



Department of Epilepsy, Movement Disorders and Physiology  
Kyoto University Graduate School of Medicine

# Annual Report

2019, 2020, 2021

April 2022



<Front cover>

Design of the cover page is the slow waveforms with different colors, which may remind you of brain waveforms and different frequencies.

Hoping to enjoy EEG wave surfing.

**Department of Epilepsy, Movement Disorders and Physiology**  
**Kyoto University Graduate School of Medicine**



**Annual Report**  
**2019, 2020, 2021**



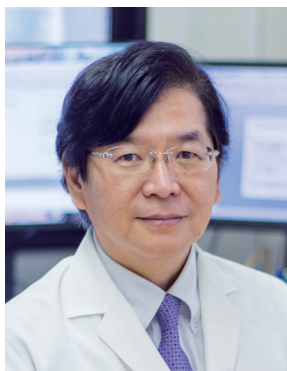
**April 2022**





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## Preface (Report of the activity)



Following the completion of the first 5 years of the Department of Epilepsy, Movement Disorders and Physiology from August 2013 to May 2018, the next 5 years of this department has started as “the Industry-Academia Collaboration Course” from June 1st, 2018. We are very pleased to make a summary report for the initial 3 years and a half, as similarly done since 2013 previously. Since the middle of this period, the beginning of 2020, the unprecedented COVID-19 pandemic disaster has swept the world and has impeded all aspects of research, clinical practice and education. Nevertheless, we could manage to continue our activity and we would like to express our sincere gratitude for the cooperation of everyone involved in and supporting this department.

First of all, we sincerely appreciate that this department has received support as “the Industry-Academia Collaboration Course” for collaborative research by Eisai Co., Ltd., and for endowment by Nihon Kohden Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and UCB Japan Co., Ltd (as listed by alphabetical order). Within the Kyoto University, we are grateful to the warmest and continuous support by the management committee by Department of Neurology (chaired by Prof. Ryosuke Takahashi), and also by the Departments of Neurosurgery (Prof. Susumu Miyamoto), Psychiatry (Prof. Toshiya Murai), Pediatrics (Prof. Toshio Heike and then Prof. Junko Takita), and Diagnostic Imaging & Nuclear Medicine (Prof. Kaori Togashi and then Prof. Yuji Nakamoto), and as an external member Eisai Co., Ltd. (Mr. Toshihisa Hanada and then Dr. Ryan Edbert Husni) for their guidance.

This course started 1) a five-year contracted collaborative research (with Eisai Co., Ltd.) in the form of an “industry-academia collaborative course”. The content can be summarized as “Clinical research on the characteristics of paroxysmal depolarization shifts (PDS) with a focus on human epilepsy, and the individualization of the action mechanisms of antiepileptic drugs, and generator mechanisms of infraslow, DC shifts and cortical spreading depolarization (CSD) for chronic epilepsy, migraine, and cerebrovascular disorders”, and the details are described separately in this report. The following items – items 2) and 3) – corresponded to the contributed matters done “Department of Epilepsy, Movement Disorders and Physiology” so far. 2) Clinical activity and education: Our objectives include multidisciplinary approaches to elucidate pathophysiology “epilepsy/movement disorders”, promotion of its treatment and highly advanced medicine, and its establishment and dissemination as a practical clinical treatment. Simultaneously, we seek to provide training and educational opportunities for specialists and clinical researchers who will play a future role in the field – both in Japan and abroad. 3) Research: Our objectives include promoting the development of both clinical neurophysiology research with clinical application and epilepsy research and treatment. It is because both are two sides of the same coin.

In item 1) mentioned above, the novel “clinical research of the characterization of PDS focused on epilepsy and the individualization of the action mechanisms of antiepileptic drugs” have been published in many international journals. PDS focused on human epilepsy are not simply giant pathological EPSP as was conventionally understood, but also it could extensively vary in duration and the degree of involvement in which humoral factors or postsynaptic membrane receptors (which act as carriers). It is understood that important information will be provided by the analyses on the clinical effects of the AMPA receptor antagonists and other drugs that have direct and indirect inhibitory mechanisms on PDS, and increasing the translatability of these results to basic experiments (Please refer to III. Activity report of this report for results of each study).

In item 2) mentioned above, we have directly contributed as much as possible within the university hospital (e.g., electrocerebral inactivity and so on) over the past years (since the start of our course in 2013) in the fields of

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EEG, epilepsy and movement disorders. We have also simultaneously directly continued contributing at the Kyoto/Kinki regional level by organizing annual EEG/EMG seminar (which is held every winter) for physicians and clinical technologists; and at a national level for annual advanced EEG teaching course (held every summer). We have accepted an average of 3-4 or more EEG/Epilepsy fellows in a year in collaboration with the department neurology in order to provide specialized education for future specialists. We have also trained 3-4 EEG/epilepsy fellowship supported and granted by The Japanese Society of Neurology since 2017 again in collaboration with the department of neurology.

In item 3) mentioned above, we have promoted domestic and international collaborative research as a member of the planning team for the new academic research of the "oscillology" (Interdisciplinary Area: Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature), as well as domestic multi-institutional collaborative research and collaborative research with overseas institutions at the Japan Agency for Medical Research and Development (AMED) (research aimed at clarifying glial function in intractable epilepsy pathologies and to prepare medical treatment guidelines).

In this annual report, I would like to analyze the current situation and conduct a self-assessment by summarizing what we have done in the last 3 and a half years since 2018 from the viewpoint of 3 important axes of clinical practice, education, and research. It could help us improve and modify the current condition, and also start the new concerns. We would greatly appreciate your any feedback to us that is very helpful for our future contribution to the patients in this planet. Finally, this annual report was created with the support of our course members and associates, and I would like to express my gratitude for them here

February, 2022

With my best wishes,



Akio IKEDA, MD, PhD. FACNS  
Chairman and Professor  
Department of Epilepsy, Movement Disorders and Physiology  
Kyoto University Graduate School of Medicine



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# Introduction

To begin with

Since the middle of this period, the beginning of 2020, the unprecedented COVID-19 pandemic disaster has swept the world and has impeded all aspects of research, clinical practice and education. Nevertheless, we could manage to continue our activity and we would like to express our sincere gratitude for the cooperation of everyone involved in this department. As in the past, detailed information is provided in this report. As such, we would appreciate it if you could take a look at it. In place of the "Introduction," I would like to summarize below what I felt was especially important about general matters related to the content of this course during the past year (from June 1, 2018 to May 31, 2021). We would appreciate it if you can provide your commentary here as well.

- 1) The Epilepsy Care Support Center (ECSC) was opened at Kyoto University Hospital
- 2) Changes in Epilepsy Treatment Conditions since 2018
- 3) The results of industry-academia collaboration research
- 4) The results of industry-academia collaboration
- 5) Oscillology research promotion, fundamentals, and clinical translatability
- 6) EEG/Epilepsy fellowship, etc.
- 7) Opportunities for specialized training in epilepsy and clinical EEG

## **1) The Epilepsy Care Support Center (ECSC) was opened at Kyoto University Hospital**

This Center (ECSC) was established on November 1, 2018, with the aims of providing comprehensive and efficient medical practice, to provide support for patients with epilepsy, and to promote clinical research on epilepsy. Activities are comprehensive including inpatients and outpatients, and the affiliated departments (epilepsy/movement disorders/physiology, neurology, pediatrics, neurosurgery, neuropsychiatry) work closely together to "see" (i.e., visualize and make transparent) epileptic treatment at Kyoto University Hospital. At the same time, it is essential to provide information on a various aspects in epilepsy care. In the past, examined patients were given handouts as needed – however, we have set up the website to provide direct downloads for use by individuals ([http://epilepsy.med.kyoto-u.ac.jp/supportcenter\\_j](http://epilepsy.med.kyoto-u.ac.jp/supportcenter_j)).

Specialized materials for healthcare professionals were also provided. Among the downloadable materials mentioned above, we would like to thank each of the participants and the associated organizations for their approval of the use of copyrighted materials. We hope that we will seek to provide epilepsy medical care and support, education, research, and information dissemination to society (see footnote for QR code).

## **2) Changes in Epilepsy Treatment Conditions since 2018**

Awareness and medical care for epilepsy have been actively promoted worldwide ever since the resolution issued at the WHO meeting in May 2015, which stated that epilepsy is an important disease that needs to be solved within the next 10 years (World Health Assembly closes, passing resolutions on air pollution and epilepsy). Epilepsy eradication was, subsequently, addressed as a side project of the WHO meeting in May 2019 – consequently, this was heavily addressed at the opening ceremonies and workshops of the biennial International Epilepsy Congress, held in Bangkok in June 2019 and sponsored by ILAE, as a global campaign of WHO.

In 2021 and hopefully in 2022, respectively, WHO resolution has been and will be done, respectively for (GLOBAL ACTION PLAN on the public health response to epilepsy2020-2030) and Intersectoral global action plan on epilepsy and other neurological disorders (IGAP)

In fiscal year 2015, the Japanese Ministry of Health, Labour and Welfare launched the "Project to Improve Cooperation in Regional Medical Care" as a three-year model project, becoming a primary project in 2019. Those hospitals which are recognized as base hospitals throughout the country expanded to >20 prefectures. As such, there was gradual progress in equal access to epilepsy treatment.

Japan Epilepsy Society (JES) has defined and have approved comprehensive epilepsy center since 2019. It has further advanced the equality and standardization of epilepsy care based on institutional standards that conform to conditions in Japan.

### 3) The results of industry-academia collaboration research

The "Clinical research on the characteristics of paroxysmal depolarization shifts (PDS) with a focus on human epilepsy, and the individualization of the action mechanisms of antiepileptic drugs, and generator mechanisms of infraslow, DC shifts and cortical spreading depolarization for chronic epilepsy, migraine, and cerebrovascular disorders" was initiated as joint research (Eisai Co., Ltd.) from June 2019. The novel "clinical research of the characterization of PDS focused on epilepsy and the individualization of the action mechanisms of antiepileptic drugs" have been published in many international journals. PDS focused on human epilepsy are not simply giant pathological EPSP as was conventionally understood, but also it could extensively vary in duration and the degree of involved in which humoral factors or postsynaptic membrane receptors (which act as carriers). It is understood that important information will be provided by the analyses on the clinical effects of the AMPA receptor antagonists and other drugs that have direct and indirect inhibitory mechanisms on PDS, and increasing the translatability of these results to basic experiments.

Throughout the first year, in particular, we clarified the characteristic action mechanisms of the AMPA receptor antagonist perampanel and its effects on cortical myoclonus, which is an epileptic pathology which maximizes perampanel expression. This was conducted as a case accumulation study which clarified multifactorial correlations among clinical symptoms, extremely characteristic effects in giant SEP, dose, therapeutic effects, clinical neurophysiological indicators, blood levels, etc., and these results were reported in international journals (Oi, K. et al. Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. *Clinical Neurophysiology*. 130 (2019)1804–1812). We have also prepared for an international collaborative study on cortical myoclonus in perampanel and conducting a clinico-physiological study of the effects of perampanel on giant SEP, an epileptic biomarker. (Please refer to Page 9 of this report)

### 4) The results of industry-academia collaboration

We have also reported the results and current status of industry-academia collaboration in this annual report. We were able to conduct fruitful collaborative research with supporting and associated companies while ensuring transparency and equality (Please refer to Page 13 of this report).

### 5) Oscillology research promotion, fundamentals, and clinical translatability

The "Understanding of Human Nature Based on Nonlinear Oscillation Phenomena" project began in 2015 and lasted 5 years as part of MEXT's research on new academic fields (area proposal type). The human brain is composed of signals for oscillatory phenomena that range from the cellular level to the integrative functions of the whole brain. It can be exemplified by a codon in the smallest unit of a gene. Normal brain function in humans manifests itself by nonlinear interactions between multi-dimensional and multi-hierarchical oscillatory phenomena, and abnormal expression of brain function has the same operating principle. Epilepsy can be viewed as a "network disease" in which an autonomous brain network suddenly over-oscillates in various dimensions and hierarchies. In this research area, we have been recording local- and broad-spectrum mass oscillation phenomena involved in normal brain function and epileptic seizure onset from the perspective of the human brain (see the following website for more details: <http://www.nips.ac.jp/oscillology/index.html>).

In the 5<sup>th</sup> year of 2019, our research area was highly rated since it newly elucidated that "chronic epileptic seizures involve not only neurons as previously understood, but actively include glia, both of which control ultra-high- and ultra-low-frequency activity, respectively, and that they are closely linked through disruption and coordination of extracellular K homeostasis".



## 6) EEG/Epilepsy fellowship, etc.

We have accepted the EEG/Epilepsy fellowship as one of the key pillars of teaching in collaboration with the department of neurology since 2011. Almost every year, 1-3 junior doctors have constantly participated in subspecialty clinical training and clinical research. Meanwhile, the fellowship provided by Japanese Society of Neurology also done in Kyoto University Hospital since 2017. It provides a support system for short-term domestic residency training in EEG/epilepsy/neurophysiology. We contributed to accept 2-3 fellowships each year i in collaboration with the department of neurology.

## 7) Opportunities for specialized training in epilepsy and clinical EEG

Professional training in clinical EEE is essential for the clinical practice of epilepsy. Not only do we provide opportunities for in-hospital clinical training, we also organize the Japanese Society of Clinical Neurophysiology (JSCN) sponsored seminar, "Advanced course EEG seminar" annually at Kyoto University. We also organized similar short course "EEG and EMG seminar" at Kyoto University Hospital.

The Kinki Region Adult Epilepsy Seminar – co-sponsored by the JES Kinki Regional Association, UCB Japan Co. Ltd., Otsuka Pharmaceutical Co. Ltd., and Nihon Kohden Co. – has been held every year since 2017 as an educational seminar for epilepsy. We hope to continue to contribute to various societies relating to epilepsy, EEG, and clinical neurophysiology. Furthermore, we would also like to contribute to provide specialized training in clinical EEG.

For the past 20 years or more, weekly EEG teaching session have been held every Wednesday from 7:00 pm, for participants from inside and outside the hospital. Since March 2020, because of COVID-19 pandemic, it has changed to web-conference system from face to face conference, and thus participants all over the country could attend.

I would be very grateful if young teachers who are interested in our programs would have a chance to visit us.

February, 2022

With my best wishes,



Akio IKEDA, MD, PhD. FACNS

Chairman and Professor

Department of Epilepsy, Movement Disorders and Physiology

Kyoto University Graduate School of Medicine

(The following is an introduction page of the Epilepsy Medical Support Center at Kyoto University Hospital.)



Pamphlet







## **Funding prospects**

Establishment      June 1st, 2018

## **Name of the Industry-Academia Collaboration Course**

Department of Epilepsy, Movement of Disorders and Physiology  
Kyoto University Graduate School of Medicine

## **Founding vision**

- 1) We clarify the pathophysiology and clinical knowledge of epilepsy and its related movement disorders, promoting the development of diagnostic and therapeutic methods, and education.
- 2) We continue to develop our ability to diagnose and treat the patients with epilepsy and movement disorders by using a variety of highly advanced techniques.
- 3) We make best efforts to offer opportunities of trainings and educations to young physicians both from Japan and abroad to foster the specialists and physician-scientists in the field of epilepsy.
- 4) As an academic department in the university hospital, we promote researches and clinical applications of clinical neurophysiology, which is essential for elucidating the pathophysiology and developing the treatment of clinical epileptology.

## **Clinical practice and Research for epilepsy and movement disorders**

- 1) Outpatient department
- 2) Inpatient evaluation (including long-term video EEG monitoring) and treatment
- 3) Promotion of epileptic surgery
- 4) Development of diagnostic methods for brain function
- 5) Development and promotion of novel treatment
- 6) Promotion of clinical trials for antiepileptic drugs
- 7) Promotion of basic neuroscience

## **Education**

- 1) Promotion of hospital-clinic collaboration with other institutes
- 2) Promotion of trainings and educations to young physicians both from Japan and abroad to foster the specialists and physician-scientists in the field of epilepsy.
- 3) Education for nurses caring epilepsy patients
- 4) Provide clinical information to patients with epilepsy and their family as well as societies.

## **Research vision**

### **Industry-Academia Collaboration**

- 1) The Effectiveness of Perampanel against Progressive Myoclonus Epilepsy
- 2) Physiological analysis for the effect of Perampanel on giant SEP as a marker of epilepsy
- 3) The migraine's mechanism and the physiological biomarker of its diagnosis and treatment

### **General**

- 1) Promotion of basic neuroscience and clinical trials about the action mechanism and effect of antiepileptic drugs.
- 2) Development of medical devices for wide-band EEG recording&analysis, and its application to elucidation of epileptogenicity
- 3) Promotion of epilepsy surgery and research on higher brain functions&its plasticity under epileptic conditions

- 4) Combined imaging and neurphysiological researches on the pathophysiology of epileptic focus
- 5) Research on the pathophysiology and treatment of movement disorders
- 6) iPS (induced pluripotent stem) cell research and animal model research on epileptogenesis
- 7) Establishment of the training programs for the advanced specialists in the related fields
- 8) Promote collaborative researches with basic and mathematical scientists to understand neural oscillations underlying both physiological brain functions and pathology

### Companies of endowment (in alphabetical order)

Eisai Co. Ltd.  
NIHON KOHDEN CORPORATION  
Otsuka Pharmaceutical Co., Ltd.  
UCB Japan Co., Ltd.

### Contact address

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E-mail: [epilepsy@kuhp.kyoto-u.ac.jp](mailto:epilepsy@kuhp.kyoto-u.ac.jp) (Secretary)  
Address: 54, Shogoin-Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, JAPAN  
TEL: (+81)-75-751-3662  
FAX: (+81)-75-751-3663

### Members of this Department and Affiliated Persons

#### <Members of Department of Epilepsy, Movement Disorders and Physiology>

Professor: Akio Ikeda, M.D., Ph.D. (Aug. 2013 -)  
Associate Professor: Masao Matsushashi, M.D., Ph.D. (Jun. 2018 -)  
Assistant Professor: Akihiro Shimotake, M.D., Ph.D. (Nov. 2016 - May 2019)  
Assistant Professor: Kiyohide Usami, M.D., Ph.D. (Apr. 2019 -)  
Secretary: Miki Watanabe  
Part-time scientist: Masako Daifu, M.D. (Jul. 2018 - Aug. 2018)  
Visiting Scientist: Tomoyuki Fumuro, Ph.D. (Dept. of Medical Technology and Sciences, School of Health Sciences at Fukuoka, International University of Health and Welfare)  
Morito Inouchi, M.D., Ph.D. (Dept. of Neurology, Kyoto Medical Center)  
Hirofumi Takeyama, M.D., Ph.D. (Dept. of Neurology, Otsu Red Cross Hospital)  
Research support personnel: Takeshi Inoue, M.D. (May 2016 – Mar. 2020. Dept. of Pediatric Neurology, Osaka city general hospital)  
Kei Sato, M.D. (Dept. of Neurology, Uji Hospital)  
Shunsuke Kajikawa, M.D. (Dept. of Neurology, Kyoto Medical Center)

#### <Affiliated members from Department of Neurology>

Associate Professor: Riki Matsumoto, M.D., Ph.D. (Aug. 2016 - Nov. 2018)  
Assistant Professor: Akihiro Shimotake, M.D., Ph.D. (Jun. 2019 -)  
Katsuya Kobayashi M.D., Ph.D. (Jan. 2016 - Aug. 2018, Sep. 2020 -)  
Medical staff: Shunichiro Neshige, M.D. (Apr. 2018 - Dec. 2018, from Department of Neurology, Hiroshima University)  
Masaya Togo, M.D., Ph.D. (Apr. 2019- Mar. 2020)  
Masako Daifu, M.D. (Sep. 2020 -)  
Mayumi Otani, M.D. (Apr. 2021 -)

## Graduate Students (Doctoral course):

Kazuaki Sato, M.D. (Apr. 2015 - Mar. 2019)  
 Kosuke Tanioka, M.D. (Apr. 2015 - Mar. 2019)  
 Masaya Togo, M.D. (Apr. 2015 - Mar. 2019)  
 Mitsuhiro Sakamoto, M.D. (Apr. 2015 - Mar. 2019)  
 Kazuki Oi, M.D. (Apr. 2017 -)  
 Mayumi Otani, M.D. (Apr. 2017 -)  
 Shunsuke Kajikawa, M.D. (Apr. 2017 -)  
 Shamima Sultana, M.D. (Apr. 2017 - Mar. 2020)  
 Tadashi Okada, M.D. (Apr. 2018 -)  
 Miwa Takatani, M.D. (Apr. 2018 -)  
 Maya Tojima, M.D. (Apr. 2018 -)

Masahiro Gotoh, M.D. (Apr. 2019 -)  
 Kozue Hayashi, M.D. (Apr. 2019 -)  
 Kyoko Hosokawa, M.D. (Apr. 2019 -)  
 Haruka Ishibashi, M.D. (Apr. 2020 -)  
 Yuki Kawamura, M.D. (Apr. 2020 -)  
 Yu Tatsuoka, M.D. (Apr. 2020 -)  
 Naoya Mimura, M.D. (Apr. 2020 -)  
 Haruo Yamanaka, M.D. (Apr. 2020 -)  
 Toshiya Takahashi, M.D. (Apr. 2021 -)  
 Yu Tamura, M.D. (Apr. 2021 -)  
 Eri Kikuchi (Apr. 2021 -)

## EEG/Epilepsy fellowship:

Takeshi Tsukamoto, M.D. (Oct. 2018 - Mar. 2019 from Dept. Neurology, Shiga University of Medical Science)  
 Kaoru Yagita, M.D. (Jan. 2019 - Mar. 2019 from Tenri Hospital)  
 Kento Matoba, M.D. (Oct. 2019 - Dec. 2019 from Dept. of Neurology, Kobe University Graduate School of Medicine)  
 Yawara Nakamura, M.D. (Apr. 2020 - Sep. 2020 from Dept. of Neurosurgery, Ehime University Graduate School of Medicine)  
 Toshiyuki Nagai, M.D. (Apr. 2021 - Dept. of Neurology, Kitasato University Hospital)

## Research student and undergraduate student:

Kei Sato, M.D. (Apr. 2018 - Mar. 2021, Dept of Neurology, Uji Hospital)  
 Hiromi Kanasaki (Apr. 2018 - Mar. 2020, Clinical psychologist, National Hospital Organization Utano National Hospital)  
 Shamima Sultana, M.D. (Apr. 2020 - May 2020 - with technical assistant)  
 Aya Demura (Apr. 2020 -, Clinical laboratory technician, National Hospital Organization Utano National Hospital)

## Medical assistant technician:

Saho Takasaki (Apr. 2017 - Mar. 2019, Dept. of Human Health Sciences)  
 Kana Furuichi (Apr. 2017 - Mar. 2019, Dept. of Human Health Sciences)  
 Asami Koyama (May 2019 - Mar. 2021, Dept. of Human Health Sciences)  
 Mizuho Takeda (May 2019 - Mar. 2021, Dept. of Human Health Sciences)  
 Yohei Yanagida (Apr. 2021 -, Dept. of Human Health Sciences)  
 Aina Inagami (May 2021 -, Dept. of Human Health Sciences)

## &lt;Affiliated members&gt;

**Department of Neurosurgery**

Associate Professor: Kazumichi Yoshida, M.D., Ph.D.  
 Senior Lecturer: Takayuki Kikuchi, M.D., Ph.D.  
 Assistant Professor: Yukihiro Yamao, M.D., Ph.D.

**Department of Clinical Laboratory Medicine**

Senior Lecturer: Takefumi Hitomi, M.D., Ph.D.  
 Assistant Professor: Masayuki Honda, M.D., Ph.D.

**Department of Respiratory Care and Sleep Control Medicine**

Assistant Professor: Hirofumi Takeyama, M.D. Ph.D. (Apr. 2017 - Mar. 2021)  
 Jumpei Togawa, M.D. (Apr. 2021 -)

## II. Outline

Members of this Department and Affiliated Persons as of Sep. 2019







# Activity report (June 2018-May 2021)

## Research activities

As a department founded on the Industry-Academia Collaboration Course, we collaborate with the industries that support us, tackling with missions to solve so-called "clinical questions", which have been raised in the daily clinical activities and have remained unsolved yet. By means of methodology used in systems neuroscience, we seek for bona-fide scientific knowledge to help develop clinical epilepsy. We participated in "Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature" and "Understanding brain plasticity on body representations to promote their adaptive functions" in Interdisciplinary Area supported by MEXT and conduct many clinical and basic researches by established and newly developed various methods with other institutes including the hospitals that deal with neurological diseases other than epilepsy.

### KEY WORDS

**General key words:** anti-epileptic drug, epilepsy, glia, epilepsy surgery, higher cortical function (motor control, praxis, language, semantic cognition, vision, will), Bereitschaftspotential (BP), cortico-cortical network, movement disorders, sleep disorders, autoimmune epilepsy, wide-band EEG, migraine

**Unique key words:** ictal DC shift, high frequency oscillation (HFO), cortico-cortical evoked potential (CCEP), cortical tremor, ictal apraxia, ictal paresis, cortical spreading depolarization (CSD), EEG-based precision medicine

### 1) Joint study with Eisai Co. Ltd.

The following three research proposals were made in collaboration with Eisai Co. Ltd. under the remit of this course.

- (A) Analysis (observational study) of the therapeutic effect of perampanel in epileptic myoclonus and elucidation of the mechanism of its action.
- (B) Clinical-physiological study of the effect of perampanel on giant SEP, an epileptic biomarker.
- (C) Pathophysiology and treatment of migraine with aura: Detection of a clinical-physiological biomarker of this condition.

Research is ongoing in both cases as of June 2021, Outstanding results have been achieved with respect to A) and B), and a summary of these and their specific research results are described below.

### Summary

In (A), we showed clinically that "a small dose of this drug is significantly effective in refractory cortical myoclonus," and the mechanism of the electrophysiological effect of perampanel obtained at the same time can be explained in terms of its temporal dispersion effect and suppression effect on paroxysmal depolarization shifts (PDS). This study was accepted for publication in Clinical Neurophysiology, and we clarified both the "theory and clinical data". <https://doi.org/10.1016/j.clinph.2019.07.006>

In (B), we showed for the first time that high-frequency oscillations (HFO) associated with giant SEP appear in benign adult-onset familial myoclonus epilepsy (BAFME), in a disease-specific manner. In pre- and post-perampanel treatment studies, giant SEP showed a decrease in amplitude and prolongation of latency, while HFO did not change significantly. This was a giant SEP, which is the PDS; in other words, a giant EPSP, which clearly reflects the pharmacological effect of perampanel. Meanwhile, once an HFO induced by PDS appears, it is stable, with no variation. This is quite consistent with the hypothesis that HFOs above 300 Hz reflect intracellular potential activity, i.e., action potential.

With regard to (C), after a thorough literature review and preparation of a study protocol were performed in the first year, this research was selected as an exploratory (budding) study in FY2020, entitled "New developments in migraines from a glial perspective: integrated analysis of slow EEG and functional MRI".

#### Study results

#### (A) Analysis of therapeutic effect of perampanel in epileptic myoclonus (observational study) and elucidation of the mechanism of its action.

[Title]

Investigation of the clinical and electrophysiological effects of perampanel on refractory cortical myoclonus

[Background and Objectives]

Perampanel (PER) has recently been reported to be useful for cortical myoclonus<sup>1-3)</sup>, but its mechanism of action and the electrophysiological changes associated with treatment remain unclear. Herein, we investigated the therapeutic effects and electrophysiological changes in patients with refractory cortical myoclonus.

[Methods]

The study subjects were 18 patients with progressive myoclonus epilepsy and Lance-Adams syndrome (LAS) with refractory cortical myoclonus who attended Kyoto University Hospital and Takeda Hospital from 2016 to 2017, and later from 2017 to 2019 as a follow-up study. Before and after the initiation of treatment, questions on myoclonus and activities of daily life (ADL) were administered, somatosensory evoked potential (SEP) was performed, and adverse effects and PER blood levels were evaluated. The SEP test measured N20, P25, and N33 latencies as well as P25 and N33 amplitudes. The correlation between the myoclonus score, ADL score, and PER blood concentration, and the change in each component before and after treatment was examined. The dose and adverse effects were also examined.

[Result]

The subjects were 18 patients, comprising 10 males, average age  $48.4 \pm 16.2$  years. Of these, 7 were Unverricht-Lundborg disease (ULD) patients, 6 benign adult familial myoclonus epilepsy (BAFME) patients, 2 dentatorubral-pallidoluysian atrophy (DRPLA) patients, One Gaucher disease patient and two LAS patients. During the observation period of  $9.15 \pm 17.2$  months, the mean PER dose was  $3.2 \pm 2.1$  mg/day, and the mean blood concentration was  $234.3 \pm 168.0$  ng/mL. The myoclonus score improved from  $2.8 \pm 0.8 \rightarrow 1.8 \pm 0.8$  ( $p < 0.001$ ), and the ADL score improved from  $13.8 \pm 7.9 \rightarrow 10.2 \pm 6.7$  ( $p < 0.001$ ). The amplitude drop of the giant SEP improved from  $13.5 \pm 6.5 \mu V \rightarrow 9.1 \pm 4.5 \mu V$  ( $p < 0.003$ ) by P25, and from  $21.2 \pm 12.1 \mu V \rightarrow 14.4 \pm 7.1 \mu V$  ( $p = 0.035$ ) by N33, showing that all underwent significant improvements. The latent time was significant for N20 only, from  $18.2 \pm 1.6$  ms  $\rightarrow 18.9 \pm 1.54$  ms ( $p = 0.007$ ). The  $\Delta$  amplitude decrease and  $\Delta$  latent time prolongation correlated significantly on both sides at P25 (right:  $P = 0.033$ ,  $\rho = -0.71$ , Left:  $P = 0.018$ ,  $\rho = -0.76$ ), suggesting the existence of temporal dispersion. In addition, delta latent time prolongation of P25 and N33 improved the ADL score (P25:  $p = 0.019$ ,  $\rho = 0.75$ , N33:  $P = 0.025$ ,  $\rho = 0.73$ ) and PER blood concentrations (P25:  $p = 0.011$ ,  $\rho = 0.79$ , N33:  $p = 0.025$ ,  $\rho = 0.73$ ), respectively. Adverse effects were observed in 8/18 patients, but all were mild. In the subsequent follow-up investigations, the observation period after initiation of the PER treatment was  $25.2 \pm 5.8$  months, and the dose increased to an average of  $3.3 \pm 2.2$  mg/day. However, the mean blood concentration was relatively low at  $335.7 \pm 229$  ng/mL, and drug tolerance was high, without serious adverse effects or any discontinuations. The myoclonus score improved further from  $2.8 \pm 0.8$  to  $1.4 \pm 0.6$  ( $p < 0.01$ ), the improved state of ADL was maintained, and the amplitude drop and latent time prolongation of the giant SEP were similar.

[Discussion]

PER acts as a selective antagonist of the AMPA receptor on the postsynaptic membrane, and suppresses nerve cell hyperexcitation by blocking the inflow of  $Ca^{2+}$ <sup>4,5)</sup>. This results in decreased inflammation of abnormal neuronal cells in the mechanism of paroxysmal depolarization shift (PDS), decreased amplitude, and prolonged latency time<sup>6)</sup>.

The correlation between the prolongation of latency time of the P25 component involved in the primary motor field and clinical items suggests that PER acts to reduce the excitability of neuronal cells in the primary motor field<sup>7)</sup>.

The additional investigation also suggests that the effects of suppressing the stimuli of the motor cortex reflected in clinical symptoms and electrophysiology are maintained over time, but further studies are required on whether PER gradually diminishes the stimuli of the motor cortex.

## [Conclusion]

A small dose of PER was useful for refractory cortical myoclonus, improving clinical parameters, and decreasing the amplitude of giant SEP, without any serious adverse effects. The prolongation of latent time of the P25 component after treatment was correlated with the amplitude decrease and clinical parameters, suggesting that PER suppresses motor cortical excitability, and that SEP may acts as a biomarker for determining treatment efficacy in the future.

## [Articles and conference reports]

- 1) Oi et al. 51st Annual Congress of the Japan Epilepsy Society, 2017
- 2) Oi et al. 60th Annual Meeting of the Japanese Society of Neurology, 2018
- 3) Neshige et al. 12th Asian and Oceania Epilepsy Congress, 2018
- 4) Kobayashi et al. Keiji Nara Epilepsy Conference, 2018
- 5) Oi et al. 53rd Annual Congress of the Japan Epilepsy Society, 2019
- 6) Oi, K. and Neshige, S. et al. Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. *Clinical Neurophysiology*. 2019;130: 1804-1812.

**(B) Clinical-physiology study of the effect of perampanel on giant SEP, an epileptic biomarker****B-1)**

## [Title]

Biomarkers of benign adult-onset familial myoclonus epilepsy (BAFME): high-frequency oscillations (HFO) in giant somatosensory evoked potentials (giant SEP)

## [Background and Objectives]

Benign adult familial myoclonus epilepsy (BAFME) is an autosomal dominant hereditary disease with a giant SEP<sup>1)</sup> containing the cortical components P25, N35 etc., as high amplitudes of the upper limb somatosensory evoked potential (SEP), which is one of the electrophysiological features of cortical reflective myoclonus. However, this has not been established as a clinically useful marker to allow differentiation from other cortical reflective myoclonus. Physiological and pathologically high frequency oscillations (HFO) are observed at SEP latent times of 20 ms and longer. However, the presence or absence and significance of the HFO that coexists with the P25 component of giant SEP (P25-HFO) have not been adequately investigated. We examined this feature, considering the possibility of its application as a biomarker of BAFME.

## [Methods]

We retrospectively examined patients with cortical myoclonus who showed giant SEP<sup>4)</sup> in upper limb SEP examinations at Kyoto University Hospital from 2008 to 2018. The presence of P25-HFO was defined as a P25-HFO with an end latency time greater than 22 ms, and a baseline SD greater than  $\pm 4$  SD for at least 4 consecutive cycles (2 cycles) after using a 400-1000 Hz bandpass filter. We compared clinical information, SEP findings, and the presence or absence of P25-HFO between BAFME and other cortical myoclonus groups, and investigated factors involved in the presence or absence of P25-HFO. The diagnostic accuracy of each factor in diagnosing BAFME was also calculated.

## [Result]

The subjects were 49 patients, including 14 men, average age  $55.8 \pm 18.3$  years; 16 had BAFME, and 33 other cortical myoclonus. In the BAFME group, P25-HFO was observed in all the subjects, with a significantly lower starting age of involuntary exercise than other cortical myoclonus groups, and use of anti-epileptic drugs, SEP amplitude, SEP amplitude after filter, and incidence of P25-HFO were high ( $p=0.043$ ,  $0.0035$ ,  $0.0001$ ,  $<0.0001$ ,  $<0.0001$ ).

In a comparison between the groups with and without P25-HFO, there were significantly more BAFME cases in the group with P25-HFO, and the P25 and N35 amplitudes were higher ( $p<0.0001$ ,  $p=0.0003$ ). Regarding the diagnostic accuracy of BAFME, P25-HFO was the highest (100% sensitivity, 87.9% specificity, 80.0% positive neutral, 100% negative neutral) compared to age at the start of involuntary movements, P25 amplitude, N35 amplitude, and the SEP amplitude after the filter.

#### [Discussion]

In BAFME, P25-HFO was observed in all cases. In previous reports investigating the presence or absence of HFO when the latent time of the upper limb giant SEP was 20 ms and beyond, HFO was not observed in mitochondrial disease<sup>5,6)</sup> or multisystem atrophy<sup>6)</sup>. However, HFO was observed in myoclonus epilepsy<sup>6-8)</sup> and Parkinsonism associated with Myoclonus<sup>6)</sup>. Our results suggest that it is possible that the previously reported myoclonus epilepsy with HFO was BAFME; the presence of P25-HFO is a highly suspicious finding for the diagnosis of BAFME, suggesting that the clinical diagnosis of BAFME may be more convenient than genetic testing. The difference in the incidence of P25-HFO in the present study suggests that the pathogenesis of giant SEP differs between BAFME and other cortical myoclonus, and further analysis of HFO may be useful in elucidating the pathogenesis of cortical myoclonus, including BAFME.

#### [Conclusion]

In the upper limb giant SEP, P25-HFO was observed and in particular, the incidence of BAFME was high. P25-HFO can be a useful biomarker for BAFME, and its analysis may be useful for elucidating the pathogenesis of cortical myoclonus. HFO analysis may be useful in elucidating the pathogenesis of cortical myoclonus.

#### [References]

- 1) Rothwell, et al. *J Neurol Neurosurg Psychiatry*. 1984;47:33-42.
- 2) Ozaki, et al. *Clinical Neurophysiology*. 2011;122:1908-1923.
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- 8) Mochizuki, et al. *Neuroscience Research*. 2003;46:485-492.

#### [Articles and conference reports]

- 1) Tojima, et al. 53rd Annual Congress of the Japan Epilepsy Society, 2019
- 2) Tojima, et al. 50th Annual Meeting of the Japanese Society of Clinical Neurophysiology, 2020
- 3) Tojima, et al. *Movement Disorders*. 2021;36:2335-2345.

### B-2)

#### [Title]

Effects of perampanel in Unverricht-Lundborg disease: long-term evaluation over time using giant somatosensory evoked potentials

#### [Case report]

A 36-year-old woman, who had difficulty walking independently due to intractable myoclonus, showed marked improvement of myoclonus after starting perampanel (PER) treatment at the age 34, enabling her to stand up and walk a few steps independently.

The results of the somatosensory evoked potentials (SEP) based on left-right medial nerve stimulation that was performed temporally from the age of 23 years to 35 years were examined retrospectively. We found that before the PER treatment had started, the latent time of P25 was unchanged, but the amplitude increased. However, after PER was started, the latent time was prolonged for the first time while the amplitude was decreased.

The latent time and amplitude of P25 continued to prolong and decrease, respectively, over time, with increases in the dose of PER.

#### [Conclusion]

In a study expanding more than 10 years, giant SEP was clinically regarded as a paroxysmal depolarization shift (PDS), and PER was shown to cause temporal dispersion of PDS, and to have "dose-dependent" and "long-term persistent and potentiating" effects.



[Articles and conference reports]

- 1) Tojima et al. 37th Annual Meeting of the Japanese Society of Neurological Therapeutics, 2019
- 2) Tojima et al. 17th Asian Oseanian Congress of Neurology, 2021
- 3) Tojima et al. Clinical Neurophysiology. 2021;132:2329-2331.

#### Appendix: International Joint Study on Perampanel in Cortical Myoclonus

We have continued discussions with Eisai Co. Ltd. on the international joint study on the therapeutic effect of perampanel on cortical myoclonus in the Asia-Oceania region of ILAE as a collaborative research project since the year prior to the launch of this collaborative research laboratory. A new clinical research law that was enacted in April 2018 has made the conduct of prospective studies extremely difficult, and changed the method towards retrospective case accumulation studies; this has triggered significant modification of all protocols.

After consulting relevant countries in the Asia-Oceania region for retrospective case accumulation studies in the form of a questionnaire, and summarizing the cooperation status of each country by the March 2019 stage, it became evident that it was probably difficult to secure sufficient cases at this time, and that it would be necessary to review the cost-effectiveness of establishing a case registration system limited to cortical myoclonus.

Subsequently, in a meeting with Eisai Inc. on May 8, 2019, it was decided to launch a new Asia-Oceania registry study of epilepsy patients and to then proceed with a format to examine the therapeutic effect of perampanel on cortical myoclonus as part of that study.

This information was presented at the ILAE executive committee meeting on June 21 and the ILAE-Asia Oceania (formerly CAO) business meeting on June 23 during the ILAE International Epilepsy Congress held in Bangkok from June 22, 2019. The content was approved in both meetings.

Subsequently, we discussed with Dr. Peter Bergin, who operates EpiNet (<https://www.epinet.co.nz/>), an epilepsy database that has already collected more than 10,000 cases mainly in New Zealand and Australia, how to build the database, and conducted a pilot operation from November 2020 to March 2021. As a result, it was decided that EpiNet would be joined by Kyoto University and ILAE-AO, with necessary modifications such as collection items, and that the registry study approved by the Research Task Force of ILAE-AO would be conducted on EpiNet. The results were reported to the ILAE Board of Directors on January 21, 2021, and approved by the ILAE-AO Board of Directors on May 29, 2021. Contract negotiations are currently underway.

This is expected to address the concerns raised by clinical research methods, and will further build a research base for solving not only the therapeutic effects of Perampanel on cortical myoclonus, but also the problems of clinical epilepsy in the Asia-Oceania region.

## 2) Pathophysiology of medically intractable epilepsy and its treatment

### a) Research for pathophysiology of intractable partial epilepsy

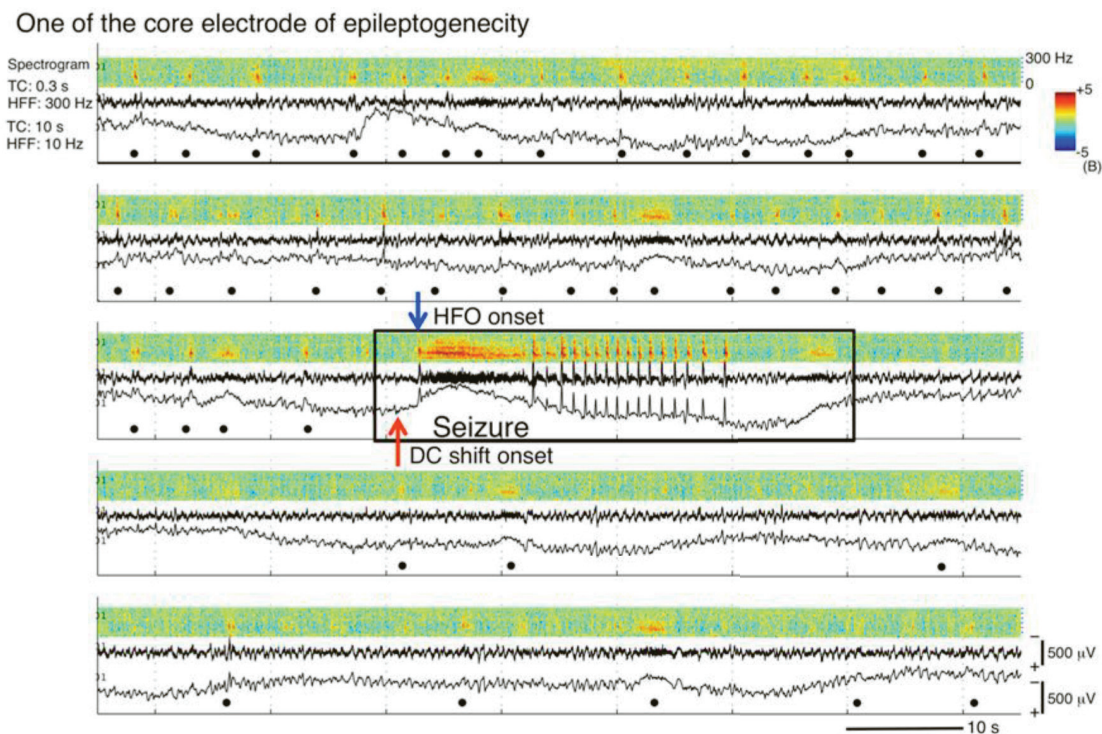
We retrospectively investigated how ictal DC shifts related to surgical outcome with 61 patients' data who had epileptic surgery in 5 institutes in Japan. We showed that the complete resection of ictal DC as well as ictal HFO contributes to favorable seizure outcome (Nakatani et al., accepted). Ictal DC shifts has been recorded by amplifier with time constant (TC) 10 sec. We analyzed that ictal DC shifts could be identified even with TC 2 sec. Furthermore, we performed cluster analysis and 2 patterns of ictal DC shifts were identified. One was a rapid development pattern, which tended to show the rapidly progressive ascending slope, and the other was a slow development pattern, which had an opposite tendency to rapid development pattern. (Kajikawa et al., 2022)

Our study about the histology of core area of ictal DC shifts revealed the downregulation of astrocytic inwardly rectifying potassium (Kir) 4.1 channel in FCD1 patients (3 out of 5 patients) (Kobayashi et al., 16th Asian Oceanian Congress of Neurology). Kir4.1 channels regulate extracellular potassium ion homeostasis. Dysfunction of Kir4.1 channel is reported to be involved in the generation of generalized tonic-clonic seizures. We showed that the antiepileptic drugs such as valproate elevate the astrocytic Kir4.1 channel expression in rats (Mukai et al., 2018). Moreover, we demonstrated that the down-regulation of Kir4.1 channels in astrocytes is involved in Lgi1 (Leucine-rich

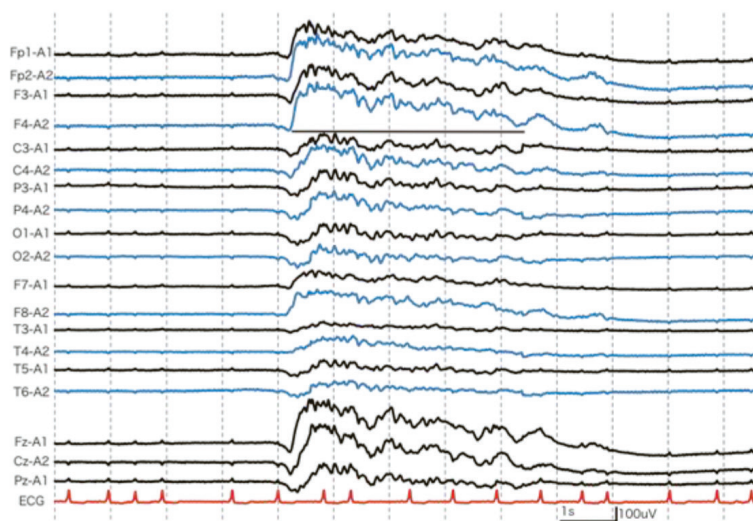
glioma-inactivated 1) mutation-induced epileptogenesis, which is prevented by valproate (Kinboshi et al., 2019).

We reported the presence of co-occurrence of interictal slow and HFOs (IIS+HFO) and its temporal changes so as to elucidate its clinical usefulness as a surrogate marker of epileptogenic zone in a patient with intractable focal epilepsy (Inoue et al., 2019, Figure 1).

In patient with hypoxic encephalopathy, the activity of 0.08 to 0.5 Hz which can be measured with a time constant of 2 seconds was defined as short infraslow activity (SISA). We reported that SISA was superimposed on the burst phase of the burst-suppression pattern and was significantly associated with acute symptomatic seizures and myoclonus after cardiac arrest (Togo et al., 2018, Figure 2).



**Figure 1:** In the middle of figure (black rectangle), one seizure occurred where ictal active DC shifts was observed; ictal negative DC shifts occurred earlier than ictal HFOs. Before the seizure, red slow (co-occurrence of slow and HFO, black dot) was significantly frequent than after seizure (cited with modification from Inoue et al., 2019).



**Figure 2:** Short infraslow activity was more clearly delineated in the setting of time constant 2 seconds than time constant 0.3 second (cited with modification from Togo et al., 2018).

We recorded the CCEPs time-locked to the phase of spike (reflecting excitation) and post-spike slow (reflecting inhibition) in interictal epileptiform discharges. We proved that the excitability of the epileptic network was dynamically modulated according to the degree of underlying internal cortical excitability by different behavior of CCEPs depending on the timing of stimuli (Kobayashi et al., in preparation). The precise generator mechanisms of epileptic spasms (ES) remain elusive. Cortico-cortical and/or subcortical network has been considered to be responsible for the semiology of ES. Integrated neurophysiological findings revealed engagement of cortico-cortical and subcortical networks in a representative patient with ES.



#### b) Research for pathophysiology of various epilepsy syndromes and their treatment

Semantic dementia studies have shown that the anterior temporal lobe (ATL) is a key structure for semantic memory. For epilepsy surgery, the dominant ventral ATL is known as the basal temporal language area, which we have been investigating (Shimotake et al., 2016). The compensational mechanism after ATL resection remains elusive. To clarify postoperative compensational course of semantic memory, semantic tasks were performed before and after surgery in patients with dominant TLE. Dominant TLE patients preoperatively showed impaired semantic memory. ATL resection resulted in immediate decline of semantic function, which generally improved within 1 year (Ota et al., in preparation).

Responsive neurostimulation (RNS) is one of the neuromodulation therapies for patients with medically refractory epilepsy in the U.S.A., which has not been yet approved in Japan. We have revealed that stimulating at or around the sites showing large connectivity with other cortical regions in CCEP for the RNS therapy resulted in better seizure outcome (Kobayashi et al., in preparation, a study under Dr. Dileep R. Nair in Epilepsy Center, Cleveland Clinic, U.S.A.).

Some epilepsy syndrome are associated with gene abnormality. Benign adult familial myoclonus epilepsy (BAFME), a penta-nucleotide repeat disease characterized by cortical tremor and infrequent generalized seizures, is one of the examples. The relationship between the pathophysiology and electrophysiological findings in BAFME remains largely unknown. Our studies revealed that a) the abnormal repeat length is mildly correlated with the frequency of posterior dominant rhythm in EEG (Tojima et al., in preparation) and b) sleep is associated with the reduction of epileptiform discharges (Table 1. Hitomi et al., 2018) in BAFME patients. Besides, the nationwide questionnaire for neurologists and epileptologists in Japan revealed that BAFME patients were found diffusely without regional accumulation. The further

Summary of the electroencephalography analysis.

	Sleep staging (min)		Number of epileptiform discharges		Frequency of epileptiform discharges (number/min)	
	Awake	SI and II	Awake	SI and II	Awake	SI and II
Pt 1	40	19	81	0	2.03	0.00
Pt 2	22	39	8	0	0.36	0.00
Pt 3	42	28	33	3	0.78	0.11
Pt 4	27	6	84	0	3.16	0.00
Pt 5	26	4	7	0	0.27	0.00
<b>Mean</b>	<b>31.3</b>	<b>19.2</b>	<b>42.6</b>	<b>0.6</b>	<b>1.3</b>	<b>0.02</b>
<b>SD</b>	<b>9.1</b>	<b>14.9</b>	<b>37.9</b>	<b>1.3</b>	<b>1.3</b>	<b>0.05</b>
						
						

SI and II: sleep stage I and II.

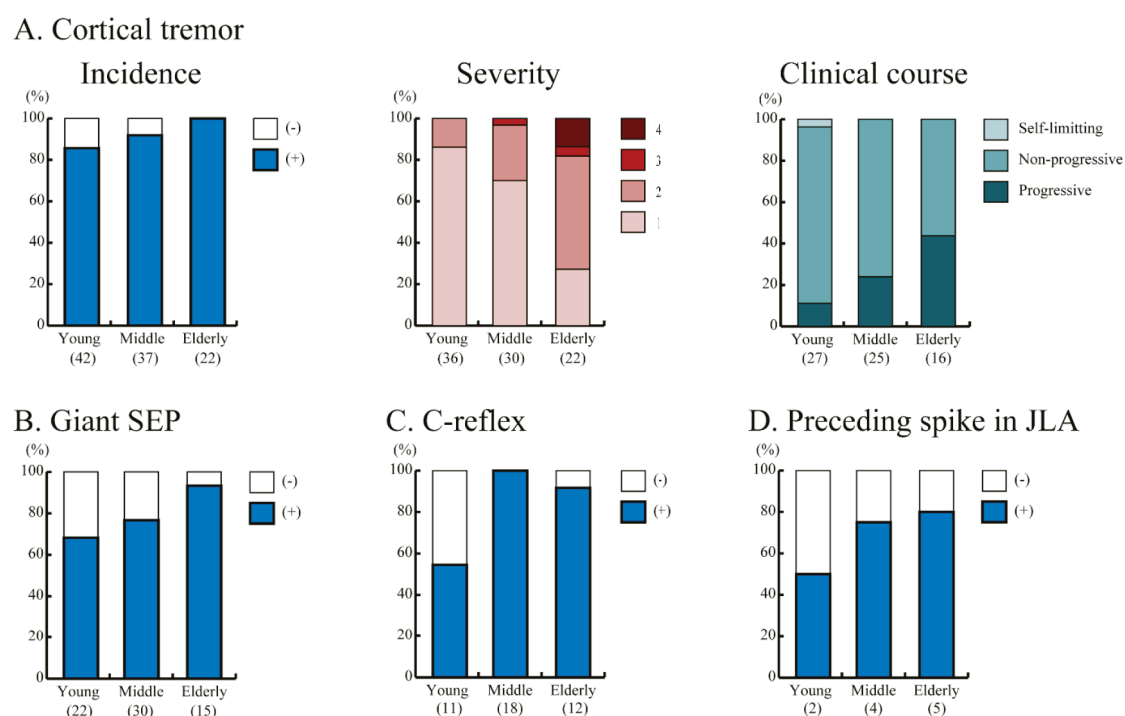
\*  $P < 0.05$  (Wilcoxon signed rank test).

**Table 1:** The frequency of epileptiform discharges significantly decreased during light sleep compared to the awake stages in patients with BAFME (cited from Hitomi et al., 2018).

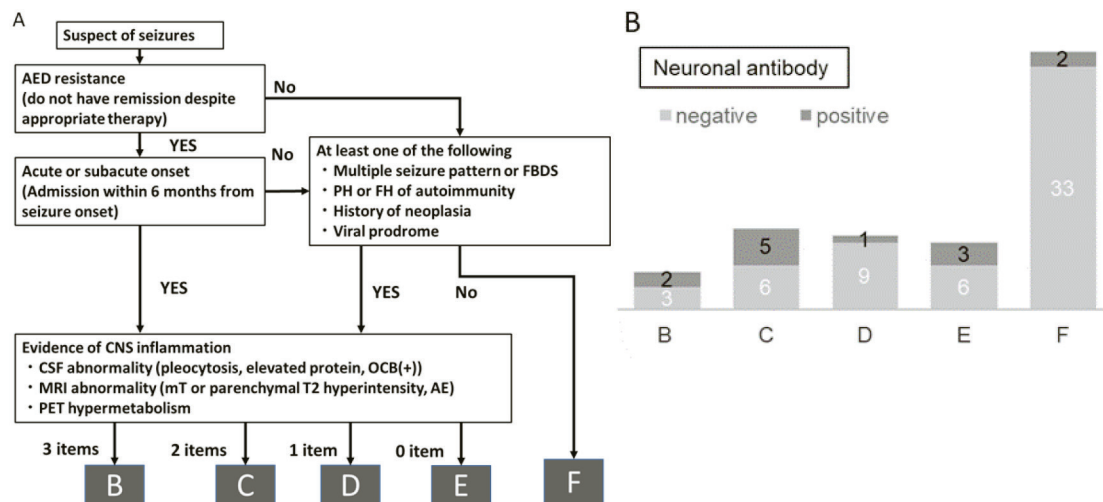
survey based on the detailed clinical information of about 100 BAFME patients clarified the pathophysiology of BAFME in Japan (Figure 3, Kobayashi et al., 2018).

The epilepsy syndrome of autoimmune etiology, namely, autoimmune epilepsy has attracted the attention in recent years, as was reflected in the new etiology of "immunity" in the Epilepsy Classification of the International League Against Epilepsy. However, no specific tests other than neuronal antibodies have been established. We examined the long term course (86-103 months) of anti-VGKC antibody positive autoimmune encephalitis, which causes autoimmune epilepsy. We measured the volume of the amygdala, hippocampus and the whole brain, demonstrating that 1) the amygdala body tends to be swollen even in the chronic phase, 2) the increase of the volume during the course can be a marker of relapse of inflammation, and 3) not only hippocampus but also cerebral atrophy will proceed unless adequate immunotherapy is performed (Honda et al., 31st International Congress of Clinical Neurophysiology). This study showed the neuroimaging is probably useful for the diagnosis of autoimmune epilepsy. Based on this observation and other studies, we proposed a diagnostic algorithm for autoimmune epilepsy and preliminarily investigated its clinical utility (Sakamoto et al., 2018, Clinical Neurology).

We applied this algorithm to 70 patients who were suspected as having autoimmune epilepsy from clinical symptoms and laboratory findings in our institute. In this two-step algorithm, the patients were initially screened by clinical features and then evaluated by laboratory findings (neuronal antibodies, CSF, MRI, FDG-PET). In this preliminary investigation, it was suggested that two or more abnormal findings in the diagnostic tests (CSF, MRI, FDG-PET) favor the diagnosis of autoimmune epilepsy (Figure 4). Recruitment of the patient cohort with comprehensive neuronal antibody testing and multivariate analysis of laboratory findings is warranted for validation and modification of the proposed algorithm.



**Figure 3.** In the nationwide survey of 101 BAFME patients, the middle-aged and elderly groups showed a higher degree of cortical tremor, suggesting a progressive tendency for this symptom (A). In addition, the positive rates in electro-neurophysiological examinations suggesting cortical hyperexcitability were higher in the middle-aged and elderly groups than those in the young group (B-D) (modified from Kobayashi et al., 2018).



**Figure 4.** A: Algorithm for diagnosis of autoimmune epilepsy without evaluation of neuronal antibody. B: Patients in each category (B-F) of the proposed algorithm without considering the findings of neuronal antibody. Dark gray bar denotes patients with positive neuronal antibody findings, and light gray bar those with negative antibody findings. The figure in each bar denotes the number of patients. (Cited with modification from Figure 2 in Sakamoto, et al., 2017, Clinical Neurology)

### 3) Mapping higher functions/network and elucidating its functional alteration under pathological condition

In epilepsy surgery, it is important to map cortical functions to preserve eloquent cortices in addition to the localization of the epileptic focus. Therefore, we need to perform comprehensive ‘system mapping’ to help neurosurgeons to make strategy of surgery for individual patients. We have made vigorous attempts at developing various techniques for mapping higher cortical functions (e.g., language, motor control etc.) and their network for clinical application.

Functional neuroimaging tells us if specific brain regions are active during certain tasks, but activation by itself does not demonstrate the necessity of those areas. In contrast, electrical cortical stimulation, a gold standard method since mid-20th century, can delineate the cortex responsible for a particular task by making functional impairment. The functional interference is temporary ( $\sim 5$ s), discretely focal ( $\sim 1$  cm<sup>2</sup>), and in sharp contrast to chronic stroke lesions that are relatively large and usually associated with cortical plastic compensation.

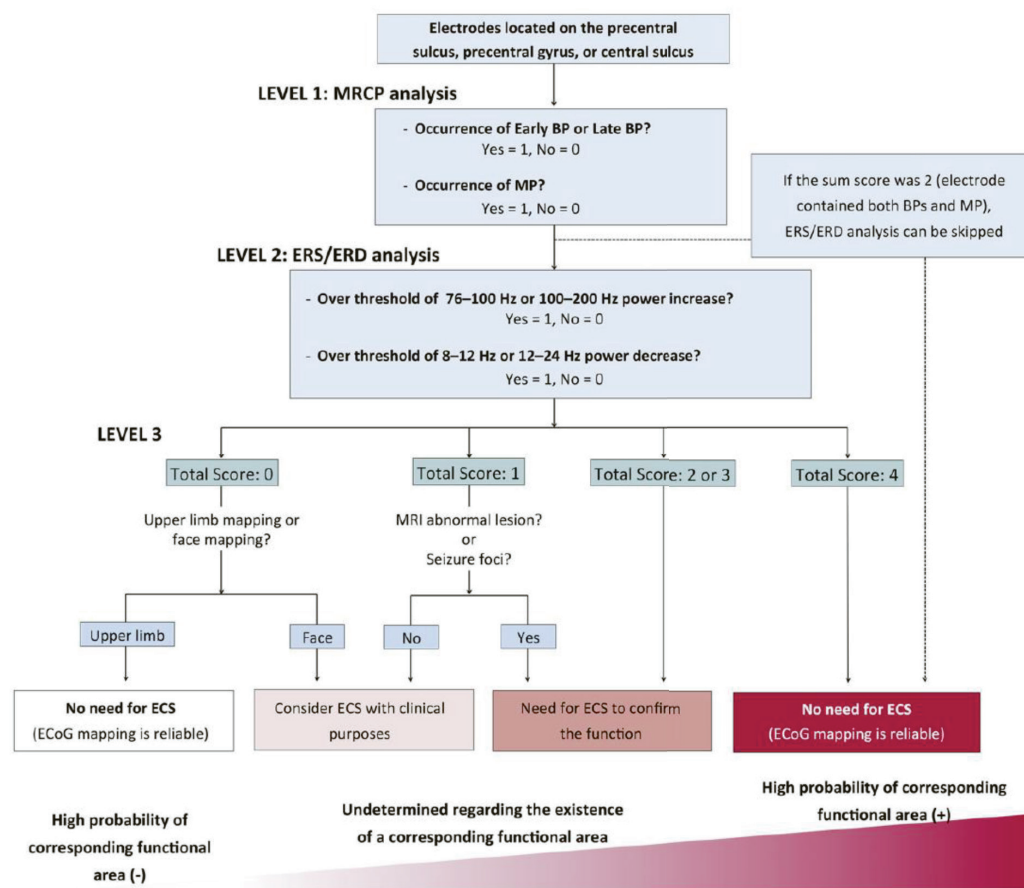
However, high frequency electrical stimulation often results in afterdischarges that delay functional mapping and harbor a risk of seizure induction. Recent technical advances have enabled us to record the cortical activities relevant to higher cortical functions with wideband EEG technology - from infraslow to high gamma activities. In our institute, in addition to the gold standard method of high frequency electrical stimulation, we perform comprehensive mapping of higher cortical functions by recording epicortical infraslow and high frequency oscillation/activity during motor or cognitive tasks.

We assessed the feasibility of multi-component electrocorticography (ECoG)-based mapping using ‘wide-spectrum, intrinsic-brain activities for identifying the primary sensori-motor area (S1-M1) for non-stimulus, less invasive functional mapping strategy, alternative to electrical cortical stimulation (ECS). We evaluated 14 epilepsy patients with subdural electrodes implantation and performed multicomponent, ECoG-based mapping involving combined analyses of the single components: movement-related cortical potential (MRCP), event-related synchronization (ERS), and event-related de-synchronization (ERD) to identify the S1-M1. As conclusions, wide-spectrum, multi-component ECoG-based mapping is feasible, having high sensitivity/ specificity relative to ECS to identify the S1-M1 (Neshige et al., 2018). In addition to this, the ECoG score, assessed by slow cortical potentials and very fast frequency band augmentations related to motor area, can identify the M1 with high sensitivity/ specificity and it is spatially concordant with ECS (Neshige et al., 2019) (Figure 5).



We incorporate cortico-cortical evoked potentials (CCEPs) to probe inter-areal functional connectivity in order to perform ‘system mapping’. CCEP is an in vivo electrical tract tracing method developed in Cleveland and Kyoto (Matsumoto et al., 2004). Single electrical stimulation (1 Hz) is applied to a part of the cortices and cortical evoked potentials, i.e., CCEPs, were recorded from adjacent and remote cortical activities through cortico-cortical connections. With this CCEP method, we can probe cortico-cortical networks involved in functional brain systems and seizure network in each individual patient. Furthermore, by gathering data of cortical functions and networks from many patients in various physiological and pathological states and analyzing them as a group, we attempt to feedback this valuable information into the system neuroscience by providing functional/connectivity references for non-invasive research.

We can also use induced evoked potential (CCEP) and high frequency activities (HFA) as a dynamic marker of cortical connectivity and excitability since it can “snapshot” the connectivity and excitability within 20-30 trials (< 1 min). We applied this method to awake and sleep cycle and found that cortical connectivity and excitability are different between wakefulness and non-REM (rapid eye movement) sleep. We analyzed CCEP-related HGA that are recorded from adjacent and remote cortical areas as a proxy of cortical excitability. We reported that the excitability changes across sleep stages and that the intensity of suppression that follows excitation was potentiated during non-REM sleep, with REM sleep being an intermediate state of wakefulness and non-REM sleep (Usami K, et al., 2015,



**Figure 5.** Algorithm of the scoring system of electrocorticographic (ECoG) mapping for primary motor cortex. The first step in the flow chart started with assessing the score from the sum of movement-related cortical potential (MRCP)/event-related synchronization (ERS)/event-related desynchronization (ERD) components and dividing the scores into four subcategories. A total score of 4 indicates a high probability of brain function, suggesting no need for electrical cortical stimulation (ECS) (rule in), and when the score was 0 in the upper limb task, the function was presumed to be ruled out (ECS not needed).

Hum Brain Mapp) and also reported that the suppression is attenuated during phasic REM, suggesting that cortical excitability transiently approaches wakefulness (Usami K, et al., 2017, SLEEP). To investigate the interaction of neural activity between whole brain network during awake and sleep, we applied SPES, which elicited corticocortical spectral responses at high-gamma frequencies (CCSR<sup>HG</sup>, 80-150Hz), by using event-related causality (ERC) analysis. We observed the greater propagation of activity from frontal to parietal lobe during slow-wave sleep, and decreased propagation within frontal lobe, but increased propagation within parietal lobe, during REM sleep. These suggest that wakefulness and sleep are associated with different patterns of propagation of neural activities across brain networks (Usami, et al., 2019, a collaborative study with Professor Nathan Crone, Department of Neurology, the Johns Hopkins University School of Medicine). By means of this method to calculate propagation of neural activities, we analyzed the brain activities during picture naming task. We observed that the difference of properties such as living or non-living affected the way information is processed in the posterior cortices (Usami K, et al., in submission). We also have been investigating the association between connectivity indexed by CCEP and ECS-related brain function or motor-related cortical potentials (MRCP) (collaboration with Professor Matsumoto, Division of Neurology, Kobe University).

We have demonstrated the central mechanisms and functional alteration under pathological condition relevant to i) the motor control (negative motor phenomena, praxis, reaching, conflict processing and response inhibition), ii) language (dorsal and ventral language networks with emphasis on semantic cognition) and iii) visual functions (retinotopic mapping by functional MRI), combined with non-invasive evaluation (functional MRI, diffusion tractography, MEG, neuropsychology). Additionally, we are now tackling with decoding of complex neural signals during various tasks in cooperation with seasoned researchers in and out of the Kyoto University (the MRC Cognition & Brain Sciences Unit, University of Cambridge, Prof. Matthew Lambon-Ralph, NICT (National Institute of Information and Communications Technology), Dr Eiichi Naito. We, (A03 “the Direct Recording of Human Neural Oscillations”, Prof. Ikeda as PI) engaged in the national research group of “Neuro-Oscillology” which was funded by Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science and Technology (MEXT). We took part in the ‘Embodied-Brain Systems Science’ funded by another grant from MEXT (A03-4, Dr. Riki Matsumoto as PI), in order to reveal the motor control and the mechanism of body representations especially in the fronto-parietal network.

#### **4) Pathogenesis of movement disorders and its treatment**

We have investigated movement disorders, mainly myoclonus and myoclonus epilepsy, by way of epidemiological, genetic and electrophysiological methods. BAFME (benign adult onset familial myoclonus epilepsy) has been investigated mainly in Japan and European countries for 20 years. The clinical pictures are as follows: i) adult onset, ii) autosomal dominant (unknown causative gene), iii) cortical (myoclonic) tremor (tremulous myoclonus), iv) infrequent generalized seizure, v) cortical reflex myoclonus disclosed by electrophysiological study. We have also been studying BAFME since it was first reported in 1990. As its name suggests, BAFME was considered to present no progression and good prognosis. However, cortical myoclonic tremor has been proved to worsen with aging. Recently, we demonstrated slow progression of the disease, based on the electrophysiological evidence. Namely, the amplitude of somatosensory evoked potential, reflecting the cortical excitability in the primary sensori-motor cortices, more exaggerated with aging in BAFME patients than normal volunteers. We also demonstrated clinical anticipation in BAFME, in which the onset of generalized seizure and cortical (myoclonic) tremor became earlier in the next generation. The anticipation in BAFME was more apparent in patients with maternal transmission. By comparing the EEG posterior dominant rhythms (PDRs) between patients with BAFME and age-matched control subjects, we showed mild diffuse encephalopathy in BAFME. The nationwide questionnaire for neurologists and epileptologists in Japan revealed that BAFME patients were found diffusely without regional accumulation. The further survey based on the detailed clinical information of about 100 BAFME patients clarify the pathophysiology of BAFME in Japan (Kobayashi et al., 2018). Based on these findings, multi-institutional study supervised by Dr. Shoji Tsuji of Tokyo University revealed the causative gene of BAFME (Ishiura et al., 2018). By comparing awake and sleep EEG, epileptiform discharges were significantly more frequent during awake period than those during sleep, which indicated a

reduction in cortical irritability during sleep period. Unverricht-Lundborg disease (ULD) showed a similar tendency, and thus BAFME and ULD may share a similar pathological mechanism of genesis of cortical irritability from the view point of vigilance change (Hitomi et al., 2018). Low-dose perampanel (PER) markedly improved myoclonus and ADL in patients with refractory cortical myoclonus. Our results suggest that SEP, particularly P25 latency, can be used as a potential biomarker for assessing the objective effects of PER on intractable cortical myoclonus (Oi et al., 2019). In BAFME patients, high frequency oscillations were superimposed on the giant components of somatosensory evoked potentials, and this electrophysiological feature was rarely seen in other cortical myoclonus patients, so we proposed as a new diagnostic method for BAFME (Tojima et al., 2021). By means of cortico-muscular coherence, we clarified that hyperexcitability of primary sensorimotor cortex and the subcortical structures such as basal ganglia and cerebellum would be involved in the generator mechanisms of cortical tremor in BAFME (in preparation). As the research of post-genome era in BAFME, we investigated the relationship among SEP parameters (latencies and amplitudes), aging and repeat length. We showed that SEP parameters were more affected by aging than repeat length (in preparation). (Maya Tojima, Kazuki Oi, Shuichiro Neshige, Katsuya Kobayashi, Takefumi Hitomi)

## 5) Joint research with different and related fields

### a) Analysis of epileptogenesis mechanisms and high-order brain function from mathematical models.

With the development of computer science, EEG data measured by digital electroencephalographs with multiple channels and wide bandwidth are being analyzed in various manners which go beyond mere observation, and are being applied for various purposes, such as epileptic focus retrieval, brain function mapping, and brain-machine interface. We work closely with researchers in this field in the basic and theoretical sciences, such as mathematics, informatics, science, and engineering. As the basis for this joint research, in the Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature of the Grant-in-Aid for Scientific Research on Innovative Areas of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), tools and waveform data are shared and analyzed among with joint researchers using a database. Meanwhile, the MEXT's Grant-in-Aid for Scientific Research (B) program, "Glia and Neurons in Comprehensive Epileptic Networks of the Human Brain", which started in FY2019, aims to validate the mechanism of epileptic seizure onset, consisting of glia and neurons, using mathematical models, brain network models, and real data.

As an individual joint study, we are conducting power spectrum analysis, chaos time series analysis, and cluster analysis of DC shifts for cortical brain wave data during and before epileptic seizures in collaboration with Dr. Namiki of Hokkaido University, and Professor Tsuda of Chubu University. Together with Professor Keiichi Ueda of the University of Toyama, we are developing and validating a mathematical model of neurons, including glia, and providing theoretical considerations on the prevention and cessation of epileptic seizures. We are further collaborating with Professors Christophe Bernard and Victor Jirsa at the University of Aix-Marseille on epileptic disease model, and with Professor Keiichi Kitashiro at the Institute of Physiological Sciences on intracranial EEG data during epileptic seizures to study information transfer between frequencies. We are further collaborating with Prof. Aoyagi's group at the Faculty of Science, Kyoto University, and Prof. Kitano's group at Ritsumeikan University to elucidate the dynamics of brain activity during epileptic seizures by permutation entropy.

The following events were held to further develop cooperative relations between the two sides.

- October 24, 2018: AEEE Study Group (Pre-Congress of the 52nd Annual Congress of the Japan Epilepsy Society, Yokohama, Japan)
- June 11, 12, 2019: Mathematical Studies of Epilepsy (Research Meeting of the Institute for Mathematical Analysis, Prof. Namiki, Hokkaido University)
- October 30, 2019: 2nd AEEE Study Group Meeting (Pre-Congress of the 53rd Annual Congress of the Japan Epilepsy Society, Kobe, Japan)

### b) Joint research on critical care EEG, CSD and brain pathology

Although studies in patients with refractory partial epilepsy have confirmed that infra-slow activity (ISA) is observed

in EEG tests, it is not clear whether this is also seen in acute brain disorders such as acute cerebral infarction, head trauma, and subarachnoid hemorrhage. However, ISA may be associated with pathological conditions including cortical spreading depolarization (CSD), which is thought to be involved in the pathogenesis of acute brain injury. We are collaborating with TMG Asaka Medical Center (Dr. Satoshi Egawa, Department of Neuro-ICU) to evaluate the neurophysiological significance of ISA in acute brain injury by examining the EEG (critical care EEG) recorded once or twice a month in the neuro-ICU. In collaboration with the Department of Neurosurgery, we are also studying the neurological symptoms and EEG abnormalities associated with abnormal perioperative cerebral perfusion in patients who have undergone revascularization surgery for cerebrovascular diseases.

## 6) Collaborators

We have been collaborating closely with the Departments that officially support our department. Other collaborators are listed below.

[Overseas]

Dr. Stéphanie Baulac, Ph.D.

Affiliation: Institut du Cerveau et de la Moelle épinière (ICM), Epilepsy Unit

Position: Research Director

Dr. Christophe Bernard, Ph.D.

Affiliation: INS - Institut de Neurosciences des Systèmes, UMR INSERM 1106, Aix-Marseille Université

Position: Team leader

Prof. Marco Catani, M.D., Ph.D.

Affiliation: Natbrain lab, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry,  
King's College London

Position: Head of the Natbrainlab, Clinical Senior Lecturer and Honorary Consultant Psychiatrist

Prof. Nathan Earl Crone, M.D.

Affiliation: Department of Neurology, Johns Hopkins University School of Medicine

Position: Professor

Prof. Matthew A. Lambon-Ralph, FRCSLT (hons), FBPSS

Affiliation: School of Social Sciences, Manchester Institute for Collaborative Research on Ageing,  
The University of Manchester

Position: Professor

Michel Le Van Quyen

Affiliation: Institut du Cerveau et de la Moelle épinière, Hôpital de la Pitié-Salpêtrière

Position: Researcher

Dr. Dileep R. Nair, M.D.

Affiliation: Epilepsy Center, Cleveland Clinic

Position: The Section Head of Adult Epilepsy and Director of Intraoperative Neurophysiologic monitoring

Dr. Marco de Curtis, M.D.

Affiliation: Fondazione IRCCS Istituto Neurologico Carlo Besta

Position: Head of Epileptology and Experimental Neurophysiology Unit, Head of Pre-clinical Neuroscience Laboratories

Dr. William Stacey, M.D., Ph.D.

Affiliation: Department of Neurology, Department of Biomedical Engineering, University of Michigan

Position: Associate Professor

[Domestic]

Dr. Satoshi Egawa, M.D., Ph.D.

Affiliation: Neurointensive Care Unit, the TMG Asaka Medical Center.

Position: Director

Koichi Fujiwara, Ph.D.

Affiliation: Department of Systems Science, Graduate School of Informatics, Kyoto University.

Position: Assistant Professor

※ As of June, 2021

Affiliation: Department of Materials Process Engineering, Nagoya University, Graduate School of Engineering

Position: Associate Professor

Dr. Hiroyuki Ishiura, M.D., Ph.D.

Affiliation: Department of Neurology, The University of Tokyo Hospital.

Position: Senior Lecturer

Dr. Masaki Izumi, M.D., Ph.D.

Affiliation: Department of Neurosurgery, Chiba Cerebral and Cardiovascular Center.

Position: Chief Doctor

Dr. Masaaki Kato, M.D., Ph.D.

Affiliation: Musashino Kokubunji Clinic.

Position: Hospital Director

Dr. Michi Kawamoto, M.D., Ph.D.

Affiliation: Department of Neurology, Kobe City Medical Center General Hospital.

Position: Director

Dr. Seiichiro Mine, M.D., Ph.D.

Affiliation: Department of Neurosurgery, Epilepsy Center, Chiba Cerebral and Cardiovascular Center.

Position: Center Director

Dr. Miho Miyajima, M.D.

Affiliation: Department of Psychosomatic and Palliative Medicine, Tokyo Medical And Dental University,  
Medical Hospital

Position: Assistant Professor



Prof. Masatoshi Nakamura, Ph.D.

Affiliation: Research Institute of Systems Control, Institute for Advanced Research and Education, Saga University

Position: Emeritus Professor (deceased)

Prof. Shigeto Nishida, Ph.D.

Affiliation: Department of Information and Communication Engineering, Faculty of Information Engineering,  
Fukuoka Institute of Technology

Position: Professor

Dr. Teiichi Onuma, M.D., Ph.D.

Affiliation: Musashino Kokubunji Clinic.

Position: Honorary Hospital Director

Prof. Yoshio Sakurai, Ph.D.

Affiliation: Laboratory of Neural Information, Graduate School of Brain Science, Doshisha University.

Position: Professor

Prof. Hiroshi Shibasaki, M.D., Ph.D.

Affiliation: Department of Neurology, Kyoto University Graduate School of Medicine

Position: Emeritus Professor

Prof. Takenao Sugi, Ph.D.

Affiliation: Institute of Ocean Energy, Saga University.

Position: Professor

Dr. Takao Takeshima, M.D., Ph.D.

Affiliation: Department of Neurology, Headache Center, Tominaga Hospital.

Position: Director

Dr. Yoshihisa Tatsuoka, M.D., Ph.D.

Affiliation: Tatsuoka Neurology Clinic.

Position: Hospital Director

Dr. Masaya Togo, M.D., Ph.D.

Affiliation: Department of Neurology, Kobe University Hospital.

Position: Assistant Professor

Prof. Shoji Tsuji, M.D., Ph.D.

Affiliation: International University of Health and Welfare.

Position: Professor

Prof. Ikuko Yano, Ph.D.

Affiliation: Department of Pharmacokinetics and Pharmaceutics, Kobe University Graduate School of Medicine.

Position: Professor

(Listed in the alphabetical order of their family names)

#### Direct recording of the neural oscillation in human brain

(Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science and Technology, Japan: Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature)

Prof. Ichiro Tsuda, Ph.D.

Affiliation: Chubu University Academy of Emerging Science.

Position: Professor

Dr. Keiichi Kitajo, Ph.D.

Affiliation: Rhythm-based Brain Information Processing Unit, RIKEN Brain Science Institute.

Position: Unit Leader

Prof. Katsunori Kitano, Ph.D.

Affiliation: Department of Human and Computer Intelligence, Ritsumeikan University.

Position: Professor

Prof. Toshio Aoyagi, Ph.D.

Affiliation: Department of Applied Analysis and Complex Dynamical Systems,  
Kyoto University Graduate School of Informatics.

Position: Professor

Prof. Tatsuya Mima, M.D., Ph.D.

Affiliation: The Graduate School of Core Ethics and Frontier Sciences, Ritsumeikan University.

Position: Professor

Prof. Hiroaki Wagatsuma, Ph.D.

Affiliation: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology.

Position: Professor

Prof. Katsuhiro Kobayashi, M.D., Ph.D.

Affiliation: Department of Child Neurology, Okayama University Graduate School of Medicine.

Position: Professor

Prof. Takashi Nagamine, M.D., Ph.D.

Affiliation: Department of Systems Neuroscience, Sapporo Medical University School of Medicine.

Position: Professor

Prof. Naoyuki Sato, Ph.D.

Affiliation: School of Systems Information Science, Department of Complex and Intelligent Systems,  
Future University Hakodate.

Position: Professor

**Neural basis of human body representation: a direct electrocorticographic recording and stimulation study.**  
**(Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science and Technology, Japan: Understanding brain plasticity on body representations to promote their adaptive functions ("Embodied-Brain"))**

Dr. Eiichi Naito, Ph.D.

Affiliation: Center for Information and Neural Networks (CiNet), National Institute of Information and Communications Technology (NICT).

Position: Research Manager

Prof. Hiroshi Imamizu, Ph.D.

Affiliation: Department of Intelligence Science and Technology, Graduate School of Informatics, University of Tokyo.

Position: Professor

Dr. Takaki Maeda, M.D., Ph.D.

Affiliation: Department of Neuropsychiatry, Keio University School of Medicine.

Position: Senior Lecturer

**The elucidation of glial function in intractable epilepsy and standardization of clinical practice guidelines. (Japan Agency for Medical Research and Development (AMED): Practical Research Project for Rare Diseases)**

Prof. Taketoshi Maehara, M.D., Ph.D.

Affiliation: Department of Neurosurgery, Tokyo Medical and Dental University.

Position: Professor

Prof. Akiyoshi Kakita, M.D., Ph.D.

Affiliation: Department of Pathology, Brain Research Institute, Niigata University.

Position: Professor

Prof. Yukihiro Ohno, Ph.D.

Affiliation: Laboratory of Pharmacology, Osaka University of Pharmaceutical Sciences.

Position: Professor

Dr. Masaki Iwasaki, M.D., Ph.D.

Affiliation: Department of Neurosurgery, National Center Hospital, National Center of Neurology and Psychiatry.

Position: Director

Dr. Hiroki Kitaura, M.D., Ph.D.

Affiliation: Department of Pathology, Brain Research Institute, Niigata University.

Position: Specially Appointed Associate Professor

Dr. Hiroshi Shirozu, M.D., Ph.D.

Affiliation: Department of Neurosurgery, Hypothalamic Hamartoma Center,  
National Hospital Organization, Nishiniigata Chuo Hospital.

Position: Center Director

Dr. Yushi Inoue, M.D., Ph.D.

Affiliation: Department of Clinical Research, Shizuoka Institute of Epilepsy and Neurological Disorders,  
National Epilepsy Center.

Position: Honorary Hospital Director

Dr. Naotaka Usui, M.D., Ph.D.

Affiliation: Department of Clinical Research, Shizuoka Institute of Epilepsy and Neurological Disorders,  
National Epilepsy Center.

Position: Chief Doctor

#### **The establishment of diagnostic criteria and treatment for post-stroke epilepsy patients.**

**(AMED: Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes Mellitus)**

Dr. Masafumi Ihara, M.D., Ph.D.

Affiliation: Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center.

Position: Director

Dr. Tomotaka Tanaka, M.D., Ph.D.

Affiliation: Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center.

Position: Doctor

Dr. Kazuki Fukuma, M.D., Ph.D.

Affiliation: Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center.

Position: Doctor

#### **Multicenter study "Prospective observational study in autoimmune epilepsy/limbic encephalitis."**

Prof. Riki Matsumoto, M.D., Ph.D.

Affiliation: Department of Neurology, Kobe University Hospital.

Position: Professor

Dr. Norio Chihara, M.D., Ph.D.

Affiliation: Department of Neurology, Kobe University Hospital.

Position: Senior Lecturer

Dr. Atsushi Hara, M.D.

Affiliation: Department of Neurology, Kobe University Hospital.

Position: Postgraduate student

Prof. Klaus-Peter Wandinger, M.D., Ph.D.

Affiliation: Department of Neuroimmunology, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein.

Position: Professor

Dr. Frank Leipoldt, M.D., Ph.D.

Affiliation: Department of Neuroimmunology, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein.

Position: Head of Neuroimmunology section

Prof. Koji Kawakami, M.D., Ph.D.

Affiliation: Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health.

Position: Professor

Ikumi Yoshida, Ph.D.

Affiliation: Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health.

Position: Senior Lecturer

Toshiki Fukasawa, M.S.

Affiliation: Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health.

Position: Assistant Professor

Dr. Kyoko Kanazawa, M.D., Ph.D.

Affiliation: Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry.

Position: Doctor

Dr. Yasukiyo Araki, M.D., Ph.D.

Affiliation: Department of Clinical Research, Shizuoka Institute of Epilepsy and Neurological Disorders,  
National Epilepsy Center.

Position: Doctor

Dr. Yoko Goji, M.D., Ph.D.

Affiliation: Neuropsychiatric Department, Aichi Medical University Hospital.

Position: Senior Lecturer

Dr. Morito Inouchi, M.D., Ph.D.

Affiliation: Department of Neurology, National Hospital Organization Kyoto Medical Center.

Position: Director

Prof. Takayuiki Kondo, M.D., Ph.D.

Affiliation: Department of Neurology, Kansai Medical University Medical Center.

Position: Professor

Dr. Takahiro Mitsueda, M.D., Ph.D.

Affiliation: Department of Neurology, Osaka City General Hospital.

Position: Director

Dr. Hajime Yoshimura, M.D., Ph.D.

Affiliation: Department of Neurology, Kobe City Medical Center General Hospital.

Position: Chief Doctor

Prof. Hiroshi Shigeto, M.D., Ph.D.

Affiliation: Division of Medical Technology, Department of Health Sciences, Graduate School of Medical Sciences,  
Kyushu University.

Position: Professor

## Educational activities

### 1) Offering the optimal education and research to Japanese and foreign physicians

#### ■ EEG/Epilepsy fellowship

With great support by the Department of Neurology, we have set up the EEG/Epilepsy fellowship for training young neurologists, neurosurgeons, pediatricians, and psychiatrists. A total of twelve adult neurologists, one pediatric neurologist, four neurosurgeons, and one general medicine doctor have already completed this fellowship. Our education covers various fields of epileptology with a focus on clinical neurophysiology. We plan to welcome foreign young doctors for fellowship training as well.

Contents of the fellowship program are listed as follows;

- 1) Training of routine EEG reading (emergency EEG as well)
- 2) Analysis of the long-term video-EEG monitoring for diagnosis and presurgical evaluation
- 3) Clinical practice of adult epilepsy
- 4) Training of medical treatment with anti-seizure medication/anti-epileptic drugs

Japanese Society of Neurology has started domestic fellowship for neurophysiological examinations (EEG) since 2016. We have contributed to accept six doctors as this fellowship.

Graduates of EEG/Epilepsy fellowship

Reiko Tsuda (June 2011 - Aug 2011)

Takeshi Inoue (Apr 2013 - Mar 2016)

Hajime Yoshimura (July 2015 - Sept 2015)

Tsuyoshi Tsukada (Oct 2015 - Mar 2016)

Daiki Fujii (Sept 2014 - Nov 2014, Feb 2016 - Mar 2017)

Masayuki Honda (Apr 2016 - Mar 2018)

Namiko Henmi (Oct 2016 - Mar 2019)

Haruo Yamanaka (Jan 2017 - Mar 2017)

Nobutaka Mukae (June 2017 - July 2017)

Norihiro Muraoka (Oct 2017 - Mar 2018)

Toshikazu Hamaguchi (May 2017 - Mar 2019)

Tomoaki Taguchi (Apr 2018 - Jun 2018)

Takashi Tsukamoto (Oct 2018 - Mar 2019)

Kaoru Yagita (Jan 2019 - Mar 2019)

Kento Matoba (Oct 2019 - Dec 2019)

Yawara Nakamura (Apr 2020 - Sept 2020)

Toshiyuki Nagai (July 2021 - Mar 2022)

Kang Yugui (Sept 2021 - Dec 2021)

#### ■ Intramural, multidisciplinary monthly case conference

In cooperation of the Departments of Neurology, Neurosurgery, Pediatrics, Diagnostic Radiology, Psychiatry, Rehabilitation, and Clinical Laboratory Medicine, and Human Brain Research Center, we have been holding the intramural, multidisciplinary monthly case conference for more than a decade. In the conference, we discuss the diagnosis and surgical indication of epilepsy patients for comprehensive epilepsy practice as a tertiary epilepsy special facility. The numbers of participants and the discussion cases are getting larger. As a training facility certified by Japan Epilepsy Society (JES), this conference is open for doctors outside the hospital to discuss their problem case or to obtain the credit to apply board examination of JES-certified epileptologist.



**■ EEG conferences and so on**

For our graduate students and EEG/Epilepsy fellows, we have been offering multifaceted educational and research trainings, such as EEG reading skills in EEG conferences twice a week, seeing outpatients and inpatients with staffs, and epilepsy/clinical neurophysiology researches. One EEG conference and research conference are held in English for training skills in English presentation. The other conference is held in Japanese and open for the in-hospital technicians and out-hospital doctors for providing them with training opportunities for the practical basic EEG reading skills (about 30-40 participants).

**■ Specialist training**

Our department has produced 23 board-certified epileptologists (JES) and 24 board-certified EEGers (JSCN) since 2013.

**■ Extramural workshops**

Regarding educational activities outside the institute, as the secretary office in general, we have organized the district EEG & EMG teaching course for the young doctors and technicians in Kansai (Kansai EEG & EMG workshop) every year since 2008. In 2015, we newly founded and organized the EEG seminar advanced course for the purpose of acquisition of specialized knowledge and reading skills in clinical EEG sponsored by the Japanese Society of Clinical Neurophysiology. We also have provided educational activities by complying the request of lectures nation-widely (please refer to the achievements for details). Staffs in our department regularly teach EEG reading and epileptology at the affiliated hospitals.

Educational seminars for industry-academia collaboration

The following is a list of seminars of at least one day per year dedicated exclusively to education, in which the lecturer team is planned to collaborate with our department.

1) Seminar Title: Industry-Academia Cooperative Educational Seminar: Kinki Adult Epilepsy Seminar

Dates: October 6, 2018; September 21, 2019; September 26, 2020 (web-based)

Co-sponsored by the Japanese Epilepsy Society Kinki Regional Meeting, UCB Japan K.K., Otsuka Pharmaceutical Co.

Abstract: In view of the lack of educational opportunities for epilepsy care and EEG in the field of neurology in the Kinki region, an educational seminar on the basics of epilepsy care was held.

The number of participants is as follows:

Specialty area	2018	2019	2020
Neurology	69	68	57
Neurosurgery	8	10	23
Psychiatry	16	2	10
Pediatrics	9	9	20
Resident	5		5
Internal medicine department		2	1
Clinical laboratory technicians and nurses			15
Total amount	107	91	131

Content covered in the program (25-40 minutes each)

**Seizure symptom**

Interview on the history of epilepsy  
Seizure video (partial seizure)  
Seizure video (generalized seizure)  
Epilepsy Case Study

**EEG interpretation**

Basics of EEG interpretation  
Actual EEG interpretation  
EEG Case Study

#### ■ EEG/Epilepsy lecture series

We have been holding the intensive lecture series of the basics of EEG and epileptology for EEG/Epilepsy fellows and young doctors.

#### ■ Joint program for the aim of the establishment of the epilepsy care and education center in Indonesia

As the industry-academia collaboration among Nihon Kohden Corporation, Eisai Co., Ltd., Kyoto University, and Tohoku University, we have been planning to help establish epilepsy medical care and education center for the 3 axes of treatment, human resource development, and research by improving epilepsy medical care in Indonesia. In January 2020, the team including Akio Ikeda and Masao Matsushashi belonging to our department visited Jakarta and held a workshop with local neurologists and neurosurgeons. We shared the current status of epilepsy treatment with each other through academic exchanges.

#### 2) Offering medical staffs' education for caring of epilepsy patients

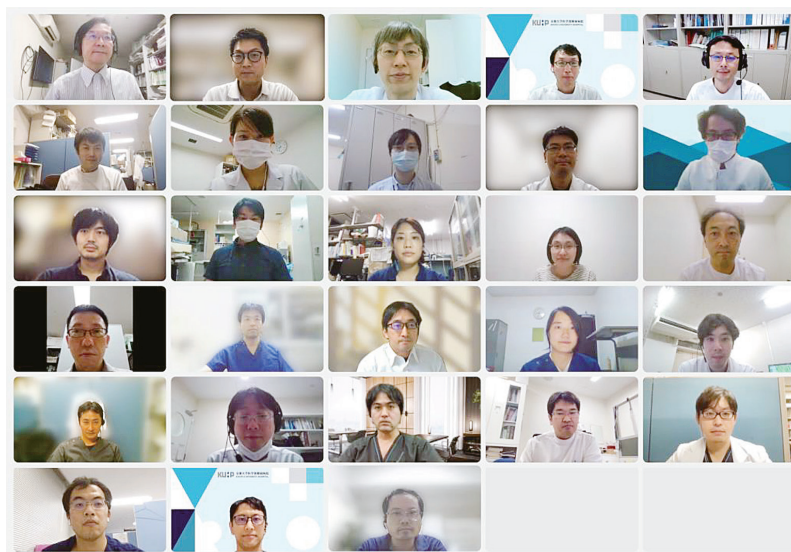
In the Kyoto University Hospital, we have offered education for epilepsy and related disorders to doctors and medical staffs. For the medical staffs in the Neurology clinic and ward, we hold comprehensive monthly lectures about pathophysiology of epilepsy, seizure semiology, and medical care of patients living with epilepsy.

#### 3) Providing patients, family and society with valuable information

We have responded to the request by the patients, family, and society in cooperation with Japan Epilepsy Association. For example, we have joined the lectures sponsored by Japan Epilepsy Association for the public, and also the continuing medical education lectures for physicians by Japan Medical Association.

#### 4) Education in the era of the COVID-19 pandemic

Due to the COVID-19 pandemic, face-to-face education has been limited since early 2020. To overcome this difficulty, we have been continuing education using web conference systems. EEG/Epilepsy lectures have been recorded and provided for residents or fellows in our hospital as e-learning materials. We started to accept the doctors as virtual fellowship of the Japanese Society of Neurology.



Interdisciplinary monthly case conference



EMU EEG conference in English



EEG conference held in Japanese

## Clinical activities

### 1) Outpatient Epilepsy Clinic. Promoting cooperation between hospitals and clinics for epilepsy care. Foundation of Integrated Epilepsy Care Support Center

As a team of specialists, we have made full efforts to provide the best care to patients suffering from epilepsy or movement disorders. Until recently, epilepsy has been recognized as a childhood-onset disease. However, with the advent of a super-aging society, epilepsy that develops in the middle-aged or elderly has become a current problem in Japan. In addition, the number of the hospitals and physicians that can offer the epilepsy care is not adequate. Moreover, it is unclear which department, neurology, neurosurgery, or psychiatry, is in charge for the adult epilepsy service. In order to offer the optimal epilepsy care, it is very important to establish the cooperation model among general physicians and epilepsy specialists for epilepsy care like that in European and North American countries. As a tertiary care institute for epilepsy in Kyoto, we have led cooperation among primary, secondary and tertiary facilities in the Kinki district (esp. in Kyoto-Shiga region) to provide a comprehensive epilepsy service with a dedicated team of neurologists, neurosurgeons, pediatricians and psychiatrists.

In 2019 and 2020, we saw about 1200 outpatients. About 250 patients were newly consulted from other hospitals and clinics in the Kinki district in 2019. 132 patients were newly consulted from other hospitals and clinics in the Kinki district in 2020. We promoted hospital-clinic cooperation by returning the referral patients to their local clinics and hospitals.

Epilepsy care and support center of Kyoto University Hospital was founded in November 2018 for the purpose of integrated support and care for the patients with epilepsy and promotion of epilepsy research. Integrated Epilepsy Care Support Center had the function not only within the institute, The center also promotes the hospital-clinic cooperation. In addition, approximately 30 kinds of brochures about the epilepsy and epilepsy care were uploaded in the homepage of the center. These brochures are open to the public, so that patients who did not visit our hospital could read the brochures. The Steering Committee of the Epilepsy Care Support Center is held regularly for the purpose of smoothly operating the Integrated Epilepsy Care Support Center.

In the fiscal years of 2019-2020, we participated in the research about the guideline to run core epilepsy centers for promoting the regional medical care cooperation system, supported by Health, Labor and Welfare Science Research Grant. Furthermore, our Kyoto University Hospital was certified as an integrated epilepsy special hospital by Japan Epilepsy Society. We will continue to collaborate with administration to more improve epilepsy care in Japan.

### 2) Inpatient evaluation and treatment for epilepsy (including video-EEG monitoring)

Since 1991, we have been running the epilepsy monitoring unit (EMU) in the Neurology Ward for evaluation of patients with epilepsy. We now have two dedicated rooms for EMU, equipped with the digital video-EEG system.

By capturing seizures with simultaneous video and EEG recording, we can perform

- i) An accurate diagnosis of epilepsy: To determine whether the seizure is epileptic or non-epileptic, including movement or psychogenic disorders,
- ii) Identification of epileptic focus: To locate the epileptic focus for epilepsy surgery in patients with medically intractable epilepsy.

In 2019, we examined 52 patients in the EMU in 2019 and 37 patients in the EMU in 2020.

In addition, we provide patients with multidisciplinary studies for comprehensive evaluation, such as 3 tesla MRI, routine EEG, FDG-PET/SPECT, MEG and neuropsychological testing. Routine EEGs were performed in 1376 patients in 2019 and 1418 patients in 2020.

### 3) Epilepsy Surgery

We have established an epilepsy surgery program with close collaboration with the Department of Neurosurgery since 1991. Since the first epilepsy surgery in 1992, we have performed more than 190 epilepsy surgeries, with the majority of patients having seizure freedom or substantial decrease of seizure leading to better QOL. We provide

each patient with the individually tailored surgery plan by incorporating the findings of the multimodal studies (see below) as well as the Wada test. The patients may proceed to the invasive presurgical evaluation with intracranial electrodes (subdural and/or depth electrodes) when the epileptic focus cannot be precisely localized (such as in cases with non-lesional MRI) or the focus is located at or around the functionally important areas such as motor or language cortices. In such cases, the patients undergo the first surgery for implantation of intracranial electrodes. After electrode implantation, the patients are evaluated for the epileptic focus (by recording seizures) and the functional cortical areas (by incorporating the state-of-art mapping techniques) for 1-2 weeks. Then, the patients undergo the second surgery for resection of the epileptic focus. The patients may undergo the awake brain surgery, where the patients wake up from anesthesia if necessary. Awake surgery has the advantage to evaluate the brain functions such as motor and language during resection and monitor the 'natural' epileptic spikes without any influence from anesthetics. Our team performed epilepsy surgery in 17 patients (including 4 patients underwent vagal nerve stimulation) in 2019, and 16 patients (including 5 patients underwent vagal nerve stimulation) in 2020.

#### **4) Examinations for epilepsy**

As the tertiary care epilepsy facility, we provide patients with the state-of-arts studies for the evaluation of epilepsy. As the comprehensive epilepsy program in the national university hospital, we incorporate the leading techniques as clinical research studies (IRB approved) for the optimal presurgical evaluations.

- Electroencephalography (EEG)
- Magnetoencephalography (MEG)
- FDG-PET (18F-fluorodeoxyglucose positron emission tomography)
- SPECT (Single photon emission computed tomography) including ictal SPECT
- 3 tesla MRI
- functional MRI (fMRI)
- EEG-fMRI (simultaneous EEG and functional MRI recording)
- Neuropsychological testing (WAIS-III, WMS-R, WAB, semantic batteries and Kanji/Kana related tasks)
- invasive EEG monitoring with intracranial electrodes

Recently, autoimmune epilepsy is regarded as one of the important cause of epilepsy. Following tests are diagnostic for autoimmune epilepsy.

- Cerebrospinal fluid / serum antibody test

#### **5) Development of novel treatments for epilepsy**

- i) Interventional Neurophysiology: Recently, neurophysiology has been highlighted for its application to treatment of various neurological diseases. In our hospital, we apply a novel interventional neurophysiology method, neurofeedback treatment, to medically intractable patients in whom epilepsy surgery is not applicable. Patients train themselves to control the brain activity (by adjusting slow EEG potentials) to suppress epileptic seizure activity. Our preliminary study shows a good efficacy as comparable to that for the Vagus Nerve Stimulation.
- ii) Promoting the clinical trials for new anti-epileptic drugs.

#### **6) Diagnosis and treatment for movement disorders**

It is also our mission to provide the optimal care for patients with movement disorders. We provide precise diagnosis using advanced diagnostic tools for better treatment of movement disorders such as tremor, myoclonus, dystonia and other involuntary movements.

The pathophysiology of movement disorders, however, is not fully understood. We have been investigating their pathophysiology and treatment in close collaboration with the Department of Neurology and Human Brain Research Center (HBRC).

**7) Simulation training of brain death determination**

Since Organ Transplant Law went into force in 1997, we, in close collaboration with the affiliated departments, have been regularly practicing the course 'Simulation-based training in brain death determination'. In this course, we simulate the management about how and what to do when the donor is found and until organs are taken. The training is highly practical for those in charge of brain death determination in our hospital. We also participated in the first case of brain death determination of Kyoto University Hospital in close collaboration with many affiliated departments.



## Social activities on academic organization

### Akio Ikeda

Board certified member of the Japanese Society of Neurology  
 Board certified member of the Japan Epilepsy Society  
 Board certified member of the American Board of Clinical Neurophysiology (ABCN)  
 Board certified member of the Japanese Society of Internal Medicine  
 Board certified member of the Japanese Society of Clinical Neurophysiology

#### MEMBERSHIPS OF ORGANIZATIONS:

Japan Epilepsy Society: President, international affairs committee (chair), clinical specialist accreditation committee, drug investigation affairs committee, membership and public relations affairs committee  
 Japanese Society of Clinical Neurophysiology: council member, EEG seminar and advanced course committee (chair),  
 Japan Neurology Society: council member, educational committee, medical care affairs committee, epilepsy guideline committee  
 Japanese Society of Human Brain Mapping: council member  
 Japanese Society of Neurotherapeutics: council member  
 ILAE CAO (Commission of Asian Oceanian Affairs): chair  
 CAO: co-chair of research task force committee, ASEPA EEG Certification Examination Board member  
 ILAE: executive committee member Research priorities task force member, ILAE/AES translational task force of the neurobiology commission of the ILAE member  
 American Clinical Neurophysiology Society (ACNS): FACNS (Councilor of American Clinical Neurophysiology), program committee, international relationship committee  
 European Neurology Society: higher cortical function subcommittee

#### EDITORIAL BOARD:

Epilepsia (associate editor)  
 Epileptic Disorders (John Libbey)  
 Neurology and Clinical Neuroscience (NCN) (associate editor)  
 International Journal of Epilepsy (Indian Epilepsy Society English Journal)  
 Journal of Epilepsy Research (JER, Korean Epilepsy Society English Journal)  
 Rinsho Shinkeigaku (Clinical Neurology)  
 Japanese Journal of Clinical Neurophysiology (field editor)  
 Epilepsy & Seizure (JES, Tokyo)  
 Epilepsy (Medical Review)

### Masao Matsuhashi

Board certified member of the Japanese Society of Internal Medicine  
 Board certified member of the Japanese Society of Neurology  
 Board certified member of the Japanese Society of Clinical Neurophysiology  
 Japanese Society of Clinical Neurophysiology: Councilor  
 Japan Biomagnetism and Bioelectromagnetics Society: Councilor  
 Japan Consortium of Clinical MEG: Committee member

**Akihiro Shimotake**

Board certified member of the Japanese Society of Neurology  
Japan Epilepsy Society: Councilor  
Japanese Society of Clinical Neurophysiology: Committee member

**Kiyohide Usami**

Board certified member of the Japanese Society of Internal Medicine  
Fellow of the Japanese Society of Internal Medicine (FJSIM)  
Board certified member of the Japanese Society of Neurology  
Board certified member of the Japan Epilepsy Society  
Board certified member of the Japan Stroke Society

## Research grants obtained from extramural sources & awards

### The ministry of Education, Culture, Sports, Science and Technology of Japan Grant-in-Aids for Scientific Research (KAKENHI)

Fiscal years 2015-2019

Grant-in-Aid for Scientific Research on Innovative Areas (Non-linear Oscillology)

Principal investigator: Akio Ikeda

Subject number: 15H05874

Fiscal years 2019-2021

Grant-in-Aid for Scientific Research (B)

Principal investigator: Akio Ikeda

Subject number: 19H03574

Fiscal years 2020-2022

Grant-in-Aid for Challenging Research (Exploratory)

Principal investigator: Akio Ikeda

Subject number: 20K21573

Fiscal years 2019-2021

Grant-in-Aid for Young Scientists (B)

Principal investigator: Akihiro Shimotake

Subject number: 19K17033

Fiscal years 2018-2019

Grant-in-Aid for Research Activity start-up

Principal investigator: Kiyohide Usami

Subject number: 18H06087, 19K21210

Fiscal years 2020-2022

Grant-in-Aid for Young Scientists (B)

Principal investigator: Kiyohide Usami

Subject number: 20K16492

Fiscal years 2019-2022

Grant-in-Aid for Young Scientists (B)

Principal investigator: Kiyohide Usami

Subject number: 19K17004

### Health Labour Sciences Research Grant

Fiscal years 2017-2019

Principal investigator: Yushi Inoue

Co-investigator: Akio Ikeda

Subject number: H29-難治等(難)-一般-010

Fiscal years 2020-2022

Principal investigator: Yushi Inoue

Co-investigator: Akio Ikeda

Subject number: 20FC1039

Fiscal years 2019-2020

Principal investigator: Jin Yamamoto

Co-investigator: Akio Ikeda

Subject number: 19GC1301

### **Japan Agency for Medical Research and Development (AMED)**

Fiscal years 2016-2018

Co-investigator: Akio Ikeda

Subject number: 16ek0210057h0001, 17ek0210057h0003

### **Others**

The Japan Epilepsy Research Foundation Research Grant

Fiscal years 2017-2019

Principal investigator: Akihiro Shimotake

The Japan Epilepsy Research Foundation Research Grant

Fiscal years 2021-2023

Principal investigator: Katsuya Kobayashi

The Fujiwara Memorial Research Foundation Research Grant

Fiscal years 2021

Principal investigator: Katsuya Kobayashi

### **Awards**

Mayumi Otani :

53<sup>rd</sup> Japan Epilepsy Society (Oct. 31- Nov. 2, 2019)

English Presentation Award [English Session: Surgery]

“Assessment of language tasks in electric cortical stimulation(ECS) for efficient functional mapping in epilepsy surgery”

Miwa Takatani :

53<sup>rd</sup> Japan Epilepsy Society (Oct. 31- Nov. 2, 2019)

Kobe Portpier Award (English Poster Award)

“Red slow detection in scalp-EEG by quantitative analysis based on visual analysis”

Daisuke Yamada:

44<sup>th</sup> Epilepsy Surgery Society of Japan (Jan. 21, 2021)

Oral presentation award

"Clinical efficiency of intraoperative electrocorticogram in the awake state during epilepsy surgery"

Maya Tojima:

44<sup>th</sup> Epilepsy Surgery Society of Japan (Jan. 21, 2021)

Poster award

"Systematic analysis of candidates of epilepsy surgery: trial of 'Specific Consistency Score' with weighting"

7th AOCCN (Asian Oceanian Congress on Clinical Neurophysiology) (Jan.31-Feb.1, 2021)

E-poster award

"Origin Of Giant Somatosensory Evoked Potentials (SEPs) Using Principal Component Analysis: P25-HFOs Were Exclusively Seen In Benign Adult Familial Myoclonus Epilepsy (BAFME)"

2021 AOCN (Asian Oceanian Congress of Neurology) (Apr.1-4, 2021)

Oral Presentation Award (Silver Award)

"Markedly suppressed and prolonged giant SEPs by perampanel: a decade-long course in Unverricht-Lundborg disease"

Kozue Hayashi:

13th Asian&Oceanian Epilepsy Congress (virtual conference; Jun.10-13, 2021)

Tadokoro Award 2021

"Slow and infraslow of scalp EEG is associated with transient neurological events (TNE) in Moyamoya disease"





## Publications

### Original articles

#### 〈English articles〉

1. H. Ishiura, K. Doi, J. Mitsui, J. Yoshimura, M.K. Matsukawa, A. Fujiyama, Y. Toyoshima, A. Kakita, H. Takahashi, Y. Suzuki, S. Sugano, W. Qu, K. Ichikawa, H. Yurino, K. Higasa, S. Shibata, A. Mitsue, M. Tanaka, Y. Ichikawa, Y. Takahashi, H. Date, T. Matsukawa, J. Kanda, F.K. Nakamoto, M. Higashihara, K. Abe, R. Koike, M. Sasagawa, Y. Kuroha, N. Hasegawa, N. Kanesawa, T. Kondo, T. Hitomi, M. Tada, H. Takano, Y. Saito, K. Sanpei, O. Onodera, M. Nishizawa, M. Nakamura, T. Yasuda, Y. Sakiyama, M. Otsuka, A. Ueki, K.I. Kaida, J. Shimizu, R. Hanajima, T. Hayashi, Y. Terao, S. Inomata-Terada, M. Hamada, Y. Shiota, A. Kubota, Y. Ugawa, K. Koh, Y. Takiyama, N. Ohsawa-Yoshida, S. Ishiura, R. Yamasaki, A. Tamaoka, H. Akiyama, T. Otsuki, A. Sano, A. Ikeda, J. Goto, S. Morishita, and S. Tsuji: Expansions of intronic TTCA and TTTA repeats in benign adult familial myoclonic epilepsy. *Nat Genet* 2018, 50(4): 581-590.
2. Takayuki Kikuchi, Yu Abekura, Daisuke Arai, Hiroyuki Ikeda, Takeshi Funaki, Akira Ishii, Kazumichi Yoshida, Yasushi Takagi, Susumu Miyamoto: A Treatment Strategy for Basilar Bifurcation Aneurysm Associated with Moyamoya Disease: A Case Successfully Treated by Combined STA-MCA Anastomosis and Stent-assisted Coil Embolization. *Journal of Neuroendovascular Therapy* 2018, 001-006.
3. Chris G. Dulla, Damir Janigro, Premysl Jiruska, Joseph V. Raimondo, Akio Ikeda, Chou-Ching K. Lin, Howard P. Goodkin, Aristeia S. Galanopoulou, Christophe Bernard, Marco de Curtis: How do we use in vitro models to understand epileptiform and ictal activity? A report of the TASK1-WG4 group of the ILAE/AES Joint Translational Task Force. *Epilepsia Open* 2018, 3: 460-473.
4. Ozlem Akman, Yogendra H. Raol, Stephane Auvin, Miguel A. Cortez, Hana Kubova, Marco de Curtis, Akio Ikeda, F. Edward Dudek, Aristeia S. Galanopoulou: Methodologic recommendations and possible interpretations of video-EEG recordings in immature rodents used as experimental controls: A TASK1-WG2 report of the ILAE/AES Joint Translational Task Force. *Epilepsia Open* 2018, 3: 437-459.
5. Takahiro Mukai, Masato Kinboshi, Yuki Nagao, Saki Shimizu, Asuka Ono, Yoshihisa Sakagami, Aoi Okuda, Megumi Fujimoto, Hidefumi Ito, Akio Ikeda, Yukihiko Ohno: Antiepileptic Drugs Elevate Astrocytic Kir4.1 Expression in the Rat Limbic Region. *Frontiers in Pharmacology* 2018, 9: 845.
6. Shinako Inaida, Kousuke Kanemoto, Shiro Tanaka, Yoko Gouji, Tomohiro Oshima, Riki Matsumoto, Akio Ikeda, Koji Kawakami: Psychogenic non-epileptic seizures in Japan: Trends in prevalence, delay in diagnosis, and frequency of hospital visits. *Epilepsy & Seizure* 2018, 10: 73-86.
7. Takefumi Hitomi, Morito Inouchi, Hirofumi Takeyama, Katsuya Kobayashi, Shamima Sultana, Takeshi Inoue, Yuko Nakayama, Akihiro Shimotake, Masao Matsushashi, Riki Matsumoto, Kazuo Chin, Ryosuke Takahashi, Akio Ikeda: Sleep is associated with reduction of epileptiform discharges in benign adult familial myoclonus epilepsy. *Epilepsy & Behavior Case Reports* 2018, 11: 18-21.
8. Masaya Togo, Takefumi Hitomi, Tomohiko Murai, Hajime Yoshimura, Masao Matsushashi, Riki Matsumoto, Michi Kawamoto, Nobuo Kohara, Ryosuke Takahashi, Akio Ikeda: Short "Infraslow" Activity (SISA) With Burst Suppression in Acute Anoxic Encephalopathy: A Rare, Specific Ominous Sign With Acute Posthypoxic Myoclonus or Acute Symptomatic Seizures. *Journal of Clinical Neurophysiology* 2018, 35: 496-503.

9. Hidemasa Matsuo, Tomohiro Handa, Michiko Tsuchiya, Takeshi Kubo, Akihiko Yoshizawa, Yuko Nakayama, Shuichi Shiga, Takefumi Hitomi, Souichi Adachi, Hiroshi Date, Toyohiro Hirai, Satoshi Ichiyama: Progressive Restrictive Ventilatory Impairment in Idiopathic Diffuse Pulmonary Ossification. *Internal Medicine* 2018, 57: 1631-1636.
10. Katsuya Kobayashi, Takefumi Hitomi, Riki Matsumoto, Masako Watanabe, Ryosuke Takahashi, Akio Ikeda: Nationwide survey in Japan endorsed diagnostic criteria of benign adult familial myoclonus epilepsy. *Seizure* 2018, 61: 14-22.
11. Hajime Yoshimura, Riki Matsumoto, Hiroyuki Ueda, Koichi Ariyoshi, Akio Ikeda, Ryosuke Takahashi, Nobuo Kohara: Status epilepticus in the elderly: Comparison with younger adults in a comprehensive community hospital. *Seizure* 2018, 61: 23-29.
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13. Shuichiro Neshige, Masao Matsushashi, Katsuya Kobayashi, Takeyo Sakurai, Akihiro Shimotake, Takefumi Hitomi, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matsumoto, Ryosuke Takahashi, Susumu Miyamoto, Hirofumi Maruyama, Masayasu Matsumoto, Akio Ikeda: Multi-component intrinsic brain activities as a safe alternative to cortical stimulation for sensori-motor mapping in neurosurgery. *Clinical Neurophysiology* 2018, 129: 2038-2048.
14. Tomoyuki Fumuro, Masao Matsushashi, Riki Matsumoto, Kiyohide Usami, Akihiro Shimotake, Takeharu Kunieda, Takayuki Kikuchi, Kazumichi Yoshida, Ryosuke Takahashi, Susumu Miyamoto, Akio Ikeda: Do scalp-recorded slow potentials during neuro-feedback training reflect the cortical activity? *Clinical Neurophysiology* 2018, 129: 1884-1890.
15. Byungin Lee for the Asian Status Epilepticus Survey Group: Treatment gap for convulsive status epilepticus in resource-poor countries. *Epilepsia* 2018, 59 suppl2: 135-139.
16. Masato Kinboshi, Saki Shimizu, Tomoji Mashimo, Tadao Serikawa, Hidefumi Ito, Akio Ikeda, Ryosuke Takahashi, Yukihiro Ohno: Down-Regulation of Astrocytic Kir4.1 Channels during the Audiogenic Epileptogenesis in Leucine-Rich Glioma-Inactivated 1 (Lgi1) Mutant Rats. *International Journal of Molecular Sciences* 2019, 20: 001-015.
17. Kiyohide Usami, Griffin W Milsap, Anna Korzeniewska, Maxwell J Collard, Yujing Wang, Ronald P Lesser, William S Anderson, Nathan E Crone: Cortical Responses to Input From Distant Areas are Modulated by Local Spontaneous Alpha/Beta Oscillations. *Cerebral Cortex* 2019, 29: 777-787.
18. Takeshi Inoue, Morito Inouchi, Masao Matsushashi, Riki Matsumoto, Takefumi Hitomi, Masako Daifu-Kobayashi, Katsuya Kobayashi, Mitsuyoshi Nakatani, Kyoko Kanazawa, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda: Interictal Slow and High-Frequency Oscillations: Is it an Epileptic Slow or Red Slow? *Journal of Clinical Neurophysiology* 2019, 36: 166-170.

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20. Masahiro Nagano, Katsuya Kobayashi, Mayumi Yamada-Otani, Akira Kuzuya, Riki Matsumoto, Jiro Oita, Makoto Yoneda, Akio Ikeda, Ryosuke Takahashi: Hashimoto's Encephalopathy Presenting with Smoldering Limbic Encephalitis. *Internal Medicine* 2019, 58: 1167-1172.
21. Shuichiro Neshige, Riki Matsumoto, Morito Inouchi, Katsuya Kobayashi, Akihiro Shimotake, Hirofumi Maruyama, Ryosuke Takahashi, Akio Ikeda: Absence of an Autonomic Sign Assists in the Diagnosis of Extratemporal Lobe Epilepsy Manifesting Generalized Convulsion with Retained Awareness. *Internal Medicine* 2019, 58: 1151-1155.
22. Shuichiro Neshige, Katsuya Kobayashi, Masao Matsuhashi, Takefumi Hitomi, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matsumoto, Susumu Miyamoto, Ryosuke Takahashi, Hirofumi Maruyama, Akio Ikeda: A rational, multispectral mapping algorithm for primary motorcortex: A primary step before cortical stimulation. *Epilepsia* 2019, 60: 547-559.
23. Masaya Togo, Masako Kinoshita: Hepatic encephalopathy revisited: Beyond the triphasic waves. *Clinical Neurophysiology* 2019, 130: 408-409.
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26. Takeyama T, Matsumoto R, Usami K, Nakae T, Kobayashi K, Shimotake A, Kikuchi T, Yoshida K, Kunieda T, Miyamoto S, Takahashi R, Ikeda A: Human entorhinal cortex electrical stimulation evoked short-latency potentials in the broad neocortical regions: Evidence from cortico-cortical evoked potential recordings. *Brain and Behavior* 2019, Sep;9(9): e01366.
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28. Kazuki Oi, Shuichiro Neshige, Takefumi Hitomi, Katsuya Kobayashi, Masao Matsuhashi, Akihiro Shimotake, Daiki Fujii, Riki Matsumoto, Shuhei Kasama, Masutaro Kanda, Yoshiaki Wada, Hirofumi Maruyama, Ryosuke Takahashi, Akio Ikeda: Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. *Clinical Neurophysiology* 2019, 130: 1804-1812.
29. Shuichiro Neshige, Katsuya Kobayashi, Masao Matsuhashi, Masaya Togo, Mitsuhiro Sakamoto, Akihiro Shimotake, Takefumi Hitomi, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matsumoto, Hirofumi Maruyama, Ryosuke Takahashi, Susumu Miyamoto, Akio Ikeda: A score to map the lateral non-primary motor area: multi-spectrum intrinsic brain activity vs. cortical stimulation. *Epilepsia* 2019, 60: 2294-2305.

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31. Takuro Nakae, Riki Matsumoto, Takeharu Kunieda, Yoshiki Arakawa, Katsuya Kobayashi, Akihiro Shimotake, Yukihiro Yamao, Takayuki Kikuchi, Toshihiko Aso, Masao Matsuhashi, Kazumichi Yoshida, Akio Ikeda, Ryosuke Takahashi, Matthew A Lambon Ralph, Susumu Miyamoto: Connectivity Gradient in the Human Left Inferior Frontal Gyrus: Intraoperative Cortico-Cortical Evoked Potential Study. *Cereb Cortex* 2020, 30: 4633-4650.
32. Takeshi Inoue, Katsuya Kobayashi, Riki Matsumoto, Morito Inouchi, Masaya Togo, Jumpei Togawa, Kiyohide Usami, Akihiro Shimotake, Masao Matsuhashi, Takayuki Kikuchi, Kazumichi Yoshida, Hisashi Kawawaki, Nobukatsu Sawamoto, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda: Engagement of cortico-cortical and cortico-subcortical networks in a patient with epileptic spasms: An integrated neurophysiological study. *Clin Neurophysiol* 2020, 131: 2255-2264.
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34. Kenji Yoshinaga, Masao Matsuhashi, Tatsuya Mima, Hidenao Fukuyama, Ryosuke Takahashi, Takashi Hanakawa, Akio Ikeda: Comparison of Phase Synchronization Measures for Identifying Stimulus-Induced Functional Connectivity in Human Magnetoencephalographic and Simulated Data. *Front Neurosci* 2020, 14: 648.
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37. Masato Kinboshi, Akio Ikeda, Yukihiro Ohno: Role of Astrocytic Inwardly Rectifying Potassium (Kir) 4.1 Channels in Epileptogenesis. *Front Neurol* 2020, 11: 626658.
38. Maria Luisa Saggio, Dakota Crisp, Jared M Scott, Philippa Karoly, Levin Kuhlmann, Mitsuyoshi Nakatani, Tomohiko Murai, Matthias Dümpelmann, Andreas Schulze-Bonhage, Akio Ikeda, Mark Cook, Stephen V Gliske, Jack Lin, Christophe Bernard, Viktor Jirsa, William C Stacey: A taxonomy of seizure dynamotypes. *eLife* 2020, 9: e55632.
39. Jong-Hyeon Seo, Ichiro Tsuda, Young Ju Lee, Akio Ikeda, Masao Matsuhashi, Riki Matsumoto, Takayuki Kikuchi, Hunseok Kang: Pattern Recognition in Epileptic EEG Signals via Dynamic Mode Decomposition. *Mathematics* 2020, 8: 481.
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43. Katsuya Kobayashi, Riki Matsumoto, Kiyohide Usami, Masao Matsuhashi, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda: Cortico-cortical evoked potential by single-pulse electrical stimulation is a generally safe procedure. *Clin Neurophysiol* 2021, 132: 1033-1040.
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## Presentations

### Congress presentations

#### ■ Invited lectures and symposium etc.

#### International presentations

1. Akio Ikeda: How to predict good responders to vagus nerve stimulation, Beijing International Pediatric Epilepsy Forum (BIPEP) 2018 (2018/04/13-15, Beijing, China).
2. Akio Ikeda: Subdurally recorded HFO may represent extracellular or intercellular activity? SIG 1: Clinical and basic researches of EEG (Discussion on the researches of Basic and clinical EEG), 23rd Korean Epilepsy Congress (KEC2018) (2018/06/15-16, Seoul, Korea).
3. Akio Ikeda: Epilepsy, neuron and glia: Is it a paradigm shift?, Presidential symposium, Issues and advanced Technologies in Epilepsy, 23rd Korean Epilepsy Congress (KEC2018) (2018/06/15-16, Seoul, Korea).
4. Akio Ikeda: Generator mechanisms of antagonist of AMPA receptor Paroxysmal depolarization shifts (PDS) vs. AED Spotlight on Perampanel, Eisai Satellite Symposium, evolving landscape in management of epilepsy: experts perspective, the 12th Asian & Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
5. Akio Ikeda: Development of EEG services: the Japanese experience, CAO A Task Force Session, CAO A's global campaign task force session: improving availability and quality of EEG in the region, the 12th Asian & Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
6. Akio Ikeda: Biomarkers of epilepsy: What approaches do we have? EEG biomarkers for neuron and glia, the 12th Asian & Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
7. Akio Ikeda: CAO A's ongoing project Perampanel on cortical myoclonus, the 12th Asian & Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
8. Akio Ikeda: Neuron, glia, and epilepsy: Is it a paradigm shift?, Epilepsy Grand Rounds, University Hospitals, Neurological Institute, School of Medicine, Case Western Reserve University (2018/07/05, Cleveland, USA).
9. Akio Ikeda: Inflammation and epilepsy, 31st Annual Scientific Meeting of The Hong Kong Neurological Society (2018/11/03-04, Hong Kong, China).
10. Akio Ikeda: The role of EEG in adult epilepsy care, Teaching course 1-4, AOCN-ASEPA EEG Workshop 16th Asian Oceanian Congress Of Neurology (2018/11/08-11, Seoul, Korea).
11. Akio Ikeda: What do different frequencies and other modalities tell us about MEG's ability to identify the extent of the epileptic zone?, American Epilepsy Society (AES) 2018 Annual Meeting (2018/11/30-12/04, New Orleans, USA).
12. Akio Ikeda: DC shifts are established tool or still research topic? Concurrent session: SIG, Wide-band EEG for epilepsy: established tool or research topic?, American Clinical Neurophysiology Society, 2019 Annual Meeting and Courses (2019/02/06-10, Las Vegas, USA).

13. Akio Ikeda: Paroxysmal depolarization shifts (PDS) vs. AED in clinical epilepsy, Unique effects of perampanel on giant SEPs, i.e., paroxysmal depolarization shifts (PDS), Pertinent investigation in epilepsy, 20th Joint conference of Indian Epilepsy Society (IES) and Indian Epilepsy Association (IEA) (2019/03/08-10, New Delhi, India).
14. Akio Ikeda: Slow EEG and HFO is long and new frontiers in clinical EEG: Ready for epilepsy and functional mapping? EEG course and workshop Organized by Subcommittee on Clinical Neurophysiology of the Hong Kong Neurological Society (2019/05/04-05, Hong Kong, China).
15. Akio Ikeda: Interpretation of epileptiform activities (focal, generalized and status epilepticus), EEG course and workshop Organized by Subcommittee on Clinical Neurophysiology of the Hong Kong Neurological Society (2019/05/04-05, Hong Kong, China).
16. Akio Ikeda: Active ictal DC shifts & red slow in epilepsy patients: Other slows among pathological DC brain potentials, International conference of cortical spreading depolarization (iCSD) (2019/7/1-3, Yokohama).
17. Akio Ikeda: Pharmaco-resistant epilepsy, How do we know the real focus? New approach by active ictal DC shifts and red slow, 5th Neuroepidemiology International Conference (2019/9/3-5, Cairo, Egypt).
18. Ikeda A: Intractable partial Epilepsy: How do we know the real focus? New approach by active ictal DC shifts and red slow, 8th CAAE (China Association Against Epilepsy) International Conference of Epilepsy (2019/10/18-20, Dingdao, China).
19. Ikeda A: Clinical, neurophysiological features & history of BAFME/FCMTE, International Conference on Familial Cortical Myoclonic Tremor With Epilepsy (FCMTE) and Repeat Expansion Diseases (2019/11/17-19, Hangzhou, China).
20. Akio Ikeda: EEG and electrophysiological monitoring: Basic and wide band EEG, 10th Advanced International Course of Clinical Epileptology (2020/8/17-28, web).
21. Akio Ikeda: Case discussion from Kyoto University Graduate School of Medicine, A dialogue across the Pacific Ocean on epilepsy cases in America and Asia, 6th Huaxia International Neurology Forum (2020/11/22, web).
22. Akio Ikeda: EEG and electrophysiological monitoring: Basic and wide band EEG, EPIC online (Indian Epilepsy Association) (2021/1/10, web).
23. Akio Ikeda: Infralow, DC Shift and High Frequency Oscillations: Established Tool or Research Topic?, 7th Asian-Oceanian Congress on Clinical Neurophysiology (2021/1/30-2/1, web).
24. Akio Ikeda: Advances in EEG Analysis - Wide-Band EEG, Dense-Array EEG and Quantitative EEG, 7th Asian-Oceanian Congress on Clinical Neurophysiology (2021/1/30-2/1, web).
25. Akio Ikeda: How to predict good responders to vagus nerve stimulation, Comprehensive Epilepsy Surgery Online Course Series-XI (2021/4/24, web).



## Domestic Presentations

## 〈English Presentations〉

26. Akio Ikeda: Clinical EEG in 21st century: a research topic or tool?. 第48回日本臨床神経生理学会学術大会 (2018/11/08-10, 東京).

## 〈Japanese Presentations〉

27. 池田昭夫: グルタミン酸受容体拮抗薬の作用機序 - 基礎と臨床の translatability-PDS と抗てんかん薬〜臨床の立場から〜. 第60回日本小児神経学会学術集会 (2018/05/31-06/02, 千葉).
28. 松本理器: 高齢者のてんかん. 第60回日本老年医学会学術集会 (2018/06/14-16, 京都).
29. 池田昭夫: 急性発作性の運動異常症でてんかん関連運動異常および PKC: てんかん発作との類似点と鑑別. 第12回日本パーキンソン病・運動障害疾患カンファレンス (2018/07/05-07, 京都).
30. 松本理器: 非てんかん性異常・意識障害. 第4回脳波セミナーアドバンスコース (2018/08/04-05, 京都).
31. 池田 昭夫: てんかんの分類と診断 (池田昭夫) (他講演者分あり). 第7回サマーてんかんセミナー (2018/09/02, 東京).
32. 松本理器, 小林環, 下竹昭寛, 吉田和道, 矢野史朗, 前田貴記, 今水寛, 池田昭夫: 島皮質障害による運動主体感の動的変容: 脳外科手術症例からの知見. 身体性システム. 脳内身体表現のモデル化からリハビリテーション. 第36回日本ロボット学会 (2018/09/05-08, 愛知).
33. 池田昭夫: てんかん診療ガイドライン2018 改訂ポイント〜高齢者てんかんを中心に. 第17回 南勢神経フォーラム (2018/09/21, 津).
34. 池田昭夫: てんかんの病歴聴取, 病歴・発作症候の記載は, 臨床神経生理学を定性的に言語化したもの. 近畿成人てんかんセミナー (2018/10/06, 大阪).
35. 山尾幸広, 松本理器, 國枝武治, 荒川芳輝, 中江卓郎, 菊池隆幸, 吉田和道, 池田昭夫, 宮本享: 術中言語白質路モニタリングにおける皮質-皮質間誘発電位の麻酔の影響-言語機能保護を目指して-. 日本脳神経外科学会 第77回学術総会 (2018/10/10-12, 仙台).
36. 松本理器: てんかん. 京都市委託事業 難病患者医療講演・相談会 (2018/10/14, 京都).
37. 宇佐美清英: Functional Brain Mapping by ECoG-Recent Development -ECoG による脳機能マッピング-この1年の動向-. 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
38. 池田昭夫: グルタミン酸と AMPA 受容体-基礎と臨床の translatability-発作原性, てんかん原性と PDS: 臨床的視点. 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
39. 池田昭夫: 生き生きとしたてんかん医療地域連携とてんかん診療拠点の役割 日本てんかん学会のミッション: てんかん診療の多様性に対しての均てん化への方策. 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
40. 松本理器, 下竹昭寛, 十河正弥, 菊池隆幸, 國枝武治, 池田昭夫: 皮質電気刺激による脳機能マッピング. 第48回日本臨床神経生理学会学術大会 (2018/11/08-10, 東京).

41. 山尾幸広, 松本理器, 國枝武治, 荒川芳輝, 中江卓郎, 菊池隆幸, 吉田和道, 池田昭夫, 宮本享: 術中脳機能モニタリング. 第48回日本臨床神経生理学会学術大会 (2018/11/08-10, 東京).
42. 池田昭夫: 診療ガイドライン2018に基づく, てんかんの診療と治療. 第20回ニューロトピックス21「てんかん」(2018/11/13, 東京).
43. 池田昭夫: 一般診療における脳卒中とてんかんの鑑別診断. 第25回東播磨脳卒中フォーラム (2018/11/15, 明石).
44. 松本理器: 臨床システム神経科学によるヒト脳病態・高次機能の解明. 分子発生学セミナー (2019/02/25, 大阪).
45. 池田昭夫: てんかん発作発現メカニズム-up to date グリア・ニューロンからみた発現メカニズム〜電気生理学のおよび臨床的アプローチ〜. グルタメートカンファランス (2019/02/03, 東京).
46. 池田昭夫: てんかんと頭痛, てんかんと片頭痛の興奮性の違いは?. 第19回埼玉頭痛研究会学術研究会 (2019/02/15, さいたま).
47. 池田昭夫: てんかんの診断と治療の最近の話題. 日本神経治療学会, 第4回神経治療研修会プログラム (2019/04/14, 京都).
48. 池田昭夫: てんかん臨床と脳波: エッセンシャル (基本的小さしておくべきコツ). てんかんプライマリーケア・セミナー in Chiba (2019/04/19, 千葉).
49. 池田昭夫: 21世紀のてんかんの診断と治療: てんかんは国民病. 第81回大阪薬科大学 公開教育講座 くすりの作用と副作用〜薬物治療における安全管理のために (43) (2019/05/19, 大阪).
50. 池田昭夫: 第16回生涯教育セミナー Hands-on「脳波」. 第60回日本神経学会学術大会 (2019/05/24, 大阪).
51. 池田昭夫: 21世紀のてんかんの診断と治療: てんかんは国民病. 第37回日本神経治療学会年次集会 (2019/11/05-07, 東京).
52. 池田昭夫: Berger から始まる今日の脳波・脳磁図の研究・臨床と今後. Berger 講演2. 第49回日本臨床神経生理学会 (2019/11/28-30, 福島).
53. 池田昭夫: てんかん発作か発作性運動異常症か, それが問題だ. 第61回日本神経学会学術大会 (2020/08/31-09/02, 岡山).
54. 人見健文, 高橋良輔, 池田昭夫: 3) 皮質性ミオクローヌスとミオクロニー発作: てんかん発作か運動異常症か. 教育コース 7 てんかん発作か発作性運動異常症か, それが問題だ. 第61回日本神経学会学術集会 (2020/08/31-09/02, 岡山).
55. 池田昭夫: てんかん: 内科治療のトピックス, 抗発作薬から抗てんかん原性薬へ. 第79回日本脳神経外科学会総会 (2020/10/15-17, 岡山 (web)).
56. 宇佐美清英, 細川恭子, 竹島多賀夫, 立岡良久, 池田昭夫: 片頭痛の病態生理研究の新展開 片頭痛の脳波研究: Back to the basic. 第50回日本臨床神経生理学会学術集会 (2020/11/26-28, 京都).
57. 人見健文, 高橋良輔, 池田昭夫: ①易しく繙くデジタル脳波の利点 (講義). 主催セミナー 1 脳波ハンズオン. 第50回日本臨床神経生理学会学術集会 (2020/11/26-28, 京都).

58. 人見健文, 小林勝哉, 高橋良輔, 池田昭夫: ミオクローヌスてんかん. アドバンスレクチャー 10. 第50回日本臨床神経生理学会学術集会 (2020/11/26-28, 京都).
59. 池田昭夫: てんかん診療の進歩の多様化. 2020年度日本神経学会関東・甲信越地区生涯教育講演会 (2020/12/06, web).
60. 池田昭夫: 日本のでんかん外科へのメッセージ: 脳神経内科と ILAE の視点から. 第44回日本てんかん外科学会 (2021/01/20-21, 新潟 (web)).
61. 池田昭夫: 集中治療のための急性期脳波モニタリングの基礎: 難治てんかんの EMU モニタリングとの比較から. 第48回日本集中治療医学会学術集会 (2021/02/12-14, web).
62. 池田昭夫: 教育コース 21 小児てんかん治療の留意点. 第62回日本神経学会学術大会 (2021/05/19-22, 京都).

## ■ Oral and poster presentations

### International presentations

1. Tomohiko Murai, Takefumi Hitomi, Riki Matsumoto, Yuki Kawamura, Masutaro Kanda, Ryosuke Takahashi, Akio Ikeda: Scalp-EEG could record both ictal DC shift and HFO even with time constant 2 sec: a case report, the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
2. Masaya Togo, Takefumi Hitomi, Tomohiko Murai, Hajime Yoshimura, Masao Matsuhashi, Riki Matsumoto, Michi Kawamoto, Nobuyuki Kohara, Ryosuke Takahashi, Akio Ikeda: Short "infraslow" activity with burst suppression in acute anoxic encephalopathy: a rare, specific ominous sign with acute post-hypoxic myoclonus or acute symptomatic seizure, the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
3. Shuichiro Neshige, Kazuki Oi, Katsuya Kobayashi, Takefumi Hitomi, Akihiro Shimotake, Daiki Fujii, Riki Matsumoto, Shuhei Kasama, Masutaro Kanda, Yoshiaki Wada, Ryosuke Takahashi, Akio Ikeda: Clinico- electrophysiological impacts of small dosage of perampanel on patients with refractory cortical myoclonus: a case series study, the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
4. Shuichiro Neshige, Katsuya Kobayashi, Masao Matsuhashi, Akihiro Shimotake, Takefumi Hitomi, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matsumoto, Ryosuke Takahashi, Susumu Miyamoto, Hirofumi Maruyama, Akio Ikeda: Rational cortical mapping algorithm for epilepsy surgery: non-stimuli, multi-intrinsic brain activities without cortical stimulation, the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
5. Takefumi Hitomi, Katsuya Kobayashi, Takeyo Sakurai, Tomohiko Murai, Shamima Sultana, Masako Kinoshita, Akihiro Shimotake, Riki Matsumoto, Ryosuke Takahashi, Akio Ikeda: A homozygotic mutation with severe benign adult familial myoclonus epilepsy (BAFME), the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
6. Takefumi Hitomi, Katsuya Kobayashi, Shuichiro Neshige, Shamima Sultana, Kei Sato, Kosuke Tanioka, Akihiro Shimotake, Riki Matsumoto, Ryosuke Takahashi, Akio Ikeda: Temporal change of electroencephalogram in benign adult familial myoclonus epilepsy (BAFME), the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).

7. Shunsuke Kajikawa, Katsuya Kobayashi, Masako Daifu, Masao Matsuhashi, Takefumi Hitomi, Yukihiro Yamao, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matumoto, Ryosuke Takahashi, Akio Ikeda: Ictal direct current shifts can be intracranially recorded even with time constant 2 seconds, the 12th Asian&Oceanian Epilepsy Congress (2018/06/28-07/01, Bali, Indonesia).
8. Mitsuhiro Sakamoto, Riki Matsumoto, Junpei Togawa, Hirofumi Takeyama, Yuichiro Hashi, Katsuya Kobayashi, Akihiro Shimotake, Frank Leypoldt, Klaus- Peter Wandering, Takayuki Kondo, Ryosuke Takahashi, Akio Ikeda: Revised diagnostic algorithm for autoimmune epilepsy without antibody testing: its proposal and validation with a retrospective cohort, 16th Asian Oceanian Congress Of Neurology (2018/11/08-11, Seoul, Korea).
9. Tamaki Kobayashi, Riki Matsumoto, Akihiro Shimotake, Masaya Togo, Yoshiki Arakawa, Yukihiro Yamao, Takayuki Kikuchi, Kazumichi Yoshida, Akio Ikeda, Shiro Yano, Takaki Maeda, Hiroshi Imamizu, Susumu Miyamoto: The role of the insula in sense of agency: supportive data from neurosurgical cases, 16th Asian Oceanian Congress Of Neurology (2018/11/08-11, Seoul, Korea).
10. Katsuya Kobayashi, Riki Matsumoto, Kiyohide Usami, Akihiro Shimotake, Masao Matsuhashi, Yukihiro Yamao, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Ryosuke Takahashi, Akio Ikeda: Underlying excitability at the focus modulates network dynamics of seizure propagation: a single-pulse electrical stimulation study time-locked to spike and post-spike slow, American Epilepsy Society (AES) 2018 Annual Meeting (2018/11/30-12/04, New Orleans, USA).
11. Shunsuke Kajikawa, Masao Matsuhashi, Katsuya Kobayashi, Takefumi Hitomi, Masako Daifu, Yukihiro Yamao, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Takao Namiki, Ichiro Tsuda, Riki Matumoto, Ryosuke Takahashi, Akio Ikeda: Ictal direct current (DC) shifts can be classified with 2 patterns: Comparison of ictal DC shifts between time constant 10 sec and 2 sec: attempt of classification with cluster analysis, American Clinical Neurophysiology Society, 2019 Annual Meeting and Courses (2019/02/06-10, Las Vegas, USA).
12. Kazuki Oi, Shuichiro Neshige, Takefumi Hitomi, Katsuya Kobayashi, Maya Tojima, Masao Matsuhashi, Akihiro Shimotake, Daiki Fujii, Riki Matsumoto, Shuhei Kasama, Masutaro Kanda, Yoshiaki Wada, Hirofumi Maruyama, Ryosuke Takahashi, Akio Ikeda: LOW-DOSE PERAMPANEL IMPROVES REFRACTORY CORTICAL MYOCLONUS BY THE DISPERSED AND SUPPRESSED PAROXYSMAL DEPOLARIZATION SHIFTS IN THE SENSORIMOTOR CORTEX. 7th Asian-Oceanian Congress on Clinical Neurophysiology (2021/01/30-02/01, web)
13. Maya Tojima, Masao Matsuhashi, Takefumi Hitomi, Kazuki Oi, Katsuya Kobayashi, Kiyohide Usami, Akihiro Shimotake, Ryosuke Takahashi, Akio Ikeda: Origin of giant somatosensory evoked potentials (SEPs) using principal component analysis: P25-HFOs were exclusively seen in benign adult familial myoclonus epilepsy (BAFME). 7th Asian-Oceanian Congress on Clinical Neurophysiology (2021/01/30-02/01, web)
14. Haruka Ishibashi, Kiyohide Usami, Shuichiro Neshige, Hirofumi Maruyama, Ryosuke Takahashi, Akio Ikeda: How to identify posterior dominant rhythm among obscuring EMG artifacts in psychogenic non-epileptic seizures: Time-frequency analysis can help us. 17th Asian Oceanian Congress of Neurology (2021/04/01-04, Taipei, Taiwan (web))
15. Maya Tojima, Shuichiro Neshige, Takefumi Hitomi, Masao Matsuhashi, Kazuki Oi, Katsuya Kobayashi, Kiyohide Usami, Akihiro Shimotake, Ryosuke Takahashi, Akio Ikeda: Markedly suppressed and prolonged giant SEPs by peramppanel: a decade-long course in Unverricht-Lundborg disease. 17th Asian Oceanian Congress of Neurology (2021/04/01-04, Taipei, Taiwan (web)).

## Domestic presentations

## 〈English Presentations〉

16. Masaya Togo, Riki Matsumoto, Takuro Nakae, Hirofumi Takeyama, Katsuya Kobayashi, Kiyohide Usami, Akihiro Shimotake, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda: Human medial parietal cortices have distinct connectivity patterns: Evidence from standardized connectivity map using cortico-cortical evoked potential, 第41回日本神経科学大会 (2018/07/26-29, 神戸).
17. Shunsuke Kajikawa, Katsuya Kobayashi, Masako Daifu, Masao Matsuhashi, Takefumi Hitomi, Yukihiro Yamao, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Riki Matsumoto, Ryosuke Takahashi, Akio Ikeda: Ictal direct current shifts with time constant (TC) 2 seconds and its comparison with TC 10 seconds: Invasive EEG data from intractable human epilepsy, 第41回日本神経科学大会 (2018/07/26-29, 神戸).
18. Makiko Ota, Akihiro Shimotake, Riki Matsumoto, Mitsuhiro Sakamoto, Masako Daifu, Takuro Nakae, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Matthew Lambon-Ralph, Akio Ikeda: Compensation of semantic memory after dominant anterior temporal lobe resection in epilepsy surgery, 第41回日本神経科学大会 (2018/07/26-29, 神戸).
19. Akihiro Shimotake, Riki Matsumoto, Katsuya Kobayashi, Takayuki Kikuchi, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Matthew Lambon-Ralph, Akio Ikeda: Visual and auditory semantic processing converges in the anterior temporal lobe, 第41回日本神経科学大会 (2018/07/26-29, 神戸).
20. Masako Daifu, Riki Matsumoto, Akihiro Shimotake, Makiko Ota, Mitsuhiro Sakamoto, Katsuya Kobayashi, Takayuki Kikuchi, Kazumichi Yoshida, Takeharu Kunieda, Ryosuke Takahashi, Matthew A. Lambon-Ralph, Akio Ikeda: Double dissociation of the semantic and phonological processing in reading Kanji and Kana words - A quantitative low-intensity cortical stimulation study, 第41回日本神経科学大会 (2018/07/26-29, 神戸).
21. Akihiro Shimotake, Riki Matsumoto, Katsuya Kobayashi, Takayuki Kikuchi, Masao Matsuhashi, Kazumichi Yoshida, Takeharu Kunieda, Susumu Miyamoto, Ryosuke Takahashi, Akio Ikeda: Functional mapping of visual and auditory semantic processing in the anterior temporal lobe, 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
22. Norihiro Muraoka, Riki Matsumoto, Katsuya Kobayashi, Ryosuke Takahashi, Akio Ikeda: A case of focal epilepsy presenting the lower jaw, 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
23. Masayuki Honda, Riki Matsumoto, Akihiro Shimotake, Yuichiro Hashi, Mitsuhiro Sakamoto, Daiki Fujii, Katsuya Kobayashi, Takahiro Mitsueda, Akira Kuzuya, Ryosuke Takahashi, Akio Ikeda: Chronological volumetry of amygdala, hippocampus and whole brain and association with clinical course in patients with anti-voltage-gated potassium channel-complex antibodies associated limbic encephalitis (VGKC-LE), 第52回日本てんかん学会学術集会 (2018/10/25-27, 横浜).
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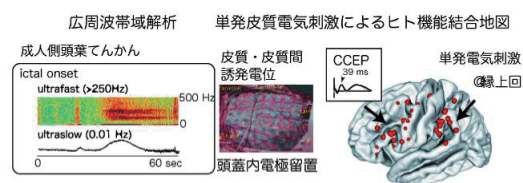
## Collaborative research activity in the Grant-in-Aid for Scientific Research on Innovative Areas: Non-linear Neuro-oscillology - Towards Integrative Understanding of Human Nature.

This five-year innovative research program has been led by Prof. Atsushi Nambu (National Institute for Physiological Sciences, Division of System Neurophysiology) and aimed to create a new academic field of Neuro-oscillology, which enables us to understand human nature. We have been devoting ourselves to researches on wideband-EEG oscillations to understand the human nature and network diseases such as epilepsy (Research Project A03: Principal Investigator Akio Ikeda) and to collaboration with the researchers of other fields including mathematical modeling, intervention and exploration groups.

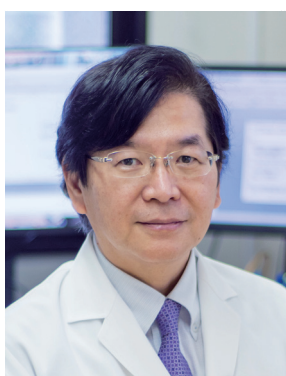
Homepage: <http://www.nips.ac.jp/oscillology/>

### A03 ヒト脳発振現象の直接記録

ヒト脳機能は多次元・多階層の発振現象の非線形的相互作用により発現する。一方、脳機能の異常発現も作動原理の根本は共通し、てんかんは、自律的な脳ネットワークが突発的に種々の次元・階層で過剰発振する「ネットワーク病」と捉えられる。本研究計画では、正常脳機能およびてんかん発作発現にかかわる局所および広域の集団発振現象をヒト脳からの直接記録で探索する。



空間的観点からは、局所神経回路(細胞外多電極記録)からシステムレベル(皮質脳波、頭皮上脳波、脳磁図)で、発達過程の観点からは、ヒトの乳児・小児・成人脳および動物モデルで比較検討する。B班と連携し、記録データからの数理モデルを構築し、正常振動現象および病態下の異常発振の作動原理と制御機構の解明を目指す。C班と連携し、外的および内的な振動制御の手法を用いて、突発性振動異常の制御を試み、介入による多次元・多階層での生理的・病的振動の変容機構を明らかにする。



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## 2<sup>nd</sup> 'Advanced ECoG/EEG Analysis in Epilepsy' symposium

As the pre-congress symposium of the 53rd annual meeting of Japan Epilepsy Society, 2<sup>nd</sup> 'Advanced ECoG/EEG Analysis in Epilepsy (AEEE)' was held cosponsored by Japan Epilepsy Society, JSPS Grant-in-Aid for Scientific Research on Innovative Areas "Neuro-oscillology", g.tec medical engineering GmbH Co., Physio-Tech Co., NIHON KOHDEN Co., Miyuki Giken Co., Unique Medical Co., Ltd.. The objective of this symposium was to facilitate the collaboration between the basic scientists and clinicians for the investigation of epilepsy pathology and normal brain function. Prof. Hiroshi Otsubo (Division of Neurology, The Hospital for Sick Children), Prof. Keiichi Kitajo (Division of Neural Dynamics, Department of System Neuroscience, National Institute for Physiological Sciences), Prof. Dean J. Krusienski (Department of Biomedical Engineering, Virginia Commonwealth University), Prof. Naoyuki Sato (Department of Complex and Intelligent Systems, Future University Hakodate), and Prof. Masayuki Hirata (Department of Neurological Diagnosis and Restoration, Osaka University) were invited as the lecturer for the symposium.



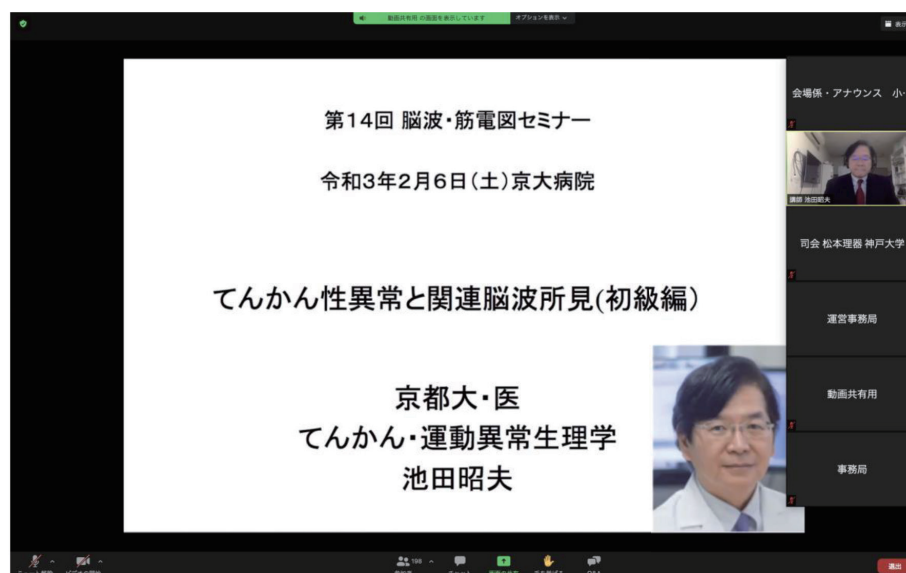
2<sup>nd</sup> AEEE symposium



## 13<sup>th</sup> and 14<sup>th</sup> electroencephalography (EEG) and electromyography (EMG) seminar

13<sup>th</sup>: February 1st, 2020, Kyoto University

14<sup>th</sup>: February 6th, 2021, Web conference



14<sup>th</sup> electroencephalography (EEG) and electromyography (EMG) seminar

## 5<sup>th</sup> and 6<sup>th</sup> advance course of electroencephalography (EEG) seminar

5<sup>th</sup>: August 31st- September 1st, 2019, Shirankaikan, Kyoto University

6<sup>th</sup>: September 5th- September 6th, 2020, Web conference

The advance course of electroencephalography (EEG) seminar was founded by Japanese Society of Clinical Neurophysiology (A committee of advance course of electroencephalography (EEG) seminar: Chair Akio Ikeda) in order to acquire specialized knowledge and technique about clinical EEG. The seminar adopted ANZAN (Australian-New Zealand Association of Neurology) style which consists of 8 sessions, and each session consists of lecture (30 min) followed by practical hands-on related to lecture (60 min). About 60 participants in 5<sup>th</sup> and 140 participants in 6<sup>th</sup> deepened their knowledge about recording and reading of clinical EEG.

EEG samples were prepared by the courtesy of ANZAN (Prof. Andrew Bleasel, Prof. Earnest Somerville, Prof. John W. Dunne, and Prof. Nicholas Lawn).



5<sup>th</sup> advance course of electroencephalography (EEG) seminar

**例1) 63才男性患者 (波形なし)**

Moderately abnormal: awake (30%)/sleep(I) (70%)

- 1) poorly organized background activity, background slow (7Hz)
- 2) intermittent, irregular slow (2-3Hz), focal right parieto-occipital, every 2-5 pages
- 3) **intermittent, irregular slow** (3-5Hz), generalized (max bifrontal), every 3-6 pages, mostly during drowsy state

中等度異常: 覚醒(30%)、睡眠(I期まで)(70%)

- 1) 背景活動の組織化の軽度不良、後頭部優位律動の徐波化(7Hz)
- 2) 間欠的不規則徐波(2-3Hz)、局在性、右頭頂後頭部、2-5ページ毎
- 3) 間欠的不規則徐波(2-3Hz)、全般性(前頭部最大)、3-6ページ毎、殆んどが傾眠期に出現

“この脳波は、軽度から中等度の非特異的なびまん性脳機能障害と、right parieto-occipitalのfocal abnormalityを示唆する”

この時点でこの患者の臨床情報と画像情報(例えば10年前の陳旧性の right parieto-occipitalの脳梗塞があり、2-3年前からの進行性の軽度の認知症症状がある)があれば、その関連についてさらに具体的に言及することができる。

講師 岸田 昭夫

6<sup>th</sup> advance course of electroencephalography (EEG) seminar

## 13<sup>th</sup> Asian & Oceanian Epilepsy Congress (AOEC)

June 10th- 13th, 2021, Web conference

Asian & Oceanian Epilepsy Congress (AOEC) has been held once every two years since the first AOEC was held in 1996. 13<sup>th</sup> AOEC, of which Akio Ikeda served as co-chair, was held as virtual congress due to COVID-19 pandemic.

## English Version of Collection of Works at the Art Exhibition around Epilepsy 2016 and 2017

The Art Exhibition around Epilepsy 2016, which was held for the first time during the 50th Congress of the Japan Epilepsy Society in 2016 based on a proposal from Dr. Yushi Inoue, chair of the congress, received an overwhelming response. The following year, the “Art Exhibition around Epilepsy 2017” was held at the 51st Congress of the Japan Epilepsy Society, which was chaired by Akio Ikeda. In order to introduce the endeavor to organize an art exhibit on epilepsy to patients with epilepsy and medical professionals from Japan and around the world, we have compiled the works of art from the 2016 and 2017 exhibitions into the English version.

<http://epilepsy.med.kyoto-u.ac.jp/art-and-epilepsy>

### Special Lecture

Lecturer: Richard C. Burgess

Affiliation: Cleveland Clinic Epilepsy Center, USA

Title: The Role of Magnetoencephalography in the  
Evaluation of Patients with Complicated Epilepsy

Sponsor: Department of Neurology, Department of  
Epilepsy, Movement disorders and Physiology,  
Kyoto, RICOH

Date: June 13<sup>th</sup>, 2018

Venue: Kyoto University Hospital



Special lecture of Richard C. Burgess

Lecturer: Edward Bertram

Affiliation: University of Virginia, USA

Title: The Evolution of surgery for epilepsy

Sponsor: Department of Neurology, Department of  
Epilepsy, Movement disorders and Physiology,  
Kyoto

Date: October 29<sup>th</sup> 2018

Venue: Kyoto University Hospital



Special lecture of Edward Bertram

Lecturer: William Gaillard

Affiliation: Georgetown University, USA

Title: fMRI mapping of language networks (for epilepsy  
populations/surgery)

Sponsor: Department of Neurology, Department of  
Epilepsy, Movement disorders and Physiology,  
Kyoto

Date: March 20<sup>th</sup>, 2019

Venue: Kyoto University Hospital



Special lecture of William Gaillard

Lecture: Takao Namiki

Affiliation: Hokkaido Graduate school of Mathematics

Title: ヒトてんかん焦点の原理を探る医数理連携

～脳波の高周波発振現象に関する数理モデル～

Sponsor: Department of Neurology, Department of  
Epilepsy, Movement disorders and Physiology,  
Kyoto

Date: July 22<sup>th</sup>, 2019

Venue: Kyoto University Hospital

Lecture: Wei Luo

Affiliation: 2nd Affiliated Hospital, School of Medicine,  
Zhejiang, China

Title: familial cortical myoclonic tremor with epilepsy  
(FCMTE) の臨床, 遺伝子, 治療

Sponsor: Department of Neurology, Department of Epilepsy,  
Movement disorders and Physiology, Kyoto

Date: November 5<sup>th</sup>, 2019

Venue: Kyoto University Hospital



Special lecture of Wei Luo



## Visiting physicians

### [Overseas]

June 13<sup>th</sup> 2018  
 Dr. Richard C. Burgess  
 Affiliation: Cleveland Clinic Epilepsy Center, USA  
 Position: Director of Magnetoencephalography  
 Laboratory

October 29<sup>th</sup> 2018  
 Dr. Edward Bertram  
 Affiliation: University of Virginia, USA  
 Position: Professor of Neurology

March 20<sup>th</sup> 2019  
 Dr. William Davis Gaillard  
 Affiliation: George Washington University Hospital,  
 Position: Professor of Neurology,

### [Domestic]

June 11<sup>th</sup>, July 22<sup>th</sup> 2019  
 Takao Namiki, Ph.D.  
 Affiliation: Department of Mathematics,  
 Hokkaido University  
 Position: Associate Professor

June 11<sup>th</sup>, 2019  
 Prof. Keiichi Ueda, Ph.D.  
 Affiliation: Department of Mathematics,  
 Toyama University  
 Position: Professor

June 11<sup>th</sup>, 2019  
 Prof. Ichiro Tsuda, Ph.D.  
 Affiliation: Department of Mathematics,  
 Chubu University  
 Position: Professor

June 12<sup>th</sup>, 2019  
 Jong-Hyeon Seo  
 Affiliation: Department of Mathematics, Chubu University  
 Position: Researcher

June 12<sup>th</sup>, 2019  
 Naoto Nakano  
 Affiliation: Department of Mathematics, Kyoto University  
 Position: Lecturer

June 12<sup>th</sup>, 2019  
 Takayuki Yamaguchi  
 Affiliation: Center for Data Science Education and  
 Research, Shiga University  
 Position: Assistant professor

**Department of Epilepsy, Movement Disorders and Physiology**  
**Kyoto University Graduate School of Medicine**  
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