Tohoku Neuroscience Global COE

Basic & Translational Research Center for Global Brain Science

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Basic & Translational Research Center for Global Brain Science

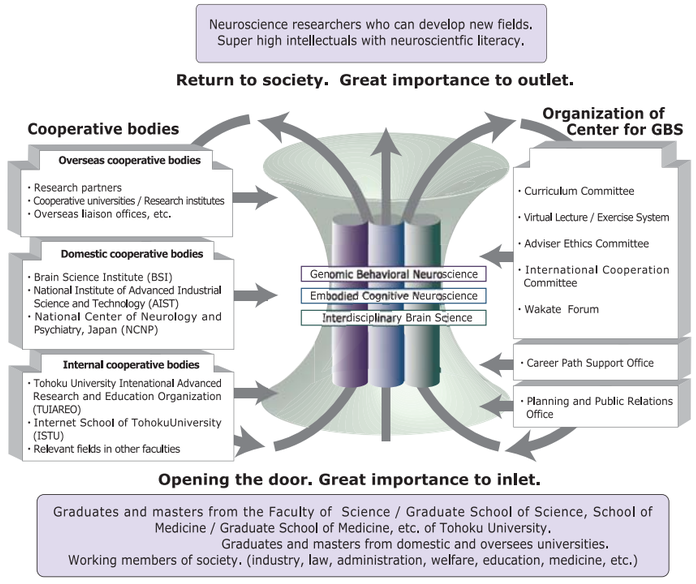
Philosophy and summary

Modern science is an international, collaborative endeavor, in which researchers from all over the world conduct cooperative projects and share their findings. To do proper science nowadays it is imperative to free up the flow of information and ideas.

The Global Centers of Excellence program, supported by Japan' s Ministry of Education, Culture, Sports, Science and Technology, provides funding to establish education and research centers at the cutting edge of scientific research and boost the international competitiveness of Japanese universities. The program is also intended to enhance the education and research functions of graduate schools and foster young scientists to become global leaders in their fields.

There are numerous COE programs nationwide, in a variety of scientific fields, including mathematics, materials science, physics, earth science and many others. The Tohoku Neuroscience COE, officially known as the Basic and Translational Research Center for Global Brain Science, is one of 13 COEs in the field of life sciences in Japan, and one of 12 currently operating at Tohoku University.

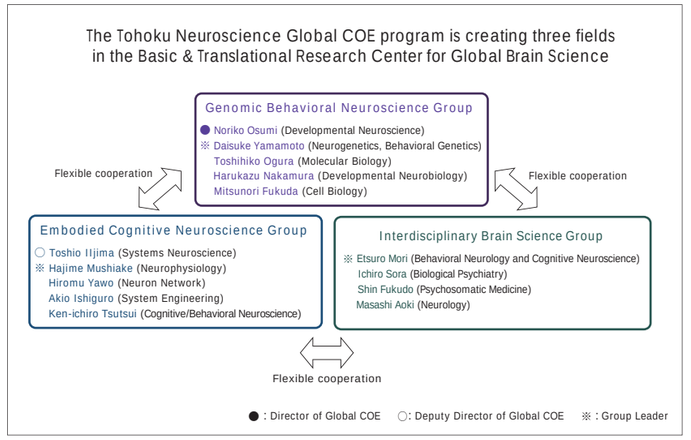
Heading up the Center is Dr. Noriko Osumi, a professor at Tohoku University' s School of Medicine and a member of the Science Council of Japan. "We want to use our program to integrate the many subfields of neuroscience, from genes, molecules, cells and neurons to larger systems, the brain and environmental factors as well," she said. "Neuroscience covers a great diversity of fields, and it can be quite hard to combine them all."



Prof. Noriko Osumi
(Director of Global COE)

The Tohoku Neuroscience Global COE is divided into three groups: Genome Behavioral Neuroscience, which studies the genetic basis of individual behavior; Embodied Cognitive Neuroscience, which focuses on cognitive function arising from the mutual operation of brain and body; and Interdisciplinary Neuroscience, which integrates a range of research, from the environment surrounding people to relationships among them. The center' s 14 professors are divided among these three groups.

Tohoku University, with its long and distinguished history in brain studies, is an appropriate venue for the Neuroscience COE. Brain scientists at the Graduate School of Life Sciences, the Graduate School of Medicine and the Institute of Development, Aging and Cancer have made the university a highly respected institution, especially in molecular, developmental and cognitive neuroscience.



"We established the Global COE because we believe there is a strong need for neuroscience in today' s society," Dr. Osumi said. Neuroscience can be applied to a variety of areas, including medicine, education, social welfare and engineering. The field has strong links to the pharmaceutical industry, and in other businesses brain science findings are used in product design and market research. The research can also be used to better understand human economic behavior, leading to better and safer products and services.

Another reason behind the COE program is that universities all over Japan are under increasing pressure to justify their research and teaching programs. "The COE organization is based on the awareness that the number of children in Japan is declining," Dr. Osumi noted. "So we have to build up our reputation, and be open to recruiting foreign students to come here."

"Also, funding from the government for national universities is being reduced. Universities now have to compete among themselves to get grants, and the COE program is one way to do this."

Reaching out

All this makes it even more imperative to train scientists to communicate effectively, and the Tohoku Neuroscience Global COE places great emphasis on international activities and community outreach. To this end, the center funds several fellowships and forums to help young scientists to gain international experience.

One, the Hasekura Fellowship, is named after Tsunenaga Hasekura, the first Japanese diplomat to make the long and dangerous journey from Japan to Rome in the 17th century to meet with the Pope. Thanks to this fellowship, the COE sends students and post-docs to attend international conferences, as well as accepting researchers from overseas.

The Wakate Forum is aimed at exposing young researchers to other fields of science through seminars that the students set up themselves. They organize the seminars, select the speakers, and invite them to come. Logistics is handled by the administrative office, but the planning and initial contacting of the invitees are done by the students. They also have seminars to present their own data to each other.

The COE is also active in career support, inviting people outside of academia, but who have trained to a high level, for example patent lawyers, pharmaceutical company executives, entrepreneurs and venture capitalists. Meeting such people can be very important to the students. In Japan, although many students graduate with PhDs every year, very few career posts in academia open up, but traditionally grad schools have trained students only for academic careers.

"There has been no system to encourage students to go out into the wider world, and the teachers don' t really know how to educate people who are not going into academia," Dr. Osumi noted. "So we invite many people working in various careers, and show the students that they can apply their training to benefit society in other fields."

(Interview, text and photo
by Robert Cameron)
2009.01.23

Tohoku Neuroscience Global COE

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International activities

Tohoku University' s Neuroscience COE places a high priority on international activities. In this day and age, international collaboration and cooperation are crucial for doing effective, cutting-edge science. The various conferences and symposiums also promote scientific progress by encouraging the free flow of information and ideas.

Some students got such an experience in October 2008, when the Tohoku Neuroscience COE held a joint forum with Fudan University in Shanghai. More than 100 people attended, most of them from Fudan U., and about 35 from Tohoku U. – 22 young scientists and the rest professors. The students were asked to submit a 1,500 word article for the proceedings journal, and while in China they each did a 15-minute talk and presented their posters.

Tohoku Neuroscience Global COE 1st International Conference in Zao "From Genes to Development and Behavior" (Jan. 2008)

"For many of the students, the poster session was their first English oral presentation. They were a little nervous, but it was really a good situation for them, though it was also quite difficult," Dr. Osumi said.

The forum was the latest event in a long history of contacts between Tohoku University and China. The renowned Chinese novelist Lu Xun studied at Tohoku U.' s medical school in 1904, and lived in Shanghai for many years. One of his professors at Tohoku University even appeared in one of his novels. "That' s one reason we held the joint forum with Fudan University," Dr. Osumi said. "The other reason, of course, is that Fudan U. has an excellent brain science institute."

The previous year, the COE held an international symposium conference at the Zao mountain ski resort area near Sendai. Eighty attendees came from seven countries. The event was organized by Prof. Daisuke Yamamoto of the Genome Behavioral Neuroscience group under the title, "From Genes to Development and Behavior." Most of the people attending were related to molecular and behavioral neuroscience.

"It was very good, because it was held at an *onsen* hot-spring resort, which provided a nice atmosphere, and everyone stayed at the same traditional *ryokan* hotel, and we were able to discuss our work until very late at night," Dr. Osumi recalled.

Attendees heard 50 poster sessions by Tohoku University students and seven lecturers invited from around the world. "It was an excellent chance for our students and post-docs to talk frankly and deeply about their research with some of the top people in the field, famous scientists that they had only known by name. It was a very precious time for them," Dr. Osumi said.

Also in 2008, the center held a retreat at the beautiful town of Matsushima near Sendai, jointly with the RIKEN research institute' s Brain Science Institute. RIKEN BSI has held a summer school for the last 10 years, which is quite well known among brain science-related researchers all over the world, and consistently attracts three times more applicants than there are places at the summer school.

"Of course, we welcome doctoral students and post-docs as well, to come to our labs," Dr. Osumi noted. "For example, one happy result of the joint workshop in Shanghai was that one of the participants from Fudan University said she wanted to come to Japan; she started as a post-doc researcher in my lab in February."

"In our COE there are quite a few foreign students and post-docs, many of whom are from Asia," Dr. Osumi said. "Tohoku University is quite famous in Asia, especially in chemistry and materials science, but the neuroscience department lately has also been making a name for itself."

There are more international activities in the pipeline. The next international conference will be in Taiwan, a joint seminar with a Taiwanese research institute, and a summer retreat will also be held again this year.

"We are planning more international symposiums and conferences, including some outside Japan. We are always encouraging students to go abroad," Dr. Osumi said.

The organizers of the Neuroscience Global COE realize that English is the language of international science, and anyone wanting to be a serious scientist has to be not only fluent in spoken and written English, but also experienced in giving effective presentations at international conferences.

"To do science we need to communicate," Dr. Osumi noted. "But our university system isn' t really set up to teach advanced communication skills. Of course, we have English teachers, who teach literature and basic conversation, but it usually does not go beyond that." To provide experience in English communication, many of the symposiums, seminars and poster sessions at the COE are given in English, and students have to give many of their presentations in English as well.

"I think this is a valuable exercise," Dr. Osumi said. "It can be a little hard for the students to do the presentations in addition to their own research projects, but this kind of on-the-job training in presentation and organizing will be helpful in their future careers."

(Interview and text by Robert Cameron)
2009.01.23

Tohoku University-Fudan University Neuroscience Workshop for Young Scientists (Oct. 2008)

Tohoku Neuroscience Global COE Summer Retreat in Matsushima (Aug. 2008)

Noriko Osumi

Global COE Director
Developmental Neuroscience

Profile

Prof. Osumi has graduated Tokyo Medical and Dental University, been conferred PhD degree from the same university, and now is a professor of Tohoku University School of Medicine since 1998. She is appointed in various governmental committees such as ethical issues, grant system development, and career paths for young scientists, and also chosen as a youngest member of Japanese Council Japan since 2005. Her research interest covers broad areas such as pre- and postnatal development of the brain and craniofacial region, and behavior of animals as models of psychiatric diseases. More specifically, she is recently eager to understand regulatory mechanisms of neurogenesis and maintenance of neural stem cells at cellular and molecular levels both in embryonic and postnatal stages. Manipulating embryos and imaging brain cells are expertise of her lab. She has translated two books into Japanese: Essential Developmental Biology by Jonathan Slack and The Birth of the Mind by Gary Marcus. She is a representative of CREST project (2005-2009) supported by JST and Global COE project (2007-2011) supported by MEXT.

Genetic and environmental mechanisms for development and maintenance of the central nervous system

In order to achieve various higher functions of the brain, several developmental processes have to be accomplished. For example, various kinds of neurons have to be generated and distributed in accurate numbers and in precise positions, and proper neural circuits have to be established among an enormous numbers of neurons. In addition to these neurons, a huge number of glial cells (astrocytes, oligodendrocytes, and microglia) are also located within the entire central nervous system (CNS), where the astrocytes interact with blood vessels to intake oxygen and nutrients and to transfer them to the neurons, oligodendrocytes myelinate neuronal axons thereby increasing speed of neuronal transmission, and microglia work in healing inflammation and wound. Most of the processes in the brain formation during embryonic periods are governed by genetic programs, yet further refinement and modification of the CNS continue postnatally. During the initial process of CNS formation when the neural tube is just closed, the region called the neural crest is established at the interface between the neural epithelium and surface ectoderm. Neural crest-derived cells differentiate multiply to make not only neurons and glia in the peripheral nervous system (PNS), but also bone, cartilage, smooth muscle and pericytes of the blood vessels in the craniofacial region. Our lab is thus working to better understand mechanisms for development of the CNS and PNS at molecular and cellular levels. Particularly, we are interested in initial brain regionalization, embryonic and adult neurogenesis (i.e., proliferation and differentiation of neural stem cells), and mechanisms for establishment and differentiation of the neural crest. Our recent curiosity in neurogenesis further includes relationship between states of neurogenesis and mental diseases because the neurogenesis is important not only in brain formation but possibly in homeostasis of brain functions.

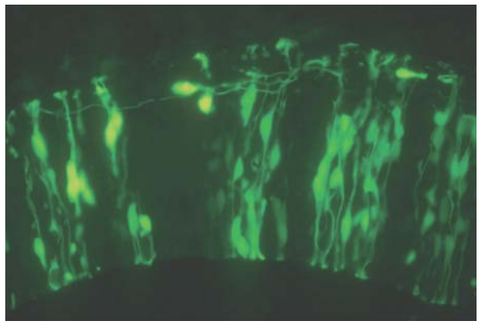

Fig. 1. Morphology of neuroepithelial cells and differentiated neurons in the developing rat hindbrain. Neuroepithelial cells are highly polarized cells with long apical and basal processes, which attach to the lumen of the ventricle and to the pial surface, respectively.

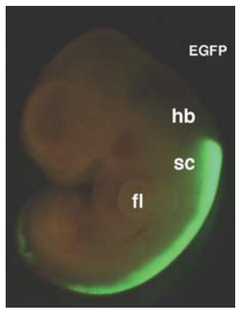

Fig. 2. Transfer of exogenous genes into cultured rat embryo. Expression vector of enhanced green fluorescent protein (EGFP) was introduced into neuroepithelial cells in the rat spinal cord. 24 hours later, the expression of EGFP protein is detected by fluorescent microscopy.

Above studies require various experimental systems, which we are actively developing. For example, we have established a unique system to transfer certain genes directly into the developing brain primordium by combining mammalian whole embryo culture and electroporation. This technique is very quick and easy compared with one using virus vectors, and has advantage in precisely transferring genes into certain regions of the brain primordium. For manipulating embryos at later stages, we perform *in utero* operation together with electroporation. Time-lapse imaging techniques are also refined to observe embryonic neural stem cells in conditions better mimicking *in vivo* situation. Behavior analyses of rodent models have been done in regards with neurogenesis within the brain development and aging and mental diseases.

Various kinds of environmental factors influence on development and maintenance of the brain. We are particularly focusing on nutrients, and analyzing effects of polyunsatulated fatty acids (e.g., DHA and arachidonic acid) on neurogenesis in animal models and cultured cells. Since exercise promotes neurogenesis in rodents possibly via enhancing blood flow, we are trying to increase neurogenesis with treating mice with antihypertensive drugs. These studies may contribute therapeutic development for prevention and treatment of mental diseases such as depression and schizophrenia that may relate with impaired neurogenesis.

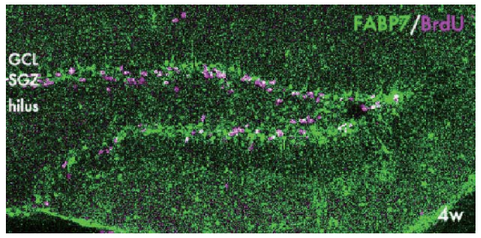

Fig. 3. Neural stem cells in the postnatal hippocampus. Proliferating neural stem/progenitor cells are labeled with BrdU (magenta) and express FABP7, a fatty acid binding protein. GCL:granule cell layer; SGZ, subgranular zone

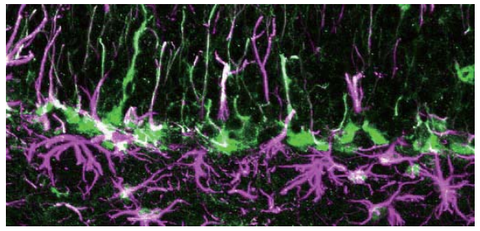

Fig. 4. Neural stem cells and astrocytes in the postnatal hippocampus. The localization of FABP7+/GFAP+ cells in the subgranular zone of the mouse hippocampal dentate gyrus at 4 weeks. These cells are considered to be nueral stem cells and astrocytes.

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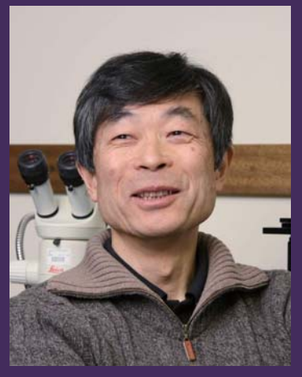
Daisuke Yamamoto

Group Leader
Behavior Genetics



Profile

Daisuke Yamamoto is a full professor of Neurogenetics at Tohoku University Graduate School of Life Sciences, Sendai, Japan. He majored in Applied Entomology and Zoology (1976) at Tokyo University of Agriculture and Technology, Japan, and after that, he did his graduate studies in Neurophysiology in Mitsubishi-Kasei Institute of Life Sciences, Machida, Tokyo, and received his D. Sc. (equivalent to Ph.D.) in 1981 at Hokkaido University Graduate School of Science. In 1980, he was employed as Junior Staff Scientist in Mitsubishi-Kasei Institute of Life Sciences, and worked there until 1999 (promoted to Group Leader in 1988). He had a postdoctoral training at Northwestern University Medical School, Chicago, USA, from 1981 to 1983. He was appointed to be Director of ERATO Yamamoto Behavior Genes Project from 1994 to 1999. Yamamoto was on the faculty of Waseda University as a full professor in 1999. He moved to Tohoku University in 2005. Yamamoto explores our long-standing question of why females and males think and behave so differently. His favorite material is a *Drosophila* mutant *fruitless*, males of which display homosexual courtship. He was the first to clone the gene *fruitless* (1996). Yamamoto is also prolific in his writing on science.

Molecular and cellular basis for the sexual dimorphism in the brain and behavior

Why females and males behave differently is a fundamental question for us. Biologists postulate that the sexual dimorphism in the brain underlies such gender differences in behavior, yet little evidence has been obtained. *Drosophila* offers a handy system for genetic dissection of complex behaviors. One of the most salient examples of sexually dimorphic behaviors in *Drosophila* is courtship behavior. When a male fly encounters a female, he immediately initiates courtship in most cases, whereas the male-male encounters provoke aggression under certain conditions. The male fly could also commence courting another male but he stops courting soon after, often switching to aggression. Such a choice between behavioral repertoires correlated with the differences in the social context must result in a switching of motor centers to be activated, and this decision-making is likely controlled by an executive neural center that is situated on a higher rung of the neural hierarchy. To explore the neural basis for decision-making, we have to identify these neural centers individually in the brain.

We will use the MARCM (Mosaic Analysis with Repressive Cell Markers) method to label a few clonal cells in the brain, to manipulate them, or to record their activity. In MARCM, the Gal4 action is repressed by the presence of Gal80 in most cells in the body, except for some clonal cells in which the Gal80-coding transgene has been recombined out during development. The cells derived from these Gal80-free clones alone express Gal4 in the animal. Gal4 is then used to drive expression of reporters, activators or inactivators of neurons. In the proposed research, we use MARCM to study physiology and anatomy of a subset of *fruitless*-expressing cells that potentially contribute to sexual dimorphisms of behavior.

The *fruitless* gene was originally identified by its remarkable phenotype of its mutants: mutant males court both males and females, yet without copulating. In some of other strains that are also mutant for the *fruitless* gene, males court males but not females. Therefore, the *fruitless* gene seems to function as a critical switch in behavioral choice in the sexual context. In fact, the *fruitless* gene is proposed to be a master control gene in organizing the brain centers for sexual behavior, for its ability to cause an “inversion” of the gender role, when male-specific forms of its transcripts are expressed in females by replacing the genomic *fruitless* gene with an engineered one.

We will identify uniquely the *fruitless*-expressing neurons by labeling individually their entire structures including dendrites and axons in addition to the cell bodies by means of the MARCM method. Based on the projection and dendritic branching patterns of *fruitless*-expressing neurons revealed by single cell labeling with this method, we should be able to distinguish groups of neurons that are functionally distinct. The neuronal clusters we define here are presumably not just the cell groups of which somata are located close proximity to each other, but represent functional units, as the members of a group share projection patterns and dendritic fields. If this is the case, we may be able to assign a specific function to each neuronal cluster. For instance, a particular cluster of fruitless-expressing neurons could play an executive role in initiating male-typical courtship behavior. We will generate small clonal patches of neurons that are masculinized in otherwise female individuals, on the assumption that a fraction of such females displays male-like courtship as a result of sexual transformation of a cell cluster that functions as the neural center to trigger the male-type sexual behavior.

This rather straightforward approach using *Drosophila* genetics will allow us to identify executive neurons governing behavioral choices in the sexual context.

Do such executive neurons for sex-specific behavior exist in humans, as well? This remains to be answered.

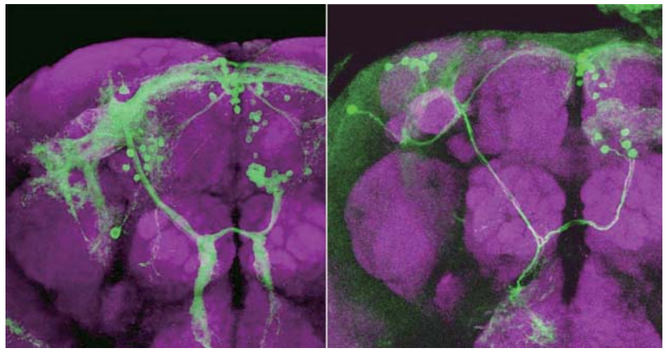


Figure: Sexually dimorphic neuronal cluster, mAL, that express *fruitless*. mAL is composed of 30 cells in males and 5 cells in females. The neurite projection and dendritic arborization of mAL are also sexually dimorphic.

Articles

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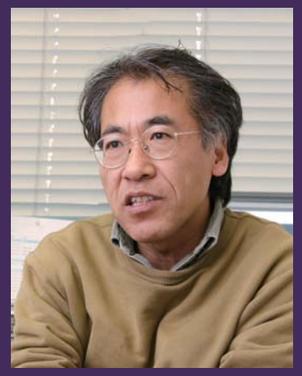
Toshihiko Ogura

Molecular Biology



Profile

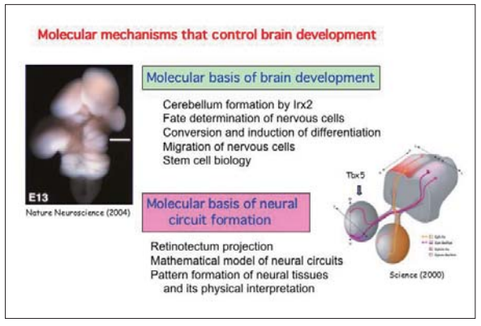
Prof. Ogura has graduated Tohoku University School of Medicine, been conferred PhD degree (Immunology) from Kyoto University, and now is a professor of Institute of Development, Aging and Cancer, Tohoku University since 2003. His research covers broad areas of developmental biology, from cardiogenesis to neurogenesis. His lab is now focusing on re-interpretation of morphogenetic movement with different viewpoints, such as mathematics and dynamics, since Prof. Ogura and his colleagues have found that physical forces are an essential parameter of morphogenesis, homeostasis and metabolism. Prof. Ogura' s lab is now trying to open a new field that has never been explored. Prof. Ogura is a faculty member of Faculty of 1000 (Neurodevelopment section).

Molecular and physical basis of pattern formation

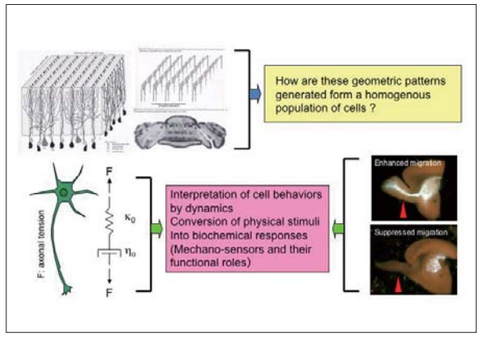
Orchestration of differentiation, migration and re-assembly of cells is one of the most fundamental aspects of pattern formation of tissues and organs, including central nervous system. We thought that these coordinated behaviors of cells are regulated by a genetic program, in which pivotal genes regulate these steps in a tight and precise manner. This also implies that careful dissection of this genetic program and detailed analyses of functions of genes should help us to understand complicated morphogenesis of tissues and organs. Nonetheless, we have just come to a point to re-evaluate our approaches and to proceed to a new field, which has never been explored.

Pattern formation, such as the Benard convection and the Taylor instability, is also extensively studied in physics and chemistry. In these cases, a homogenous group of molecules can form orderly patterns. In another case, oxidative and reductive states repeat in an oscillatory way, known as the (Belousov-Zhabotinsky) B-Z reaction. These indicate that autonomous mechanisms do exist even in developing embryos, some of which were already studied extensively by Turing and Meinhard.

We have been exploring molecular mechanisms of pattern formation of vertebrate embryos, with central nervous system, limb bud and heart as model organs, and with several key transcription factors as our keen interest. Nonetheless, we have noticed that extensive analyses on the genetic programs are not sufficient for understanding thoroughly the dynamic pattern formation of developing embryos. Recently, we have identified that several proteins change their shapes and conformation in response to physical forces that are generated by cells, hereby such strains trigger next biochemical responses. We are now studying this novel mechanism to understand functional roles of physical forces generated by cells and sensed by cells.



1) Molecular mechanisms of brain formation. Induction of cerebellum by an Iroquois homeodomain transcription factor, Irx2. Fate determination of neural stem cells and their differentiation and migration.
2) Molecular mechanisms of neural network formation. Retinotectum projection regulated by Tbx5. Migration of neuronal cells.



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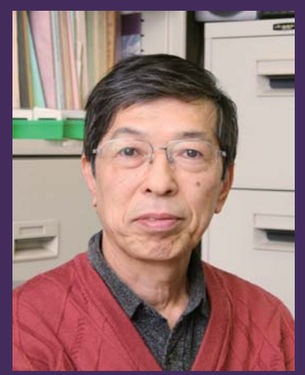
Harukazu Nakamura

Developmental Neurobiology



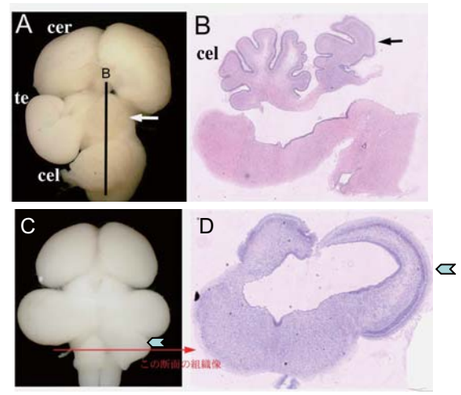
Profile

Prof. Nakamura graduated from Kyoto University in 1971. After graduation he had been working at the Department of Anatomy of Kyoto Prefectural University and Hiroshima University for 17 years. He got his phD in Hiroshima University. He then became a professor of Biology at Kyoto Prefectural University of Medicine, and moved to Institute of Development, Aging and Cancer, Tohoku University in 1994. He has participated in the Graduate School of Life Sciences from the first (2001). He learned micromanipulation of chick embryos from Prof. Nicole Le Douarin (1979-1980), and has been working on brain pattern formation in chick embryos since then. He established the system of gene transfer to living chick embryos by electroporation in ovo, which revived the chick embryo as a model animal for developmental biology, and this method is now a routine technique in the study of developmental biology. His team greatly contributed to understanding the mechanisms of brain pattern formation. He headed the 'Brain Pattern Formation' team of Grant-in-Aid for Scientific Research on Priority Areas- of the Ministry of Education, Culture, Sports, Science and Technology of Japan during 1999-2004. He has been a chief editor of Development, Growth & Differentiation, the official journal of Japanese Society of Developmental Biologists (JSDB). He organized Annual Meeting of JSDB in 2005. He edited and published a book, Electroporation and Sonoporation in Developmental Biology, from Springer, Japan, in 2009. He published books sharing authorship, 'Neuroscience, editor Masao Ito, from Miwa Shoten' ; and 'Standard Cell Biology, from Igaku Shoin' . He also translated textbooks into Japanese, 'Human Embryology of Larsen' and 'Physiologie du Neurone, eds Tritsch et al., Doin editeru-Paris' .

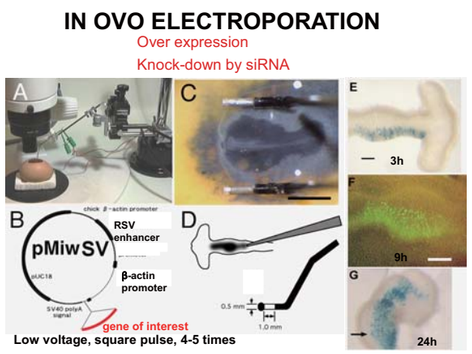
Understanding the mechanisms of vertebrate brain plan

We have been interested in the regionalization of the vertebrate central nervous system (CNS). We have developed a very effective gene transfer system in chick embryos, in ovo electroporation. This system is so effective for misexpression of the gene of interest that the chick embryo is revived as a model animal for developmental biology. The system is applied in other animals, and become routine technique in developmental biology. siRNA system has enabled us to silence the expression of the target gene, which could also be applied by electroporation.

We have studied the mechanisms of regionalization of the optic tectum and cerebellum. It is now accepted that the fate of the brain vesicles is determined by combination of the transcription factors expressed, and that organizing molecule emanated from the local organizing center regulates expression of the transcription factors to determine the fate of the adjacent region. Midbrain hindbrain junction (isthmus) functions as a local organizing center emanating Fgf8. We have shown that strong Fgf8 activates Ras-ERK signaling pathway to induce cerebellar differentiation. If this signaling pathway is disrupted by dominant negative form of Ras, the optic tectum differentiates in place of cerebellum. But this signaling pathway should be regulated precisely for mesencephalon metencephalon boundary formation. If it overflows the boundary shifts anteriorly, and if the signaling is repressed the boundary shifts posteriorly. We have also shown that the region where Otx2, Enl and Pax2 are expressed differentiates as mesencephalon. Repressive interaction between Pax6 and En1/Pax2, and between Otx2 and Gbx2 determines the di-mesencephalic and mes/metencephalic boundary, respectively. We are now interested in downstream signal transduction of Fgf8 in the midbrain and hindbrain. We also pay attention to the polarity formation in the tectum.



Fate change of the mesencephalon to the cerebellum by Fgf8b (A, B), and reverse by dominant negative form of Ras (C, D). These figures suggest that strong Fgf8 signal activates Ras-ERK signaling pathway to differentiate a cerebellum.



Chick embryos had been used as a model animal of experimental embryology, but difficulty in manipulating the embryo while in the uterus interfered with molecular approach to the embryo (such as production of transgenic chick or of gene-knock-out chick). Development of gene transfer by electroporation in ovo in our lab revived chick embryos as a model animal of modern developmental biology. Combination of siRNA and electroporation made it possible to knock-down a targeted gene expression. Moreover, we can now integrate transgene by transposon system, and follow long term effects of the tranfered gene. Now we can carry out gain and loss of function of a gene of interest in chick embryos at desired place and stage of the chick embryo.

Articles

1) Suzuki-Hirano, A., Sato, T. and Nakamura, H. Regulation of isthmic Fgf8 signal by Sprouty2. ***Development***, 132, 257-265 (2005)
2) Sato, T. and Nakamura, H. The Fgf8 signal causes cerebellar differentiation by activating Ras-ERK signaling pathway. ***Development***, 131, 4275-4285 (2004)
3) Sato, T., Araki, I., Nakamura, H. Inductive signal and tissue responsiveness to define the tectum and the cerebellum. ***Development***, 128, 2461-2469 (2001)
4) Katahira, T., Sato, T., Sugiyama, S., Okafuji, T., Araki, I., Funahashi, J., and Nakamura, H. Interaction between Otx2 and Gbx2 defines the organizing center for the optic tectum. ***Mech. Dev***, 91, 43-52 (2000)
5) Nakamura, H. Regionalisation of the optic tectum: Combination of the gene expression that defines the tectum. ***Trends Neurosci***, 24, 32-39 (2001)

Mitsunori Fukuda

Cell Biology

Profile

Prof. Fukuda has graduated from Tohoku University, been conferred PhD degree from the University of Tokyo, and now is a professor of Tohoku University, Graduate School of Life Sciences since 2006. He was the recipient of the 2004 Young Scientist Award from the Japanese Biochemical Society, the 2006 Young Scientist Award from the Kao Foundation for Arts and Sciences, and the 2007 Young Scientist Award from the Molecular Biology Society of Japan. He is currently a member of the advisory and editorial boards of two international journals, *Journal of Biochemistry* and *International Journal of Medical Engineering and Informatics*. His research interest is to understand the mechanism of "membrane traffic", in which membrane-wrapped substances (e.g., organelles) are transported within the cell, at the molecular level. More specifically, he is now focusing on the molecular mechanism of neurotransmitter release in neurons and melanin transport in melanocytes. He is a member of the Global COE project (2007-2011) supported by MEXT.

Membrane traffic and brain function

The human body comprises a great many cells, each of which contains many subcellular units known as organelles (e.g., nucleus, the Golgi apparatus, and endoplasmic reticulum). Signals are exchanged frequently between cells and between organelles through "membrane traffic", in which membrane-wrapped substances are transported. However, much remains unknown about this process. Our laboratory focuses on the secretory phenomena (i.e., transport of secretory vesicles in neurons and endocrine cells), the autophagic pathway (i.e., a catabolic cellular process), and the melanin transport in melanocytes and tries to identify "key molecules" responsible for these membrane trafficking events. The aim of our research is to elucidate the molecular mechanism of membrane traffic by use of molecular biology, cell biology, biochemistry, and molecular imaging techniques.

We have previously shown that an abundant synaptic vesicle protein synaptotagmin I (Syt I) regulates synaptic vesicle exocytosis (i.e., neurotransmitter release) and endocytosis in neurons (Fig. 1). Syt I consists of a single N-terminal transmembrane domain and C-terminal tandem C2 calcium/phospholipid-binding domains (named C2A domain and C2B domain). These two C2 domains are functional domains of Syt I, because functionally blocking antibody against the C2A domain (or the C2B domain) inhibited synaptic vesicle fusion step (or synaptic vesicle recycling step) (*Proc. Natl. Acad. Sci. USA* (2000) 97, 14715-14719; *Proc. Natl. Acad. Sci. USA* (2004) 101, 17855-17860).

We have recently identified novel synaptotagmin -related molecules that contain tandem C2 domains at the C terminus (named Slp, synaptotagmin-like protein) and their related protein Slac2 (Slp homologue lacking C2 domains). Both Slp and Slac2 contain the conserved domain (named SHD, Slp homology domain) at their N terminus, and we found that the SHD functions as an effector domain for small GTPase Rab27A, which is specifically present on melanosomes in mammalian skin melanocytes (*Structure* (2008) 16, 1478-1490). We further found that two Rab27A effectors, Slac2-a/melanophilin and Slp2-a, are abundantly expressed on melanosomes and sequentially regulate melanosome transport in melanocytes (*Nature Cell Biol*. (2004) 6, 1195-1203). Slac2-a simultaneously interacts with Rab27A on the melanosome and with an actin-based motor myosin Va, and the resultant tripartite protein complex (Rab27A・Slac2-a・myosin Va) mediates actin-based melanosome transport (*Mol. Cell. Biol.* (2003) 23, 5245-5255). After actin-dependent melanosome transport, the second Rab27A effector Slp2-a promotes the anchoring of melanosomes to the plasma membrane of melanocytes through direct interaction of the C2A domain with phosphatidylserine (PS) (Fig. 2).

In addition to melanosome transport, Rab27 has recently been shown to be involved in the transport of secretory vesicles in a wide variety of secretory cells, including neurons, endocrine cells, exocrine cells, and immune cells. For example, Rab27A regulates docking of hormone granules to the plasma membrane in neuroendocrine PC12 cells through interaction with rabphilin and Slp4-a/granuphilin-a (*J. Biol. Chem*. (2005) 280, 39253-39259; *Mol. Biol. Cell* (2006) 17, 2101-2112). Rab27 is also involved in the transport of recycled synaptic vesicles to the release site in the squid giant synapse (*Proc. Natl. Acad. Sci. USA* (2008) 105, 16003-16008).

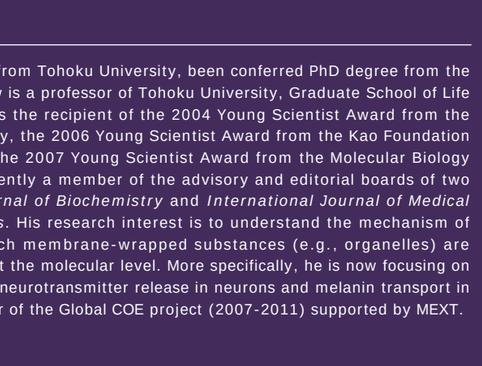


Fig. 1. Role of synaptotagmin I in synaptic vesicle transport in neurons (*Molecular Mechanisms of Exocytosis* (2006) pp. 42-61, Regazzi, R., ed., Landes Bioscience, Austin, TX).

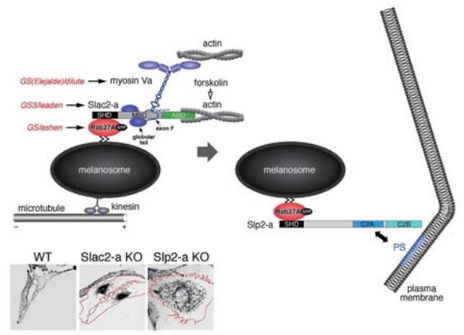


Fig. 2. Role of Rab27A and its effectors in melansome transport in melanocytes (*J. Biochem*. (2005) 137, 9-16).

Articles

1) Itoh, T., Fujita, N., Kanno, E., Yamamoto, A., Yoshimori, T. and Fukuda, M. Golgi-resident small GTPase Rab33B interacts with Atg16L and modulates autophagosome formation. *Mol. Biol. Cell*, 19, 2916-2925 (2008)
2) Yu, E., Kanno, E., Choi, S., Sugimori, M., Moreira, J.E., Llinás, R.R. and Fukuda, M. Role of Rab27 in synaptic transmission at the squid giant synapse. *Proc. Natl. Acad. Sci. USA*, 105, 16003-16008 (2008)
3) Tsuboi, T. and Fukuda, M. The Slp4-a linker domain controls exocytosis through interaction with Munc18-1・syntaxin-1a complex. *Mol. Biol. Cell*, 17, 2101-2112 (2006)
4) Kuroda, T.S. and Fukuda, M. Rab27A-binding protein Slp2-a is required for peripheral melanosome distribution and elongated cell shape in melanocytes. *Nature Cell Biol*, 6, 1195-1203 (2004)
5) Llinás, R.R., Sugimori, M., Moran, K.A., Moreira, J.E. and Fukuda, M. Vesicular reuptake inhibition by a synaptotagmin I C2B domain antibody at the squid giant synapse. *Proc. Natl. Acad. Sci. USA*, 101, 17855-17860 (2004)

Toshio Iijima

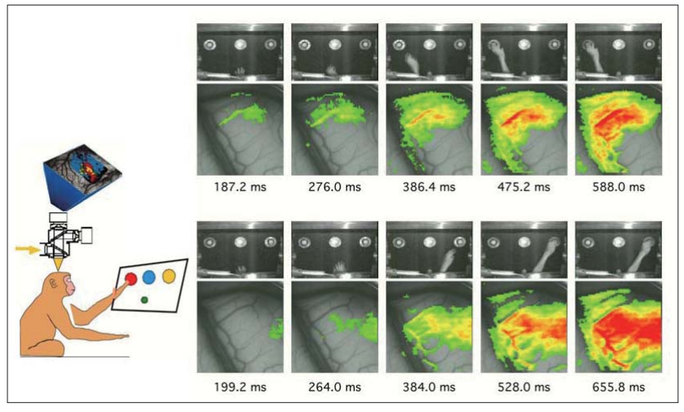
Global COE Deputy Director
Systems Neuroscience

Profile

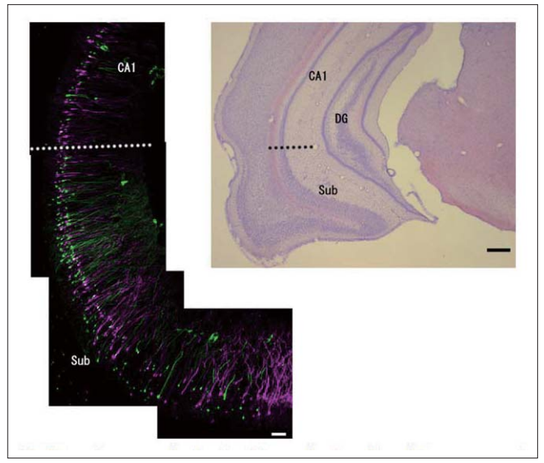
Graduated from the Doctorial Course in the Graduate School of Science, Tohoku University. Worked as Research Assistant Professor at the University of California Los Angeles, researcher at the Electrotechnical Laboratory, Ministry of International Trade and Industry (present National Institute of Advanced Industrial Science and Technology (AIST)), Manager of the Biofunction Research Office, Chief Research Officer, professor at the University of Tsukuba Medical Branch, etc. and became professor at Tohoku University Graduate School of Life Science. Vice-President of Tohoku University (Life Sciences and Research ethics), Dean of Tohoku University Graduate School of Life Sciences. Councilor of Tohoku University. Received the Hiroshi Irisawa Memorial JJP Award from the Physiological Society of Japan (1998), etc

Elucidation of functional architecture of the brain

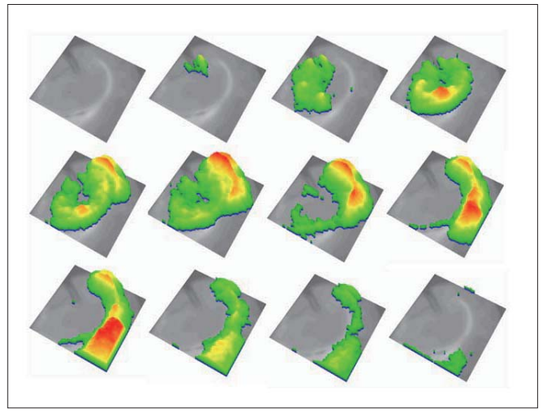
Understanding of our mind has long been a big subject of human beings. Recent advances of analytical technique for the brain mechanisms may allow us to answer the question “what is mind” in the near future, through the knowledge of the brain now being accumulated. On the way to the final goal, it seems to be essential for us to elucidate the functional architecture of the brain for the better understanding of the brain. Based on this concept, we are studying the neuronal bases of higher brain function, such as the learning and memory, the motor control and the processing of various sensory inputs. In addition, the developments of new technique with virus vectors and of the brain machine interface are now going on.



A high-speed real-time optical imaging of neural activity in the MI of monkey during target reaching hand movement



Studies of neuronal circuit with newly developed trans-synaptic tracing method using virus vectors



Propagation of neural activity in the entorhinal-hippocampal slice preparation visualized with a high-speed optical imaging

Articles

1) Ishikawa, T., Sato, T., Shimizu, A., Tsutsui, K., de Curtis, M., Iijima, T. Odor-driven activity in the olfactory cortex of an in vitro isolated Guinea pig whole brain with olfactory epithelium. *J. Neurophysiol*, 97, 670-679 (2007)
2) Kajiwara, R., Takashima, I., Witter, M.P., Mimura, Y., Iijima, T. Amygdala input promotes the spread of excitatory neural activity from the perirhinal cortex to the entorhinal/hippocampal neurocircuit: An optical imaging study. *J. Neurophysiol*, 89, 2176-2184 (2003)
3) Iijima, T., Witter, M.P., Ichikawa, M., Tominaga, T., Kajiwara, R., Matsumoto, G. Entorhinal-Hippocampal Interactions Revealed by Real-Time Imaging. *Science*, 272, 1069-1232 (1996)
4) Vranesic, I., Iijima, T., Ichikawa, M., Matsumoto, G., Knopfel, T. Signal transmission in the parallel fiber-Purkinje cell system visualized by high-resolution imaging. *Proc. Natl. Acad. Sci. USA*, 91, 13014-13017 (1994)
5) Iijima, T., Ciani, S., Hagiwara, S. Effect on the external pH on Ca Channels: Experimental studies and theoretical considerations using a two-site, two ion model. *Proc. Natl. Acad. Sci.USA*, 83, 654-658 (1987)

Hajime Mushiake

Group Leader
Neurophysiology

Profile

Prof. Mushiake has graduated Tohoku University School of medicine and received PhD from the same university. His career started as a research associate since Dr. Jun Tanji moved to Tohoku University in 1987. The main theme of his research was to understand functions of higher-ordered motor cortices including the supplementary motor area and premotor areas. For 1989-1993, he worked abroad as a postdoctoral fellow in the State University of New York in Syracuse under supervisory of Dr. Peter Strick and investigated functions of the basal ganglia and cerebellum. From 1993-1996, he worked as a researcher of PRESTO, sponsored by JST and started to investigate neural mechanisms underlying problem-solving behavior. Since 2005, he has been a professor of Department of Physiology of Tohoku University as a successor of Professor Tanji. Now his research interest covers neural mechanisms underlying voluntary actions and cognitive behavior. He also collaborates with engineering researchers in an interdisciplinary approach based of embodied cognitive science. He has recently published a textbook of motor learning and rehabilitations with Dr. Kubota and Dr.Miyai in Japanese: Brain and Learning

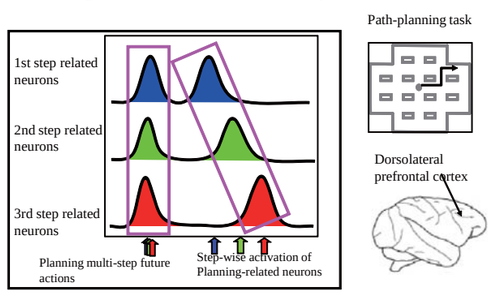
Neural mechanisms underlying problem solving

General scope of our study is to understand how the brain works in goal-directed behavior. Recent progress in cognitive science and system neuroscience has significantly altered concepts of how the brain works to achieve functional operations required for cognition, action, memory and emotion. The time is ripe for studying the integrative aspects of brain function in detail using analytical methods. In our department, we have been investigating how individual areas in the cerebral cortex take part in generating purposeful motor behavior. Our main interest is to investigate cellular mechanisms to construct spatial and temporal patterns of activity required to plan to solve various cognitive problems.

As a result of recent studies, it has been established that multiple areas exist in the cerebral cortex that are crucially involved in controlling motor behavior. Our goal is to clarify how individual areas take part in determining what motor act to select and prepare, and how to generate spatial and temporal motor patterns from the viewpoint of embodied cognitive science. According to this view, any organism, such as a human or animal, or even a robot, is considered an embodied agent that interacts with its environment. To achieve our goal, we employ physiological techniques such as analyzing the activity of single cells in motor task behavior in primates, pharmacological techniques to apply chemical substances in situ, or histological techniques.

Recent findings from our laboratory: 1. We have found similarities and differences in neuronal activity in the premotor cortex and supplementary motor area compared to that in the primary motor cortex, in relation to a variety of motor acts. 2. We have defined the presupplementary motor cortex (pre-SMA) using physiological criteria, and found differences in the activity properties of cells in the pre-SMA and the SMA.3. We found that the SMA and premotor cortex are involved differently in preparing and controlling sequential and continuous movements. 4. We found that neuronal activity in the SMA and pre-SMA are particularly useful for preparing multiple movements in a different order. We also found that the pre-SMA cells are particularly active in updating a new behavioral sequence. 5. We found that the cingulate motor area, mostly its rostral part, is crucially involved in selecting appropriate movements on the basis of reward evaluation. 6. We found that the rostral part of the cingulated motor area is involved in reward-based motor selection. 7. We have found physiological properties that characterize the supplementary eye field, in comparison with the frontal eye field. 8. We have found neuronal activity which reflect behavioral guidance by integrative function in the prefrontal cortex. 9. We found that cellular activity in the superior parietal lobule reflected the number of self-movement executions. 10. We have found neuronal activity, which reflect goal-setting, planning, in a problem-solving task in the prefrontal cortex. 11 We found that the prefrontal cortex in involved in planning multiple sequence of action based on action-category. 12 We found that discharge synchrony was transiently enhanced during the transition of behavioral goal representations of prefrontal neurons.

Planning and executive function in the prefrontal cortex



The prefrontal cortex is involved in planning multi-step future actions and executing planed actions.

Embodied cognitive science and neuroscience

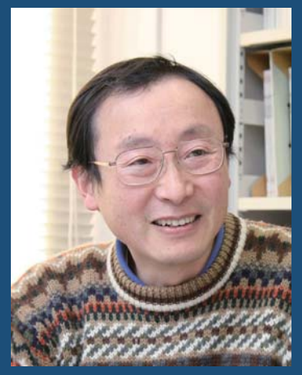
The frontal lobe is divided into several areas. We investigate its cognitive functions such as problem-solving, decision-making, and motor control from the view point of Embodied cognitive science using Neurophysiological approaches.

Articles

1) Shima K, Isoda M, Mushiake H, Tanji J. Categorization of behavioral sequences in the prefrontal cortex. *Nature*, 445:315-8 (2007)
2) Mushiake H, Saito N, Sakamoto K, Itoyama Y, Tanji J. Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. *Neuron*, 50:631-41 (2006)
3) Saito N, Mushiake H, Sakamoto K, Itoyama Y, and Tanji J. Representation of immediate and final behavioral goals in the monkey prefrontal cortex during an instructed delay period. *Cerebral Cortex*, 15:1535-46 (2005)
4) Shima K, Mushiake H, Saito N, Tanji J. Role for cells in the presupplementary motor area in updating motor plans. *Proc.Nctl. Acad.Sci.USA*, 93:8694-8698 (1996)
5) Mushiake H, Inase M, Tanji J. Neuronal activity in the primate premotor, supplementary and precentral motor cortex during visually guided and internally determined sequential movements. *J. Neurophysiol*, 66:705-718 (1991)

Hiromu Yawo

Neuron Network



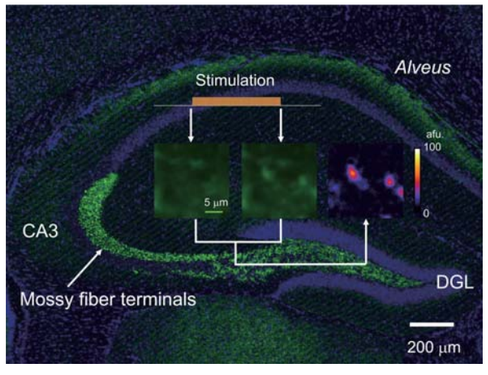
Profile

Dr. Hiromu Yawo graduated Kyoto University Graduate School of Medicine in 1981, being given PhD under the thesis “How a nerve fiber repairs its cut end: involvement of phospholipase A2.” He thereafter collaborated with Prof. Motoy Kuno in Kyoto University as an instructor of physiology. In 1985 he received an award from the Center for Cellular and Molecular Neurobiology in Washington University School of Medicine in St. Louis, USA (McDonnell Research Fellowship). Under collaboration with Prof. Dale Purves he started studies on the neuronal network plasticity. In 1995 he became a professor of Tohoku University School of Medicine. He has been a professor of Tohoku University Graduate School of Life Sciences since 2001. He organized a research team investigating “Presynaptic mechanisms of learning and memory” as a Director of the Program of Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency (JST) from 1999 to 2005. His major aim of research is to understand the molecular and cellular mechanisms underlying the neuronal network plasticity.

From neuron to network - Shedding light in the black box

The brain consists of many types of neurons which make a complex network. This idea was first proposed by Ramon y Cajal more than 100 years ago. However, it is still unresolved how the network activities are integrated into the brain’ s function, the mind. Using genetic engineering techniques we have developed new optical recording methods which visualizes the network activities (Araki et al. 2005). We plan to manipulate activities of individual neurons by light as well as to record them optically, and to reveal how they are integrated in the network. The neuronal network is also dynamically regulated by its environment as well as by its activity itself. We will investigate the cellular and molecular mechanisms regulating the network dynamics.

In the neuronal network of the central nervous system (CNS) the synaptic transmission is regulated by the vesicle exocytosis and endocytosis. This vesicular dynamics is associated with the changes of intra-vesicular pH and can be visualized by the fluorescence of synaptopHluorin (SpH), a pH-sensitive GFP fused to the lumenal aspect of VAMP-2. We have generated several SpH transgenic mouse lines in which the SpH expression is regulated by the neuron specific Thy-1.2 promoter or Cre/loxP recombination system. In one of them SpH was specifically expressed in the mossy fiber (MF) terminals of the hippocampus. Recently we found that there are distinct two vesicle pools, the resting pool which is resistant to exocytosis, and the releasable pool and that the fidelity of synaptic transmission is ensured by the rapid supply from the reserve subpopulation of releasable pool (Suyama et al. 2007).

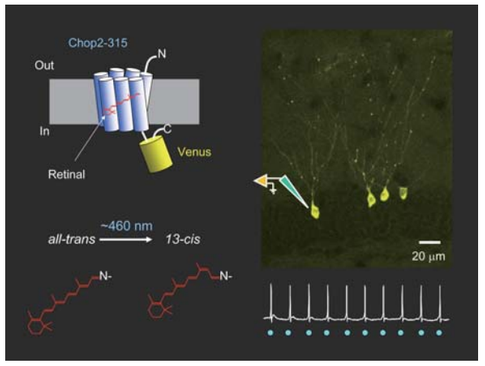


Optical analysis of synaptic acitivities using synaptopHluorin
We have generated a transgenic mouse which express synaptopHluorin (SpH, green), a optical probe reporting vesicular dynamics, selectively in the mossy fiber terminals of the hippocampus. Neurons are also stained their nuclei (DAPI, blue). The repetitive stimulation of mossy fiber axons increases the SpH fluorescence in the individual presynaptic terminals (insets left and middle). This change is shown in the difference image (inset right, pseudocolor ratings).

During phototaxic and photophobic movements of unicellular green algae, light is perceived by archaeal-type rhodopsins which are localized in small regions of the plasma membrane, called eyespots. Two rhodopsins were isolated from *Chlamydomonas reinhardii*, channelrhodopsin (ChR) 1 and 2. ChR2 has a peak light absorbance at 460 nm and forms a non-selective cation channel, the gating of which is triggered by the photoisomerization of the all-trans retinal to 13-cis configuration. We expressed ChR2 exogenously in the hippocampal neurons of a living mouse (Ishizuka et al. 2006). A brief illumination by a blue LED light depolarized these neurons over threshold to evoke action potential which is phase-locked with the light pulses.

With its high resolution in space and time, its large dynamic range and its convenience this photostimulation method would fulfill all the requirements for artificial stimulation of neurons, namely generality, speed, localization and parallelism. Since ChR2 is relatively small and encoded in a single gene, it could be expressed in a specific subset of neurons under regulations of cell-type-specific promoters. It would, thus, open many potential applications, for both in vitro and in vivo studies of neuronal network, artificial manipulations of neuronal activity for the development of informational modules and possibly the development of non-invasive therapeutic instruments of bypassing interrupted neuronal connections.

Retinitis pigmentosa (RP) refers to a group of diseases in which a gene mutation results in death of rod photoreceptors followed by gradual death of cones. Approximately 1 in 4,000 people are affected by this disease. Symptoms include night blindness, loss of the peripheral visual field and of central vision. Although photoreceptor cells are almost degenerated in the eyes of RP patients, other retinal neurons including retinal ganglion cells (RGC) are preserved. These remaining neurons are possibly made photosensitive by genetically engineering to express ChR2. When ChR2 was expressed in the retina of the aged Royal College of Surgeons (RCS) rat, one of classic model animals of recessively inherited RP, some of visual responses were shown to be restored (Tomita et al. 2007). It is thus suggested that the ChR2 transduction method would provide a new strategy to treat some RP symptoms.



Photostimulation of neurons
Top, left: The hypothetical structure of channelrhodopsin 2 (ChR2, 1-315) which is tagged with Venus, one of GFP derivatives, at its C-terminus.
Bottom, left: ChR2 has a peak light absorbance at 460 nm and forms a non-selective cation channel, the gating of which is triggered by the photoisomerization of the all-trans retinal to 13-cis configuration.
Top, right: The dentate granule cells expressing ChR2-Venus in the hippocampus of a living mouse.
Bottom, right: Induction of patterned action potentials by blue LED light pulses (blue circles).

Articles

1) Wang, H., Sugiyama, Y., Hikima, T., Sugano, E., Tomita, H., Takahashi, T., Ishizuka, T., Yawo, H. Molecular determinants differentiating photocurrent properties of two channelrhodopsins from *Chlamydomonas*. *J Biol Chem*. (in press) (2009)
2) Suyama, S., Hikima, T., Sakagami, H., Ishizuka, T., Yawo, H. Synaptic vesicle dynamics in the mossy fiber-CA3 presynaptic terminals of mouse hippocampus. *Neuroscience Research*, 59, 481-490 (2007)
3) Tomita, H., Sugano, E., Yawo, H., Ishizuka, T., Isago, H., Narikawa, S., Kügler, S., Tamai, M. Visual responses in aged dystrophic RCS rats were restored by AAV-mediated channelopsin-2 gene transfer. *Invest Ophthalmol Vis Sci*, 48, 3821-3826 (2007)
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5) Kamada, M., Li, R.-Y., Hashimoto, M., Kakuda, M., Okada, H., Koyanagi, Y., Ishizuka, T., Yawo, H. Intrinsic and spontaneous neurogenesis in the postnatal slice culture of rat hippocampus. *European Journal of Neuroscience*, 20, 2499-2508 (2004)

Akio Ishiguro

System Engineering

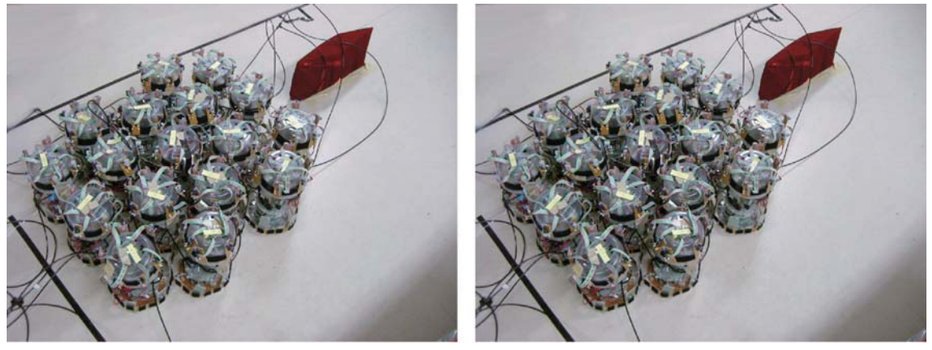
Profile

Prof. Ishiguro has received PhD degree from Nagoya University in 1991. From 1991 to 1997, he was with Nagoya University as an assistant professor. From May 1997 to 2006, he was an associate professor of the same university. In 1997, he was a visiting professor at artificial intelligent laboratory (Prof. Rolf Pfeifer) in University of Zurich, Switzerland. Since April 2006, he has been a professor of the Graduate School of Engineering, Tohoku University. His research interests are in embodied artificial intelligence, autonomous decentralized control, nonlinear science, robotics, and biophysics. He received 2004 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS2004) Best Paper Award.

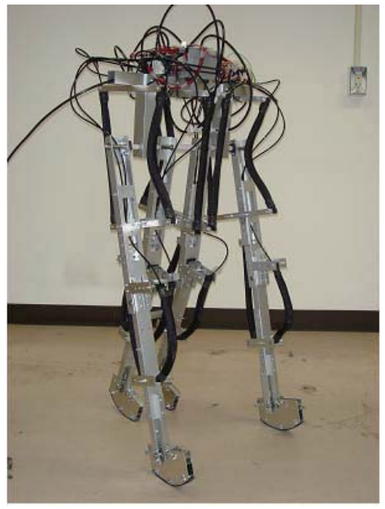
Intelligence emerged through the interaction between brain, body and environment
- Synthetic approach with building robotic agents -

The behavior of an embodied agent emerges through the interplay between its brain (i.e. control system), body (i.e. mechanical system), and the environment. Considering the fact that the brain and body, which are normally the targets to be designed for robotic agents, are positioned at the source of this interaction, they should be treated with an equal emphasis. However, despite their tight interdependency, these two systems have been investigated in isolation so far. In light of these facts, we have been investigating the brain-body interaction. More specifically, our interests are summarized as twofold: 1) how the brain and its body should be coupled so as to emerge useful functionalities such as adaptivity?; and 2) to what extent the brain should be responsible for the generation of behavior? In order to investigate the above, we employ a synthetic approach with the use of robots, i.e. understanding by building robotic agents. The research topics currently underway are as follows:

- A modular robot that exhibit amoeboid locomotion
- Self-assembly inspired from the biological developmental process
- Self-repair
- Adaptive control of bipedal locomotion
- A biped robot that enables stable and adaptive running
- Seamless transition between walking and running



Prototype of a modular robot developed.
Left: the initial state.
Right: negotiating the obstacle by dynamically deforming the morphology.



A walking robot developed for understanding the mechanism of adaptive motion control.

Articles

1) D. Owaki and A. Ishiguro, Mechanical Dynamics That Enables Stable Passive Dynamic Bipedal Running, *Journal of Robotics and Mechatronics*, Vol.19, No.4, pp.374-380 (2007)
2) A. Ishiguro, M. Shimizu, and T. Kawakatsu, A Modular Robot That Exhibits Amoebic Locomotion, *Robotics and Autonomous Systems*, Vol.54, pp.641-650 (2006)
3) S. Tokura, A. Ishiguro, T. Kawashima, and S. Okuma, Hardware Implementation of Neuromodulated Neural Network for a CPU-less Autonomous Mobile Robot, *Advanced Robotics*, Vol.20, No.12, pp.1341-1358 (2006)
4) M. Shimizu, A. Ishiguro, M. Takahashi, T. Kawakatsu, Y. Masubuchi, and M. Doi, Adaptive Shape Reconfiguration of a Decentralized Motile System Exploiting Molecular Dynamics and Stokesian Dynamics Methods, *Journal of Robotics and Mechatronics*, Vol.16, No.3, pp.271-277 (2004)
5) A. Ishiguro, A. Fujii, and P. Eggenberger Hotz, Neuromodulated Control of Bipedal Locomotion Using a Polymorphic CPG Circuit, *Journal of Adaptive Behavior*, Vol.11, No.1, pp.7-17 (2003)

Ken-ichiro Tsutsui

Cognitive/Behavioral Neuroscience

Profile

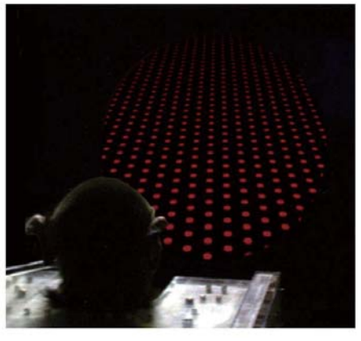
Assoc. Prof. Ken-Ichiro Tsutsui graduated, and received his Ph.D. in Experimental Psychology, from the University of Tokyo. Since then he has been studying the neural mechanisms of higher cognitive functions, first as a JSPS Fellow in the Department of Physiology, Nihon University School of Medicine, next as a Research Associate in the Department of Anatomy, University of Cambridge, and presently as an Associate Professor in the Tohoku University Graduate School of Life Sciences. He was awarded the Japan Neuroscience Society Young Investigator Award in 2003 for his series of studies on the neural mechanisms of three-dimensional vision. He uses theories and concepts in behavioral and cognitive psychology with electrophysiological, neurochemical, and neuroimaging techniques, in order to investigate the neural mechanisms of higher cognitive functions. His current research interests cover parietal-prefrontal interactions for 3D vision and mental image manipulation, prefrontal-inferotemporal interactions for categorization and inference, and prefrontal-limbic-striatal interactions for reward processing and decision-making.

Neural basis of higher cognitive function

We are interested in the neural background of various cognitive functions. We combine behavioral, electrophysiological, and neuroimaging techniques in order to investigate the relations between behavior and neural activity at the level of single neurons and individual brain regions. Our research interest covers wide range of cognitive processes, such as:

1. Three-dimensional vision (parietal association cortex)
2. Categorical reasoning, decision making (prefrontal cortex)
3. Reward representation, incentive learning, neuroeconomics (cortex - basal ganglia - brainstem interactions)

A certain cognitive function cannot be attributed to a specific brain structure. Rather than that, harmonic interactions of various brain structures are necessary for any cognitive function. In order to thoroughly understand the neural background of a cognitive function, it is very important to investigate this dynamic process taking place in the brain. The basic strategy of our research is to first develop a suitable behavioral task to examine the target cognitive function, and then to perform electrophysiological recordings in various brain regions using primates and/or rodents as subjects. By comparing the properties of the neuronal activity recorded in different brain regions, we can build up a model of neural circuit connecting within and between multiple brain regions underlying the cognitive function. The results obtained by the electrophysiological recordings can be confirmed in humans at the level of brain regions by neuroimaging experiments using the same behavioral task.



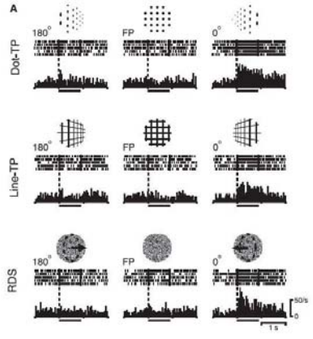


Fig.1
A monkey looking at a three-dimensional visual stimulus (left) and the activity of a 3D surface orientation selective neuron in the parietal area CIP (right) (from Tsutsui et al., *Science* 2002)

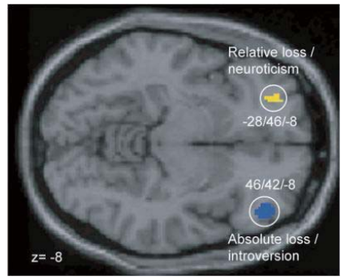


Fig.2
Activations of lateral orbitofrontal cortex for financial loss correlated with personality factors (introversion/neurotilism). (Fujiwara et al., *Eur J Neurosci* (2008))

Articles

1) Fujiwara J, Tobler, PN, Taira M, Iijima T, Tsutsui KI. Personality-dependent dissociation of absolute and relative loss processing in orbitofrontal cortex. *European Journal of neuroscience*, 27, 1547-52 (2008)
2) Tsutsui KI, Taira M, Sakata H. Neural mechanisms of three-dimensional vision. *Neuroscience Research*, 51, 221-229 (2005)
3) Tsutsui KI, Jiang M, Sakata H, Taira M. Short-term memory and perceptual decision for three-dimensional visual features in the caudal intraparietal sulcus (Area CIP). *Journal of Neuroscience*, 23, 5486-5495 (2003)
4) Tsutsui KI, Sakata H, Naganuma T, Taira M. Neural correlates for perception of 3D surface orientation from texture gradient. *Science*, 298, 409-412 (2002)
5) Tsutsui KI, Jiang M, Yara K, Sakata H, Taira M. Integration of perspective and disparity cues in surface-orientation-selective neurons of area CIP. *Journal of Neurophysiology*, 86, 2856-2867 (2001)

Etsuro Mori

Group Leader
Behavioral Neurology/Cognitive Neuroscience

Profile

Dr. Mori received his M.D. and Ph.D. from Kobe University School of Medicine and has been a professor of Tohoku University Graduate School of Medicine since 2003. He completed an internship, residency, and fellowship in neurology at Kobe University Hospital and Hyogo Brain and Heart Center at Himeji. He has done research on stroke at the Department of Molecular and Experimental Medicine at Scripps Clinic and Research Foundation (La Jolla, CA, USA), and on dementia at Hyogo Institute for Aging Brain and Cognitive Disorders. He has broad interests in stroke, dementing disorders, behavioral neurology, and the interface of neuroscience and society, and has written 450 articles, and chapters on stroke, dementia or behavioral neurology. He serves on the Executive Committees of the Japan Stroke Society, Japan Neuropsychological Association, Japan Society for Higher Brain Dysfunction, and the Japan Neuropsychyatric Association. He has participated in numerous clinical trials in acute ischemic stroke. He was a co-principal investigator or a member of the Executive/Steering Committee for JET, MELT, J-ACT, J-ACT II, SINPHONI, and J-COSMIC. In addition, he is on the editorial board of various prominent journals, including Cerebrovascular Disorders and Journal of Neuroimaging.

Behavioral Neurology and Cognitive Neuroscience

Department of Behavioral Neurology and Cognitive Neuroscience was founded in 1994 as a part of Division of Disability Science, Tohoku University Graduate School of Medicine. We also have a responsibility for the clinic of the Tohoku University Hospital. Our section have graduate programs for medical students and postgraduate programs for graduate students from various areas including neuroscience, psychology, rehabilitation sciences, and education, and provides unique opportunities to study and research functions of the brain and mind and its relation.

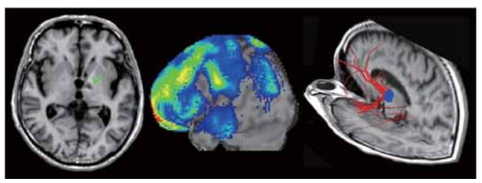
Core Research Interest

1. Clinical neuropsychology

Our clinical studies covers wide range of neuropsychological and behavioral neurological themes including emotion, attention, memory, language, praxis, visuospatial function, frontal lobe functions, and dementia. Aims of our clinical studies are; to clarify the level of dysfunction that each patient shows using detailed neurological and neuropsychological examinations tailored for the individual, to examine localization and severity of brain damage by neuroimaging techniques such as MRI, PET and SPECT, and to understand neuronal mechanisms underlying each higher cerebral function. Furthermore we devise methods for treatment for each patient using those findings. We have published important findings concerning brain-mind relation and its disorder in leading journals.

2. Neuroimaging studies

In addition to clinical studies mentioned above, functional neuroimagings such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) enable us to measure brain activity associated with various cognitive functions in humans. The joint complementary use of neuroimaging and neuropsychology offers a fundamental advantage over either technique in isolation. Research interests were focused so far on memory processes and executive functions, but are now expanding into other basic cognitive domains, activation study in brain damaged, and pharmacological fMRI.



1. Lesion-circuit disruption-cortical hypoperfusion-dysfunction relationship.

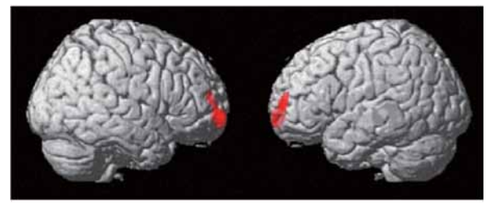
A clinico-anatomical study was carried out in a patient with an infarct in the genu of the internal capsule (→) causing semantic memory deficits and behavioral derangement. A SPECT revealed decreased cerebral blood flow in the frontal and anterior lobes, a stereotaxic MRI tractgraph demonstrated the anterior and inferior thalamic peduncles from the capsular genu to the frontal and anterior temporal cortices.

3. Research on neurobehavioral aspects of neurological diseases

Studies focusing on cognitive and behavioral problems in patients with various neurological diseases and brain injury elucidated neuronal basis and solutions of the problems. Structural and functional brain imagings figured out the neural basis of the deficits of memory, language, and executive functions and behavioral symptoms in dementing illnesses (e.g., Alzheimer' s disease, frontotemporal lober degeneration, idiopathic normal pressure hydrocephalus), neurological diseases (e.g., Parkinson' s disease), and neurodevelopmental disorders (e.g., Prader-Willi syndrome).

4. Neuro-nosometrics and clinical trial for neurological and cognitive disorders

It is increasingly important to measure cognitive and behavioral dysfunctions after emerging the concepts of evidence-based medicine and translational research. Study on measures of cognitive and behavioral dysfunctions as well as sensori-motor deficits caused by brain damage (neuro-nosometrics) is an important research field, which we are centrally involved in. Neuro-nosometrics covers not only evaluation of neuronal dysfunctions but also detection of possible effects of an intervention. We are now engaged in several nation-wide cooperative clinical trials for stroke and Alzheimer's disease as core investigators for study design and analysis of clinical outcome. Furthermore, we are organizing a new physician-leading clinical trial of a compound for patients with aphasia.



2. Patients with Parkinson' s disease have difficulty telling lies due to dysfunction of the prefrontal cortices.

It has been believed that patients with Parkinson' s disease have characteristic personal traits including seriousness and honesty. Patients with Parkinson' disease have difficulty making deceptive responses on an experimental deception task compared with healthy people. The patients' task performance was correlated with the glucose hypometbolism in the prefrontal cortices measured by 18F-fluorodeoxyglucose PET.

Articles

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2) Abe N, Suzuki M, Mori E, Itoh M, Fujii T. Deceiving others: distinct neural responses of the prefrontal cortex and amygdala in simple fabrication and deception with social interactions. *J Cogn Neurosci*, 2007 Feb;19(2):287-95.

3) Nishio Y, Kazui H, Hashimoto M, Shimizu K, Onouchi K, Mochio S, Suzuki K, Mori E. Actions anchored by concepts: defective action comprehension in semantic dementia. *J Neurol Neurosurg Psychiatry*, 2006 Dec;77(12):1313-7.

4) Abe N, Suzuki M, Tsukiura T, Mori E, Yamaguchi K, Itoh M, Fujii T. Dissociable roles of prefrontal and anterior cingulate cortices in deception. *Cereb Cortex*, 2006 Feb;16(2):192-9.

5) Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, Mori E. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? *Am J Psychiatry*, 2005 Apr;162(4):676-82.

Ichiro Sora

Biological Psychiatry

Profile

Ichiro Sora, M.D., Ph.D. is Professor and Chairperson, Department of Biological Psychiatry, Tohoku University Graduate School of Medicine since 2002. Dr. Sora is also guest researcher at National Institute on Drug abuse, USA since 1999. He provides government service as members of advisory committees such as regulation of addictive drug, pharmaceutical and medical safety since 2006. Dr. Sora is trained as a psychiatrist (MD, 1982, PhD, 1986 Okayama University Medical School). His current research examines issues in molecular neurobiology of mental disorders. Dr. Sora is principle investigator of the major study of drug abuse, schizophrenia and attention deficit hyperactive disorder, funded by government grants from MHLW and MEXT.

Molecular Neurobiology of Mental Disorders

It is very useful to develop animal models of neuropsychiatric disorder, which are able to investigate pathophysiology, responsability to medication, and various symptoms of neuropsychiatiric disorder, although there are no sufficient animal models to reflect overall symptoms of psychiatric patients. Recently molecular genetic method, which targets specific genes of mice and delete them, has been established. We introduce here usefulness and recent acknowledgement of these knockout mice as animal models of neuropsychiatric disorder.Monoamine neurotransmission is affected by antipsychotics or antidepressants, so it is said to play a crucial role in pathophysiology of neuropsychiatric disorders. Dopamine transporter(DAT), serotonin transporter(SERT), and norepinephrine transporter are located on plasma membrane of pre-synaptic region. They rapidly reuptake extracellular monoamine and regulate the neurotransmission.

Drugs of abuse are able to elicit compulsive drug-seeking behaviors upon repeated administration, which ultimately leads to the phenomenon of addiction. Evidence indicates that the susceptibility to develop addiction is influenced by sources of reinforcement, variable neuroadaptive mechanisms, and neurochemical changes that together lead to altered homeostasis of the brain reward system. Addiction is hypothesized to be a cycle of progressive dysregulation of the brain reward system that results in the compulsive use and loss of control over drug taking and the initiation of behaviors associated with drug seeking. Cocaine, amphetamine, and many other psychostimulants are believed to produce their stimulating and addictive effects mainly by increasing the extracellular levels of dopamine in the brain reward areas through the interaction with DAT. Mice lacking DAT are hyperactive and psychostimulants do not increase further their locomotor activity. However, these mice still self-administer cocaine, as well as show conditioned place preference for cocaine, indicating that the drug's rewarding effects are not abolished. These data showed that although both DAT and SERT participate in cocaine's reward, DAT has more important role in this drug's effect. Studies in monoamine transporter knockout mice paint a picture of considerable complexity in the actions of cocaine.

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous neuropsychiatric syndrome of inattention, hyperactivity, and impulsivity, typically of juvenile onset. We've engineered the dopamine transporter knockout(DAT-KO) mice, which exhibit spontaneous behavioral hyperactivity compared to wild-type mice. Hyperactivity in DAT-KO mice is associated with high extracellular DA concentration because of lacking DA uptake by DAT. Recently, an association between polymorphisms in the noncoding regions of the human DAT and ADHD has been suggested. So DAT-KO mice has a possibility of animal model of ADHD. Treatment for ADHD has involved the use of psychostimulants that paradoxically serve to attenuate the hyperactivity and often improve cognitive performance. DAT-KO mice also showed a decrease in locomotion in response to amphetamine, methylphenidate, and cooaine. Despite the similarities between DAT-KO mice and ADHD, their phenotypes are not completely identical. It is not appropriate to explain the pathogenesis of ADHD with only monoamine transporters, other parameters that underlie the hyperactivity should be evaluated.

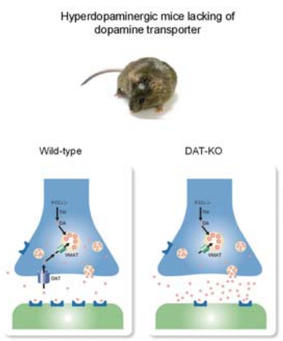

Figure 1.
The dopamine transporter (DAT) functions to limit extracellular dopamine through reuptake of released dopamine. In mutant mice lacking the DAT, extracellular dopamine levels are persistently elevated, which induces hyperdopaminergic neurotransmission.

Exposure to drugs of abuse, such as amphetamine cause experience-dependent change in their behavioral effects. One example is 'behavioral sensitization', a process in which repeated intermittent administration of drugs causes increased responsiveness to their stimulant and rewarding effects. Repeated administration of the drug leads to increasing locomotor activity and stereotyped behavior in animal. Sensitization is a model of neural plasticity within which drug-induced changes in complex behavior can be linked to drug-induced changes in molecular processes.

Schizophrenia is one of the major psychiatric disorders, which shows psychotic symptoms of hallucination, delusion, and blunted affection. As most of antipsychotics for treatment of schizophrenia have potency as dopamine antagonists, "dopamine hypothesis" is well known to explain pathophysiology of schizophrenia. Prepulse inhibition (PPI) is reported to be disrupted and be one of the physiological characteristics in schizophrenics. PPI is a phenomenon in which the startle response is reduced when the startle stimulus is preceded by a low-intensity prepulse. Disruption in PPI is suggested to reflect the abnormality of sensorimotor gating. Recently PPI paradigm has been used as one of the measurements in developed animal models of schizophrenia. For example, drug treatment of direct and indirect dopamine agonists or DATKO mice, which significantly increases dopaminergic neurotransmission, is disrupted in PPI.

Opiate analgesics are widely used and abused drugs. Individual differences in opiate sensitivity can hamper effective pain treatments and increase risks of drug abuse. Although genetic factors might affect individual differences in opiate sensitivity, scientific evidence for specific genetic mechanisms that underlie these differences has been sparse. Recent studies using inbred and knockout mice have revealed that the mu opioid receptor (MOR) gene has a mandatory role in the analgesic and addictive properties of opiate drugs. More than 100 polymorphisms have been identified in the human MOR gene, some of which are related to vulnerability to drug dependence in some populations. Rapid advances in this research field are leading to improved understanding of the relationships between gene polymorphisms and opiate sensitivities that will enable more-accurate prediction of the opiate sensitivity and opiate requirements in individual patients.

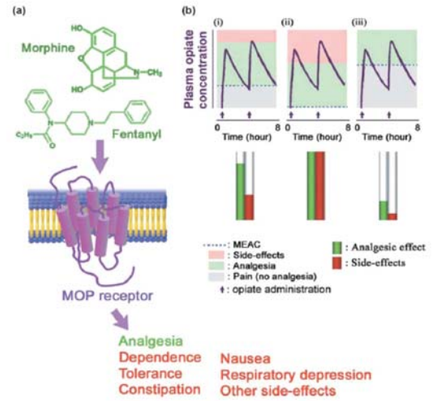

Figure 2.
(a) Opiate analgesics, such as morphine and fentanyl, act mainly on mu opioid receptor (MOR) and induce analgesia together with adverse side-effects such as dependence, tolerance, constipation, nausea and respiratory depression. (b) Opiate sensitivity differs among individuals at least partly because of the differences in the MOR gene. Although the plasma opiate concentration after its administration (arrows) changes in the same manner in different patients (i-iii), the clinical response can differ between patients because of 5-10-fold inter-patient differences in the minimal effective analgesic concentration (MEAC) (dashed blue line).

Articles

1) Uhl GR, Drgon T, Liu QR, Johnson C, Walther D, Ujike H, Komiyama T, Harano M, Sekine Y , Inada T, Ozaki N, Iyo M, Iwata N , Yamada M, Sora I, Chen CK, Liu HC, Lin SK. Genome-wide association for methamphetamine dependence: convergent results from two samples. *Arch Gen Psychiatry*, 65(3):345-355 (2008)

2) Fukushima S, Shen H, Hata H, Ohara A, Ohmi K, Ikeda K, Numachi Y, Kobayashi H, Hall FS, Uhl GR, Sora I. Methamphetamine-induced locomotor activity and sensitization in dopamine transporter and vesicular monoamine transporter 2 double mutant mice. *Psychopharmacology*, 193(1):55-62 (2007)

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5) Sora I, Hall FS, Andrews AM, Itokawa M, Li XF, Wei HB, Wichems C, Lesch KP, Murphy DL, Uhl GR. Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *Proc Natl Acad Sci USA*, 98: 5300-5305 (2001)

Shin Fukudo

Psychosomatic Medicine

Profile

Professor Fukudo graduated Tohoku University School of Medicine (MD) and was given PhD degree from the same university. He is a professor and director of Behavioral Medicine, Tohoku University since 1999 and has been recognized as one of the distinguished researchers of stress-related disorders and brain-gut interactions. His achievements include earlier conceptualization of disorders of brain-gut interactions and identifying key molecules of interoception. He uses many modalities to measure both the brain and the gut including positron emission tomography, functional magnetic resonance imaging, evoked potential, electroencephalogram, gastrointestinal manometry, barostat, electrical stimulation of the gut, and testing of autonomic function. He searches genes that regulate brain-gut function. He also developed several animal models of disordered brain-gut interactions. He is one of members of international Rome III committee for functional gastrointestinal disorders. He is known as a recipient of the Early Career Award of the American Psychosomatic Society in 1994 and Prize for Science and Technology, Research Category, the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science, and Technology of Japan in 2006.

Research on stress and brain—Gut interactions

The great social benefit is expected if we can clarify the pathophysiology of stress-related disorders and coping program against it with brain science. The mission of the Department of Behavioral Medicine is to promote basic and clinical research on the relationships among health, illness, and behavior. Our research targets at any diseases that are influenced by psychosocial stress but mainly focuses on physiology of stress and pathophysiology of stress-related disorders.

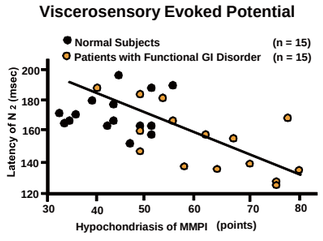
Mind is results of brain function and development of the brain needs the peripheral organs both in the individual aspects and in the evolutional aspects. All environmental information is input to the peripheral organs at first, conducted to the brain as the sensory signal, and processed in the brain. The perception and emotion arise during this process. Emotion consists of changes in the function of the peripheral organs via autonomic nervous system and endocrine as well as subjective feeling. Feedback or feedforward processing among the specific brain structures and between the brain and the peripheri forms further emotion. This response is considered to be partially determined with genes and epigenetic factors including combination and/or magnitude of the stimuli, developmental process, influence of pathogen, and so on. Individuals cope with environmental changes by behavior. The magnitude of the response is regulated in the normal range as the healthy condition. Deviated response out of the normal range is manifested as the stress-related disorder.

This concept is well applicable to irritable bowel syndrome (IBS), one of disorders of brain-gut interactions, as . We found stress-induced exaggeration of gastrointestinal motility and correlation between reduced alpha-power percentage in elecroencephalogram and indices of gastrointestinal motility under stress. Fear conditioning by combination of the sound and electrical stimulation induced fine movements of the colon simultaneously with increased regional cerebral blood flow in the anterior cingulate cortex, insula, and prefrontal cortex using positron emission tomography (PET). Conversely, the thalamus, anterior cingulate cortex, insula, and prefrontal cortex were activated by stimulation of the colon. Therefore, perception signal from the visceral organ or psychosocial stressor activates the common limbic and paralimbic structures. Interestingly, patients with IBS show aberrant regional activation of the brain in response to the visceral stimulation. We tried to modify the visceral perception as the bottom-up processing with the top-down processing of the brain and succeeded to prove it using viscerosensory evoked potential and PET imaging. Subjective sensation and feeling were modified as well.

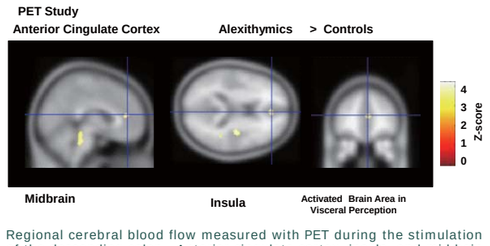
What kinds of substance regulate the brain-gut interactions is also one of the main interests of our group. We performed gene analysis and found that polymorphism of the serotonin transporter gene at least in part regulated negative emotion. Moreover, differential brain response was detected depending on the polymorphism of the serotonin transporter gene. Administration of corticotropin-releasing hormone (CRH) to IBS patients induces exaggerated secretion of adrenocorticotropic hormone and exaggerated motility of the colon. Administration of CRH antagonist improves exaggerated motility of the colon, visceral perception, anxiety, reduced alpha-power percentage in elecroencephalogram, and PET imaging in IBS patients. Increased input of the signal to the colon made rats have exaggerated colonic motility, increase noradrenaline release in the hippocampus, and be anxious. In this animal model of IBS, CRH antagonist was effective to alleviate the pathophysiology.

We are also exploring psychological trauma, maternal deprivation, alexithymia, mucosal sensitization, and histamine H1 receptor distribution on the pathophysiology of the stress-related disorders like eating disorders. Moreover, we are developing applicable program for clinical practice; psychotherapy including cognitive behavioral therapy, hypnotherapy, etc, based on the evidence. We plan to proceed to further clarification of the pathophysiology of stress-related disorders, finding way of regulation of key molecule of stress response, and developing coping program against it with brain science.

Figure 1. Brain-Gut Interactions-1

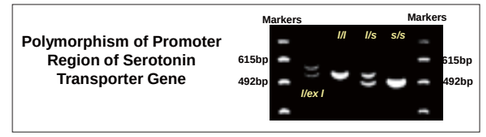


Viscerosensory evoked potential (VSEP) by summation of electroencephalogram under the electrical stimulation of the esophagus. Late component of VSEP N2 in FGID patients showed shorter than that in controls. N2 negatively correlated with somatization (Kanazawa M, et al. *JAMA* 286: 1974-5, 2001).

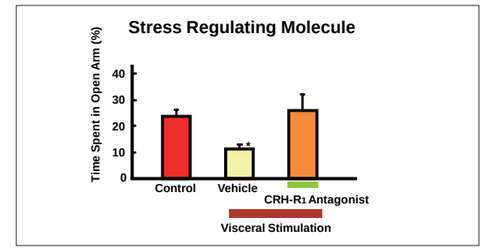


Regional cerebral blood flow measured with PET during the stimulation of the descending colon. Anterior cingulate cortex, insula, and mid bain were more activated in alexithymic subjects than in non-alexithymic subjects (Kano M et al., *Pain* 132: 252-63,2007).

Figure 2. Brain-Gut Interactions-2



Analysis of serotonin transporter gene polymorphism. Electrophoresis showed bands *of I/extra-I, I/I, I/s, and s/s.* This polymorphism relates to the negative emotion of stress-related disorders including IBS patients (Mizuno T, et al. *J Psychosom Res* 60: 91-7, 2006).



Corticotropin-releasig hormone (CRH) is a brain-gut peptide derived from the paraventricular nucleus of the hypothalamus. Stimulation of the colon makes rats less spent time in the open arm of the elevate plus maze, indicating anxiety-like behaviors, compared with controls. Administration of specific CRH-R1 antagonist reverses visceral stimulation-dericed anxiety (Saito K, et al. *Gastroenterology* 129: 1533-43, 2005).

Histamine H1 receptor binding in the brain measured with 11C-doxepin-PET. Control women showed more H1 receptor binding than control men. Patients with anorexia nervosa had increased H1 receptor binding in the amygdala (Yoshizawa M et al. *Biol Psychiatry* Sep 22, 2008 [Epub]).

Articles

1) Yoshizawa M, Tashiro M, Fukudo S, Yanai K, Utsumi A, Kano M, Karahasi M, Endo Y, Morisita J, Sato Y, Adachi M, Itoh M, Hongo M. Increased brain histamine H1 receptor binding in patients with anorexia nervosa. *Biol Psychiatry*, (2008) Sep 22 [Epub ahead of print]

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Masashi Aoki

Neurology

Profile

Dr. Aoki graduated Tohoku University School of Medicine (MD) and was given PhD degree from the same university. For 1996-1998, he worked abroad as a postdoctoral fellow and Instructor in Neurology in Massachusetts General Hospital under supervisory of Dr. Robert H Brown Jr. and investigated the genetics for amyotrophic lateral sclerosis and muscular dystrophy. He has been recognized as one of the distinguished researchers of neurological disorders. He is known as a recipient of ALS Foundation, Japan ALS Association in 1995, the Nakabayashi Trust for ALS Research in 1999 and the award from Japan Intractable Disease Research Foundation in 2001.

Development of motor neuron restorative therapy in amyotrophic lateral sclerosis using hepatocyte growth factor

Amyotrophic lateral sclerosis (ALS) is an adult onset neurodegenerative disorder characterized by the death of upper and lower motor neurons. Mutations in Cu/Zn superoxide dismutase (SOD1) have been linked to some familial cases of ALS[1]. In familial ALS kinders with mutations in the SOD1 gene, the age of onset of weakness varies greatly but the duration of illness appears to be characteristic to each mutation. For example, in patients with the L84V mutation, the average life expectancy is less than 1.5 year after the onset of symptoms, whereas patients harboring the H46R mutation have an average life expectancy of 18 years after the disease onset. In view of the evidence supporting the idea that familial ALS variants of SOD1 enzymes acquire toxic properties, the variations in the duration of illness in the different kinders might arise because each mutation imparts different degrees of toxicity to the mutant protein[2].

We developed rats that express a human SOD1 transgene with two different ALS-associated mutations (G93A and H46R) develop striking motor neuron degeneration and paralysis. The larger size of this rat model as compared with the ALS mice will facilitate studies involving manipulations of spinal fluid (implantation of intrathecal catheters for chronic therapeutic studies; CSF sampling) and spinal cord (e.g., direct administration of viral- and cell-mediated therapies) (Fig 1) [4].

Figure 1.
Intrathecal administration of HGF to transgenic (Tg) rats protects against neurodegeneration. Some experimental manipulations are difficult in Tg mice because of size limitations. However, this Tg rat model allows routine implantation of infusion pumps for intrathecal drug delivery. This route of administration bypasses the blood–brain barrier, allowing rapid access to potential binding sites for the test compound in the spinal cord.

Hepatocyte growth factor (HGF) is one of the most potent survival-promoting factors for motor neurons. To examine its both protective effect on motor neurons and therapeutic potential, we administered human recombinant HGF (hrHGF) by continuous intrathecal delivery to G93A transgenic (Tg) rats at onset of paralysis for 4 weeks. Intrathecal administration of hrHGF attenuates motor neuron degeneration and prolonged the duration of the disease by 63 % (Fig.2, 3) [6]. Our results indicated the therapeutic efficacy of continuous intrathecal administration of hrHGF in Tg rats. The results should prompt further clinical trials in ALS using continuous intrathecal administration of hrHGF. We are making efforts in evaluating several adverse effects of the hrHGF treatment on primates using marmosets on the way to clinical trials of HGF for ALS patients.

Positional cloning of the gene for Miyoshi myopathy and limb-girdle muscular dystrophy

Miyoshi myopathy (MM) is an autosomal recessive distal muscular dystrophy characterized by mid-to late childhood or early adulthood onset, with preferential involvement of the calf muscles and highly elevated levels of the enzyme serum creatine kinase (CK). In 1998, we identified that the dysferlin gene is mutated in MM[3]. It has 55 exons and 6,243-bp nucleotides in an open reading frame predicted to encode 2,080 amino acids. This gene is also mutated in families with limb girdle muscular dystrophy 2B[3]. We reported the genotype-phenotype correlations in Japanese patients with MM[5].

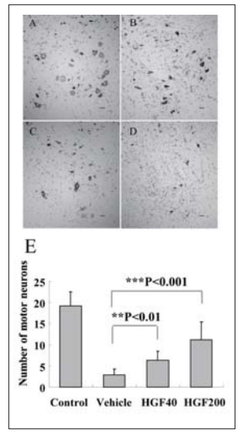

Figure 2.
Intrathecal administration of HGF to G93A Tg rats from 100 days old (the age at which pathological changes of the spinal cord appear but animals show no clinical weakness) showed a protective effect against motor neuron death[6].(A–D) Histological evaluation of the anterior horn with Nissl staining at 130 days old. The anterior horn of the lumbar cord of non-Tg rats (A), 200 μg human recombinant HGF (hrHGF) treated (B), 40 μg hrHGF-treated (C), and vehicle-treated G93A Tg rats (D) (scale bar, 40 μm). (E) Quantitative morphometric evaluation of surviving motor neurons of the fifth lumbar anterior horn at 130 days old. We counted neurons that were >40 μm in diameter. Significantly larger numbers of motor neurons survived in hrHGF-treated G93A Tg rats (P<0.01 and P<0.001, 40 μg and 200 μg hrHGF, respectively) as compared with vehicle-treated G93A Tg rats.

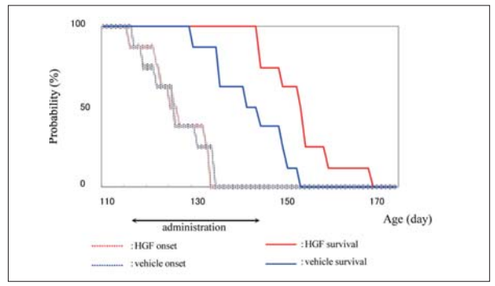

Figure 3.
Intrathecal administration of HGF from 115 days old (just before disease onset) retarded disease progression[6]. Survival periods were 143.25±17.0 d in the vehicle-treated group (solid blue line) and 154.3±16.4 d in the 200 μg hrHGF-treated group (solid red line). Survival of hrHGF-treated animals was significantly extended (P=0.0135), although there were no significant differences in onset (dotted lines, P=0.6346).

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1) Aoki M, Ogasawara M, Matsubara Y, Narisawa K, Nakamura S, Itoyama Y, Abe, K. Mild ALS in Japan associated with novel SOD mutation. *Nature Genet,* 5:323-4 (1993)

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Hasekura Fellowship

Support for short- and mid-term research vists to/from abroad

Purpose

One of the major aims of this GCOE program is to help graduate students and junior scientists develop outstanding scientific communication skills within and outside of the research community, as well as unparalleled research skills in their fields of expertise. Collaborative experiences with colleagues having different cultural and educational backgrounds will undoubtedly broaden the perspectives of young researchers and spark enthusiasm for acquiring the theoretical and technical capabilities they will need to become world-class scientists. Attendance at international meetings will provide them with opportunities to realize the strengths and weaknesses of their own research by exposing them to the global standards in their fields. Japanese society and the Japanese scientific community remain "exotic" from the perspective of Western standards. For example, we focus on team efforts more and tend to avoid criticizing others explicitly. This and other traditions survive in part because of the uniqueness of the Japanese language. Although this protection fostered the development of a uniquely Japanese culture, it also hampered Japan's transition to an "open" society, in which unrestricted discussion among members underlies any decision-making.

Aiming to open the Japanese scientific community, we implemented an educational program in which graduate students and junior scientists are encouraged to seek new ways to reconcile Japanese traditions to global standards in a variety of scientific achievements. Toward this end, we established the Hasekura fellowship program to support short- and mid-term visits to foreign countries by GCOE graduate students and junior scientists for collaborative research and attendance at scientific meetings. The Hasekura fellowship also supports visits by established researchers as well as graduate students and junior researchers from abroad to our GCOE laboratories for the same purposes.

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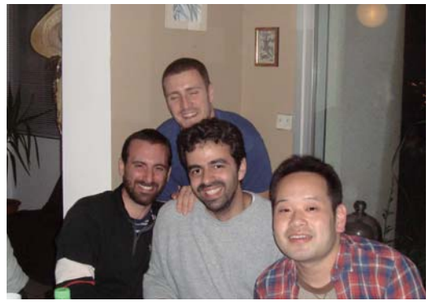


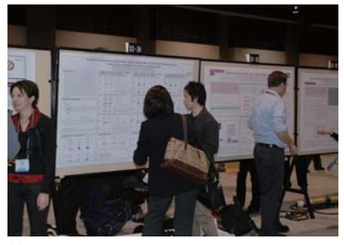
02

01 Mr. Ashiwin Shanker Shetty was invited to Prof.Osumi's lab to study patterning and formation of the cerebral cortex.

02 A student has studied at the lab in Dijon, France, for three months.

Hasekura Tsunenaga -SAMURAI who went to Rome in 16th Century

This fellowship program is named after Tsunenaga Hasekura (1571-1622), a samurai in the early Edo era (1603-1867). Ieyasu Tokugawa (1543-1616), the founding Shogun of the Edo era, rescued the crew of a Spanish ship stranded near the Pacific coast of Japan, and sent them back to Spain with a newly constructed ship. This stimulated the exchange of missions between the two countries. In 1613, Masamune Daté (1567-1636), the Daimio samurai serving as the local governor of the Tohoku area (its capital city was Sendai), sent a historic mission, called the Keicho Embassy, to Spain. It was Tsunenaga Hasekura who headed the Keicho Embassy, together with the famous Spanish explorer Sebastian Vizcaino (1548-1624). Accompanied by more than 180 sailors they set sail aboard the galleon *San Juan Bautista,* built in Japan, and spent more than two years at sea before arriving in Rome, where Tsunenaga Hasekura met the Pope. Many of the Japanese sailors involved in this trip eventually became naturalized citizens of Spain, and in the small town of Coria del Rio, several hundred people having the last name Japón or Xapón, indicative of being descendants of the Japanese sailors, are now living. Before the Keicho Embassy, only a limited number of missions to the Western world had been sent from Japan. Soon after the Keicho Embassy, the second Shogun, Hidetada Tokugawa (1579-1632), closed the country, beginning an isolation policy that lasted for 250 years. Thus, the Keicho Embassy headed by Tsunenaga Hasekura represents a surprising endeavor to change Japanese society through adventurous explorations of the world.



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03 The annual meeting 2008 of Society for Neuroscience, Washington, DC. Several doctoral students made poster presentations.

04 Several graduate students of the global COE attended IEEE, the huge annual conference on electronics, and made presentations.

05 A graduate student made an oral presentation at Digestive Disease Week 2008 in San Diego.

Fellowship achievements

Researchers who wish to visit laboratories in other countries, attend international meetings, or invite leading scientists from abroad to our GCOE laboratories, must submit an application for a Hasekura fellowship to the GCOE office. The submitted applications are evaluated by GCOE's international affairs committee. In the past two fiscal years, Hasekura fellowships have enabled 31 graduate students, 6 postdoctoral fellows, and 7 assistant professors of the GCOE laboratories to participate in international collaborations and/or meetings. Moreover, 1 established scientist and 8 graduate students and junior scientists from around the world visited our laboratories under this program. The total budget for the Hasekura fellowships in that two-year period was over 20 million yen. We hope that more and more young researchers will benefit from the Hasekura fellowships for the development of their careers as professional scientists.

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