World Premier International Research Center Initiative (WPI)
FY 2017 WPI Project Progress Report

Host Institution	The University of Tokyo	Host Institution Head	Makoto Gonokami
Research Center	International Research Center for Neurointelligence (IRCN)	Center Director	Takao Kurt Hensch

Summary of State of WPI Center Project Progress (write within **2 pages**)

1. Conducting research of the highest world level

The International Research Center for Neurointelligence (IRCN) seeks an advanced understanding of human intelligence (HI) through the elucidation of basic principles underlying neural circuit development and the pathology of psychiatric disorders caused by anomalies in this process. In turn, we aim to promote a next-generation artificial intelligence (AI) based on these principles of neural circuit maturation and function in the brain.

Laboratories in IRCN aim to (1) elucidate fundamental principles and learning rules underlying neural circuit development, (2) advance the understanding of pathophysiology of psychiatric disorders caused by impaired HI, and (3) contribute to the development of next-generation AI based on the principles of development and function of multimodal neuronal connections in the brain.

Our major activities in FY2017 were as follows. **In the Development Study Unit,** Yukiko Gotoh clarified the regulation of neural stem cell quiescence; Masanobu Kano demonstrated synchronous synapse elimination and the contribution of progranulin-Sort1 signaling; Kazuo Emoto identified novel genes involved in elimination and remodeling of dendrites; Kenichi Ohki demonstrated functional segregation of visual streams during mouse cortical development; and Kuniyoshi Sakai investigated mechanisms in human the 2nd language learning process. **In the Technology Development Unit**, Yasushi Okada, Haruo Kasai, Arthur Konnerth, and Shoji Takeuchi advance state-of-the-art neural circuit analysis technology. Especially, Takeuchi assembled an artificial neural circuit. **In the Neurodevelopmental Disorder Pathology Unit**, Kiyoto Kasai uses human structural and functional MRI and developed biomarkers potentially used for the early psychosis. Takao Hensch pursues novel, circuit-based etiological insights and treatments for these cognitive disorders using preclinical models. **In the Mathematical Information Systems Unit**, Hiroki Ueda developed a mouse brain atlas with almost all cells detected by his original brain clarification technique; Kazuyuki Aihara and Masashi Sugiyama analyzed neural network with dynamic synapses and brain dynamics, and seek the chance to create next-generation AI technology based on the newly elucidated principles of neural circuit development in the brain.

2. Advancing fusion of various research fields

Interdisciplinary cooperation is a prerequisite for understanding highly complex brain functions and elucidating pathology of disorders due to their dysfunction from a neurodevelopmental perspective. There are few interdisciplinary research centers designed to promote collaboration between globally-renowned basic neuroscientists, physicians, and AI researchers with a long-term goal of understanding HI and creating next-generation AI principles. Thus, IRCN would become a world-leading research center with unique scientific mission and profound social impact. Cross-disciplinary communication among researchers have been engaged through the First IRCN International Symposium held on 12/17, 2017 at the Hongo Campus with 192 participants, and the First IRCN Retreat held on 3/17-18, 2018 at Yokohama City with 89 participants, including PIs, affiliated faculties, young scientists, graduate students and undergraduate students. The both events above were designed for exchange of ideas and information on research subjects, techniques and resources. To support interdisciplinary research collaboration, we tightly communicate each other by weekly PI meeting every Monday morning.

3. Establishing international research environment

IRCN satellite at the Boston Children's Hospital (hereafter BCH) was launched on October 20th in

2017 supported by collaboration agreement. IRCN research conferences and meetings were all held in English. An attractive IRCN website has been set up and the press releases has been made to advertise IRCN's research achievements to the world. In order to enhance the visibility of the IRCN, IRCN administrative staff attended WPI's outreach symposium and the annual meeting of AAAS in February, 2018. IRCN successfully recruited Dr. Yazaki-Sugiyama (hiring from 4/1) as a new PI, who is highly attractive internationally. A multilingual secretariat provides foreign researchers with various services according to the model of Kavli IPMU. IRCN sponsored the first IRCN international symposium held at the Hongo Campus on Dec. 17th, 2017. There were in total 192 participants including 5 from outside Japan. The 1st IRCN Retreat was held on Mar. 17th to 18th at the Institute Onward Soken, Yokohama. There were 89 participants including Keynote guest speakers. The IRCN and Reischauer Institute of Harvard University are preparing for a summer internship program starting in May, 2018.

4. Reforming the research organization

IRCN, as a core originator in the University's reform along with Kavli IPMU, synchronizes with the following reform of the host institution. IRCN actively adopts the new system of employee employment conditions of UTokyo challenges (shorter work time if requested, annual salary system, etc) to support employees' life styles and promote service-oriented attitude. Several IRCN researchers from outside Japan have been newly accepted to UTokyo residence, which helps to further recruit excellent researchers. IRCN adopted newly established the URA certification system in UTokyo for the skill up of their activities. IRCN along with Kavli IPMU has established a support system for the international exchange of the undergraduate students to stimulate their global senses.

5. Efforts to secure the center's future development over the mid- to long-term

Organization: We set up IRCN under the UTokyo Institutes for Advanced Study (UTIAS). We secured space within the university to build it out, and established an administrative office with reference to the Kavli IPMU, so as to be immediately responsive to the Director's decisions. Two Deputy Directors support the Director for smooth operation and swift decision making. The Administrative Director provides administrative services necessary for the IRCN research activities. In addition, Steering Committee and Scientific Board have been established. The President of UTokyo supports to hire six skilled administrative staffs for IRCN to grow into a sustainable institute. Fourteen principal investigators (PIs) organize the four research units. Their deep synergy has started to produce new interdisciplinary researches as described in the item 2 of this progress report. Early recruitment of young researchers and postdoctoral fellows was achieved by approximately 60% of the final target number set in March, 2022. IRCN successfully recruited a new female PI, Dr. Yoko Yazaki-Sugiyama, starting from April 2018, as a project associate professor studying 'critical period' of the brain circuit. Her work will give a hint to create the new generation of AI.

Core Facilities: In order to develop into the joint research center, IRCN established advanced equipment rooms and laboratories: ES-mouse/virus Core, Imaging Core and Data Science Core Facilities. They provide the usage of large-scale advanced equipment by skilled Core Managers and the technical staffs.

Satellite and Institutional Collaborations: The IRCN satellite was set up in the Boston Children's Hospital, an affiliated hospital of the Harvard University, by a written agreement. It aims to understand pathologies of psychiatric disorders and to develop treatments, mainly collaborating with the Neurodevelopmental Disorder Pathology Unit. We have been seeking strategic collaborations with RIKEN AIP Center, RIKEN Brain Science Institute (BSI, currently CBS), and RIKEN Quantitative Biology Center (QBiC, currently a part of BDR).

External Funds: Japanese PIs received in total of 999 million-yen of competitive grants from Grants-in-Aid for Scientific Research, AMED, and JST, and 61 million-yen funded by the host university in FY2017.

Contribution of the host university: The University promised to provide full- fledged support for IRCN as one of the most important units in the University. IRCN, as a member of UTIAS, has been given a status of "special district" within the University. Like the other two UTIAS, IRCN has discretion in recruiting researchers and budgetary requests to MEXT in cooperation with the Faculty of Medicine. IRCN thus acts as an autonomous unit in the University and pioneers the University's organization reform. Specifically, the University secures spaces for IRCN, and supports the development of core facilities, and administration staffs' and a part of PIs' salaries (61 million-yen) to assure the sustainability of IRCN.

* Please describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 criteria, please place emphasis on the following:
  (1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusing fields).
  (2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
  (3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long-term.

1. Conducting research of the highest world level

* Regarding the criteria used when evaluating the world level of center, please note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

The International Research Center for Neurointelligence (IRCN) seeks an advanced understanding of human intelligence (HI) through the elucidation of basic principles underlying neural circuit development and the pathology of psychiatric disorders caused by anomalies in this process. In turn, we aim to promote a next-generation artificial intelligence (AI) based on these principles of neural circuit maturation and function in the brain.

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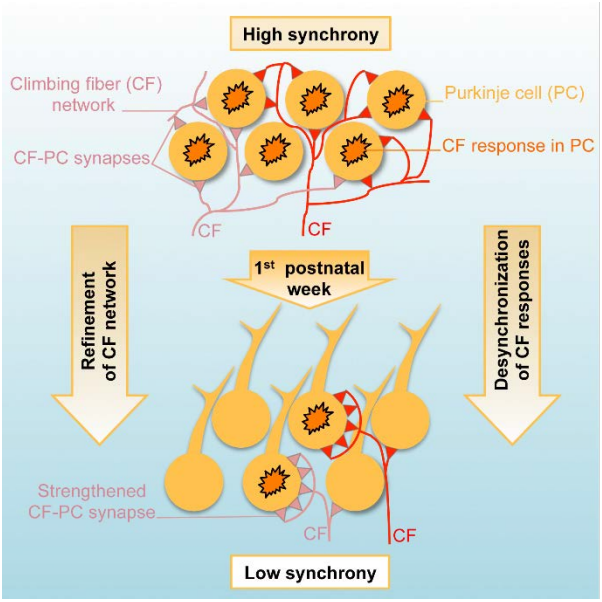
- **Development Study Core Unit:** Seven PIs use their individual model systems to pursue the fundamental principles of neural circuit development as well as the neural basis of language, a representative function of HI.

Yukiko Gotoh studies regulation of neural stem cell fate**:**

In the adult mammalian brain, the subependymal zone (SEZ) of the lateral ventricles is the largest neurogenic niche, where neural stem cells (NSCs) generate neurons. In this study, we found that Notch3 plays an important role in the maintenance of quiescent NSCs (qNSCs), while Notch1 has been reported to act as a regulator of actively cycling NSCs. Furthermore, we found that Notch3 is specifically expressed in qNSCs located in the lateral and ventral walls of the lateral ventricles and regulates neuronal production of NSCs in a region-specific manner. Our results indicate that Notch3, by maintaining the quiescence of a subpopulation of NSCs, confers a region-specific heterogeneity among NSCs in the adult SEZ (Kawai et al. J. Neurosci. 2017).

Masanobu Kano studies synapse elimination in postnatal development:

Formation of immature contacts followed by strengthening of a limited subset of early-formed synapses and the massive elimination of redundant ones, a process known as "synaptic pruning" or "synapse elimination". Kano lab is pursuing the principles and cellular mechanisms of synapse elimination in the developing cerebellum. Kano group found that the climbing fiber to Purkinje cell network is extensively remodeled during postnatal development. Using *in vivo* two-photon calcium imaging, they demonstrated that *in vivo* population activity of Purkinje cells in response to climbing fiber synaptic inputs is highly synchronized in newborn mice and massively desynchronized during the first postnatal week due to climbing fiber network refinement. (Good et al., Cell Reports 21: 2066–2073, 2017. See the scheme on the right). Kano group also demonstrated that progranulin, a multi-functional growth factor implicated in frontotemporal dementia, strengthens developing climbing fiber synaptic inputs and counteracts their elimination from postnatal day 11 to 16. Progranulin derived from Purkinje cells acts retrogradely onto its putative receptor Sort1 on climbing fibers. Purkinje cell-specific progranulin knockout mice show mild deficit in motor coordination and reduction in the



extension of climbing fiber synapses along Purkinje cell dendrites. These results suggest that progranulin-Sort1 signaling strengthens and maintains developing climbing fiber inputs, and may contribute to selection of single "winner" climbing fibers that survive synapse elimination (Uesaka et al., Neuron 97, 1–10, 2018).

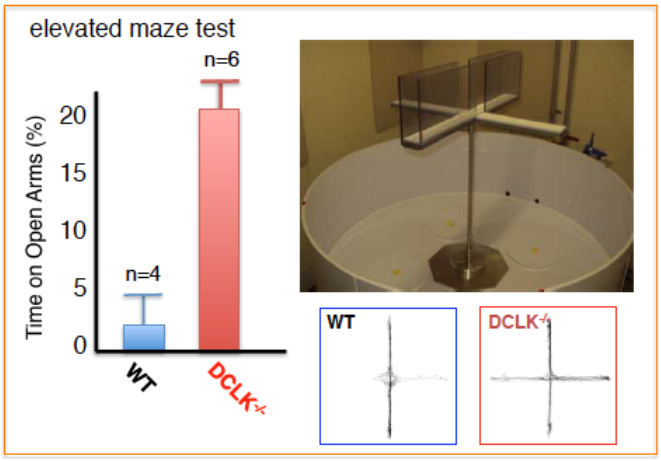
Kazuo Emoto studies elimination and remodeling of dendrites:

Molecular and cellular basis for neural remodeling in the brain development

During the postnatal development of the human brain, many neurons exhibit massive elimination of unwanted connectivity by pruning of particular synapses and neurites, and such neural remodeling appears to be necessary for functional maturation of neural circuits, as patients of neurodevelopmental disorders often has defects in the postnatal neural remodeling. We currently utilize mice and fruit fly as model animals to study molecular and cellular mechanisms underlying neuronal remodeling. In mice, we have developed a new technique to visualize and manipulate the secondary neurons (MT cells) in the olfactory circuits using AAV-mediated gene transduction method. Using this system, we described in detail how dendrite remodeling proceeds in the developing MT cells (Togashi et al. in preparation). Fruit flies typically remodel existing neural circuits, including degeneration and regeneration of particular synapses/neurites, during metamorphosis (Yoshino et al. *Curr. Biol.* 2017). Using this model, we performed a non-biased genetic screen and identified novels genes involved in pre- and post-synaptic elimination, respectively (unpublished).

Establishment and characterization of a novel mouse model with ADHD-like behavior

ADHD (attention deficit/hyperactivity disorder) is a mental disorder of the neurodevelopmental type that is characterized by problems paying attention, excessive activity, or difficulty controlling behavior. Pathological mechanisms of ADHD remain largely elusive. To study the neuronal mechanisms and find new drug targets, ADHD genetic models should be very useful. Recent GWAS studies suggest a strong interaction between ADHD patients and mutations in the *doublecortin-like kinase (dclk)* genes. In FY2017, we have established DCLK knockout (KO) mice and reported anatomical differences in the neural development between wild-type and DCLK KO mouse (Koizumi et al. *Dev. Neurobiol.* 2017). In parallel, we performed multiple behavior tests (battery tests) and revealed that DCLK KO mice displayed reduced anxiety and increased impulsivity (unpublished), which is characteristic to ADHD patients. It is thus likely that DCLK KO mouse is a novel model for ADHD, and our studies on DCLK KO mice may provide novel insights into the neural basis of ADHD. Also, DCLK KO mice might serve as a platform for screening drugs for treating ADHD.



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A behavior test (elevated maze test) for anxiety revealed that DCLK KO mice show reduced anxiety compared to wild-type control.

Takao Hensch and **Kenichi Ohki** study neural circuit development in the cerebral cortex:

The Hensch lab has identified inhibitory interneurons that mediate developmental critical period plasticity in the neocortex. Here, he focuses on the primary auditory system to reveal circuit dynamics for tonotopic map changes, which lay the foundation for phoneme perception in humans. While fast-spiking basket cells in layer 4 establish critical period timing, this microcircuit is effectively gated by descending inhibitory connections from layer 1. These 5-HT3-receptor bearing cells are a hub for top-down neuromodulatory input, such as acetylcholine acting on nicotinic receptors that are effectively dampened by Lynx1 protein as critical periods close. Notably, these cells were found also to receive a topographic bottom-up projection from the auditory thalamus, but unlike layer 4 cells fail to exhibit plastic reorganization while orchestrating plasticity in the layers below. These

findings were published in FY2017 (Takesian et al, Nature Neurosci.*). A role for inhibitory interneurons is lacking from most current A.I. systems.

*Takesian, A.E., Bogart, L.J., Lichtman, J.W. & **Hensch, T.K.** (2018) Inhibitory circuit gating of auditory critical period plasticity. *Nature Neurosci.* 21:218-227.

The Ohki lab examines functional segregation and development of mouse higher visual areas. This work will be the foundation of what we study in IRCN about mouse higher visual areas. Recent studies suggest that higher visual areas in the mouse visual cortex are segregated anatomically into two visual streams, likely analogous to the ventral and dorsal streams in primates. However, functional characterization of mouse higher visual areas are still sketchy. Moreover, it is unknown when the functional segregation of higher visual areas occurs during development. Thus, Ohki lab investigated spatiotemporal selectivity of higher visual areas and their development using wide-field calcium imaging. We found that lateral higher visual areas in the anatomical ventral stream shared similar spatiotemporal selectivity, whereas the spatiotemporal selectivity of anterior and medial higher visual areas in the anatomical dorsal stream was not uniform and these areas were segregated functionally into multiple groups. This functional segregation of higher visual areas developed and reached an adult-like pattern ~10 days after eye opening. These results suggest, not only the functional segregation of ventral and dorsal streams, but also the presence of multiple substreams in the dorsal stream, and indicate that the functional segregation of visual streams occurs gradually after eye opening. The work was published in this FY 2017 (Murakami et al., 2017).

Haruo Kasai studies reinforcement learning for multimodal association**:**

We are also extending dopamine effects on synaptic (Yagishita et al., Science 2014) and behavioral learning of the spiny projection neurons in the nucleus accumbens. In addition to these in vivo works, we keep studying more basic mechanisms of synaptic functions in slice preparations. You can find one example in section 2 below.

Kuniyoshi Sakai studies cerebral mechanisms of human language information processing:

Previous studies have reported correlated activations during learning a second language (L2), but the demonstration of causal changes has been limited. We thus examined brain activation changes due to L2 acquisition for a relatively short period, during which general changes may not be expected. Moreover, we focused on the strongest possible effects of studying abroad. Participants were 14 students (6 females, aged 18-30 years), who were staying in Japan (> 5 months) and learning Japanese through the EF (Education First, Stockholm) courses. Their first languages were various, including German, French, and Swedish. We divided the students into two groups, for whom the orders of two different sets of Japanese reading tests were switched (A to B, or B to A). The use of two different sets excluded the involvement of habituation effects due to repeating the same stimuli. The interval between these two test sets was at least 40 days, one in the earlier period of the courses (Pre: 2-3 months after the start of stay), and the other in the later period (Post: 4-5 months after the start). We used a 3.0 T MRI system (GE Healthcare), and the fMRI data were analyzed using the SPM12 software. The participants answered the tests in the MRI scanner by pressing one of four buttons. Both reading test sentences and answering questions were set as target events, which were compared with the intertrial interval in a second-level analysis (i.e., random-effects analysis). During both Pre and Post periods, we observed significant activation in the higher language areas, i.e., the left inferior frontal cortex and left lateral premotor cortex, as well as in the visual cortex spanning bilateral occipital and parietal cortices (FWE corrected $p < .0001$). We found that activated voxels in both of these language and visual regions greatly decreased from Pre to Post periods. These results indicate that the activation decrease is caused by learning a second language abroad.

- **Technology Development Unit:** Yasushi Okada, Haruo Kasai, Arthur Konnerth, and Shoji Takeuchi develop the most advanced neural circuit analysis technologies for probing neural circuit development in cooperation with the Development Study Core Unit.

Yasushi Okada is responsible for establishing and improving imaging technologies including high spatio-temporal resolution microscopy and probes:

We have developed a novel method for the non-invasive force measurements in the living axon (patent pending, manuscript under review). With this method, we have examined how many motor proteins are exerting force during the axonal transport, which serves as the basic logistics of

the neuronal development and morphogenesis. We have also applied the live cell imaging techniques and super-resolution imaging for the axonal transport, ribbon synapse in cone photoreceptor cells or the chromatin conformation and dynamics.

Haruo Kasai is responsible for single synapse manipulation technology and enabling measurement of synapse fluctuations:

We are extending our works on synaptic memory probes, initially called AS-probe (Hayashi-Takagi et al., Nature 2015), which can label recently enlarged spines selectively, and induce light-dependent shrinkage to test the involvement of the enlarged synapses in specific behavioral tasks. We have shipped out the probe over 40 laboratories in the world, and have heard about some successes. Meanwhile, our goal is to improve the probe for broader and more challenging applications, for example, multi-color labeling of learning circuits. One major drawback for this is that the AS-probe is often toxic in vivo, particularly when we replace Venus with other chromophores, such as mTurquoise (CFP). We think this is due to the direct fusion of the probe with PSD95, which is functional, and fusion proteins may have deleterious effects when expressed in highly active synapses in vivo. We are now taking a new strategy in the targeting of the probe to spines, and improving the situation. We are also finding a better way of photoactivation (PA) than the original PA-Rac1 whose molecular mechanisms for shrinkage are not well understood. Meanwhile, to our surprise, we found a new way to apply the same principle to axons to label the presynaptic boutons. It seems that the bouton probe labels recently enlarged boutons with synaptic contact with enlarged spines. We are now clarifying the mechanisms for the specific labeling of the probe to the enlarged boutons. Thus, we have now both spine and bouton probes, and we can eventually extend our methods to label both pre- and post-synaptic neurites, and might be used to label the local learning circuits.

Arthur Konnerth and **Shoji Takeuchi** are responsible for the simultaneous measurement of the activity of a number of living neurons in the brain of animals:

Arthur Konnerth and his colleague will investigate the role of the cerebellum for brain function and the general implications for cognition. Together with the Kano lab, they will pursue a project under the headline “The cerebellum as a timing machine”. The main focus will be the analysis of the olivo-cerebellar circuit and its role of as a pacemaker in the brain. While the Kano lab will deal with the development of this circuit, particularly with synapse elimination of the inferior olive-derived climbing fibers, the Konnerth lab will concentrate of the synaptic functions of Purkinje cells in the mature cerebellum. So far the following progress has been made: 1. Meeting with Prof Kano in Tokyo for defining experimental strategies and main goals 2. Purchase of devices for high-speed two-photon imaging setup 3. Hiring of Dr. Beomjong Song as a lab member (starting at May 1, 2018)

Shoji Takeuchi and his colleague developed some elemental technologies which might contribute to research of IRCN in FY2017. The technologies include 3D tissue culture, continuous monitoring of biologically important small molecules, and stem cells and neural network engineering. Particularly, in the neural network engineering area, we developed a mobile microplate to control the functional morphologies of a single neuron (axon/dendrite) which can be assembled as an artificial neural circuit. The microplates were fabricated by standard lithography process and lift-off technique using aluminum, parylene, and gelatin on a glass substrate. As shown in Figure 1, single neurons were successfully patterned on the microplates which have circular areas (cell body part) and long arms (axon area). The microplates were physically connected using a micromanipulator to form a synaptic connection, which was confirmed by immunostaining the neurons. The connection was also confirmed by measuring a synchronized fluorescent signal from fluorescent proteins expressed in the neurons. We believe this method will be useful to develop an artificially designed brain on a chip.

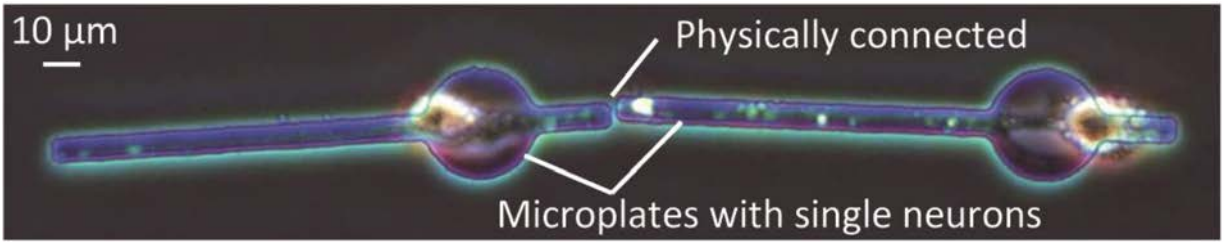


Figure 1. Single neurons patterned on microplates which are physically connected to form a synaptic connection.

- **Neurodevelopmental Disorder Pathology Unit:**

Kiyoto Kasai aims to elucidate the pathology of ASD and schizophrenia in living humans by structural and functional imaging analyses using MRI:

Using multi-modality neuroimaging and clinical neurophysiology, K. Kasai et al. have investigated pathophysiology of early psychosis and developed biomarkers potentially useful for clinical settings. Using mismatch negativity (MMN) event-related potential as auditory cortical function, Koshiyama et al. showed that the MMNs were stable through the early course of the disorder (Schizophrenia Research, 2017). Sasabayashi et al. demonstrated that increased gyrification in the occipital lobe may be a candidate biomarker for prediction of psychosis onset (Biological Psychiatry, 2017; media coverage in Nikkei Newspaper). Koike et al. found that near-infrared spectroscopy (NIRS), previously approved as a diagnostic tool for depressive state under the health coverage system in Japan may be also useful in diagnosing early psychosis (Psychiatry and Clinical Neurosciences, 2017).

Takao Hensch at Boston Children's Hospital pursues bench-to-bedside research for neuro-developmental disorders. In particular, they have identified potential circuit-based treatments for cognitive disorders using model animals of ASD and schizophrenia development based on critical period timing manipulation. They translate their breakthrough insights into the biological basis of critical periods for brain development into the clinic, transcending traditional departmental boundaries. Ongoing projects include: cognitive consequences of repeated pediatric anesthetic exposure (with Dr. Charles Berde, Anesthesiology & Emery Brown, MGH), longitudinal electrographic biomarkers to track excitatory-inhibitory imbalance in autism spectrum disorders (with Dr. Charles Nelson, Developmental Medicine), and the reopening of juvenile brain plasticity to correct amblyopia ("lazy eye") after the age of 10 (with Dr. David Hunter, Ophthalmology). With IRCN scientists and collaborators (e.g. Nancy Kopell, Boston University), they will apply sophisticated computational modeling and machine learning (A.I.) approaches to better characterize the underlying circuit dynamics and processes to inspire innovative therapies.

- **Mathematical Information Systems Unit:**

Hiroki Ueda investigates the regulation and principles hidden beneath complicated biological phenomena using mathematical analysis, and also attempts the comprehensive description and analysis of neural circuits in part or whole brain, using his original brain clarification technique:

Hiroki Ueda and collaborators developed a point-based mouse brain atlas (CUBIC-Atlas) with a newly developed tissue clearing and expanding protocol and high-magnitude imaging microscopy. Most effective chemicals to achieve both tissue swelling and matching of refractive indices were screened and selected from 1650 candidates. CUBIC was compatible with fluorescent proteins and a customized microscope system with light-sheet illumination realized rapid subcellular-resolution imaging over the entire brain (Fig. 1). Almost all cells in the brain were detected and classified based on anatomical annotation of the Allen Brain Atlas (Fig. 2)

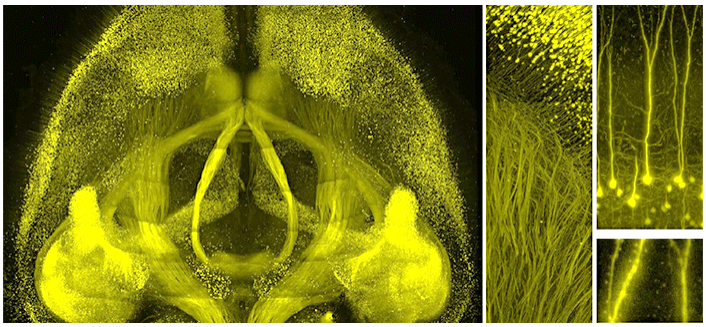


Fig. 1 Volumetrically rendered image of Thy1-YFP mouse brain, captured by customized light-sheet-fluorescent microscope (left) and magnified/detailed views (right 3 panels).

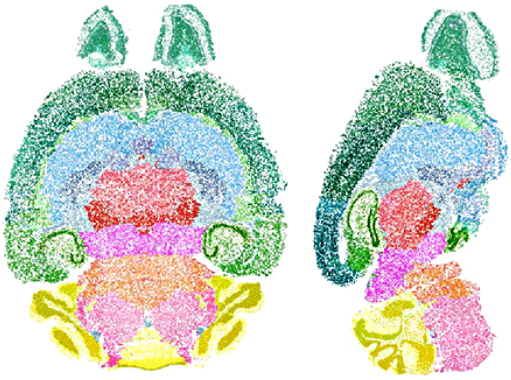


Fig. 2 Horizontal (left) and sagittal view (right) of CUBIC-Atlas. Cells in mouse brain was represented as points and anatomically annotated in colors.

Kazuyuki Aihara and **Masashi Sugiyama** seek to create next-generation AI technology based on the regulation of neural circuit development in the actual brain. In addition, Aihara aims at understanding brain pathology by modeling psychiatric disorders according to the regulation of neural circuit development:

Kazuyuki Aihara conducted the following studies.

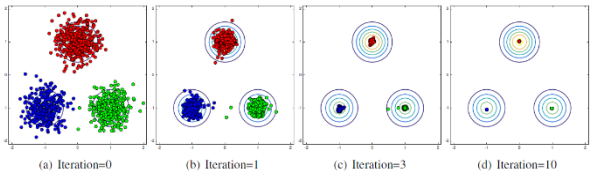
(1) Computational neuroscience: Bifurcation analysis of neural networks with dynamic synapses, task-dependent recurrent dynamics in visual cortex, and sparsely encoded associative memory with short-term synaptic dynamics.
(2) Data analysis of brain dynamics: Atypical network development patterns in children with autism spectrum disorder, and single-sample dynamical network biomarkers.
(3) Nonlinear dynamics of artificial neural networks: Robustness and fragility of coupled oscillator networks, combinatorial optimization dynamics of optoelectronic neural networks, spiral waves in chaotic neural networks, and partially unstable attractors in networks of forced integrate-and-fire oscillators.
(4) Development of nonlinear time series analysis: Definition of distance for marked point process data, a Hawkes process model with a time-dependent background rate, differential entropy, and dimensionless embedding.

He also studied hardware implementation of neural networks such as configurable qualitative-modeling-based silicon neuron circuits as joint research with NEC through Social Cooperation Programs between UTokyo and NEC on Brain-Morphic AI to Resolve Social Issues.

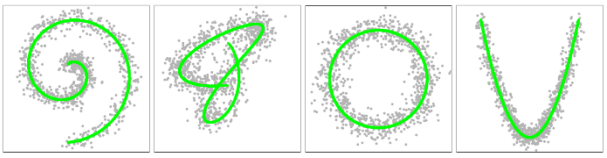
Masashi Sugiyama's research goal is to advance the current machine learning technologies based on neuroscientific findings. To do so, we need to put together two completely different topics into the same framework: the limitations of current machine learning technologies described in a mathematical form and neuroscientific findings coming from physiological experiments.

The first year of our research was devoted to promoting discussion between these two different groups of researchers. In particular, we discussed neuroscientific studies about auditory systems and visualization of brains with members of Ueda Lab., information coding in brains with members of Ohki Lab., mathematical modelling of brains with members of Aihara Lab., and molecular-level brain development with members of Gotoh Lab., and we introduced our computer-scientific machine learning studies to many IRCN members.

In terms of machine learning research which may potentially have relation to IRCN, we have been working on the problems called mode-seeking clustering and density ridge estimation, which are both aimed at some “peaks” of the data probability density function. Existing approaches first estimate the density from data and then compute its derivative. However, a good density estimator does not necessarily produce a good density-derivative estimator and thus the existing approaches do not necessarily work well. To cope with this problem, we proposed to directly estimate the density derivative without estimating the density itself and demonstrated its usefulness both theoretically and experimentally.



Mode-seeking clustering


Density ridge estimation

2. Advancing fusion of various research fields

Interdisciplinary cooperation between life science, medicine, linguistics, mathematics, and information science is a prerequisite for understanding highly complex brain functions and elucidating the pathology of brain diseases. Neurointelligence, a new discipline that IRCN proposes, is an integration of research on neural circuit development, technology development for probing neural circuits, studying psychiatric disorders, and AI research.

The world-class PIs in IRCN organizes four research units: Development Study Core Unit, Technology Development Unit, Neurodevelopmental Disorder Pathology Unit, and Mathematical Information Systems Unit. The units with distinct disciplines are expected to maintain close mutual relationships, as specified below.

(i) Technology Development Unit develops state-of-the-art advanced techniques of neural circuit analysis and measurement, including fluorescent and (bio) luminescent probes, manipulation of single synapse, and simultaneous measurement of the activity of a number of neurons, to support neural circuit studies in the Development Study Core Unit. Ueda group has developed CUBIC protocols and whole-wide brain imaging facilities. They are widely available for researchers in IRCN. Collaborative research has been already started or in progress for virus-labeled brains after in vivo experiments.

(ii) Development Study Core Unit pursues the development of neural circuits and study of learning rules in cooperation with the Technology Development Unit, which serves as a basis for exploration of novel AI models in cooperation with the Mathematical Information Systems Unit. The Kano group has started a collaboration with the Gotoh group on an electrophysiological examination of the cerebral cortex-specific FGF knockout mouse. The Kano lab is now investigating whether there are any abnormalities in the functions of excitatory and inhibitory synapses in the cortex of the mutant mice. Emoto group plans to collaborate with Fujiwara and Aihara groups to develop a novel neural network model that reflects the human brain development. Haruo Kasai has just started a collaboration with Dr. Radostin Danev who is an affiliated faculty of IRCN, and is a world expert of cryo-EM. The question is that we have been studying ultrafast exocytosis in presynaptic terminal, and finding the distinct organization of SNARE proteins in the active zone vs. conventional secretory cells using FRET/FLIM of SNAREs (Nat Com, 2015). Kasai's results indicate that a high-order oligomerization of SNAREs exists in the active zone in situ, and it is necessary for ultra-fast exocytosis confirmed with electrophysiological methods (submillisecond). Prof. Hiroshi Tokumaru in Tokushima University has recently found that SNAREs and synaptotagmin complexes can efficiently assemble in the presence of another specific protein, and look for someone to work with cryo-EM. These supra-molecular SNARE complexes may give crucial biophysical bases of ultrafast exocytosis. These structural and future theoretical studies are fundamental to the human intelligence which utilizes millisecond signal transmission in the synapses in the brain. This atomic level study will eventually lead us to design better synaptic optoprobes for delineation of the learning circuits.

(iii) Mathematical Information Systems Unit creates next-generation AI based on the regulation of neural circuit development in the brain in cooperation with the Development Study Core Unit, and systematically analyzes a large amount of data obtained by the Core Units, utilizing methods based on mathematical science and AI. Aihara and Hirata (Affiliated Associate Professor of IRCN) started collaborative research (1) with Kiyoto Kasai on detecting early warning EEG signals of transition from UHR (Ultra-High Risk for psychosis) to FES (First-Episode Schizophrenia) in schizophrenic patients on the basis of bifurcation theory, (2) with Gotoh on identifying temporal change of the three-dimensional structures of chromosomes to understand how an embryo develops its neural system, and (3) with Ohki on characterizing

chaotically transitive spatio-temporal dynamics in the visual cortex of marmoset monkeys.

(iv) Neurodevelopmental Disorder Pathology Unit works together with the Mathematical Information Systems Unit and aims at understanding psychiatric disorders by modeling based on rules of neural circuit development. This will further help to perform quantitative analysis of images and physiological data from psychiatric patients aiming at establishing objective criteria for diagnosis. Kiyoto Kasai group has started collaborative research with Aihara and Hirata group on the detection of early warning EEG signals of transition from UHR (Ultra-High Risk for psychosis) to FES (First-Episode Schizophrenia) on the basis of bifurcation theory.

Cross-disciplinary communication among researchers mentioned above were engaged through the First IRCN International Symposium held on 12/17, 2017 at the Hongo Campus with 192 participants, and the First IRCN Retreat held on 3/17-18, 2018 at Yokohama City with 89 participants, including PIs, affiliated faculties, young scientists, graduate students and undergraduate students. The both events above were designed for exchange of ideas and information on research subjects, techniques and resources. In addition, we tightly communicate each other by weekly PI meeting every Monday morning.

3. Establishing international research environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:

- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers; number and state of visiting researchers; exchanges with overseas entities
- Proactive efforts to raise the level of the center's international recognition
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

To build a visible international research center, IRCN is advancing toward the establishment of multi-level enterprise by researchers, students and administrative staff. IRCN Scientific Board (SB) and Steering Committee (SC) successfully recruited Dr. Yazaki-Sugiyama (hired from 4/1) as a new PI, who has recent high international visibility in the birdsong field. The collaboration Agreement regarding the conduct of those specific IRCN activities at the Boston Children's Hospital (hereafter BCH) was entered into by and between BCH and IRCN, and thus, IRCN satellite at BCH was launched on October 20th in 2017. It is not only effective in networking with foreign researchers and research institutes, but will also provide opportunities for young researchers to improve their careers. The interactions between foreign and Japanese members, research conferences and meetings were held all in English. An attractive IRCN website has been set up and press releases have been made to advertise IRCN's research achievements to the world. In order to enhance the visibility of the IRCN, IRCN administrative staff attended WPI's outreach symposium and the annual meeting of AAAS in February, 2018.

Strategy for staffing foreign researchers: The Director, supported by SC and SB, has been putting highest effort on recruitment of young foreign researchers with high motivation and ability. After recruitment, the Director will help the recruited scientists realize outstanding achievement during their term at IRCN and become a strong candidate for faculty or post-doctoral positions at other globally leading research institutions. Attractive job conditions are offered for foreign researchers with an annual salary system based on their competence and performance.

Strategy for establishing an international research environment and administration system, and the support system for researchers from overseas: To support foreign scientists to adapt to the Japanese grant system, we lowered hurdles associated with daily life. Startup funds are provided for starting the work. Information for grant writing and management of accepted grants set up to encourage foreign scientists to apply for external grants. A multilingual secretariat provides foreign researchers with various services according to the model of Kavli IPMU. Examples include a website for information on daily life, accompanying researchers to city offices, banks, real estate agents, etc., orientation services, Japanese language classes, online safety education, and a 24-hour emergency medical telephone service provided by the university, including that for their family members.

International research conferences: IRCN sponsored the first IRCN international symposium held at the Hongo Campus on Dec. 17th, 2017. There were in total 192 participants including 5 from outside Japan. In addition, the 1st IRCN Retreat was held on Mar. 17th to 18th at the Institute Onward Soken, Yokohama. There were 89 participants including Keynote guest speakers. These activities

later developed into several collaboration mentioned in the Item 2 of this progress report. The IRCN and Reischauer Institute of Harvard University are preparing for a summer internship program starting in May, 2018. These meetings have been promoting exchange of researchers among the core IRCN, its satellite and other institutes.

Measures to ensure that top-caliber researchers from around the world can work comfortably in carrying out their research: IRCN's administrative staff help researchers to prepare application forms for research grants. The preexisting system of university research administrators (URAs) in UTokyo supports human resources necessary for IRCN administration. IRCN by itself has set up the Research Strategy Office to provide training and full support for successful writing of grant proposals. Administrative staffs also support grant management and report preparation. Insuring and locating of housing and daycare are also supported.

4. Reforming the research organization

* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Please describe the center's operation and the host institution's commitment to the system reforms.

IRCN, as a core originator in the University's reform along with Kavli IPMU, synchronizes with the following reform of the host institution.

- IRCN will introduce the position of Executive Director to aid the Director and manage day-to-day scientific collaboration and globalization efforts. A high-level candidate with broad overview of the interdisciplinary fields represented in the center will be recruited in FY2018.
- New administration staff system of UTokyo will attempt to promote service-oriented attitude. IRCN actively adopts a new system of employment conditions (shorter/flexible work time if requested, annual salary system, etc) to support employees' life styles.
- Several IRCN researchers from outside Japan have been newly accepted to UTokyo residence. This priority acceptance will help to further recruit excellent researchers.
- The UTokyo has established the URA certification system. IRCN will use this system to encourage URA to improve skills as a research administrator. In fact, a new URA, who was recruited in FY2017 and hired in FY2018, is looking forward to receiving lectures in this system.
- Initiatives including the establishment of WINGS will enable education of graduate students under IRCN's outstanding international research environment. In conjunction, IRCN along with Kavli IPMU has established a support system of the international education of undergraduate students. Taking advantage of this system, IRCN has prepared to accept undergraduate students from Harvard University at the UTokyo for 10 weeks in FY2018 to stimulate the global sensibilities of UTokyo students.
- According to "University of Tokyo: Vision 2020", the University has been trying to attain financial independence with efficient management and resource expansion by utilization of land assets, promoting industry- university cooperation, etc. Secured budgets have been used for the promotion of excellent research and strategic investment in IRCN, specifically for the IRCN spaces, development of core facilities (e.g. fMRI), IRCN staffs' and a part of PIs' salaries, and so on.

5. Efforts to secure the center's future development over the mid- to long-term

* Please address the following items, which are essential to mid- to long-term center development:
- Future Prospects with regard to the research plan, research organization and PI composition; prospects for the fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends
- Host institution's organizational reforms carried out for the Center's autonomous administration simultaneously with the creation of the Center.

Organization: We define the startup period from FY 2017 to FY 2019 to establish management organization and research units. Immediately after award decision in October, we followed university procedures to set up IRCN under the UTokyo Institutes for Advanced Study (UTIAS). We secured space within the university to build it out. We quickly established an administrative office with reference to the Kavli IPMU, so as to be immediately responsive to the Director's decisions. As the Executive Board members, two Deputy Directors support the Director for smooth operation and swift

decision making, and the Administrative Director provides administrative services necessary for the execution of IRCN activities. In addition to the EB, Steering Committee (SC) and Scientific Board (SB) have been established to maintain close contact. The President of the University of Tokyo supports to hire six President's discretionary staffs with advanced skills recruited from headquarter for IRCN to grow into a sustainable institute.

Fourteen world-class principal investigators (PIs) from UTokyo and research institutes overseas organize the four research units: Development Study Core Unit, Technology Development Unit, Neurodevelopmental Disorder Pathology Unit and the Mathematical Information Systems Unit. We frequently communicate each other with the help of web-conferencing system to catalyze collaborations with other groups within the IRCN, which will contribute to the future success of the center. Their deep synergy produces a new dimension of studies, which have been developed as described in the item 2 of this progress report. Early recruitment of young researchers and postdoctoral fellows was achieved by approximately 60% of the final target number set in March, 2022.

In addition, IRCN successfully recruited a new female PI, Dr. Yoko Yazaki-Sugiyama, starting from April 2018, as a project associate professor in the Development Study Core Unit. She will be collaborating with Dir. Hensch to investigate developmental mechanisms by manipulation of the time windows called ‘critical period’ in the songbird. She tackles several questions: what is happening in the juvenile brain when it is receptive to accruing new information, why does this time window close, and is it possible to extend or re-open it. The critical period deeply concerns neural circuit plasticity with synaptic development and pruning, which are lacking in current artificial intelligence. Thus, her work will give new hints to create next-generation AI.

Core Facilities: In order to develop into a welcoming, shared research center, the IRCN established several advanced equipment rooms and laboratories named as the core facilities: ES-mouse/virus Core, Imaging Core and Data Science Core Facilities. Two additional cores, Science Writing and fMRI Cores, are to be set up in FY2018. They facilitate fee-for-service usage of large-scale advanced equipment by skilled Core Managers and the supporting staffs. The ES-mouse/virus Core Facility assists ES cell manipulation and the creation of new disease model mice using an ES cell line established by Ueda group, promoting joint research between IRCN inside and outside researchers. It also generates and provides recombinant AAVs for monitoring the neural cell migrations and the neural circuit plasticity. The Imaging Core Facility provides the easy access to the advanced microscopes, including rapid scope, two-photon, confocal, and all-in-one microscopes in FY2017, and STED microscope in FY2018. The Data Science Core Facility provides the access to the supercomputer built in IRCN and supports the mathematical data analysis.

Satellite and Institutional Collaborations: The IRCN satellite has been set up in the Boston Children’s Hospital, an affiliated hospital of the Harvard University, by a written agreement that was originally scheduled to be concluded in FY2018. It aims to understand pathologies of psychiatric disorders and to develop treatments, mainly collaborating with the Neurodevelopmental Disorder Pathology Unit. In addition to Takao Hensch, Michela Fagiolini heads the mouse Neurodevelopmental Behavioral Core facility where she performs preclinical analysis of Mecp2-deficient models of Rett syndrome, and Charles Nelson performs behavior analysis, electrophysiology, and functional imaging of ASD in children.

We are seeking a chance to collaborate with RIKEN. Sugiyama in the Mathematical Information Systems Unit is also the director of RIKEN Center for Advanced Intelligence Project (AIP Center). This facilitates collaboration with both the UTokyo AI Center and RIKEN AIP Center. We have been continuing to negotiate the collaboration with RIKEN Brain Science Institute (BSI, currently CBS), which has been just established. We also seek strategic collaboration with RIKEN Quantitative Biology Center (QBiC, currently BDR) in future.

External Funds: Japanese PIs received competitive grants from Grants-in-Aid for Scientific Research, AMED, and JST. Examples include Specially Promoted Research (Kano), Scientific Research on innovative Areas (Emoto, K. Kasai), Scientific Research (S) (Gotoh, H. Kasai, Ueda, Ohki, Aihara, Takeuchi), Brain Mapping by Integrated Neurotechnologies for Disease Studies (Ohki, Ueda, K. Kasai), and Strategic Basic Research Project–CREST (H. Kasai). In total of 999 million-yen of external budget and 61 million-yen funded by the host university were used for IRCN activities in FY2017. In addition, the Office for Research Strategy (ORS) gathers information from domestic and foreign funding

agencies and foundations to boost IRCN activities. Three URAs have been recruited in FY2017, and start their activities from FY2018. IRCN is exploring chances to collaborate with pharmaceutical and experimental instruments companies. These activities will support the future sustainable operation of the center.

Contribution of the host university: The University supports to maintain and expand IRCN. In "The University of Tokyo: Vision 2020", President Gonokami sets "expansion and establishment of internationally renowned bases for research" as one of the important action plans. This is expected to materialize one of the basic principles, "synergy between excellence and diversity". The third mid-term objectives/plans of the University state that the University will form "research centers that can contribute in solving issues in both academic and social domains, with pioneering, prompt, agile, and practical approaches". This plan also states that "research centers objectively recognized by their excellence, such as UTIAS, are prioritized for support from the University." In fact, the President of UTokyo strongly supports the center and regards IRCN as one of the most important units in the University and has promised to provide full- fledged support. IRCN, as a member of UTIAS, has been given a status of "special district" within the University. Like the other two UTIAS, IRCN has discretion in recruiting researchers and budgetary requests to MEXT in cooperation with the Faculty of Medicine. IRCN thus acts as an autonomous unit in the University and pioneers the University's organization reform. Specifically, the University secures spaces for IRCN, and supports the development of core facilities (e.g. fMRI purchase), and administration staffs' and a part of PIs' salaries (61 million-yen) to assure the sustainability of IRCN.

6. Others

* In addition to the above 1-5 evaluation items, only if there is anything else that deserves mention regarding the center project's progress, please note it.

To advertise IRCN's activities to the scientific community and the public, we newly established IRCN Web site, https://ircn.jp/ and https://ircn.jp/en/. Through these web sites, we have been announcing our schedule of International Symposia, Workshops, Retreat, Ceremony and bi-weekly Science Salon, which starts from May, 2018.

7. Center's response to the follow up results in last year

* Transcribe the item from the "Advice/ recommendations" section in the site visit report and "Actions required and recommendations" in the Follow-up report, then note how the center has responded to them.
* For the center launched in FY 2017, please describe the status of response to the pointed items in "Major points that need to be improved" of "The screening result for WPI centers launched in FY 2017."
* However, if you have already provided this information, please indicate where in the report.

Q1: It is vital that the Director make a full commitment to keeping the promised 80% effort. He should physically stay for at least 50% of his total working hours at the Tokyo center to execute leadership, which only the director can perform, over the project. This degree of effort should be reached as soon as possible. Some form of agreement between Harvard University, Boston Children's Hospital, and the University of Tokyo to approve the Director's participation in the WPI center at these levels is needed.
A1: Dir. Hensch spends time at UTokyo on a regular basis to oversee management of the entire center while also leading the Boston Children's Hospital (Harvard Medical School) satellite. In particular, the president's office will be responsible for increasing his physical presence at UTokyo to an adequate level, a minimum of 50% of his total working hours, as soon as practicable. The office has successfully negotiated with Boston Children's Hospital a memorandum of understanding (MOU) with UTokyo. Dir. Hensch regularly communicates with us through a Web conferencing system every Monday morning. We frequently use e-mails for tight communications. For example, Dir. Hensch sent an average of 100 E-mails to UTokyo and received more than 250 mails per month (average 15.9 mails/working day). Finally, a new position of Executive Director will be created in FY2018 to assist the Director on a daily basis at UTokyo to foster scientific collaboration and globalization.

Q2: Prof. Masashi Sugiyama is also the Director of the Center for Advanced Intelligence Project at RIKEN. Though his effort for IRCN was initially stated as 80% in the application form, he said in the hearing that it would be 16%. Therefore, your proposal should be revised to reflect his hearing statement. Furthermore, a concrete plan to ensure that Prof. Sugiyama will actually be able to contribute to IRCN should be presented with respect to his effort.

A2: Prof. Sugiyama's "Biographical Sketch of Principal Investigator" was fixed to be 16% for IRCN according to the suggestion. This question 2 is closely related to question 3, therefore, we will continue to explain this issue on the A3.

Q3: The PIs from the University of Tokyo belong to 4 graduate schools and 1 institute scattered among the Hongo, Komaba and Kashiwa campuses. Several PIs (e.g., Prof. Y. Okada, Prof. H. Ueda) are also cross-appointed with domestic institutes, especially RIKEN. While this is a welcome move by the University of Tokyo to engage in a novel research system that transcends the barrier of traditional departments, a concrete plan to ensure that the PIs can devote the promised effort to WPI activities needs to be presented.

A3: Bi-weekly progress report by young scientists and students is being held on Hongo campus and shared through the Web conferencing software from May 23rd, 2018. Several PIs, who have laboratories outside the Hongo Campus, will maintain their own offices and desks within the IRCN under one roof. These PIs regularly visit to the IRCN and communicate with the help of data-sharing tools and a Web conferencing system. As the IRCN becomes fully established, we expect that research carried out by each PI will have a greater impact on the center as a whole, and that this will automatically result in increased effort ratios.

Q4: Given its Brain Science Institute, Quantitative Biology Center and Center for Advanced Intelligence Project, RIKEN has significant overlap with IRCN in research objectives and personnel. A strategic collaboration between IRCN and RIKEN should be mutually beneficial and thoroughly conceptualized. If realized, it could lead to global leadership in neurointelligence without overlapping investment in Japan as a whole.

A4: IRCN is seeking strategic collaboration with the RIKEN Brain Science institute (BSI, currently CBS) and RIKEN Quantitative Biology Center (QBiC, currently a part of BDR). We have reached out to the Directors of RIKEN. Dr. Sugiyama, Director of the RIKEN Center for Advanced Intelligence Project (AIP), will become a hub for communication between AIP and IRCN. IRCN members have also started to collaborate with the Yokohama RIKEN Omics Science Center (OSC).

Q5: Management will be the key in achieving the project's ambitious goals. To support the Director, a powerful deputy director and/or administrative director will be needed. A strong administration will also be needed to guide the diverse assemblage of individuals and to organize the overall project.

A5: Now, we have two senior deputy Directors (DDs), Profs. Kano and Emoto, and an Administrative Director (AD), Dr. Kagawa, who has job experiences at MEXT and AMED. In addition, an IRCN Executive Director (=Senior URA, Project Professor) will join us from May 21st, 2018 to strongly support the IRCN Director. Together, they help the Director communicate with other IRCN members while the Director is occupied with outside tasks, such as running satellites and international outreach activities. IRCN has established the following organizations for the Director to receive advice: an Executive Board (EB), consisting of AD and two DDs, for smooth operation and swift decision making. The Steering Committee (SC) serves as a personnel committee for faculty. The Scientific Board (SB), consisting of all PIs, is responsible for approval of the Director's decisions and their execution. We will set up additional sub-committees as it becomes necessary. The SB meeting is held regularly every Monday morning combined with a Web conferencing system.

Q6: The President of the University of Tokyo promises to make the center a scientific hub connecting various institutions abroad and within Japan via frequent exchange of young researchers. This commitment should be realized. The success of this project is important not only for the University of Tokyo but also for the entire science community in Japan.

A6: In order to enhance the students' mobility and to promote research collaboration in all academic fields, IRCN is playing a role as a leading institute to have a university-wide agreement between UTokyo and Harvard. We have prepared a draft of this umbrella agreement (MoU). Already in summer FY2018, six Harvard students will undertake internships at IRCN labs. UTokyo will support the lodging and staying budget for international exchange of undergraduate students. The IRCN core facilities provide common equipment to promote collaborative research not only in UTokyo but also throughout the scientific community of Japan.

Appendix 1 FY2017 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2017. (Note: The list should be for the calendar year, not the fiscal year.)

A. WPI papers

(1) Original articles

1 Good JM, Mahoney M, Miyazaki T, Tanaka KF, Sakimura K, Watanabe M, Kitamura K, Kano M (2017) Maturation of cerebellar Purkinje cell population activity during postnatal refinement of climbing fiber network. Cell Reports, 21: 2066-2073

2 Kawai H, Kawaguchi D, Benjamin DK, Kitamoto T, Yamaguchi M, Gotoh Y, Furutachi S (2017) Area-Specific Regulation of Quiescent Neural Stem Cells by Notch3 in the Adult Mouse Subependymal Zone. J Neurosci., 37: 11867-11880

3 Koike S, Satomura Y, Kawasaki S, Nishimura Y, Kinoshita A, Sakurada H, Yamagishi M, Ichikawa E, Matsuoka J, Okada N, Takizawa R, Kasai K (2017) Application of functional near infrared spectroscopy as supplementary examination for diagnosis of clinical stages of psychosis spectrum. Psychiatry Clin Neurosci, 71: 794-806

4 Koshiyama D, Kirihara K, Tada M, Nagai T, Koike S, Suga M, Araki T, Kasai K (2017) Duration and frequency mismatch negativity shows no progressive reduction in early stages of psychosis. Schizophr Res, 190: 32-38

5 Sasabayashi D, Takayanagi Y, Takahashi T, Koike S, Yamasue H, Katagiri N, Sakuma A, Obara C, Nakamura M, Furuichi A, Kido M, Nishikawa Y, Noguchi K, Matsumoto K, Mizuno M, Kasai K, Suzuki M (2017) Increased Occipital gyrification and development of psychotic disorders in individuals with an at-risk mental state: a multicenter study. Biol Psychiatry, 82: 737-745

6 Yoshino J, Morikawa R, Hasegawa E, Emoto K (2017) Neural circuitry that evokes escape behavior in response to nociceptive stimuli in Drosophila larvae. Curr Biol, 27: 2499-2504

7 Koizumi H, Fujioka H, Togashi K, Thompson J, Yate J, Gleeson J, Emoto K (2017) DCLK1 phosphorylates the microtubule-associate protein MAP7D1 to promote axonal elongation in cortical neurons. Dev Neurobiol, 77: 493-510

B. WPI-related papers

(1) Original articles

8 Sasaki H, Kanamori T, Hyvärinen A, Niu G, Sugiyama M (2017) Mode-seeking clustering and density ridge estimation via direct estimation of density-derivative-ratios. Journal of Machine Learning Research, to appear

9 Hashimoto N, Ito YM, Okada N, Yamamori H, Yasuda Y, Fujimoto M, Kudo N, Takemura A, Son S, Narita H, Yamamoto M, Tha KK, Katsuki A, Ohi K, Yamashita F, Koike S, Takahashi T, Nemoto K, Fukunaga M, Onitsuka T, Watanabe Y, Yamasue H, Suzuki M, Kasai K, Kusumi I, Hashimoto R (2017) The effect of duration of illness and antipsychotics on subcortical volumes in schizophrenia: Analysis of 778 subjects. Neuroimage: Clin, 17: 563-569

10 Eriguchi Y, Kuwabara H, Inai A, Kawakubo Y, Nishimura F, Kakiuchi C, Tochigi M, Ohashi J, Aoki N, Kato K, Ishiura H, Mitsui J, Tsuji S, Doi K, Yoshimura J, Morishita S, Shimada T, Furukawa M, Umekage T, Sasaki T, Kasai K, Kano Y (2017) Identification of candidate genes involved in the etiology of sporadic Tourette syndrome by exome sequencing. Am J Med Genet B Neuropsychiatr Genet, 174: 712-723

11 Shoji T, Aihara K, Yamamoto Y (2017) Quantum model for coherent Ising machines: Stochastic differential equations with replicator dynamics. PHYSICAL REVIEW A, 96(5), 53833: 1-8

12 Yamamura A, Aihara K, Yamamoto Y (2017) Quantum model for coherent Ising machines: Discrete-time measurement feedback formulation. PHYSICAL REVIEW A, 96(5), 53834: 1-8.

(2) Review articles

13 Yamamoto Y, Aihara K, Leleu T, Kawarabayashi K, Kako S, Fejer M, Inoue K, Takesue H (2017) Coherent Ising machines-optical neural networks operating at the quantum limit. NPJ QUANTUM INFORMATION, 3, 49: 1-15

C. Previously published important WPI-related papers

14 Murakami T, Matsui T, Ohki K (2017) Functional Segregation and Development of Mouse Higher Visual Areas. J Neurosci, 37:9424-9437

15 Aihara S, Yoshida T, Hashimoto T, Ohki K (2017) Color Representation Is Retinotopically Biased but Locally Intermingled in Mouse V1. Front Neural Circuits, 11:22

16 Ishida T, Niu G, Sugiyama M (2017) Learning from complementary labels. In I. Guyon, U. V. Luxburg, S. Bengio, H. Wallach, R. Fergus, S. Vishwanathan, R. Garnett (Eds.), Advances in Neural Information Processing Systems, 30 : pp.5644-5654

17 Horev I, Yger F, Sugiyama M (2017) Geometry-aware principal component analysis for symmetric positive definite matrices. Machine Learning, 106(4): pp.493-522

18 Miyazaki T, Yamasaki M, Hashimoto K, Kohda K, Yuzaki M, Shimamoto K, Tanaka K, Kano M, Watanabe M (2017) Glutamate transporter GLAST controls synaptic wrapping by Bergmann glia and ensures proper wiring of Purkinje cells. Proceedings of National Academy of Sciences of the United States of America, 114: 7438-7443

19 Choo M, Miyazaki T, Yamazaki M, Kawamura M, Nakazawa T, Zhang J, Tanimura A, Uesaka N, Watanabe M, Sakimura K, Kano M (2017) Retrograde BDNF to TrkB signaling promotes synapse elimination in the developing cerebellum. Nature Communications, 8: 195

20 Kano M, Watanabe T (2017) Type-1 metabotropic glutamate receptor signaling in cerebellar Purkinje cells in health and disease. F1000Research (F1000 Faculty Rev) , 6:416

21 Nagai T, Kirihara K, Tada M, Koshiyama D, Koike S, Suga M, Araki T, Hashimoto K, Kasai K (2017) Reduced mismatch negativity is associated with increased plasma level of glutamate in first-episode psychosis. Sci Rep, 7(1):2258

22 Sawada K, Kanehara A, Sakakibara E, Eguchi S, Tada M, Satomura Y, Suga M, Koike S, Kasai K (2017) Identifying neurocognitive markers for outcome prediction of global functioning in ultra-high-risk for psychosis and first episode psychosis. Psychiatry Clin Neurosci, 71: 318-327

23 Yahata N, Kasai K, Kawato M (2017) Computational neuroscience approach to biomarkers and treatments for mental disorders. Psychiatry Clin Neurosci, 71: 215-237

24 Kasai K, Ando S, Kanehara A, Kumakura Y, Kondo S, Fukuda M, Kawakami N, Higuchi T (2017) Strengthening community mental health services in Japan. Lancet Psychiatry, 4: 268-270

25 Kasai K, Fukuda M (2017) Science of recovery in schizophrenia research: brain and psychological substrates of personalized value. npj Schizophrenia, 3: 14

26 Ohta S, Koizumi M, Sakai KL (2017) Dissociating effects of scrambling and topicalization within the left frontal and temporal language areas: An fMRI study in Kaqchikel Maya. Front. Psychol. 8, 748: 1-14

27 Yamamoto K, Sakai KL (2017) Differential signatures of second language syntactic performance and age on the structural properties of the left dorsal pathway. Front. Psychol. 8, 829: 1-13

28 Hirata Y, Aihara K (2017) Dimensionless embedding for nonlinear time series analysis. PHYSICAL REVIEW E, 96, 3, 32219: 1-15

29 Duan F, Watanabe K, Yoshimura Y, Kikuchi M, Minabe Y, Aihara K (2017) Detection of atypical network development patterns in children with autism spectrum disorder using magnetoencephalography. PLOS ONE, 12(9), e0184422: 1-25.

30 Amigo JM, Hirata Y, Aihara K (2017) On the limits of probabilistic forecasting in nonlinear time series analysis II: Differential entropy. CHAOS, 27(8), 83125: 1-9.

31 Omi T, Hirata Y, Aihara K (2017) Hawkes process model with a time-dependent background rate and its application to high-frequency financial data. PHYSICAL REVIEW E, 96(1): 12303.

32 Liu X, Chang X, Liu R, Yu X, Chen L, Aihara K (2017) Quantifying critical states of complex diseases using single-sample dynamic network biomarkers. PLOS COMPUTATIONAL BIOLOGY, 13(7), e1005633: 1-21.

33 Hirata Y, Aihara K (2017) Improving time series prediction of solar irradiance after sunrise: Comparison among three methods for time series prediction. SOLAR ENERGY, 149: 294-301.

34 Li Y, Oku M, He G, Aihara K (2017) Elimination of spiral waves in a locally connected chaotic neural network by a dynamic phase space constraint. NEURAL NETWORKS, 88: 9-21

35 Sase T, Katori Y, Komuro M, Aihara K (2017) Bifurcation Analysis on Phase-Amplitude Cross-Frequency Coupling in Neural Networks with Dynamic Synapses. FRONTIERS IN COMPUTATIONAL NEUROSCIENCE, 11(18), 1830: 1-19

36 Nagata M, Hirata Y, Fujiwara N, Tanaka G, Suzuki H, Aihara K (2017) Smoothing effect for spatially distributed renewable resources and its impact on power grid robustness. CHAOS, 27(3), 33104: 1-7

37 Leleu T, Yamamoto Y, Utsunomiya S, Aihara K (2017) Combinatorial optimization using dynamical phase transitions in driven-dissipative systems. PHYSICAL REVIEW E, 95(2), 22118: 1-18.

38 Birkner A, Tischbirek CH, Konnerth A (2017) Improved deep two-photon brain imaging. Cell Calcium, 64: 29-35

39 Tischbirek CH, Birkner A, Konnerth A (2017) In vivo deep two-photon imaging of neural circuits with the fluorescent Ca2+ indicator Cal-590. J Physiology, 595: 3097-3105

40 Keskin AD, Kekuš M, Adelsberger H, Neumann U, Shimshek D, Song B, Zott B, Peng T, Förstl H, Staufenbiel M, Nelken I, Sakmann B, Konnerth A, Busche MA (2017) BACE inhibition-dependent repair of Alzheimer's pathophysiology. Proc Nat Acad Sci USA 114: 8631–8636

41 Midori KN, Hiroaki O, Shoji T (2017) Rod-shaped Neural Units for Aligned 3D Neural Network Connection, Advanced Healthcare Materials, 6, 1700143

42 Chiba K, Chien K, Sobu Y, Hata S, Kato S, Nakaya T, Okada Y, Nairn AC, Kinjo M, Taru H, Wang R, Suzuki

T (2017) Phosphorylation of KLC1 modifies interaction with JIP1 and abolishes the enhanced fast velocity of APP transport by kinesin-1. Mol Biol Cell, 28:3857-3869

43 Nozaki T, Imai R, Tanbo M, Nagashima R, Tamura S, Tani T, Joti Y, Tomita M, Hibino K, Kanemaki MT, Wendt KS, Okada Y, Nagai T, Maeshima K (2017) Dynamic Organization of Chromatin Domains Revealed by Super-Resolution Live-Cell Imaging. Mol Cell. 67:282-293

2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY2017 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

1) Konnerth, Plenary Lecture at The 40th Annual Meeting of the Japan Neuroscience Society,Tokyo 2017/7/20-23
2) Gotoh, Epigenetic control of neural precursor cell fate, Keystone Symposia, Regenerative Biology and Applications, The University of Hong Kong, Hong Kong, China 2017/10/15-19
3) Takeuchi, Keynote Speech at Cell fiber technology for in vitro 3D tissue fabrication, Biofabrication 2017, 2017/10/16
4) Emoto, "Calcium signaling in spatio-temporal regulation of neuronal development and remodeling" The 48th NIPS international Symposium (Okazaki, Japan) 2017/10/31.
5) Aihara, Mathematical Modelling of Complex Systems and its Applications, SNU Electric Power Research Institute, Seoul National University, 2017/11/13.
6) Takeuchi, Lipid bilayer on a chip for biohybrid sensors, The 6th Bioscience and biotechnology International Symposium on a new epoch of membrane science and technology: interface between living and non-living systems, 2018/1/10
7) Ueda, "Whole-body and whole-organ clearing and imaging with single-cell resolution toward organism-level systems biology in mammals", Asia Pacific Bioinformatics Conference (APBC), Yokohama, 2018/1/16
8) Okada, "Development and application of high-speed super-resolution and single-molecule imaging for cell biology studies" at SPIE BioS, Moscone convention center (San Francisco), 2018/1/29
9) Kano, Invited lecture at Mechanisms of activity-dependent synapse elimination in the developing cerebellum, The 8th Brain Research Institute International Symposium, 2018/2/10
10) Kano, Invited lecture at Multiple phases of activity-dependent synapse elimination in the developing cerebellum, The 4th Symposium of NEUROSCIENCE NETWORK IN KOBE, 2018/2/16

3. Major Awards

- List up to 10 main awards received during FY2017 in order from the most recent.
- For each, write the recipient's name, name of award, and year issued.
- In case of multiple recipients, underline those affiliated with the center.

1) Konnerth, Senior-Professorship of the Hertie Foundation (1 Million Euro), 2017
2) Aihara, JSIAM (The Japan Society for Industrial and Applied Mathematics) Achievement Award, 2017
3) Minghao Nie, Takeuchi lab, Excellent Presentation Award for Young Researchers, Micro-Nano Science & Technology Division, The Japan Society of Mechanical Engineers, 2017
4) Okada, Commendation for Science and Technology by the Minister of Education、Culture、Sports、Science and Technology, 2017
5) Ohki, Inoue Prize for Science, 2017
6) Ueda, Innovator of the Year, 2017

Appendix 2　FY 2017 List of Principal Investigators

NOTE:

・Underline names of principal investigators who belong to an overseas research institution. Place an asterisk (*) by names of investigators considered to be ranked among world's top researche

・In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

		<Results at the end of FY2017>				**Principal Investigators Total: 14**	
Name	Age	Affiliation (Position title, department, organization)	Academic degree specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center Director Takao Kurt Hensch*	51	Director, Project Professor,International Research Center for Neurointelligence,The University of Tokyo Institutes for Advanced Study	PhD Neurophysiology	80	October 2017	stayed at the center two times in FY2017,usually stays at Boston Children's Hospital satellite, and very often communicates by 10 emails per day and once a week videoconference Promote IRCN's interests universities, research institutions, and academic societies around the world	manages and directs center's operations
Masanobu Kano*	61	Deputy Director, International Research Center for Neurointelligence,The University of Tokyo Institutes for Advanced Study Professor, Department of neurophysiology, Division of Functional Biology, Graduate School of Medicine, The University of Tokyo	M.D. & Ph.D. Neurophysiology	80	October 2017	usually stays at center and participates in the center's activities as Deputy Director and an Executive Board member	
Kazuo Emoto*	49	Deputy Director, International Research Center for Neurointelligence,The University of Tokyo Institutes for Advanced Study Professor, Department of Biological Sciences, Graduate School of Science, the University of Tokyo	PhD Neural Network	80	October 2017	usually stays at Graduate School of Science next to the center building, and participates in the center's activities as Deputy Director and an Executive Board member	

Name	Age	Affiliation (Position title, department, organization)	Academic degree specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Kazuyuki Aihara*	63	Professor, Department of Informatics and Electronics, Institute of Industrial Science, the University of Tokyo	PhD Biological Information Systems	80	October 2017	usually stays at Institute of Industrial Science and participates in the center's activities as a Steering Comittee member	
Haruo Kasai*	61	Professor, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, the University of Tokyo	MD & PhD Neurophysiology	80	October 2017	usually stays at center and participates in the center's activities as a Steering Comittee member	
Kiyoto Kasai*	47	Professor, Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo	MD & PhD Neuroimaging and Early Intervention for Schizophrenia	80	October 2017	usually stays at The University of Tokyo Hospital and participates in the center's activities as a Steering Comittee member	
Kenichi Ohki*	46	Professor, Department of Integrative Physiology, Division of Functional Biology, Graduate School of Medicine, the University of Tokyo	MD & PhD Neuroscience	80	October 2017	usually stays at center and participates in the center's activities as a Steering Comittee member	
Arthur Konnerth*	64	Director, Institute of Neuroscience, Technical University of Munich	MD & PhD Neurophysiology	50	October 2017	joins 1st IRCN RETREAT and regularly communicates by emails.	Send 1 young scientists(2days) Recruit young scientists
Yukiko Gotoh*	54	Professor, Department of Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, the University of Tokyo	PhD Neural Stem Cells	80	October 2017	usually stays at Graduate School of Pharmaceutical Sciences and participates in the center's activities	

Name	Age	Affiliation (Position title, department, organization)	Academic degree specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Kuniyoshi Sakai*	53	Professor, Department of Basic Science, Graduate School of Arts and Sciences, the University of Tokyo	PhD Neurobiology of Language	80	October 2017	usually stays at Graduate School of Arts and Sciences and participates in the center's activities	
Yasushi Okada*	49	Professor, Department of Physics, Graduate School of Science, the University of Tokyo	M.D. & Ph.D. Bioimaging	32	October 2017	usually stays at Graduate School of Science and participates in the center's activities	
Shoji Takeuchi*	45	Professor, Department of Mechanical and Biofunctional Systems, Institute of Industrial Science, the University of Tokyo	PhD Biohybrid Systems	80	October 2017	usually stays at Institute of Industrial Science and participates in the center's activities	
Masashi Sugiyama*	43	Professor, Department of Complexity Science and Engineering, Graduate School of Frontier Sciences, the University of Tokyo	PhD Statistical Machine Learning	16	October 2017	usually stays at Graduate School of Frontier Sciences and participates in the center's activities	
Hiroki Ueda*	42	Professor, Department of Systems Pharmacology, Division of Functional Biology, Graduate School of Medicine, the University of Tokyo	MD & PhD Systems Biology	80	October 2017	usually stays at center and participates in the center's activities	

*Percentage of time that the principal Investigator will devote to his/her work for the center vis-à-vis his/her total working hours (total time for whole working activities including education, medical services, and others as well as research).

Researchers unable to participate in project in FY 2017

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken
Rachel Wong	Professor, Department of Biological Structure, School of Medicine, University of Washington	-	Because the work at the Affiliation became very busy compared with the time of application	joins in the Symposium etc

Appendix 3-1 FY 2017 Records of Center Activities

1. Researchers and center staffs, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Regarding the number of researchers at the Center, please fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

Dr. Yazaki-Sugiyama, currently an Associate Professor at the OIST, is joining the IRCN as a new PI (cross appointment) from April, 2018. Dr. Kondo, currently a Lecturer at the Faculty of Medicine of the University of Tokyo, and Dr. Fujiwara, currently an Assistant Professor at Tokyo University of Science, are joining the IRCN as core managers/associate professors from April, 2018. Dr. Ukai, currently a Senior Research Scientist at RIKEN, is joining the IRCN as a core manager/associate professor from May, 2018.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
Harvard University / Boston Children's Hospital	Takao Kurt Hensch	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN	Hiroki Ueda, Yasushi Okada, Masashi Sugiyama	

2. Securing external research funding*

External research funding secured in FY2017

Total: 923,057,021 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.

* External research funding includes "Grant-in-Aid for Scientific Research," funding for "commissioned research projects," and for "joint research projects" as listed under "Research projects" in Appendix 3-2, Project Expenditures.

Grant-in-Aid for Scientific Research, etc.: 255,212,206 yen
Commissioned Research Projects, etc: 580,123,427 yen
Joint Research Projects: 15,450,191 yen
Others (donations. etc): 72,271,197 yen

The acquired large-scale research grants for FY2017
AMED Brain Mapping by Integrated Neurotechnologies for Disease Studies (Hiroki Ueda): 142,058,482 yen
JST CREST (Haruo Kasai): 77,537,909 yen
Grant-in-Aid for Specially Promoted Research (Masanobu Kano): 57,000,000 yen
AMED Strategic Research Program for Brain Science (Yukiko Gotoh): 54,900,000 yen
Social Cooperation Program: Brain-Morphic AI to Resolve Social Issues (Kazuyuki Aihara): 52,457,708 yen

3. International research conferences or symposiums held to bring world's leading researchers together

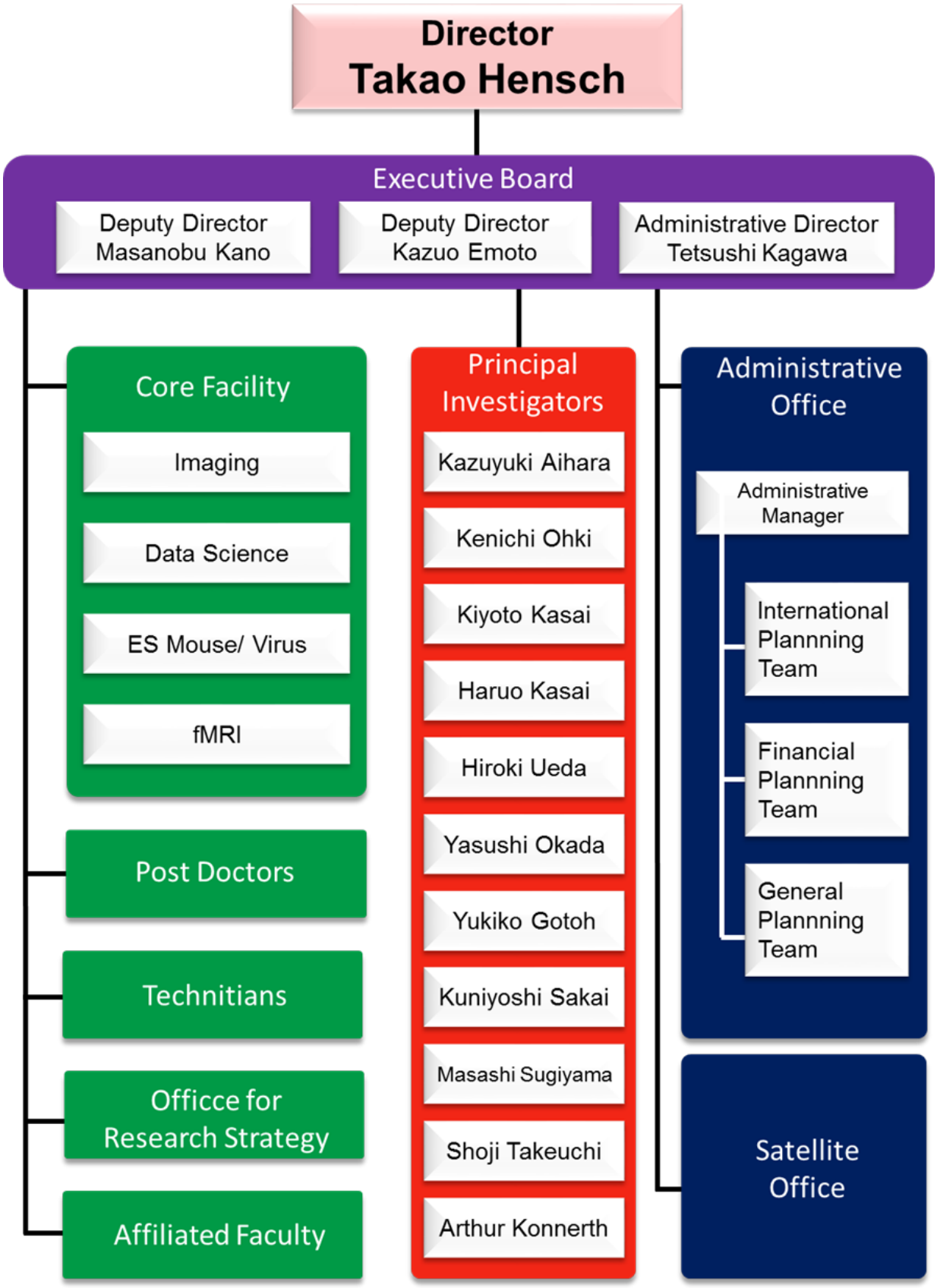
- Indicate the number of international research conferences or symposiums held in FY2017 and give up to three examples of the most representative ones using the table below.

FY 2017: 2 meetings

Major examples (meeting titles and places held)	Number of participants
The 1st IRCN International Symposium at Ito International Research Center, Hongo Campus, UTokyo	From domestic institutions: 187 From overseas institutions: 5
The 1st IRCN Retreat at The Institute Onward Soken, Yokohama	From domestic institutions: 86 From overseas institutions: 3
	From domestic institutions: OO From overseas institutions: OO

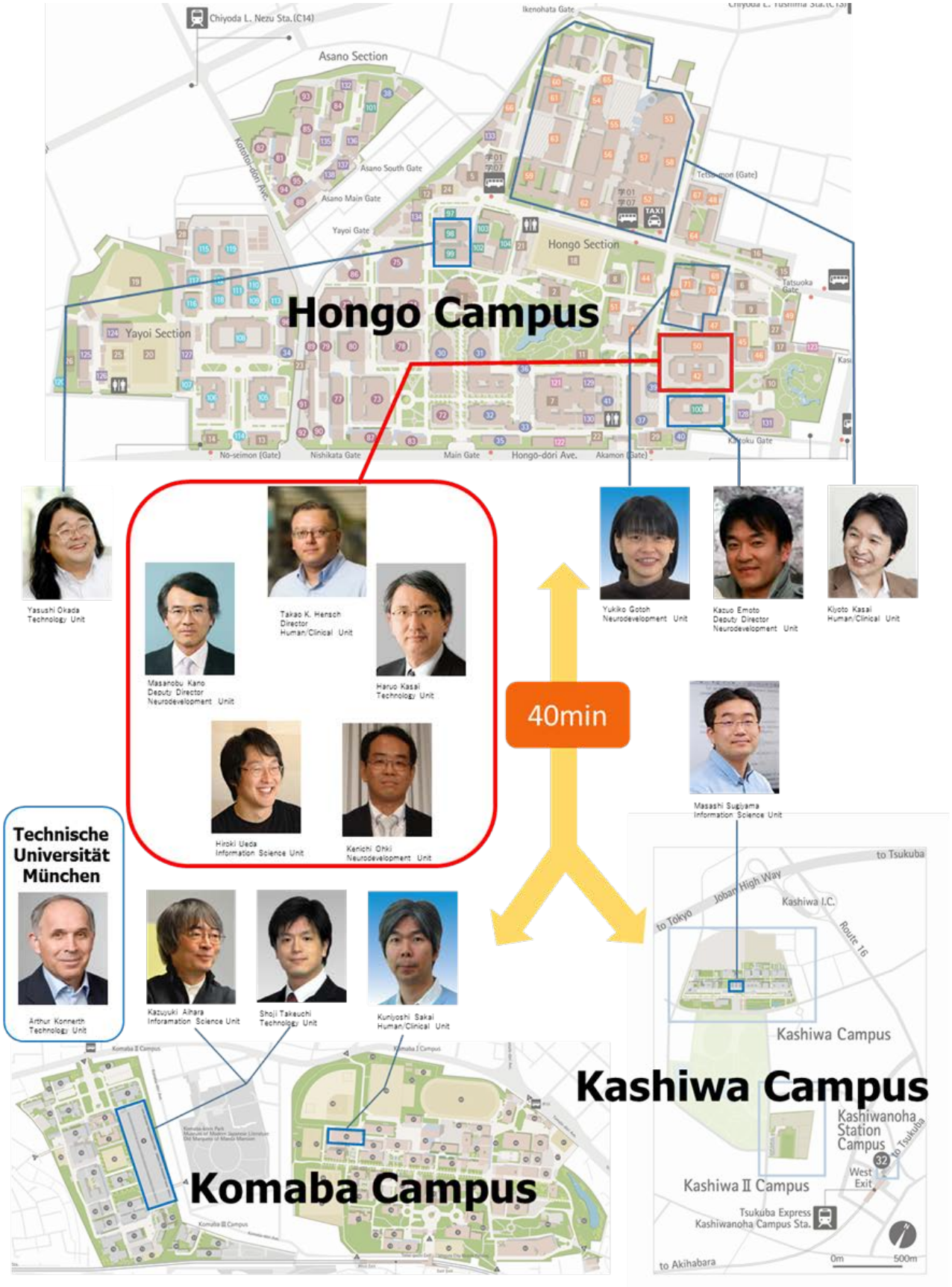
4. Center's management system

- Please diagram management system in an easily understood manner.
- If any changes have been made in the management system from that in the latest "center project," please describe them. Please describe any important changes made in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).



5. Campus Map

- Please draw a simple map of the campus showing where the main office and principle investigator(s) are located.



Appendix 3-1a FY 2017 Records of Center Activities

1. Researchers and other center staffs, satellites, partner institutic

1-1. Number of researchers and other center staffs

* Please fill in the number of researchers and other center staffs in the table blow.
* Please describe the final goals for achieving these numbers and dates when they will be achieved.

a) Principal Investigators（full professors, associate professors or other researchers of comparable standing)

(persons)

	At beginning of project	At end of FY 2017	Final goal (Date: March, 2022)
Researches from within the host institution	12	12	11
Foreign researchers invited from abroad	2	2	4
Researchers invited from other Japanese institutions	0	0	2
Total principal investigators	14	14	17

b) Total members

	At beginning of project		At end of FY2017		Final goal (Date: March, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	27		71		70	
Overseas researchers	3	11.1	25	35.21	19	27.14
Female researchers	4	14.8	17	23.94	17	24.29
Principal investigators	14		14		17	
Overseas PIs	2	14.3	2	14.29	4	23.53
Female PIs	1	7.14	1	7.143	2	11.76
Other researchers	13		57		53	
Overseas researchers	1	7.69	23	40.35	15	28.3
Female researchers	3	23.1	16	28.07	15	28.3
Research support staffs	0		0		20	
Administrative staffs	3		6		10	
Total number of people who form the "core" of the research center	30		77		100	

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the “Total Cost” column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the “Amount covered by WPI funding” column, enter the amount covered by WPI within the total amount.
* In the “Personnel,” “Project activities,” “Travel,” and “Equipment” blocks, the items and details may be changed to coincide with the project’s actual content.

(Million yens)

Cost Items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total Costs	Amount covered by WPI funding
Personnel	Center director and Administrative director	11	11
	Principal investigators (no. of persons):12	46	0
	Other researchers (no. of persons):9	10	10
	Research support staffs (no. of persons):4	2	2
	Administrative staffs (no. of persons):5	16	1
	Subtotal	85	24
Project activities	Cost of satellite organizations (no. of satellite organizations):1	42	42
	Cost of international symposiums (no. of symposiums):2	6	6
	Rental fees for facilities	10	10
	Cost of consumables	39	39
	Cost of Fixtures	23	23
	Cost of utilities	1	1
	Cost of public relations	1	1
	Cost of Core Facility established	34	34
	Other costs	8	8
	Subtotal	164	164
Travel	Domestic travel costs	1	1
	Overseas travel costs	5	5
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):4	2	2
	Travel cost for scientists on secondment (no. of domestic scientists):OO (no. of overseas scientists):OO		
	Subtotal	8	8
Equipment	Depreciation of buildings	1	1
	Depreciation of equipment	6	6
	Subtotal	7	7
Research projects (Detail items must be fixed)			
	Grants-in-Aid for Scientific Research, etc.	276	0
	Commissioned research projects, etc.	636	0
	Joint research projects	16	0
	Ohers (donations, etc.)	72	0
	Subtotal	1,000	0
Total		1,264	203

Costs (Million yens)

WPI grant in FY 2017	600
Costs of establishing and maintaining facilities	142
Establishing new facilities (Number of facilities: , OO m²)	0
Repairing facilities (Number of facilities: , 906 m²)	142
Others	0
Cost of equipment procured	262
Multiphoton microscope system 2 sets	58
Femtosecond laser 2 sets	44
GPGPU Server for Deep Learning 1 set	16
Takekru Storage Server 1 set	10
Laser System for Lightsheet Microscope 1 set	10
All-in-one Fluorescence Microscope 1 set	10
Others	114

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc.), indirect funding, and allocations from the university’s own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by Grants-in-Aid or under commissioned research projects or joint research projects, the amounts should be entered in the “Research projects” block.

2) Costs of Satellites and Partner institutions

(Million yens)

Cost Items	Details	Total Costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):OO		
	Other researchers (no. of persons):6		
	Research support staffs (no. of persons):OO		
	Administrative staffs (no. of persons):OO		
	Subtotal	20	20
Project activities	Subtotal	22	22
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		42	42

Exchange rate at the time of remittance @\ 112

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the “Total Cost” column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the “Amount covered by WPI funding” column, enter the amount covered by WPI within the total amount.
* In the “Personnel,” “Project activities,” “Travel,” and “Equipment” blocks, the items and details may be changed to coincide with the project’s actual content.

(Million yens)

Cost Items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total Costs	Amount covered by WPI funding
Personnel	Center director and Administrative director	10,488,416	10,488,416
	Principal investigators (no. of persons):12	46,288,859	0
	Other researchers (no. of persons):9	10,099,677	10,099,677
	Research support staffs (no. of persons):4	1,964,240	1,964,240
	Administrative staffs (no. of persons):5	15,981,721	725,281
	Subtotal	84,822,913	23,277,614
Project activities	Cost of satellite organizations (no. of satellite organizations):1	41,860,000	41,860,000
	Cost of international symposiums (no. of symposiums):2	5,741,328	5,741,328
	Rental fees for facilities	10,100,500	10,100,500
	Cost of consumables	39,419,171	39,419,171
	Cost of Fixtures	22,757,595	22,757,595
	Cost of utilities	974,216	974,216
	Cost of public relations	701,162	701,162
	Cost of Core Facility established	34,642,061	34,642,061
	Other costs	7,650,888	7,650,888
	Subtotal	163,846,921	163,846,921
Travel	Domestic travel costs	1,189,682	1,189,682
	Overseas travel costs	5,116,218	4,873,912
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):4	2,281,189	2,281,189
	Travel cost for scientists on secondment (no. of domestic scientists):OO (no. of overseas scientists):OO		
	Subtotal	8,587,089	8,344,783
Equipment	Depreciation of buildings	968,839	633,037
	Depreciation of equipment	5,944,100	5,944,100
	Subtotal	6,912,939	6,577,137
Research projects (Detail items must be fixed)			
	Grants-in-Aid for Scientific Research, etc.	275,876,206	0
	Commissioned research projects, etc.	635,879,550	0
	Joint research projects	15,450,191	0
	Ohers (donations, etc.)	72,271,197	0
	Subtotal	999,477,144	0
Total		1,263,647,006	202,046,455

Costs (Million yens)

WPI grant in FY 2017	600,000,000
Costs of establishing and maintaining facilities	142,041,693
Establishing new facilities (Number of facilities: , OO m²)	0
Repairing facilities (Number of facilities: , 906 m²)	142,041,693
Others	0
Cost of equipment procured	262,488,989
Multiphoton microscope system 2 sets	57,996,000
Femtosecond laser 2 sets	43,981,920
GPGPU Server for Deep Learning 1 set	15,994,800
Takekru Storage Server 1 set	9,990,000
Laser System for Lightsheet Microscope 1 set	9,990,000
All-in-one Fluorescence Microscope 1 set	9,763,740
Others	114,772,529

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc.), indirect funding, and allocations from the university’s own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by Grants-in-Aid or under commissioned research projects or joint research projects, the amounts should be entered in the “Research projects” block.

2) Costs of Satellites and Partner institutions

(Million yens)

Cost Items	Details	Total Costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):OO		
	Other researchers (no. of persons):6		
	Research support staffs (no. of persons):OO		
	Administrative staffs (no. of persons):OO		
	Subtotal	20,234,475	20,234,475
Project activities	Subtotal	21,625,525	21,625,525
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		41,860,000	41,860,000

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Appendix 4 FY 2017 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2017 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2018 and not described in Appendix 1.

Overseas Satellite 1 **Name** (Total: OO papers)

1)
2)
3)
4)

Overseas Satellite 2 **Name** (Total: OO papers)

1)
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2017. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2017		1	2		
		0	0		

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2017	0				
	1				

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2017					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2017					

Appendix 5 FY 2017 Visit Records of World Top World-level Researchers from Abroad

* If top world-level researchers have visited/ stayed at the Center, please provide information on them in the below table.
* To determine whether the researcher is a "top world-level researcher," please see the standard stipulated in the Application Guideline.

Total: 6

	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
1	Rachel Wong	58	Professor, Department of Biological Structure, University of Washington	Ph.D., Neuroscience	2015 Allen Distinguished Investigator Award (shared with T. Reh, F. Rieke) 2016 Brian Boycott Prize in Retinal Neurobiology and Visual Processing (FASEB)	12/15-18, 2017	participation in symposium and giving a talk
2	Gabriel Kreiman	44	Professor, Harvard Medical School/Boston Children's Hospital	Ph.D., Biology	2015 Pisart Award for Vision Research 2016 McKnight Award for Neuroscience	12/15-18, 2017	participation in symposium and giving a talk
3	Gavin H. Whitelaw	38	Professor, Executive Director Edwin O. Reischauer Institute of Japanese Studies, Harvard University	Ph.D., Anthropology	2009-Present Executive Board Member, Association of Asian Studies/Asian Studies Conference Japan (ASCJ).	12/17, 2018	participation in symposium
4	Yosuke Morishima	40	Professor, University of Bern	M.D,. & Ph.D., Medicine	Group leader at Division of Systems Neuroscience Psychopathology,Translational Research Center, University Hospital of Psychiatry	12/15-18, 2017	participation in symposium and giving a talk
5	Mayumi Kimura	57	Group leader, Max-Planck Max Planck Institute of Psychiatry	M.D,. & Ph.D., Medicine	Group leader at Division of Systems Neuroscience Psychopathology,Translational Research Center, University Hospital of Psychiatry	1/5, 2018	short-term stay for meeting for appointment
6	Arthur Konnerth	64	Director, Institute of Neuroscience, Technische Universita¨t Mu¨nchen	Ph.D., Medical	2015 Brain Prize (shared with Winfried Denk, Karel Svoboda and David Tank)	3/15-19, 2018	participation in retreat and giving a talk as a principal investigator
7	Reiko Mazuka		Research Professor in the Department of Psychology and Neuroscience, Duke	Ph.D., Developmental Psychology	2004-Present, Laboratory Head Laboratory for Language Development, RIKEN Brain ScienceInstitute 2013-Present, Research Professor Department of Psychology & Neuroscience, Duke University	3/17-18, 2018	participation in retreat and giving a talk
8							
9							
10							

Appendix 6 FY2017 State of Outreach Activities

* Using the table below, show the achievements of the Center's outreach activities in FY2017(number of activities, times held).
* Describe those activities that have yielded novel results or that warrant special mention in the "Special Achievements" space below.
* In appendix 7, list and describe media coverage (e.g., articles published, programs aired) in FY2017 resulting from press releases and reporting.

Activities	FY2017 (number of activities, times held)
PR brochure, pamphlet	Asia research news 2018
Lectures, seminars for general public	IRCN 1st International Science Symposium
Teaching, experiments, training for elementary, secondary and high school students	N/A
Science café	Starting from May 23rd, 2018
Open houses	N/A
Participating, exhibiting in events	WPI Science Symposium, AAAS Annual Meeting
Press releases	3 scientific press release (Drs. Kano, Ueda) 2 institutional press release (Launch of IRCN, announcement of science symposium)

<Special Achievements>
Launch of IRCN Website

Appendix 7 FY 2017 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2017 resulting from press releases and reporting.

	Date	Types of Media (e.g., newspaper, television)	Description
1	2017-08-25	television	TV program "Shiten Ronten" on NHK giving the commentary on AI and brain
2	2017-11-12	newspaper	Nikkei Shimbun "Kasai et al. conducted a multi-center MRI study on ultra-high risk individuals for developing schizophrenia, and found that increased cortical gyrification may be a promising biomarker for prediction of psychosis onset.
3	2017-12-19	news website	Eurekalert! "University of Tokyo International Research Center for Neurointelligence holds first annual symposium"
4	2017-12-19	news website	Science Newsline Technology "University of Tokyo International Research Center for Neurointelligence holds first annual symposium"
5	2018-01-09	press release	Press release at IIS entitled "To jump or not to jump: Impact of renewables and trading on power grid frequency fluctuations" (Announcement on the publication of the article "Non-Gaussian power grid frequency fluctuations characterized by Lévy-stable laws and superstatistics" in Nature Energy
6	2018-01-09	newspaper	Nagasaki Shimbun "Non-Gaussian power grid frequency fluctuations characterized by Lévy-stable laws and superstatistics" in Nature Energy
7	2018-01-09	newspaper	Ise Shimbun "Non-Gaussian power grid frequency fluctuations characterized by Lévy-stable laws and superstatistics" in Nature Energy
8	2018-01-12	newspaper	Nikkan Kogyo ShimbunI "Non-Gaussian power grid frequency fluctuations characterized by Lévy-stable laws and superstatistics" in Nature Energy
9	2018-01-16	newspaper	Nikkei Business Daily "Non-Gaussian power grid frequency fluctuations characterized by Lévy-stable laws and superstatistics" in Nature Energy
10	2018-03-09	newspaper	Kagaku shimbun "Constructing of Single-cell resolution Whole-brain Atlas"
11	2018-03-12	newspaper	Nikkei shimbun "Observation of fluorescent-labeled cells in the well-cleared mouse brain"
12	2018-03-15	news website	ALZFORUM "Compact Mouse Brain Atlas: A New Tool for Studying Neurodegeneration?"
13	2018-03-22	journal	Nature "In addition to the Kavli Institute for the Physics and Mathematics of the Universe, the International Research Center for Neurointelligence was selected in 2017 as our second WPI centre"