson's disease, is found in fish, and the amyloid precursor protein, a molecular factor in Alzheimer's disease, exists in fish and insects as well. In our laboratory, we integrate the study of various research subjects, primarily focusing on small fish species. We combine the cutting-edge neuroscience and evolutionary approaches, leveraging the esteemed Brain Bank of our institute, and employing research methodologies that cannot be replicated by AI for the next 20 to 50 years. We strive to unravel the evolutionary origins of brain disorders and establish a fundamental understanding of the pathophysiology rooted in the comprehension of the physiological functions of molecular factors that underlie these disorders.

- 1. Conquering difficult diseases.
- 2. Supporting individuals with disabilities.
- 3. Leaving a significant mark on the history of
- science.

By shedding light on the essence of brain disorders, we aim to expand our research achievements to areas such as industry-academia collaboration, drug development research, and preventive medicine, making substantial contributions to the treatment of brain disorders and the promotion of healthy longevity. Furthermore, we actively propose approaches to foster coexistence with disabilities and aging.

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 also dedicated to training competent researchers. BRI is also dedicated to research in the clinical area to advance medicine.



Niigata Junior Doctor Training School

BRI gave science talks in October 2022 as part of the master's program of "the Niigata Junior Doctor Training School", a STEM education program aiming at fostering the budding scientists. 42 pupils, from the 5th grade elementary school to junior high, participated in a lecture session by two BRI researchers. Alongside with that, two 6th-graders from the doctoral program visited BRI on a regular basis and took part in trainings and experiments to work on scientific research projects.



Niigata Nouken Seminar for Neuroscience

Every year, BRI holds Niigata Nouken Seminar for Neuroscience, formerly known as Summer Seminar. The 52nd meeting was held online in March 2023. The event included self-introductions by graduate students and newly joined researchers, a special lecture with Dr. Yasuhiro Iba of Hokkaido University, and presentations by Niigata Junior Doctor Training School pupils.



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.



Science Education

Partnering with the local Super Science High Schools specified by MEXT, BRI scientists visit local highschools to give lectures on neuro science. BRI is working to nurture the next generation of global researchers by introducing the attractive world of neuroscience.



Brain Research Institute



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